European
Neuroendocrine
Association

16th Congress of the European Neuroendocrine Association

10-13 September 2014
Sofia, Bulgaria

ENEA 2014

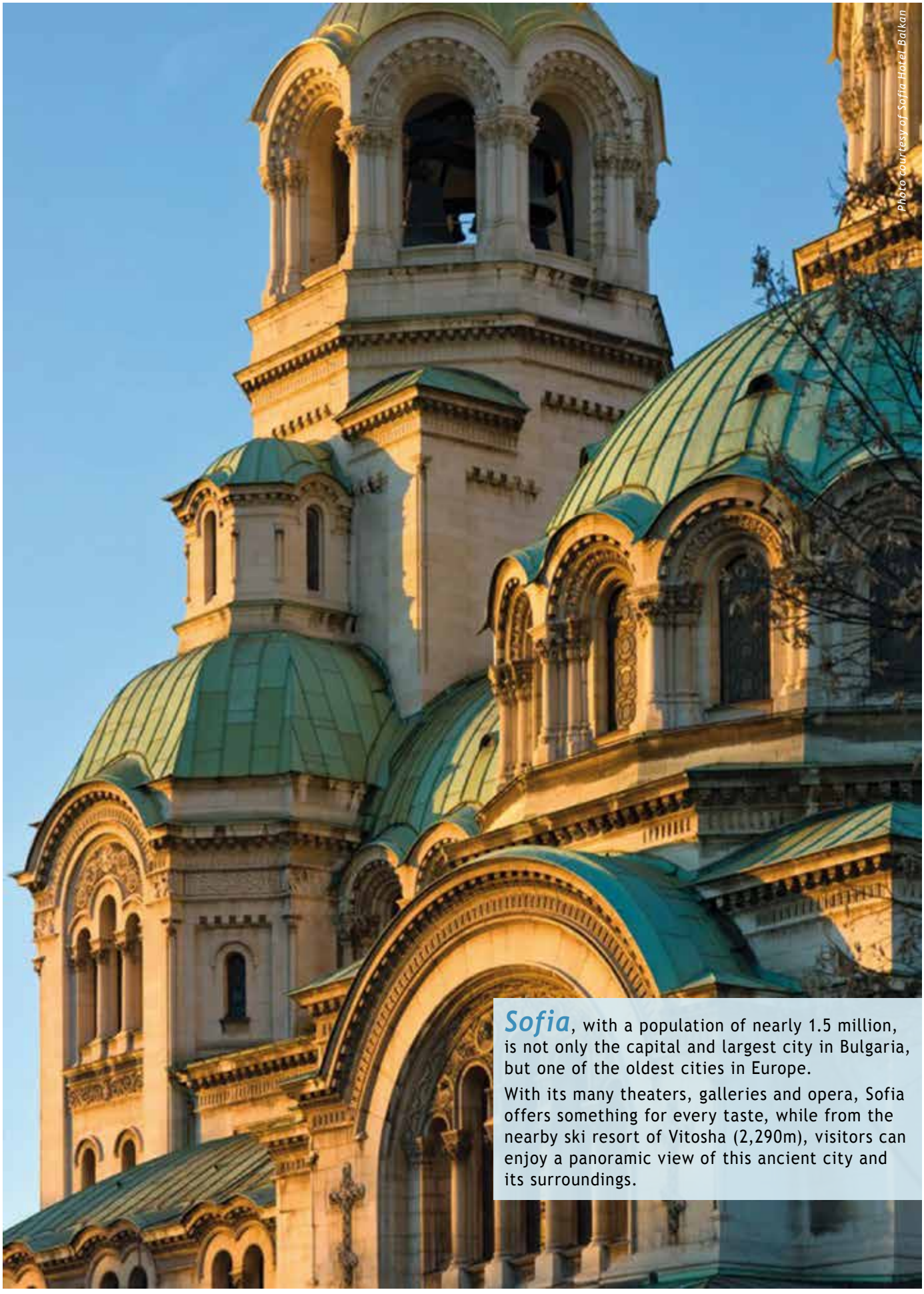

Photo courtesy of Sofia Hotel Balkan

Sofia, with a population of nearly 1.5 million, is not only the capital and largest city in Bulgaria, but one of the oldest cities in Europe.

With its many theaters, galleries and opera, Sofia offers something for every taste, while from the nearby ski resort of Vitosha (2,290m), visitors can enjoy a panoramic view of this ancient city and its surroundings.

ENEA 2014

Sofia, Bulgaria

16th Congress of the European Neuroendocrine Association

Organizing Secretariat & Registration

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European Neuroendocrine Association

Günter K. Stalla (DE) President
Annamaria Colao (IT) President elect
Albert Beckers (BE) Secretary
Philippe Chanson (FR) Treasurer

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Marek Bolanowski (PL)
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Albeto M. Pereira (NL)
Monica Roberto Gadelha (BR)
Ilan Shimon (IL)
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Sabina Zacharieva (BG)

Program Organizing Committee Members:

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Sabina Zacharieva (LOC, BG)
Maria C. Zatelli (IT)
Marek Bolanowski (PL)
Diego Ferone (IT)
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Onno C. Meijer (NL)
Jacques Young (FR)
Juan P. Martinez-Barbera (GB)
Maria A. Tichomirowa (LU)

Local Organizing Committee Members:

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A-M. Borissova
A. Elenkova, Secretary
G. Kirilov
Ph. Kumanov
M. Marinov
E. Nachev
M. Orbetzova
A. Tomova

Welcome message

Dear colleagues and friends,

On behalf of the European Neuroendocrine Association it is a great pleasure to welcome you to the 16th Meeting of the European Neuroendocrine Association here in Sofia, Bulgaria, one of the oldest capitals of Europe, from 10th until 13th of September 2014. We hope to continue the successful tradition of bringing together worldwide specialists who are interested in Neuroendocrinology. The objectives of the Congress are to offer a platform for experts to discuss the diagnosis, management, and treatment of neuroendocrine diseases and exposes the state of art research in the field of neuroendocrinology. The lectures and workshops will be presented by a group of distinguished international speakers. For the first time, the focus of the program will be on the neuroendocrinology of the HPA axis, appetite control, and pituitary development. We are convinced that the scientific program is of interest to physicians and basic scientists alike scientists with an interest in Neuroendocrinology.

We are excited and honored to host so many participants in Sofia for what promises to be a vibrant and significant congress.

Sincerely yours,

Günter K. Stalla
President of ENEA

Alberto M. Pereira
Chair POC

Sabina Zacharieva
Chair LOC

Content

Congress venue
Sofia Hotel Balkan
5, "Sveta Nedelya" square,
1000 Sofia, Bulgaria

General Information

OFFICIAL LANGUAGE

The official language of the Congress is English.

PARTICIPATION

The Congress will be open to all physicians, basic scientists, residents and students interested in the field.

ACCESS TO THE CONGRESS

Participants should wear the identification badge collected at the Secretariat Desk upon registration during all meeting sessions and events.

CERTIFICATE OF ATTENDANCE

A certificate of attendance will be given to all participants.

CITY ACCESSIBILITY

Sofia Airport is an international facility that receives flights from Europe and the world. Transfer time to the city centre is approximately 20 minutes. In the city of Sofia it is recommended to use Public Transportation or Taxi. More information can be obtained over **www.bulgariatravel.org**.

GUIDELINES FOR POSTER PRESENTERS

Posters are required to be prepared and printed in the following format:
Format: **Portrait** Height: **130 cm** Width: **90 cm**

All accepted posters will be accessible to delegates in the poster exhibition area which is located in **Hall Serdica**.

Each poster will receive a specific number, assigning it to the respective poster wall. Material for mounting posters will be provided.

Poster mounting times are as follows:
Wednesday, September 10, from 10:00 to 18:00 or
Thursday, September 11, from 07:30 to 09:30

NOTE that all posters have to be mounted by Thursday, September 11, at 09:30 the latest!

Presenters are kindly requested to remove their posters on Saturday, September 13, by 12:00.

Posters not removed by then will be disposed of.

REGISTRATION

	BEFORE July 13, 2014	AFTER July 13, 2014	ON-SITE
ENEA non Members	550 EUR	600 EUR	700 EUR
ENEA Members	450 EUR	500 EUR	600 EUR
Trainees / Nurses / Students	200 EUR	250 EUR	300 EUR
Accompanying Persons	200 EUR	200 EUR	200 EUR

OPERATING HOURS: REGISTRATION COUNTER

The Registration Counter is situated in the Main Lobby of Hotel Balkan

10.9.	10:00 - 19:30
11.9.	07:15 - 18:30
12.9.	08:15 - 17:45
13.9.	08:00 - 13:30

AUDIOVISUAL FACILITIES AND Media Check

Rooms are equipped with videoprojectors and PC (**PowerPoint**). **Powerpoint is the preferred format** for presentations. Speakers are kindly requested to avoid the use of their personal computer for the presentation.
In the Media Check Room speakers can check their presentation at several work stations. All presenters are required to check in at the Media Check **at least one hour before** the scheduled talk, or the day before if your talk is early the next morning

The Media Check is located in xxxxxxxxxxxx, and will be open at the following times:

10.9.	10:00 - 19:00
11.9.	07:15 - 18:30
12.9.	08:15 - 16:30
13.9.	08:00 - 12:30

INTERNET POINT

A **free internet point** will be available for all registered participants.

LUNCHES AND COFFEE BREAKS

They will be served following the schedule of the scientific program in the **Sredetz Room** and the **exhibition area**.

EXHIBITION

10.9.	13:00 - 18:00
11.9.	08:00 - 18:00
12.9.	08:30 - 17:30
13.9.	08:30 - 13:00

Programme**OVERVIEW**

Wednesday 10 September

Time	ROYAL Hall 1	ROYAL Hall 2	ROYAL Hall 3	RILA Room
13:30 - 13:45	OPENING CEREMONY			
13:45 - 14:15	**PLENARY LECTURE** Cortisol pulsatility: from neuroendocrine mechanisms to transcriptional responses, behavioural adaptation and replacement in humans *Stafford Lightman*			
14:15 - 14:45	**PLENARY LECTURE** Neural control of chronic stress adaptation *Jim Herman*			
14:45 - 15:05	Coffee Break			
15:05 - 17:05	**SYMPOSIUM 1** **Hypercortisolism in the brain: to what extent are the effects reversible?**	Oral Presentation 1		
15:05 - 15:35	Differential effects of chronic high cort on different brain regions *N. Sousa*	Oral Presentation 1.1 Oral Presentation 1.2		
15:35 - 16:05	Neurogenesis and apoptosis in relation to stress hormones *M. Khoel*	Oral Presentation 1.3 Oral Presentation 1.4		
16:05 - 16:35	Structural and functional in vivo brain analysis *N. van der Wee*	Oral Presentation 1.5 Oral Presentation 1.6		
16:35 - 17:05	Cushing as a model for the effects of hypercortisolism in the brain *E. Resmini*	Oral Presentation 1.7 Oral Presentation 1.8		
17:05 - 17:25	Coffee Break			
17:25 - 19:25	**SYMPOSIUM 2** **The 'brite' side of neuroendocrinology**	Oral Presentation 2		
17:25 - 17:55	Brite is the new brown *N. Petrovic*	Oral Presentation 2.1 Oral Presentation 2.2		
17:55 - 18:25	The brite-ness within: white to brite adipocyte inter-conversion *C. Wolfrum*	Oral Presentation 2.3 Oral Presentation 2.4		
18:25 - 18:55	When cold, fat gets hot: brown adipose tissue, thermogenesis and metabolism *P. Nuutila*	Oral Presentation 2.5 Oral Presentation 2.6		
18:55 - 19:25	Central regulation of metabolism via brown adipose tissue *P. Rensen*	Oral Presentation 2.7 Oral Presentation 2.8		
19:25	Welcome Reception			

Poster Exhibition	SERDICA Hall
Catering	SREDETZ Hall
Exhibition Area	LOBBIES/CORRIDORS

Thursday 11 September

Time	ROYAL Hall 1	ROYAL Hall 2	ROYAL Hall 3	RILA Room
08:00 - 09:00	**MEET THE EXPERT** Cushing's disease management in patients without visible pituitary lesion *A. Tabarin*	**MEET THE EXPERT** Hyperprolactinaemia is not always a prolactinoma *D. Maiter*	**MEET THE EXPERT** Management of comorbidities in acromegaly *P. Chanson*	**MEET THE EXPERT** Craniopharyngioma *M. Buchfelder*
09:00 - 10:10	Novartis Industrial Symposium			
10:10 - 10:30	Coffee Break			
10:30 - 12:30	**SYMPOSIUM 3** **Pituitary tumorigenesis: from mice to the human**	Oral Presentation 3 and Featured Poster Presentation (FPP)		
10:30 - 11:00	Pituitary stem cells and tumours *C. Andoniadou*	Oral Presentation 3.1 Oral Presentation 3.2 Oral Presentation 3.3		
11:00 - 11:30	Involvement of RSUME in the neovascularisation of pituitary tumors *U. Renner*	FPP 1 FPP 2 FPP 3 FPP 4 FPP 5 FPP 6 FPP 7 FPP 8		
11:30 - 12:00	Epigenomics *W.E. Farrell*			
12:00 - 12:30	Pituitary tumors: why do they behave so indolent? *S. Melmed*			
12:30 - 13:30	Lunch, Poster session			
13:30 - 15:30	**SYMPOSIUM 4** **Cushing's disease: developments in disease monitoring**	Oral Presentation 4: Say it with a tweet: The ENEA Youngsters		
13:30 - 14:00	Overview of Cushing's related morbidity *M. Yaneva*	Oral Presentation 4.1 Oral Presentation 4.2		
14:00 - 14:30	A focus on thromboembolic complications *J.O.L. Jorgensen*	Oral Presentation 4.3 Oral Presentation 4.4		
14:30 - 15:00	Tools for monitoring disease activity: clinical and patient-related outcomes (data from the Ercusyn) *E. Valassi*	Oral Presentation 4.5 Oral Presentation 4.6		
15:00 - 15:30	Cortisol in scalp hair *E. van Rossum*	Oral Presentation 4.7 Oral Presentation 4.8		
15:30 - 15:50	Coffee Break			
15:50 - 17:50	**SYMPOSIUM 5** **Clinical: Pituitary tumors: Fertility & Pregnancy**	Oral Presentation 5		
15:50 - 16:20	Fertility issues in patients with pituitary tumors *M. Bronstein*	Oral Presentation 5.1 Oral Presentation 5.2		
16:20 - 16:50	Pituitary insufficiency, treatment and monitoring *G. Vila*	Oral Presentation 5.3 Oral Presentation 5.4		
16:50 - 17:20	Acromegaly & Prolactinoma *A. Colao*	Oral Presentation 5.5 Oral Presentation 5.6		
17:20 - 17:50	Cushing *M. de Castro*	Oral Presentation 5.7 Oral Presentation 5.8		
18:00 - 19:00	ViroPharma Industrial Symposium			

Programme**OVERVIEW**

Friday 12 September

Time	ROYAL Hall 1	ROYAL Hall 2	ROYAL Hall 3	RILA Room
08:30 - 09:30	**MEET THE EXPERT** Pitfalls in pituitary imaging *J-F. Bonneville*	**MEET THE EXPERT** A critical re-evaluation of adult GHD *U. Feldt-Rasmussen*	**MEET THE EXPERT** Treatments of NETs *G. Kaltsas*	**MEET THE EXPERT** Management of water and electrolytes imbalance after pituitary surgery *M. Hannon*
09:30 - 10:00	**PLENARY LECTURE** Neuroendocrine control of appetite by gut hormones: a critical view *U. Pagotto*			
10:00 - 10:20	Coffee Break			
10:20 - 12:20	**SYMPOSIUM 6** **EYRC: Whatsapp with pituitary adenomas? The EYRC perspective**	Oral Presentation 6		
10:20 - 10:35	Medical treatment of prolactinomas: what drug, when should we start and when should we stop?" *R. Auriemma*	Oral Presentation 6.1		
10:35 - 10:50	Coagulation abnormalities in patents with CS *T. Dusek*	Oral Presentation 6.2		
10:50 - 11:05	Glucocorticoid pulsatility crucially maintains glucocorticoid receptor signalling in the rodent brain and the neuroendocrine response to stress *A. Sarabdjitsingh*	Oral Presentation 6.3		
11:05 - 11:20	miRNAs or not miRNAs: what role in pituitary tumors? *E. Gentilin*	Oral Presentation 6.4		
11:20 - 11:35	How IGF-I, insulin and gut hormones impact on pituitary function…and dysfunction *M. D. Gahete*	Oral Presentation 6.5		
11:35 - 11:50	Pathology and the management of pituitary adenomas *R. Buslei*	Oral Presentation 6.6		
11:50 - 12:05	Comparative analysis of different treatment outcome in acromegaly. Results from the Bulgarian Acromegaly Database *S. Vandeva*	Oral Presentation 6.7		
12:05 - 12:20	How should a patient harbouring a non-functioning pituitary adenoma with residual tumor after surgery be managed? *L. Vieira Neto*	Oral Presentation 6.8		
12:20 - 13:20	Lunch, Poster session			

Poster Exhibition	SERDICA Hall
Catering	SREDETZ Hall
Exhibition Area	LOBBIES/CORRIDORS

Time	ROYAL Hall 1	ROYAL Hall 2	ROYAL Hall 3	RILA Room
13:20 - 15:20	**SYMPOSIUM 7** **Development and plasticity of hypothalamus-pituitary axes**	Oral Presentation 7		
13:20 - 13:50	Embryo development of corticotroph cells: role of Pax7 *J. Drouin*	Oral Presentation 7.1 Oral Presentation 7.2		
13:50 - 14:20	Hypothalamic development and postnatal neurogenesis *S. Blackshaw*	Oral Presentation 7.3 Oral Presentation 7.4		
14:20 - 14:50	Genetics and phenotype in congenital hypothalamic-pituitary disorders *M. Dattani*	Oral Presentation 7.5 Oral Presentation 7.6		
14:50 - 15:20	Epigenetic control of CRH expression *A. Chen*	Oral Presentation 7.7 Oral Presentation 7.8		
15:20 - 15:40	Coffee Break			
15:40 - 16:10	**PLENARY LECTURE** Pituitary gland and a hypothalamus on a dish *D. Cai*			
16:10 - 17:40	General Assembly ENEA			

Saturday 13 September

Time	ROYAL Hall 1	ROYAL Hall 2	ROYAL Hall 3	RILA Room
08:30 - 09:30	**MEET THE EXPERT** Preclinical models for pituitary drug development *T. Florio*	**MEET THE EXPERT** Familial pituitary adenomas *C.A. Stratakis*	**MEET THE EXPERT** Primary and secondary hypophysitis *F. Golkowski*	**MEET THE EXPERT** How to optimize the chance to obtain an EU grant? *J. Epp*
09:30 - 10:00	**PLENARY LECTURE** Molecular pituitary tumor signature: new targets with clinical implications *E. Arzt*			
10:00 - 10:20	Coffee Break			
10:20 - 12:20	**SYMPOSIUM 8** **New molecular developments in endocrine related cancer**	Oral Presentation 8		
10:20 - 10:50	beta arrestin and G-protein coupled rec kinase2 expression in NET: role in receptor trafficking and regulation of response to somatostatin analogues *F. Gatto*	Oral Presentation 8.1 Oral Presentation 8.2		
10:50 - 11:20	Molecular targets in pheochromocytoma *M. Manelli*	Oral Presentation 8.3 Oral Presentation 8.4		
11:20 - 11:50	Circulating tumor cells as potential markers in neuroendocrine tumors *T. Maijer*	Oral Presentation 8.5 Oral Presentation 8.6		
11:50 - 12:20	MENX as model of development of NET: from hyperplasia to carcinoma *N. Pellegata*	Oral Presentation 8.7 Oral Presentation 8.8		
12:20 - 12:50	**PLENARY LECTURE** Factors that determine sensitivity and resistance to medical intervention in pituitary tumors *L. Hofland*			
12:50 - 13:30	Poster Prizes & Closing Ceremony			

Poster Exhibition	SERDICA Hall
Catering	SREDETZ Hall
Exhibition Area	LOBBIES/CORRIDORS

Wednesday 10 September

Welcome Party, 19:30

Location - Central Department Store (TZUM) of Sofia. Situated just a short walk (100-140m) from Hotel Balkan it offers also a chance to view some recently discovered ruins from Roman times.

Thursday 11 September

Official Dinner, 19:30

Location - a Traditional Bulgarian Restaurant, **The Watermill**, situated in the foothills of Mount Vitosha. Tickets cost 60.00 € per person and include bus transfer, dinner and folklore programme. Buses will depart from the parking lot of Hotel Balkan at 19.30, 30 minutes after the end of the last session of the Congress. Departure of bus transfer from the restaurant to Hotel Balkan: 22:30 - 23:00, after the end of the folklore programme.

Friday 12 September

Opera Concert, 18:30

The Opera concert is sponsored by the Union Bulgarian Bank (UBB) and will be free for the delegates of the Congress. A special invitation will be found in the congress bag. Venue: Sofia National Opera. Distance - about 1 km (map on the invitation). 18.30 h - Welcome drinks, 19.30 h - Opera concert

Additionally we have prepared some surprises:

1. 13:30 to 13:45 on 10/09/2014 – OPENING

Welcome note with two songs by the female folk group from Sofia, winners of UNESCO awards.

2. 19.25 on 10/09/2014 - OFFICIAL OPENING

After greetings and speeches of official guests – a short concert with old Bulgarian songs, composed by the first Bulgarian medieval composer John Koukouzeles in 11-12 century, will be performed by a male church choir. This unique experience will be followed by the Welcome party in the neighboring building of the Central Department Store of Sofia.

3. 13:30 on 13/09/2014 – CLOSING

Greetings with a unique Bulgarian song included in the Golden records of Voyager 1 spacecraft and performed by a famous Bulgarian folk singer.

11,12,13,14 September

DAY TRIPS to local places of interest

People in group	Plovdiv	Bachkovo Monastery	Rila Monastery	Sofia
1-2	240 €	270 €	240 €	
3-6	270 €	300 €	270 €	100 €
7-12	300 €	330 €	300 €	

Prices include transportation and guide service, but do not include entrance fees for the museums.

Wednesday 10 September

ROYAL Hall 1

13:30-13:45
OPENING CEREMONY

ROYAL Hall 1

13:45-14:15
PLENARY LECTURE

Chair: Francesco Cavagnini, Milan, Italy
Ashley Grossman, Oxford, United Kingdom

Cortisol pulsatility: from neuroendocrine mechanisms to transcriptional responses, behavioural adaptation and replacement in humans

Stafford Lightman, Bristol, United Kingdom

ROYAL Hall 1

14:15-14:45
PLENARY LECTURE

Chair: Alberto M. Pereira, Leiden, The Netherlands
Jens Otto Jorgensen, Aarhus, Denmark

Neural control of chronic stress adaptation

James P. Herman, Cincinnati, USA

14:45 - 15:05 Coffee Break

15:05-17:05 SYMPOSIUM 1

ROYAL Hall 1

Hypercortisolism in the brain: to what extent are the effects reversible?

Chair: Susan M. Webb, Barcelona, Spain
Onno C. Meijer, Leiden, The Netherlands

15:05 - 15:35
Differential effects of chronic high cort on different brain regions
Nuno Sousa, Braga, Portugal

15:35 - 16:05
Neurogenesis and apoptosis in relation to stress hormones
Muriel Koehl, Bordeaux, France

16:05 - 16:35
Structural and functional in vivo brain analysis
Nicolaas J. A. van der Wee, Leiden, The Netherlands

16:35 - 17:05
Cushing as a model for the effects of hypercortisolism in the brain
Eugenia Resmini, Barcelona, Spain

17:05 - 17:25 Coffee Break

15:05-17:05 ORAL PRESENTATION 1

ROYAL Hall 2

Chair: Marianne Andersen, Copenhagen, Denmark
Christian Strasburger, Berlin, Germany

15:05
Abstract-ID: 525
MOLECULAR CHARACTERIZATION OF TUMORS IN THE GC RAT MODEL OF ACROMEGALY
David Cano, Seville, Spain

15:20
Abstract-ID: 235
PITUITARY ADENOMAS CONTAIN A SIDE POPULATION WITH 'TUMOR STEM CELL'-ASSOCIATED CHARACTERISTICS
Freya Mertens, Leuven, Belgium

15:35
Abstract-ID: 477
THE GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE RECEPTOR (GIPR) REGULATES GH-SECRETION IN SOMATOTROPINOMAS
Gianluca Occhi, Padua, Italy

15:50
Abstract-ID: 431
INVOLVEMENT OF CELL SENESCENCE AND THE SENESCENCE-ASSOCIATED SECRETORY PHENOTYPE IN THE NON-CELL AUTONOMOUS INDUCTION OF PITUITARY TUMOURS
Jose Mario Gonzalez Meljem, London, United Kingdom

16:05
Abstract-ID: 404
THE ROLE OF HYPOXIA-INDUCIBLE FACTOR SIGNALING IN ACROMEGALIC TUMOR PATHOGENESIS
Kristin Lucia, Munich, Germany

16:20
Abstract-ID: 301
C-TERMINAL HSP90 INHIBITORS RESTORE GLUCOCORTICOID SENSITIVITY IN CUSHING'S DISEASE
Mathias Riebold, Munich, Germany

16:35
Abstract-ID: 297
ROLE OF THE BRAIN IN NEUROENDOCRINE REGULATIONS IN ONTOGENESIS
Michael Ugrumov, Moscow, Russia

16:50
Abstract-ID: 167
RECONSTRUCTION OF NEURONAL DEATH BY USING STEM CELL THERAPY FOLLOWING HYPOXIC–ISCHEMIC BRAIN DAMAGE IN THE RAT
Mohammad Reza Nikravesh, Mashhad, Islamic Republic Of Iran

Wednesday 10 September

ROYAL Hall **1**

17:25-19:25
SYMPOSIUM 2

The 'brite' side of neuroendocrinology

Chair: Ad Hermus, Nijmegen, The Netherlands
Marily Theodoropoulou, Munich, Germany

17:25 - 17:55
Brite is the new brown
Natasa Petrovic, Stockholm, Sweden

17:55 - 18:25
The brite-ness within: white to brite adipocyte inter-conversion
Christian Wolfrum, Schwerzenbach, Switzerland

18:25 - 18:55
When cold, fat gets hot: brown adipose tissue, thermogenesis and metabolism
Pirjo Nuutila, Turku, Finlsnd

18:55 - 19:25
Central regulation of metabolism via brown adipose tissue
Patrick Rensen, Leiden, The Netherlands

ROYAL Hall **2**

17:25-19:25
ORAL PRESENTATION 2

Chair: Irena Ilovaiskaia, Moscow, Russia
Marianne Klose, Copenhagen, Denmark

17:25
Abstract-ID: 396
CHOROID PLEXUS SYNTHESIZES TESTOSTERONE FROM ANDROSTENEDIONE: REGULATION OF 17BHSD3 BY THE SEX HORMONE BACKGROUND.
Telma Quintela, Covilhá, Portugal

Abstract-ID: 437
A GLUCOCORTICOID RECEPTOR HAPLOTYPE THAT ENHANCES GLUCOCORTICOID SENSITIVITY IS ASSOCIATED WITH INCREASED RISK OF METABOLIC SYNDROME: THE LIFELINES COHORT STUDY
Vincent Wester, Rotterdam, The Netherlands

Abstract-ID: 569
INTRAADRENAL ACTH IN BILATERAL MACRONODULAR ADRENAL HYPERPLASIA CAUSING CUSHING'S SYNDROME
Estelle Louiset, Mont-Saint-Aignan, France

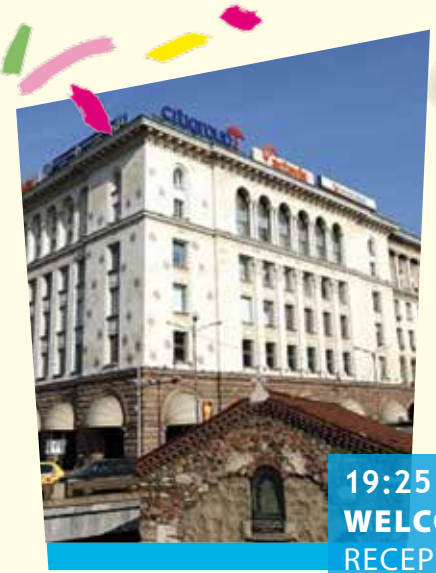
Abstract-ID: 118
PSYCHOLOGICAL MORBIDITY AND IMPAIRED QUALITY OF LIFE IN PATIENTS WITH STABLE TREATMENT FOR PRIMARY ADRENAL INSUFFICIENCY: CROSS-SECTIONAL STUDY AND REVIEW OF THE LITERATURE
Cornelie Andela, Leiden, The Netherlands

Abstract-ID: 311
GLUCOCORTICOID TREATMENT IN CONGENITAL ADRENAL HYPERPLASIA: SHORT AND LONG-TERM EFFECTS OF THE SWITCH FROM CONVENTIONAL GLUCOCORTICOIDS TO „DUAL RELEASE" HYDROCORTISONE ON METABOLIC AND HORMONAL PROFILE, QUALITY OF LIFE AND TREATMENT COMPLIANCE
Chiara Simeoli, Naples, Italy

Abstract-ID: 309
EFFECT OF SWITCH FROM CONVENTIONAL GLUCOCORTICOIDS TO "DUAL RELEASE HYDROCORTISONE" (DR-HC) ON METABOLIC PROFILE AND QUALITY OF LIFE IN ADULT PATIENTS WITH SECONDARY ADRENAL INSUFFICIENCY (SAI): RESULTS OF THREE MONTHS FOLLOW-UP
Chiara Simeoli, Naples, Italy

Abstract-ID: 435
BROWN ADIPOSE TISSUE VOLUME IS MARKEDLY LOWER IN HEALTHY LEAN ADOLESCENTS FROM SOUTH ASIAN COMPARED TO WHITE CAUCASIAN ORIGIN
Mariette Boon, Leiden, The Netherlands

Abstract-ID: 281
RESULTS OF REGISTER OF PATIENTS WITH CUSHING'S SYNDROME IN THE REPUBLIC OF UZBEKISTAN
Gulchekhra Narimova, Tashkent, Uzbekistan



19:25
WELCOME
RECEPTION

Central Department Store (TZUM) of Sofia

Thursday 11 September

08:00 - 09:00
MEET THE EXPERT

ROYAL Hall 1	ROYAL Hall 2	ROYAL Hall 3	RILA Room
Cushing's disease management in patients without visible pituitary lesion Antoine Tabarin *Bordeaux, France*	**Hyperprolactinaemia is not always a prolactinoma** Dominique Maiter *Brussels, Belgium*	**Management of comorbidities in acromegaly** Philippe Chanson *Paris, France*	**Craniopharyngioma** Michael Buchfelder *Erlangen, Germany*

A satellite symposium on the occasion of the
16th Congress of the European NeuroEndocrine Association

Satellite Symposium

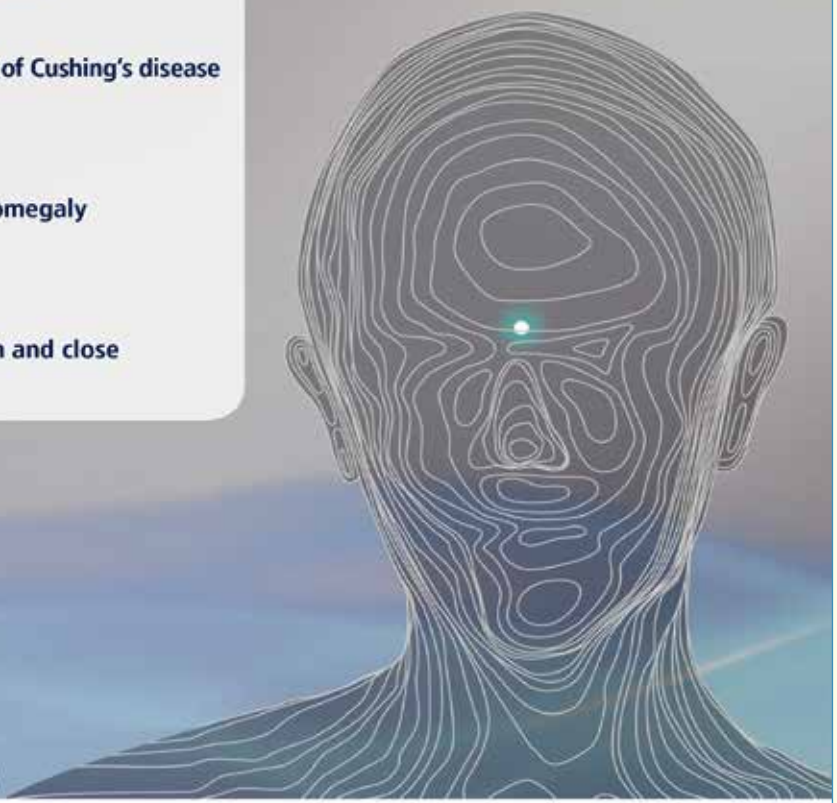
Treatment approaches in pituitary tumours

Thursday 11 September 2014
09:00–10:10

Sofia Hotel Balkan, Sofia, Bulgaria

Co-chairs:
Annamaria Colao (Italy) and Maria Fleseriu (USA)

09:00–09:05	**Welcome and introduction** Maria Fleseriu
09:05–09:30	**The medical treatment of Cushing's disease** Maria Fleseriu
09:30–09:35	**Q&A**
09:35–10:00	**New insights into acromegaly** Annamaria Colao
10:00–10:05	**Q&A**
10:05–10:10	**Symposium conclusion and close** Annamaria Colao



This medical education event is intended for non-US healthcare professionals (HCPs)

NOVARTIS
PHARMACEUTICALS

Thursday 11 September

10:10 - 10:30 Coffee Break

ROYAL Hall **1**

10:30-12:30
SYMPOSIUM 3

Chair: Hugo Vankelecom, Brussels, Belgium
Attila Patócs, Budapest, Hungary

PITUITARY TUMORIGENESIS: FROM MICE TO THE HUMAN

10:30 - 11:00
Pituitary stem cells and tumours
Cynthia L. Andoniadou, London, United Kingdom

11:00 - 11:30
Involvement of RSUME in the neovascularisation of pituitary tumors
Ulrich Renner, Munich, Germany

11:30 - 12:00
Epigenomics
William E. Farrell, Stoke-on-Trent, United Kingdom

12:00 - 12:30
Pituitary tumors: why do they behave so indolent?
Shlomo Melmed, Los Angeles, USA

ROYAL Hall **2**

10:30-12:30
ORAL PRESENTATION 3
and Featured Poster Presentation

Chair: Maria Fleseriu, Portland, USA
Marek Bolanowski, Wroclaw, Poland

10:30
Abstract-ID: 384
ASSOCIATION OF SPLICING VARIANTS OF THE SOMATOSTATIN AND GHRELIN SYSTEMS WITH THE EVOLUTION AND AGRESSIVENESS OF HUMAN NEUROENDORINE TUMORS
Raul Luque, Cordoba, Spain

10:45
Abstract-ID: 535
ANTI-TUMOR EFFICACY OF SOMATOSTATIN ANALOGUES (SSAS) IN PATIENTS WITH NEUROENDOCRINE TUMOURS (NETS) ACCORDING TO KI-67 SCORE: A MULTICENTRIC STUDY FROM ELIOS (EDUCATIONAL LEARNING INVESTIGATIONAL OBSERVATIONAL STUDY)
Antongiulio Faggiano, Napoli, Italy

11:00
Abstract-ID: 410 FFP
EXPRESSION AND ROLE OF RSUME IN ANGIOGENIC FACTOR PRODUCTION IN HUMAN PANCREATIC NEUROENDOCRINE TUMORS
Yonghe Wu, Munich, Germany

11:15
Abstract-ID: 449
ADRENAL INSUFFICIENCY IN CORTICOSTEROIDS USE: SYSTEMATIC REVIEW AND META-ANALYSIS
Leonie Broersen, Leiden, The Netherlands

11:20
Abstract-ID: 389 FFP
ROLE OF LEPTIN AND GHRELIN IN STRESS-RELATED PSYCHOPATHOLOGICAL SYMPTOMS IN FEMALE PATIENTS
Diana Vandeva, Sofia, Bulgaria

11:25
Abstract-ID: 175 FFP
RECONSTRUCTION OF NEURONAL DEATH BY USING STEM CELL THERAPY FOLLOWING HYPOXIC–ISCHEMIC BRAIN DAMAGE IN THE RAT
Mahdi Jalali, Mashhad, Islamic Republic Of Iran

11:30
Abstract-ID: 240 FFP
CLINICAL APPLICATION OF SPECT-CT IMAGING IN PATIENTS WITH THYROID PATHOLOGY
Sonya Sergieva, Sofia, Bulgaria

11:35
Abstract-ID: 52 FFP
GENE EXPRESSION PROFILING IN HUMAN ACTH-SECRETING PITUITARY TUMORS
Francesca Pecori Giraldi, Milan, Italy

11:40
Abstract-ID: 350 FFP
A FAMILY WITH FAMILIAL ISOLATED PITUITARY ADENOMA (FIPA) AND PARAGANGLIOMA
Galina Yordanova, Varna, Bulgaria

11:45
Abstract-ID: 93 FFP
ALTERATIONS IN DIURNAL RHYTHMICITY IN PATIENTS TREATED FOR NONFUNCTIONING PITUITARY MACROADENOMA; A CONTROLLED STUDY AND LITERATURE REVIEW
Sjoerd Joustra, Leiden, The Netherlands

11:50
Abstract-ID: 308 FFP
EVALUATION OF DIAGNOSTIC TEST USING THE SYNTHETIC ANALOGUE OF LH-RH (BUSERELINE) IN THE DIFFERENTIAL DIAGNOSIS OF RETARDED PUBERTY IN ADOLESCENTS
Kamil Gilyazetdinov, Tashkent, Uzbekistan

12:30 - 13:30 Lunch, Poster session

Thursday 11 September

ROYAL Hall **1**

13:30-15:30
SYMPOSIUM 4

Chair: Marco Boscaro, Padua, Italy
Stylianos Tsagarakis, Athens, Greece

Cushing's disease: developments in disease monitoring

13:30 - 14:00
Overview of Cushing's related morbidity
Maria Yaneva, Sofia, Bulgaria

14:00 - 14:30
A focus on thromboembolic complications
Jens Otto Jorgensen, Aarhus, Denmark

14:30 - 15:00
Tools for monitoring disease activity: clinical and patient-related outcomes (data from the Ercusyn)
Elena Valassi, Barcelona, Spain

15:00 - 15:30
Cortisol in scalp hair
Elisabeth F. C. van Rossum, Rotterdam, The Netherlands

ROYAL Hall **2**

13:30-15:30
ORAL PRESENTATION 4

Chair: Maria K.Tichomirowa, Warken, Luxembourg
Gianluca Tamagno, Dublin, Ireland

Say it with a tweet: The ENEA Youngsters

13:30
Abstract-ID: 446
GLUCOCORTICOIDS DIFFERENTIALLY MODULATE BETA ARRESTIN 1 AND BETA ARRESTIN 2 EXPRESSION IN CORTICOTROPH TUMOR CELLS
Federico Gatto, Genoa, Italy

13:45
Abstract-ID: 119
PATIENTS WITH ADRENAL INSUFFICIENCY HATE THEIR MEDICATION: CONCERNS AND STRONGER BELIEFS ABOUT THE NECESSITY OF HYDROCORTISONE INTAKE ARE ASSOCIATED WITH MORE NEGATIVE ILLNESS PERCEPTIONS
Cornelie Andela, Leiden, The Netherlands

14:00
Abstract-ID: 152
CIRCADIAN RHYTHM MODULATES BODY FAT MASS THROUGH BROWN ADIPOSE TISSUE ACTIVITY
Rosa van den Berg, Leiden, The Netherlands

14:15
Abstract-ID: 97
GROWTH HORMONE INDUCES CHEMORESISTANCE IN HUMAN ENDOMETRIAL CANCER CELL LINES INVOLVING ERK 1/2 AND PKCDELTA.
Giulia Zuolo, Ferrara, Italy

14:30
Abstract-ID: 313
NEUROENDOCRINE ASPECTS OF CUTANEOUS MELANOMA: EXPRESSION OF SOMATOSTATIN RECEPTORS AND EFFECTS OF PASIREOTIDE ON MELANOMA CELL LINES VIABILITY, PROLIFERATION AND CELL CYCLE
Gaia Cuomo, Naples, Italy

14:45
Abstract-ID: 395
QOL IN ACROMEGALY: DEPRESSION AND ANXIETY, BUT NOT BIOCHEMICAL CONTROL, ARE PROMISING MODIFIABLE VARIABLES FOR TARGETING REDUCED QOL
Victor Geraedts, Munich, Germany

15:00
Abstract-ID: 385
QOL IN CUSHING'S DISEASE: DEPRESSION AND ANXIETY, BUT NOT BIOCHEMICAL CONTROL, ARE PROMISING MODIFIABLE VARIABLES FOR TARGETING REDUCED QOL
Mareike Stieg, Munich, Germany

15:15
Abstract-ID: 198
EXTRA-PITUITARY NEOPLASMS IN AIP MUTATION POSITIVE INDIVIDUALS: FINDINGS IN A LARGE COHORT OF FAMILIAL ISOLATED PITUITARY ADENOMA (FIPA) AND YOUNG-ONSET SPORADIC PITUITARY ADENOMA PATIENTS
Laura Cristina Hernández Ramírez, London, United Kingdom

15:30 - 15:50 Coffee Break

Thursday 11 September

ROYAL Hall **1**

15:50-17:50
SYMPOSIUM 5

Chair: Ilan Shimon, Tel Aviv, Israel
Elena Grineva, St. Petersburg, Russia

Clinical:
Pituitary tumors: Fertility & Pregnancy

15:50 - 16:20
Fertility issues in patients with pituitary tumors
Marcello D. Bronstein, Sao Paulo, Brazil

16:20 - 16:50
Pituitary insufficiency, treatment and monitoring
Greisa Vila, Vienna, Austria

16:50 - 17:20
Acromegaly & Prolactinoma
Annamaria Colao, Naples, Italy

17:20 - 17:50
Cushing
Margaret de Castro, Sao Paulo, Brazil

ROYAL Hall **2**

15:50-17:50
ORAL PRESENTATION 5

Chair: Laura Cristina Hernández Ramírez, London, United Kingdom
Jacques Young, Le Kremlin-Bicêtre, France

15:50
Abstract-ID: 527
THE COUPLED DEXAMETHASONE-DESMOPRESSIN TEST, A USEFUL ADDITIONAL TOOL TO ADAPT FOLLOW-UP TO T HE RISK OF POSTOPERATIVE RECURRENCE IN CUSHING'S DISEASE
Thierry Brue, Marseille, France

16:05
Abstract-ID: 515
PERIOPERATIVE THROMBOPROPHYLAXIS IN CUSHING'S DISEASE: WHAT WE DID AND WHAT WE ARE DOING.
Mattia Barbot, Padua, Italy

16:20
Abstract-ID: 508
PATIENT REPORTED OUT-COME IN POSTTRAUMATIC PITUITARY DEFICIENCY
Marianne Klose, Copenhagen, Denmark

16:35
Abstract-ID: 506
IS CLINICAL PRACTICE REFLECTIVE OF ACROMEGALY TREATMENT GUIDELINES? RESULTS FROM A SURVEY OF TREATING PHYSICIANS IN 45 COUNTRIES
Diego Ferone, Genoa, Italy

16:50
Abstract-ID: 339
COOPERATIVE EFFECT OF THE HORMONE 5-HYDROXYTRYPTAMINE (SEROTONIN) AND ENDOTHELIN-1 ON CONTRACTILE BEHAVIOUR OF ISOLATED HUMAN MESENTERIC ARTERIES: NEW INSIGHT
Daniela Dimitrova, Sofia, Bulgaria

17:05
Abstract-ID: 158
RESTING-STATE FUNCTIONAL CONNECTIVITY OF THE NEUROCIRCUITRY OF STRESS IN PATIENTS WITH REMISSION OF CUSHING'S DISEASE
Steven van der Werff, Leiden, The Netherlands

17:20
Abstract-ID: 470
A SINGLE-CENTER, OPEN-LABEL, PHASE II, PROOF-OF-CONCEPT STUDY WITH PASIREOTIDE LAR IN PATIENTS WITH PROGRESSIVE MEDULLARY THYROID CANCER (MTC) AND THE COMBINATION WITH RAD001 UPON PROGRESSION
Antongiulio Faggiano, Naples, Italy

17:35
Abstract-ID: 214
CRANIOPHARYNGIOMA: 13 YEARS OF MULTIDISCIPLINARY MANAGEMENT IN SEVILLE (SPAIN)
Eva Maria Venegas Moreno, Seville, Spain

18:00 - 19:00

ViroPharma

INDUSTRIAL **SYMPOSIUM**

Cortisol Replacement

The absence of a suitable biomarker with which to tailor GC replacement therapy in patients with AI has resulted in variability of the therapeutic regimens adopted in routine clinical practice. **Dr. Simunkova** will present the EURADRENAL consortium consensus document that sets treatment goals for patients with AI in the attempt at trying to reduce this variability.

Professor Oster will discuss why cortisol is critically important to synchronise all the body functions and how not respecting the time profile of cortisol replacement may have a host of adverse effects, particularly on metabolism and cardiovascular function.

Until recently, it has not been possible to mimic the physiological cortisol profile – with conventional immediate-release hydrocortisone therapy – **Professor Stalla** will explain the rationale behind the development of PLENADREN® (Hydrocortisone modified-release tablets) in order to provide reliable and consistent serum cortisol levels that better mimic the physiological cortisol profile compared to immediate release replacement therapy, and his clinical experience with this novel drug todate.

The aftermath after being diagnosed with adrenal insufficiency: follow-up and management of adrenal crises
Dr. Katerina Simunkova, Bergen, Norway

Circadian rhythms with key implications on clinical practice in AI.
Prof. Dr. Henrik Oster, Lübeck, Germany

A novel oral glucocorticoid replacement for adult patients with adrenal insufficiency using a dual release hydrocortisone formulation
Prof. Günter K. Stalla, Munich, Germany

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INTSP/IN/PLE/14/0006 Date of preparation August 2014

Friday 12 September

08:30 - 09:30
MEET THE EXPERT

ROYAL Hall 1

Pitfalls in pituitary imaging
Jean-Francois Bonneville
Fontain, France

ROYAL Hall 2

A critical re-evaluation of adult GHD
Ulla Feldt-Rasmussen
Copenhagen, Denmark

ROYAL Hall 3

Treatments of NETs
Gregory Kaltsas
Athens, Greece

RILA Room

Management of water and electrolytes imbalance after pituitary surgery
Mark Hannon
Washington, USA

09:30-10:00 **ROYAL Hall 1**
PLENARY LECTURE

Chair: Aart J. van der Lely, Rotterdam, The Netherlands
Philippe Chanson, Paris, France

Neuroendocrine control of appetite by gut hormones: a critical view
Uberto Pagotto, Bologna, Italy

10:00 - 10:20 Coffee Break

ROYAL Hall 1

10:20-12:20
SYMPOSIUM 6

EYRC: Whatsapp with pituitary adenomas?
The EYRC perspective

Chair: Maria Chiara Zatelli, Ferrara, Italy
Maria Tichomirowa, Warken, Luxembourg

10:20 - 10:35
Medical treatment of prolactinomas: what drug, when should we start and when should we stop?"
Renata Auriemma, Naples, Italy

10:35 - 10:50
Coagulation abnormalities in patents with CS
Tina Dusek, Zagreb, Croatia

10:50 - 11:05
Glucocorticoid pulsatility crucially maintains glucocorticoid receptor signalling in the rodent brain and the neuroendocrine response to stress
Angela Sarabdjitsingh, Utrecht, The Netherlands

11:05 - 11:20
miRNAs or not miRNAs: what role in pituitary tumors?
Erica Gentilin, Ferrara, Italy

11:20 - 11:35
How IGF-I, insulin and gut hormones impact on pituitary function...and dysfunction
Manuel Gahete Ortiz, Cordoba, Spain

11:35 - 11:50
Pathology and the management of pituitary adenomas
Rolf Buslei, Erlangen, Germany

11:50 - 12:05
Comparative analysis of different treatment outcome in acromegaly. Results from the Bulgarian Acromegaly Database
Silvia Vandeva, Sofia, Bulgaria

12:05 - 12:20
How should a patient harbouring a non-functioning pituitary adenoma with residual tumor after surgery be managed?
Leonardo Vieira Neto, Rio de Janeiro, Brazil

ROYAL Hall 2

10:20-12:20
ORAL PRESENTATION 6

Chair: Rosario Pivonello, Italy
Zhanna E. Belaya, Moscow, Russia

10:20
Abstract-ID: 215
LACK OF THE ARYL HYDROCARBON RECEPTOR INTERACTING PROTEIN (AIP) GENE MUTATION IN YOUNG TURKISH PATIENTS WITH SPORADIC PROLACTINOMAS.
Sema Yarman, Istanbul, Turkey

10:35
Abstract-ID: 245
THE ROLE OF MGMT AND MSH6 EXPRESSION IN TEMOZOLOMIDE TREATMENT OF FUNCTIONING PITUITARY ADENOMAS
Alexander Micko, Vienna, Austria

10:50
Abstract-ID: 108
MARKERS OF PROLIFERATION AS PROGNOSTIC FACTORS IN PITUITARY TUMOURS
Agata Baldys-Waligorska, Krakow, Poland

11:05
Abstract-ID: 242
MOSCOW REGION ACROREGISTRY UPDATE 2014
Alexander Dreval, Moscow, Russia

11:20
Abstract-ID: 216
SCREENING OF ACROMEGALY IN PATIENTS WITH SLEEP APNEA SYMPTOMS
Eugenia Resmini, Barcelona, Spain

11:35
Abstract-ID: 244
ASYMMETRIC DIMETHYLARGININE LEVELS IN ADULTS WITH GROWTH HORMONE DEFICIENCY ARE NOT ASSOCIATED WITH TRADITIONAL CARDIOVASCULAR RISK FACTORS
Ivayla Uzunova, Sofia, Bulgaria

11:50
Abstract-ID: 112
THERAPEUTIC OPTIONS AND OUTCOME OF PATIENTS WITH CUSHING'S DISEASE AFTER FAILURE OF INITIAL TRANSSPHENOID SURGERY
Stylianos Tzagarakis, Athens, Greece

12:05
Abstract-ID: 114
FETAL AND GESTATIONAL OUTCOME IN PATIENTS WITH PITUITARY ADENOMAS
Zuleyha Karaca, Kayseri, Turkey

12:20 - 13:20 Lunch, Poster session

Friday 12 September

ROYAL Hall **1**

13:20-15:20
SYMPOSIUM 7

Development and plasticity of hypothalamus-pituitary axes

Chair: Juan Pedro Martinez-Barbera, London, United Kingdom
Thierry Brue, Marseille, France

13:20 - 13:50
Embryo development of corticotroph cells: role of Pax7
Jacques Drouin, Montreal, Canada

13:50 - 14:20
Hypothalamic development and postnatal neurogenesis
Seth Blackshaw, Baltimore, USA

14:20 - 14:50
Genetics and phenotype in congenital hypothalamic-pituitary disorders
Mehul T. Dattani, London, United Kingdom

14:50 - 15:20
Epigenetic control of CRH expression
Alon Chen, Munich, Germany

ROYAL Hall **2**

13:20-15:20
ORAL PRESENTATION 7

Chair: Sabina Zacharieva, Sofia, Bulgaria
Marcello D. Bronstein, Sao Paulo, Brazil

13:20
Abstract-ID: 220
PREDICTIVE VALUE OF SOME GROWTH FACTORS AND CYTOKINES IN PITUITARY ADENOMAS
Iliana Atanasova, Sofia, Bulgaria

13:35
Abstract-ID: 424
A RISK ASSESSMENT MODEL FOR VENOUS THROMBOEMBOLISM IN PATIENTS WITH CUSHING'S SYNDROME
Marialuisa Zilio, Padua, Italy

13:50
Abstract-ID: 262
THE GENDER DIFFERENCE IN THE GROWTH OF PROLACTIN TUMORS IS RELATED TO ESTROGEN RECEPTOR ESR1: CLINICAL, PATHOLOGICAL AND MOLECULAR ARGUMENTS IN A COHORT OF 89 PATIENTS.
Etienne Delgrange, Mont-sur-Meuse, Belgium

14:05
Abstract-ID: 418
CHANGES OF PLASMA RENIN ACTIVITY AND PLASMA ADRENALINE CONCENTRATION DURING NEURONAL NITRIC OXIDE SYNTHASE INHIBITION IN SPONTANEOUSLY HYPERTENSIVE RATS
Radoslav Girchev, Sofia, Bulgaria

14:20
Abstract-ID: 280
DISTURBED SLEEP-WAKE RHYTHMICITY IN PATIENTS PREVIOUSLY TREATED FOR NONFUNCTIONING PITUITARY MACROADENOMAS
Sjoerd Joustra, Leiden, The Netherlands

14:35
Abstract-ID: 370
MEN1 AND PITUITARY ADENOMAS IN CHILDREN AND YOUNG ADULTS
Tatjana Isailovic, Belgrade, Serbia

14:50
Abstract-ID: 365
CAVERNOUS AND INFERIOR PETROSAL SINUS SAMPLING IN THE PREOPERATIVE EVALUATION OF ACTH-DEPENDENT CUSHING'S SYNDROME.
Uliana Tsoi, St. Petersburg, Russia

15:05
Abstract-ID: 448
HYPOTHALAMIC-PITUITARY-OVARIAN AXIS REACTIVATION BY KISSPEPTIN-10 IN HYPERPROLACTINEMIC WOMEN WITH CHRONIC HYPOGONADOTROPIC AMENORRHEA.
Jacques Young, Le Kremlin-Bicêtre, France

15:20 - 15:40 Coffee Break

ROYAL Hall 1

15:40-16:10
PLENARY LECTURE

Chair: Juan Pedro Martinez-Barbera, London, United Kingdom
Annamaria Colao, Naples, Italy

Pituitary gland and a hypothalamus on a dish

Dongsheng Cai, New York, USA

ROYAL Hall 1

16:10-17:40
General Assembly ENEA

Saturday 13 September

08:30 - 09:30 MEET THE EXPERT

ROYAL Hall 1

Preclinical models for pituitary drug development

Tullo Florio
Genoa, Italy

ROYAL Hall 2

Familial pituitary adenomas

Stylianos Tsagarakis
Athens, Greece

ROYAL Hall 3

Primary and secondary hypophysitis

Filip Gołkowski
Krakow, Poland

RILA Room

How to optimize the chance to obtain an EU grant?

Julia Epp
Garching, Germany

09:30-10:00 PLENARY LECTURE — ROYAL Hall 1

Chair: *Günter K. Stalla, Munich, Germany*
Jacques Drouin, Montreal, Canada

Molecular pituitary tumor signature: new targets with clinical implications

Eduardo Arzt, Buenos Aires, Argentina

10:00 - 10:20 Coffee Break

10:20-12:20 SYMPOSIUM 8

ROYAL Hall 1

Chair: Diego Ferone, Genoa, Italy
Albert Beckers, Liege, Belgium

New molecular developments in endocrine related cancer

10:20 - 10:50
beta arrestin and G-protein coupled rec kinase2 expression in NET: role in receptor trafficking and regulation of response to somatostatin analogues
Federico Gatto, Leiden, The Netherlands

10:50 - 11:20
Molecular targets in pheochromocytoma
Massimo Mannelli, Florence, Italy

11:20 - 11:50
Circulating tumor cells as potential markers in neuroendocrine tumors
Tim Meyer, London, United Kingdom

11:50 - 12:20
MENX as model of development of NET: from hyperplasia to carcinoma
Natalia Pellegata, Munich, Germany

10:20-12:20 ORAL PRESENTATION 8

ROYAL Hall 2

Chair: Nienke Biermasz, Leiden, The Netherlands
Thierry Brue, Marseille, France

10:20
Abstract-ID: 423
CORRELATION BETWEEN INTRAOCULAR PRESSURE AND PLASMA AND SALIVARY CORTISOL VALUES IN PATIENTS WITH CUSHING'S SYNDROME
Marialuisa Zilio, Padua, Italy

10:35
Abstract-ID: 455
HIGH PREVALENCE OF AUTOIMMUNE THYROID DISEASES IN WOMEN WITH PROLACTINOMAS: SHOULD THE ROUTINE SCREENING FOR THYROID DYSFUNCTION BE INTRODUCED IN THESE PATIENTS?
Atanaska Elenkova, Sofia, Bulgaria

10:50
Abstract-ID: 467
EFFECTIVENESS OF PASIREOTIDE TREATMENT IN PATIENTS WITH CUSHING'S DISEASE: A NATIONAL EXPERIENCE BASED ON CLINICAL PRACTICE
Rosario Pivonello, Naples, Italy

11:05
Abstract-ID: 445
PASIREOTIDE LAR CAN MAINTAIN BIOCHEMICAL CONTROL IN PATIENTS WITH ACROMEGALY: RESULTS FROM THE EXTENSION OF A RANDOMIZED PHASE III STUDY (PAOLA)
Annamaria Colao, Naples, Italy

11:20
Abstract-ID: 494
NEUROPROTECTIVE EFFECT OF BOSWELLIA SERRATA AND ITS ACTIVE CONSTITUENT ACETYL 11-KETO BETA BOSWELLIC ACID AGAINST ISCHEMIA-INDUCED CYTOTOXICITY
Ahmad Ghorbani, Mashhad, Islamic Republic Of Iran

11:35
Abstract-ID: 530
ROLE OF FILAMIN-A IN SOMATOSTATIN RECEPTOR 2 (SST2) SIGNALING AND EXPRESSION IN GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOR CELLS
Andrea Lania, Rozzano, Italy

Saturday 13 September

11:50
Abstract-ID: 543
THE STIMULATION OF MUSCARINIC ACETYLCHOLINE RECEPTORS INHIBITS DIFFERENTIATION OF MOUSE INDUCED PLURIPOTENT STEM CELLS TO NEURAL PROGENITOR CELLS
Yasuhiro Watanabe, Tokorozawa, Japan

12:05
Abstract-ID: 148
EARLY ENDOCRINE ALTERATIONS REFLECT PROLONGED STRESS AND PROBABLY PREDICT ONE-YEAR FUNCTIONAL OUTCOME IN PATIENTS WITH SEVERE BRAIN INJURY
Marina Djordje, Copenhagen, Denmark

ROYAL Hall **1**

12:20-12:50
PLENARY LECTURE

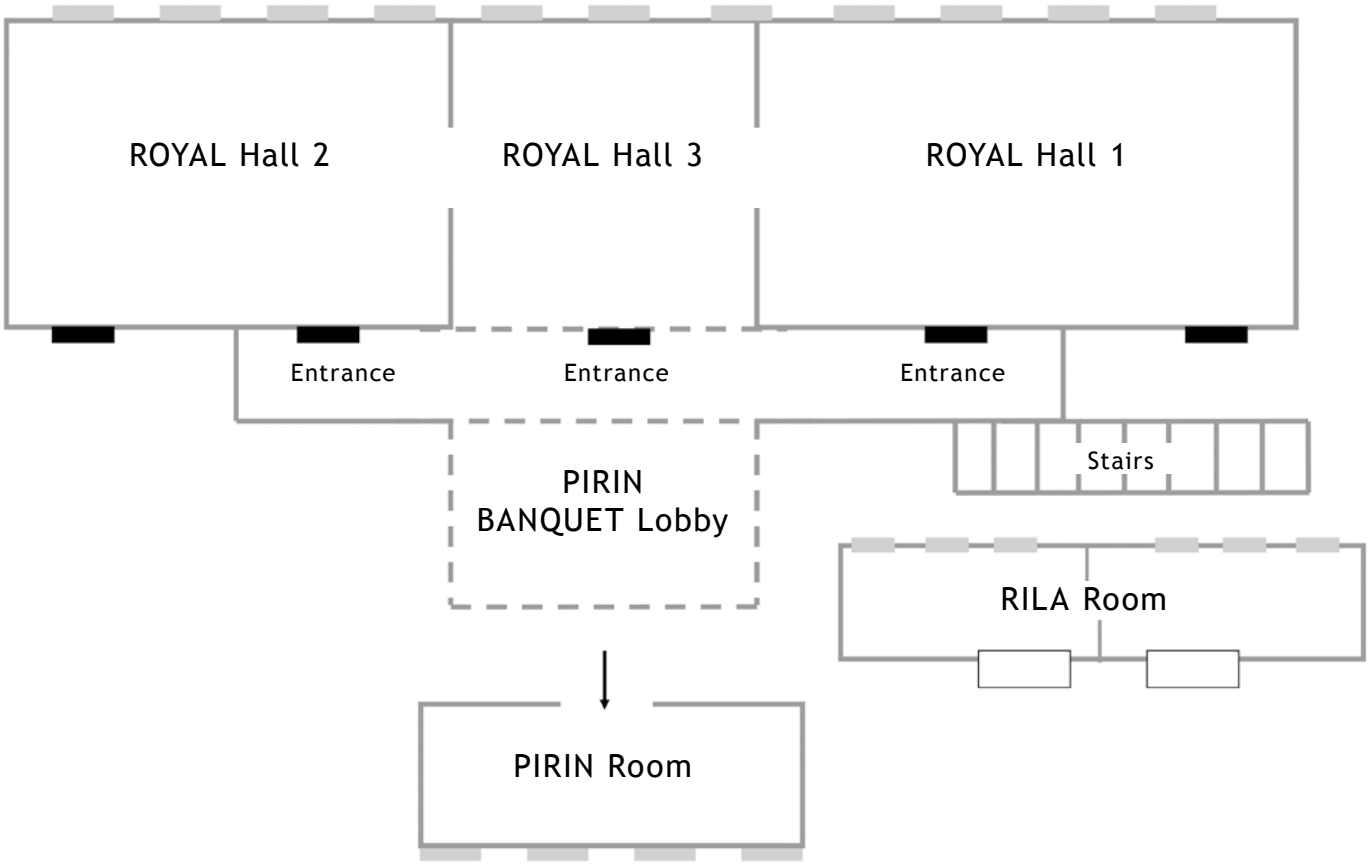
Chair: Ettore degli Uberti, Ferrara, Italy
Monica Gadelha, Rio de Janiero, Brazil

Factors that determine sensitivity and resistance to medical intervention in pituitary tumors
***Leo J. Hofland**, Rotterdam, The Netherlands*

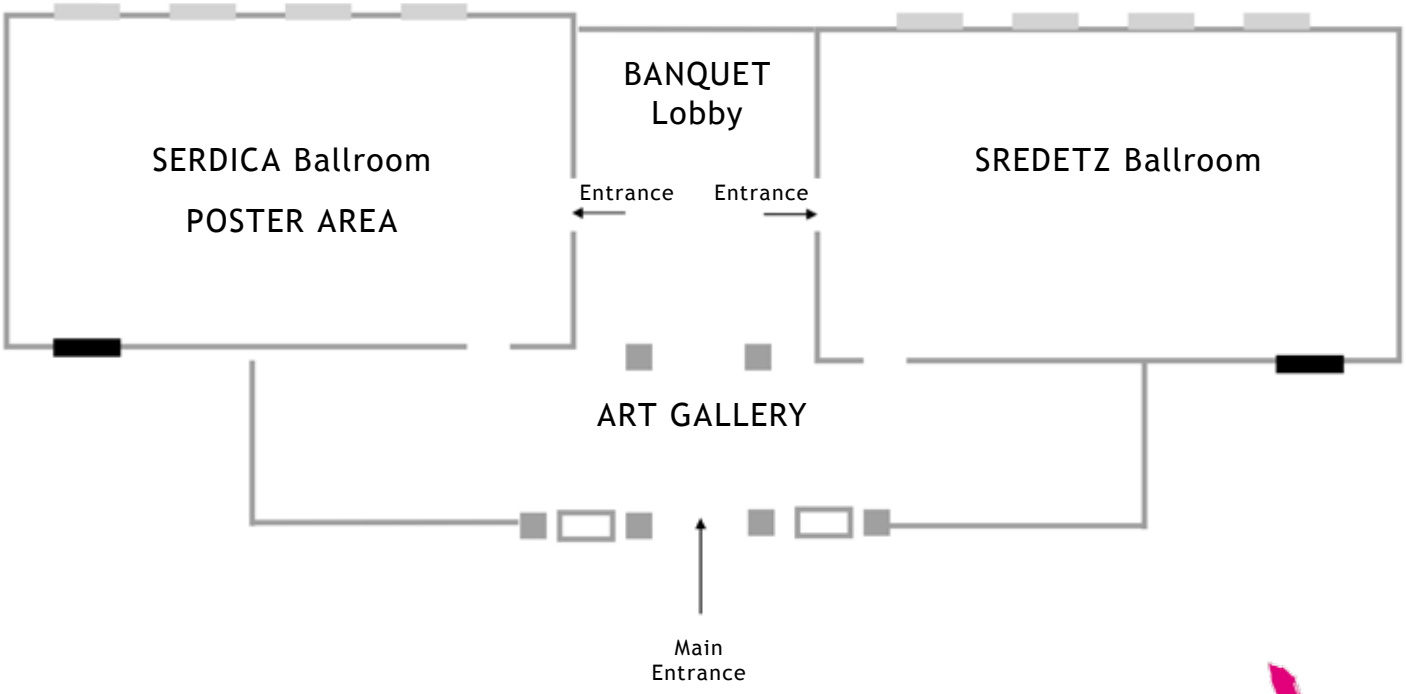
ROYAL Hall **1**

12:50 - 13:30
POSTER PRIZES
& CLOSING CEREMONY

FIRST Floor



GROUND Floor



16th Congress
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Neuroendocrine
Association

ABSTRACTS

ORAL PRESENTATION 1

Abstract-ID: 525

MOLECULAR CHARACTERIZATION OF TUMORS IN THE GC RAT MODEL OF ACROMEGALY

David Cano[1], Juan Francisco Martin-Rodriguez[1], Eva Venegas-Moreno[1], Marcin Balcerzyk[2], Manuel Gahete[3], Justo Castaño[3], Raul Luque[3], Alfonso Soto-Moreno[1], Alfonso Leal-Cerro[4]

[1]Instituto de Biomedicina de Sevilla (Ibis), University Hospital Virgen del Rocío/Consejo Superior de Investigaciones Científicas/University of Sevilla ; Division of Endocrinology, Virgen del Rocío University Hospital, Seville, Spain
[2]Cyclotron Unit, Centro Nacional de Aceleradores, University of Seville, Spain
[3]Department of Cell Biology, Physiology and Immunology, University of Cordoba, Instituto Maimónides de Investigación Biomédica de Córdoba (Imibic), Hospital Universitario Reina Sofia (Hurs); Ciber Fisiopatología de la Obesidad Y Nutrición, Córdoba
[4]Instituto de Biomedicina de Sevilla (Ibis), University Hospital Virgen del Rocío/Consejo Superior de Investigaciones Científicas/University of Sevilla

Subcutaneous implantation of GH-producing GC cells in female Wisth-Furth rats results in acromegalic phenotype. This animal model of acromegaly has been known for almost two decades and largely used to study the effects of chronic GH exposure on target tissues. However, little is known about the kinetics of tumor cell growth and information at the molecular level is scarce. In this study, immunochemistry, molecular biology and imaging techniques were used to characterize in detail the tumors formed in this animal model of acromegaly.

GC cells were injected sc into the flank of 7-week-old rats. Tumors became palpable 2–3 weeks after implantation. For *in vivo* assessment of tumor growth and metabolism, microPET scans with ^{18}F-FDG and [^{11}C]Met were conducted at 1, 2, 4 and 8 weeks after implantation. A 1.5-2 fold increase in glucose uptake and [^{11}C]Met accumulation was localized in the site of injection 1 week after implantation. Highest peaks of these radiotracers at this site were found 2 weeks after implantation. At 4 weeks, microPET scans revealed evidence of tumor necrosis.

Immunohistochemical and qPCR analysis conducted on tumor samples confirmed the tumors to be composed exclusively of GH-producing cells with no evidence of activation of expression of other pituitary hormones. Analysis of somatostatin receptor subtypes expression revealed that Sstr2 was highly expressed followed by Sstr1. Tumor cells displayed marked beta-catenin and N-cadherin membrane levels, a finding consistent with the low metastastic potential of the somatotroph tumors. Interestingly, tumor cells expressed pituitary progenitor cells markers Sox2 and Sox9.

Altogether, our results show molecular similarities between GC-implanted tumors and human somatotroph adenomas. Thus, subcutaneous injection of GC cells might be a useful model to study the mechanisms of somatotroph adenoma tumorigenesis as well as to evaluate compounds for in vivo antitumoral activity.

Abstract-ID: 235

PITUITARY ADENOMAS CONTAIN A SIDE POPULATION WITH 'TUMOR STEM CELL'-ASSOCIATED CHARACTERISTICS

Freya Mertens[1], Lies Gremeaux[1], Qiuly Fu[1], Johan van Loon[2], Marie Bex[3], Carolina Cristina[4], Damasia Becú-Villalobos[5], Hugo Vankelecom[1]

[1]Dept. Development and Regeneration, Research Unit Stem Cell Research, Ku Leuven
[2]DIV. Neurosurgery, Uz Leuven
[3]DIV. Endocrinology, Uz Leuven
[4]National University of the Northwest of Buenos Aires Province (Unnoba)
[5]Lab. Pituitary Regulation, Biology and Experimental Medicine Institute, National Research Council of Argentina (Ibyme-Conicet)

Pituitary adenomas cause severe health problems by hormone hypersecretion and compressive and invasive behavior. Little is known on pituitary tumor pathogenesis. The 'cancer stem cell' (CSC) model posits that tumors contain a subpopulation of cells that drive cancer behavior and progression. We started to search for CSC (or better here, 'tumor stem cells') in resected human pituitary adenomas using the side population (SP) methodology. SP cells are identified as Hoechst^{low} cells using FACS. In several tumor types, the SP is enriched in (candidate) CSC.

We detected a SP in all pituitary tumors analyzed (~2% of the cells; n=60). Further phenotyping also revealed the presence of CD31$^+$ endothelial cells (6-95%) and CD45$^+$ hematopoietic cells (0.2-67%) in the SP. Genome-expression analyses of the CD31$^-$/CD45$^-$ SP (~0.5% of all CD31$^-$/CD45$^-$ adenoma cells) exposed upregulation of several 'tumor stemness' markers and of genes pointing to epithelial-mesenchymal transition (EMT), a major driver of CSC.

The pituitary adenomas were found to contain self-renewing sphere-forming cells - a property of 'tumor stem cells' -, which segregated to the CD31$^-$/CD45$^-$ SP. Since human pituitary adenoma cells do not grow in immunodeficient mice neither in culture, we further turned to the (mouse) pituitary tumor cell line AtT20. The cell line contains a SP (~1%) and induces tumor growth after subcutaneous injection in SCID mice. The AtT20 SP shows upregulated expression of the pituitary stem-cell marker Sox2, a finding also observed in the human CD31$^-$/CD45$^-$ SP. The relationship between pituitary stem cells and tumors is now investigated in the dopamine-receptor D2 knock-out (*Drd2-/-*) mouse, developing prolactinomas. Finally, the EMT-regulatory Cxcr4 pathway appears positively involved in AtT20 xenograft-tumor growth.

In conclusion, we detected a SP in pituitary tumors displaying 'tumor stem cell'-associated characteristics. Our findings may lead to a better understanding of pituitary tumor pathogenesis, and to new therapeutic targets.

Abstract-ID: 477

THE GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE RECEPTOR (GIPR) REGULATES GH-SECRETION IN SOMATOTROPINOMAS

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Somatic mutations in the GNAS1 gene (GNAS^{mut}), encoding the a-subunit of the heterotrimeric stimulatory G protein (Gas), represent the most common genetic alteration so far indentified in GH-secreting pituitary adenomas. By inducing high levels of the second messanger cAMP, even without a specific stimuli, GNAS^{mut} induce GH synthesis/secretion and exert a mitogenic role by promoting GHRH-mediated somatotroph proliferation.

Recently we demonstrated that the glucose-dependent insulinotropic polypeptide receptor (GIPR) in overexpressed in about one third of GH-secreting pituitary adenomas, and in nearly half of cases appeared to be associated with a paradoxical increase in GH after an oral glucose tolerance test (OGTT). In addition, our finding that high GIPR levels and GNAS1 mutations appear to be mutually exclusive suggests that these two events could be part of the same pathogenic mechanism, with cAMP being one of the principal players.

In the present study we aimed to in-vitro confirm the role of GIPR in mediating the paradoxical response of GH after OGTT in acromegalic patients. Primary cultures from nineteen somatotropinomas obtained after transsphenoidal surgery have been used as cellular model to evaluate GIPR expression, GNAS1 mutational status, and GIP ability to induce GH-secretion. The possible association between GIP and somatostatin analogues (SA) responsiveness have also been evaluated.

Seven of nineteen patients presented paradoxical increase in GH (mean increase 84% ± 42%) and in four GNAS1 mutation-negative somatotropinomas

it was associated with GIPR overexpression and to an in-vitro significant increase of GH (55% ± 23%, p<0.05) after GIP stimulation. *GNAS*^{mut} were instead observed in nearly two thirds of cases with low GIPR expression. Among the twelve patients without paradoxical increase all but one were unresponsive to GIP and in one case a missense mutation in codon 227 (Q227L) of *GNAS1* gene have been observed. Apparently no differerences in SA responsiveness have been detected comparing GIP-responsive versus GIP-unresponsive tumors.

In conclusion here we demonstrated that GIPR is able to mediate the paradoxical GH response in a significant proportion of acromegalic patients and that its overexpression in never associated to *GNAS*^{mut}. Further functional studies on cellular models of GH-secreting pituitary adenomas are however now needed to establish whether the GIPR overexpression is merely associated with a paradoxical rise in GH during OGTT or is more generally involved in the pathogenesis of GH-secreting pituitary adenomas.

Abstract-ID: 431

INVOLVEMENT OF CELL SENESCENCE AND THE SENESCENCE-ASSOCIATED SECRETORY PHENOTYPE IN THE NON-CELL AUTONOMOUS INDUCTION OF PITUITARY TUMOURS

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Adamantinomatous craniopharyngioma (ACP) is a paediatric pituitary tumour that is characterised by high recurrence rates and frequent invasion of adjacent brain structures, leading to a long-term compromise in the patient's quality of life. Our group has developed two mouse models for human ACP by expressing oncogenic beta-catenin in either embryonic pituitary precursors (*Hesx1*$^{Cre/+}$;*Cnntb1*$^{lox(ex3)/+}$) or in adult pituitary progenitor/stem cells (*Sox2*$^{CreERT2/+}$;*Cnntb1*$^{lox(ex3)/+}$). Notably, lineage tracing experiments show that the developing tumours are not derived from the progenitor/stem cells sustaining the oncogenic mutation, suggesting that a paracrine mechanism underlies tumour formation. Using our ACP mouse models, we gather evidence that the targeted cells undergo oncogene-induced senescence and show SA-β-galactosidase staining, p53 (*Trp53*) activation and over-expression of cell cycle inhibitors such as p21 (*Cdkn1a*). Oncogenic beta-catenin also causes DNA damage as evidenced by the up-regulation of γH2A.X. Importantly, senescent cells activate a Senescence-Associated Secretory Phenotype (SASP), resulting in the expression of multiple secreted factors including pro-inflammatory cytokines such as IL1, IL6 and IL8 analogues. Additionally, the SASP coincides with the expansion of stromal and immune cell-types during tumour formation. We also provide evidence that this mechanism is relevant to human ACP, as beta-catenin-acummulating cells show strong expression of p53, p21 and γH2A.X by immunohistochemistry. Our observations suggest that in mouse and human ACP, the activation of the P53 pathway may mediate the onset of senescence in pituitary progenitor/stem cells, preventing them from over-proliferating, while the resulting SASP and inflammatory response promote the formation of a pro-oncogenic environment that leads to the paracrine transformation of tumour cells. Testing our hypotheses in a conditional knockout of P53 in our ACP models will provide novel insight into the mechanisms of pituitary tumourigenesis and help identify targets for the treatment of human craniopharyngioma.

Abstract-ID: 404

THE ROLE OF HYPOXIA-INDUCIBLE FACTOR SIGNALING IN ACROMEGALIC TUMOR PATHOGENESIS

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The survival and growth of solid tumors is greatly dependent upon adaptations which not only favor the continued proliferation of neoplastic cells themselves, but also their surrounding microenvironment. One of the most pivotal challenges solid tumors face is the inevitable decrease in oxygen delivery resulting from the outgrowth of proliferating cells beyond the extension of their original blood supply. Adaptive processes which allow tumor cells to survive under hypoxic conditions include the production of growth factors such as vascular endothelial growth factor (VEGF), which trigger the sprouting of new vessels into the tumor mass.

The aim of the study was to characterize the vascularization system in pituitary macroadenomas. The vascularization of 15 acromegalic and 17 nonfunctioning pituitary tumors were examined by CD31 immunohistochemistry and VEGF secretion by ELISA. Acromegalic tumors had low CD31 immunoreactivity scores, indicating low vascularization, but presented with high VEGF-A secretion. VEGF-A expression is transcriptionally regulated by the hypoxia-inducible-factor 1a (HIF1A), therefore we examined the tissue expression of HIF1a in acromegalic tumors and have found increased expression compared to the normal pituitary. We focused on elucidating the effects of HIF1a overexpression on critical parameters of acromegalic tumor pathogenesis such as cell viability, and growth hormone promoter activity using the GH3 somatotrophinoma cell line. HIF1a overexpression increased cell viability compared to mock transfected cells as measured by WST-1 assay and growth hormone promoter activity. GH transcription is under the positive control of the cAMP cascade. HIF1a increased cAMP responsive element (CRE) transcriptional activity, as measured by luciferase promoter assay, implicating HIF1a in the transcriptional regulation of growth hormone in acromegalic tumors.

Taken together, our results demonstrate that the overexpression of HIF1a as it can be found in human acromegalic tumors exerts important influences on several aspects of tumor pathophysiology including cell viability and growth hormone regulation. Therefore, HIF1a may pose an interesting target which may help sensitize acromegalic tumor cells to pharmacological therapy.

Abstract-ID: 301

C-TERMINAL HSP90 INHIBITORS RESTORE GLUCOCORTICOID SENSITIVITY IN CUSHING'S DISEASE

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Cushing's disease (CD) is a severe neuroendocrine condition caused by partially glucocorticoid (Gc) resistant corticotroph adenomas of the anterior pituitary. No safe and efficacious pharmacologic treatment exists to combat Gc-resistance, the central pathogenic mechanism in CD. The molecular chaperone Hsp90 directly regulates the function of GR, and aberrant expression levels of Hsp90 impede GR activity. To date, the role of Hsp90 in GR signaling has never been investigated in corticotroph adenomas.

We show by immunohistochemical staining that the inducible Hsp90α isoform is strongly overexpressed in biopsy specimens of corticotroph adenomas from CD patients as compared to the normal human pituitary. This finding enabled us to elucidate the role of Hsp90 overexpression in corticotroph adenoma cells through pharmacologic inhibition. The N-terminal Hsp90 inhibitor 17-AAG induces GR protein degradation and abolishes all aspects of GR function. In sharp contrast, Novobiocin and the recently identified C-terminal Hsp90 inhibitor MPP-482 increase the amount of mature receptor that binds agonist, without influencing its cellular

protein level. This effect is caused by dissociation of the GR::Hsp90-complex through the C-terminal Hsp90 inhibitors, and results in the potentiation of GR activity. In primary cultures of human corticotroph adenomas, MPP-482 enhances the suppression of ACTH production mediated by GR. Finally, MPP-482 shows antitumorigenic and plasma ACTH lowering effects in a mouse model for Cushing's disease, thereby relieving hypercortisolism and related symptoms.

We show here that C-terminal Hsp90 inhibitors potentially restore Gc-sensitivity in an experimental model of CD through a novel mechanism of action. This work presents the proof-of-concept that MPP-482 could be a safe pharmaceutical treatment for patients with this disease.

Abstract-ID: 297

ROLE OF THE BRAIN IN NEUROENDOCRINE REGULATIONS IN ONTOGENESIS

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According to the current concept of development of the neuroendocrine system, the brain is involved in neuroendocrine regulations only after its final maturation due to the establishment of the hypothalamic control of adenohypophysial hormone secretion. It is believed that at the earlier stage of ontogenesis, biologically active substances (BAS), synthesized in the brain exert only autocrine and paracrine influence on the neuron genesis and expression of a specific phenotype of the differentiating target neurons. We have formulated and proven at studying the rats the alternative hypothesis that the brain from the beginning of the neuron genesis and secretion of BAS up to the establishment of interneuronal synaptic connections and closing the blood brain barrier functions as a multipotent endocrine organ. During this period, the brain neurons secrete into the general circulation dozens, if not hundreds of BAS, which provide a direct endocrine regulation of the development and functioning of peripheral target organs and the brain itself (autoregulation). In the light of this concept, the development of target cells in peripheral organs and in the brain is under the double control, intraorganic paracrine, on the one hand, and endocrine by the brain-derived BAS, on the other. Only after the final development of hypothalamic peptidergic and monoaminergic neurons and the hypophysial portal circulation as well as closing the blood brain barrier - at the latest stage of the brain development, the hypothalamic control of secretion of adenohypophysial tropic hormones is established that is a characteristic of adult mammals.

Thus, the developing brain before closing the blood brain barrier in ontogenesis operates as a multipotent endocrine organ, providing an endocrine regulation of the development and functioning of peripheral target organs and the brain itself.

Abstract-ID: 167

RECONSTRUCTION OF NEURONAL DEATH BY USING STEM CELL THERAPY FOLLOWING HYPOXIC–ISCHEMIC BRAIN DAMAGE IN THE RAT

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Introduction: hypoxic–ischemic (HI) is one of most important injuries in the human neonate at birth and stem cell therapy is one of the hopeful perspectives for treatment against this injury.

Methods: The possible therapeutic potential of human umbilical cord blood stem cells (HUCBSCs) was evaluated in 7 days rats subjected to the right common carotid occlusion, a model of neonatal hypoxic ischemic (HI) brain damage. Seven days after HI, rats received either saline solution or 4×105

HUCB cells intravenously. After two weeks, rats were assessed using two motor tests. Subsequently, rats were killed for histologic and immunohistochemical analyses. Animals who did not receive any injection or surgeries were used as a control group.

Results: Immunohistochemical evaluations revealed HUCB cells located in rat brain and behavioral assessment also shown that a significant improvement in group that received HCBSCs.

Conclusion: Intravenous transplantation can be a future line in treatment of infants with hypoxic who are exposed to irreversible damages. These results show that treatment by HCBSCs in young hypoxic–ischemic brain injury is a feasible and efficacious method for cell therapy with potential for clinical use.

Key words: Neuronal death, Stem cell, Hypoxic-ischemic, Rat.

ORAL PRESENTATION 2

Abstract-ID: 396

CHOROID PLEXUS SYNTHESIZES TESTOSTERONE FROM ANDROSTENEDIONE: REGULATION OF 17BHSD3 BY THE SEX HORMONE BACKGROUND.

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Objectives: Neurosteroids have been emerging as important regulators of numerous central nervous system functions, playing essential roles in protecting the brain from insults such as neurodegeneration or ischemia. The choroid plexus (CP) forming a physical interface between the peripheral blood and the cerebrospinal fluid (CSF), regulate the uptake of nutrients, hormones and several other compounds from the peripheral blood into the CSF, and play pivotal roles in repair processes following trauma. There are evidences that CP is a target of sex steroid hormones, which regulate the expression of some proteins with impact in neuroprotection in this tissue. Unlike other brain regions, there are no current indications that CP may produce sex hormones as well, but a recent cDNA microarray analysis of the CP transcriptome showed that several enzymes involved in steroidogenesis are expressed in this tissue. Therefore, we tested the capacity of CP explants to synthesize testosterone and analyzed the expression of steroidogenic enzymes in response to the hormonal background.

Methods: This study evaluates the presence of steroidogenenic enzymes in rat CP using RT-PCR, immunohistochemistry, Western blot and immunofluorescence. In addition, we assessed the production of neurosteroids by rat CP explants from tritiated androstenedione using thin layer liquid chromatography.

Results: We demonstrate the presence of mRNA transcripts for P450scc (Cyp11A1), P450aro (Cyp19A1), 17βHSD3 (HSD17B3) and 5α-reductase (SRD5A1 and SRD5A2). Protein expression of enzymes required for testosterone synthesis in CP was also confirmed using immunohistochemistry and Western blot. Moreover, we demonstrate that CP explants are capable of converting [3H]-androstenedione to testosterone. Finally, to assess dynamic changes in the expression patterns of 17βHSD3, real-time RT-PCR was performed in CP of female and male rats subjected to gonadectomy. We show that the 17βHSD3 enzyme is up-regulated in female and male rat CP, suggesting that the peripheral hormonal background modulates the synthesis of testosterone in CP.

Conclusions: Collectively these data show that the CP has the potential to synthesize testosterone, thereby being able to regulate the hormonal content of the CSF, counterbalancing changes in peripheral hormone levels.

Abstract-ID: 437

A GLUCOCORTICOID RECEPTOR HAPLOTYPE THAT ENHANCES GLUCOCORTICOID SENSITIVITY IS ASSOCIATED WITH INCREASED RISK OF METABOLIC SYNDROME: THE LIFELINES COHORT STUDY

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Background: An excess of glucocorticoids (e.g. Cushing's syndrome) often presents with features of metabolic syndrome. Sensitivity to glucocorticoids is partly determined by polymorphisms in the glucocorticoid receptor (GR). These polymorphisms may therefore affect the risk for metabolic syndrome. We examined the association between functional GR polymorphisms and presence of metabolic syndrome.

Subjects and methods: In 13.386 adult Dutch individuals from the LifeLines Cohort study (58.2% female; median age 47, IQR 40 – 55), functional GR polymorphisms (BclI, N363S, ER22/23EK, GR-9beta and TthIIII) were genotyped using GWAS imputation with 1000 Genomes as a reference set. Using PHASE, GR haplotypes were constructed. Using logistic regression with a stepwise backwards elimination approach, the association between metabolic syndrome (ATPIII criteria) and each GR haplotype was tested, with age, sex, education level and smoking status as covariates.

Results: Six GR haplotypes accounted for 99.7% of all haplotypes found, with frequencies similar to those in our previous studies. We found a significant contribution of GR haplotype 5 (P<0.001), which contained polymorphism N363S (rs56149945), on the presence of metabolic syndrome in interaction with age, sex and education status. Stratification for education status showed that haplotype 5 increased the risk of metabolic syndrome in people with low (OR 1.47, 95% CI 1.08 – 2.01) but not in people with middle or high education status (OR 0.84, 95% CI 0.64 – 1.09 and OR 0.84, 95%CI 0.55 – 1.31, respectively). The influence of haplotype 5 declined with increasing age (OR per year increase 0.97, 95%CI 0.96 – 0.99).

Conclusion: a GR haplotype that is known to be related with increased glucocorticoid sensitivity was associated with increased risk of metabolic syndrome in interaction with education level. Our results indicate a significant gene-environment interaction, in which a genetic constitution predisposing for metabolic syndrome (a hypersensitive GR) is predominantly expressed in the presence of low education status.

Abstract-ID: 569

INTRAADRENAL ACTH IN BILATERAL MACRONODULAR ADRENAL HYPERPLASIA CAUSING CUSHING'S SYNDROME

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Illicit expression of membrane receptors for circulating regulatory factors, such as gastric inhibitory polypeptide (GIP), luteinizing hormone (LH) and serotonin (5HT) receptors, has been well documented in bilateral macronodular adrenal hyperplasias (BMAHs) causing Cushing's syndrome. In addition, we have observed an abnormal expression of ACTH in some steroidogenic cells in two BMAH tissues. The aim of the present study was to investigate the role of local production of ACTH in the control of steroidogenesis in a series of 30 BMAH tissues. Expression of pro-opiomelanocortin (POMC) mRNA and ACTH-like immunostaining were detected in all tissues studied. ACTH co-localized with 17hydroxylase, the HDL-cholesterol receptor SR-B1, prohormone convertase 1 and secretogranin II immunoreactivities in clusters of cells disseminated throughout hyperplasia tissues. Perifusion experiments demonstrated that adrenal slices spontaneously released detectable amounts of ACTH in a pulsatile fashion. ACTH secretion was significantly increased in vitro by GIP, hCG and 5-HT in tissues previously sensitive in vivo to the stimulatory action of food intake, hCG and 5-HT4 receptor agonists. In addition, measurement of ACTH concentrations in plasma obtained from two BMAH patients during adrenal vein sampling showed a significant ACTH gradient versus periphery indicating that BMAH tissues actually secrete ACTH in vivo. The ACTH receptor antagonists corticostatin and ACTH(7-38) reduced basal as well as GIP-induced cortisol production from perifused hyperplasia tissues. These data indicate that, in BMAH tissues, ACTH released by a subpopulation of steroidogenic cells exerts an intraadrenal stimulatory tone on cortisol secretion. They also suggest that macronodular bilateral adrenal hyperplasia may be regarded as a cause of ACTH-dependent Cushing's syndrome due to ectopic expression of corticotropin within the adrenal cortex. *This work was supported by grants from INSERM, Assistance Publique des Hôpitaux de Paris, the COMETE network, the Société Française d'Endocrinologie and Novo Nordisk Laboratory.*

Abstract-ID: 118

PSYCHOLOGICAL MORBIDITY AND IMPAIRED QUALITY OF LIFE IN PATIENTS WITH STABLE TREATMENT FOR PRIMARY ADRENAL INSUFFICIENCY: CROSS-SECTIONAL STUDY AND REVIEW OF THE LITERATURE

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Context: A high prevalence of psychological morbidity and maladaptive personality as well as impaired quality of life (QoL) is observed in patients with and without hydrocortisone dependency following (cured) Cushing's syndrome. However, it is currently unclear whether a similar pattern is present in patients with chronic glucocorticoid replacement for primary adrenal insufficiency (PAI).

Objective: To evaluate psychological functioning, personality traits, and QoL in patients with PAI.

Design and subjects: A cross-sectional study including 54 patients with stable treatment for PAI and 54 healthy matched controls. Both patients and controls completed questionnaires on psychological functioning (Apathy Scale, Irritability Scale, Mood and Anxiety Symptoms Questionnaire short-form, and Hospital Anxiety and Depression Scale), personality traits (Dimensional Assessment of Personality Pathology short-form), and QoL (Multidimensional Fatigue Inventory, Short-Form 36, EuroQoL-5D, Nottingham Health Profile, and Physical Symptom Checklist).

Results: Patients with PAI suffered from more psychological morbidity (i.e. irritability and somatic arousal) and QoL impairments compared with controls (all P<0.01). There were no differences regarding maladaptive personality traits between patients and controls. However, there was a strong and consistent positive association between the daily hydrocortisone dose and prevalence of maladaptive personality traits (i.e. identity problems, cognitive distortion, compulsivity, restricted expression, callousness, oppositionality, rejection, conduct problems, social avoidance, narcissism, and insecure attachment, all P<0.05). There was also a strong relation

between the mean daily hydrocortisone dose and both psychological morbidity (i.e. depression, P<0.05) and QoL impairments (i.e. general health perception, several measures of physical functioning, and vitality, all P<0.05).

Conclusion: Patients with stable glucocorticoid replacement therapy for PAI report psychological morbidity and impaired QoL. Psychological morbidity, impaired QoL, and maladaptive personality traits were all associated with higher hydrocortisone dosages.

Abstract-ID: 311

GLUCOCORTICOID TREATMENT IN CONGENITAL ADRENAL HYPERPLASIA: SHORT AND LONG-TERM EFFECTS OF THE SWITCH FROM CONVENTIONAL GLUCOCORTICOIDS TO „DUAL RELEASE" HYDROCORTISONE ON METABOLIC AND HORMONAL PROFILE, QUALITY OF LIFE AND TREATMENT COMPLIANCE

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Life-long glucocorticoid (GC) treatment is needed in patients with 21-hydroxylase deficiency congenital-adrenal-hyperplasia (CAH) to replace cortisol and to prevent hyperandrogenism. CAH is associated with metabolic syndrome (MS), probably due to cortisol overexposure, caused by multiple daily GC doses, an impaired QoL and poor treatment compliance (TC). The current study aimed at investigating the impact of the switch from twice/thrice daily GCs to once daily dual-release-hydrocortisone (DR-HC) on metabolic and hormonal profile, QoL and TC in CAH patients. Twenty-four CAH patients (16F, 8M, 19-39yrs), chronically treated with hydrocortisone (10-40mg/day) or prednisone (6.25-12.5mg/day) and switched to DR-HC (10-40mg/day) entered the study. Metabolic and hormonal profile, QoL and TC were evaluated before and after 3 and 6 month-DR-HC in 24 and 17 patients, respectively. Insulin resistance (IR) was evaluated by HOMA-IR whereas MS by IDF. QoL and TC were investigated using specific questionnaires. After 3 months, fasting-glucose (p=0.04) and HDL-cholesterol (p=0.018) significantly improved. After 6 months, fasting-glucose (p=0.007) and HOMA-IR (p=0.057) significantly improved. A clear diagnosis of MS, performed in one patient at baseline, was not confirmed after 6 months. Other metabolic parameters did not significantly change. No significant change in ACTH, cortisol, 17-OH progesterone and androgens and no clinical worsening of hyperandrogenism were observed. General health perception, vitality and working ability ameliorated in 37, 25 and 21% of patients respectively after 3 months and in 12, 23 and 23% after 6 months. Depression and body pain perception improved in 21 and 25% of patients respectively after 3 months and in 23 and 35% after 6 months. TC improved at both evaluations moving from low to medium adherence. In conclusion, the switch from conventional GCs to DR-HC improves metabolic parameters, QoL, TC, maintaining an optimal hormone control in CAH patients, suggesting that DR-HC might ensure a better clinical management of CAH.

Abstract-ID: 309

EFFECT OF SWITCH FROM CONVENTIONAL GLUCOCORTICOIDS TO "DUAL RELEASE HYDROCORTISONE" (DR-HC) ON METABOLIC PROFILE AND QUALITY OF LIFE IN ADULT PATIENTS WITH SECONDARY ADRENAL INSUFFICIENCY (SAI): RESULTS OF THREE MONTHS FOLLOW-UP

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Adrenal Insufficiency (AI) requires life-long glucocorticoid (GC) treatment, which is associated with an increased risk of metabolic syndrome (MS), probably due to cortisol overexposure for multiple drug daily doses, together with an impairment of QoL. Moreover treatment compliance (TC) is reported to be suboptimal in AI patients. The current study aimed at investigating the impact of the switch from twice/thrice daily conventional GCs to once daily dual-release-hydrocortisone (DR-HC) treatment on metabolic profile, QoL and TC in a cohort of patients with secondary AI (SAI). Twelve patients (6F, 6M, 37-70 yrs) chronically treated with cortisone acetate (12.5-75 mg/day) or hydrocortisone (15 mg/day) entered the study and switched to DR-HC (15-60 mg/day). Metabolic parameters were evaluated in the entire group of 12 patients whereas QoL and TC were evaluated in a subgroup of 6 patients before and after 3 months of DR-HC. Visceral Adiposity Index (VAI) was calculated according to Amato and co-workers, whereas MS was assessed in line with IDF criteria. QoL and TC were investigated using specific questionnaires. At 3-month-follow-up, HDL-cholesterol (p<0.001), triglycerides (p=0.021) and VAI (p=0.001) significantly improved and a trend to a significant improvement was also found for total (p=0.087) and LDL (p=0.063) cholesterol. Waist circumference, fasting-glucose, diastolic and systolic blood pressure did not significantly change. A clear diagnosis of hypertension and MS, performed in 3 patients (25%) at baseline, was confirmed only in one (8.3%) case after 3 months. QoL improved in all 6 patients. Particularly, general health perception ameliorated in all patients, whereas vitality, working ability, depression and body pain perception in 2 of 6 (33.3%) patients. TC also improved, changing from low to medium adherence. In conclusion, the switch from conventional GCs to DR-HC rapidly improved lipid profile, VAI, prevalence of hypertension and MS, QoL and TC, suggesting a better clinical management of SAI patients

Abstract-ID: 435

BROWN ADIPOSE TISSUE VOLUME IS MARKEDLY LOWER IN HEALTHY LEAN ADOLESCENTS FROM SOUTH ASIAN COMPARED TO WHITE CAUCASIAN ORIGIN

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Background: South Asians have a higher risk of developing type 2 diabetes than white Caucasians. Though the underlying cause is still poorly understood, it is assumed that an ethnic susceptibility towards a disturbed energy metabolism might be present. Brown adipose tissue (BAT) has emerged as an important player in energy metabolism by combusting fatty acids and glucose towards heat. We, therefore, hypothesized that a low total BAT activity might underlie the susceptibility for T2DM in South Asians.

Methods: BAT volume and activity were measured in young healthy lean adolescents (mean age 24.1 ± 0.6 years) from South Asian (n=12) and white Caucasian (n=12) origin, matched for BMI, using cold-induced ^{18}F-FDG-PET-CT-scans. Furthermore, REE, non-shivering thermogenesis (NST) and plasma parameters were assessed.

Results: REE was lower in South Asian compared to white Caucasian adolescents (-32%, P<0.005). Cold exposure significantly increased NST in white Caucasians (+20%, P<0.005), but not in South Asians. Furthermore, a significant cold-induced increase in plasma FFA levels appeared in white Caucasians only (+50%, P<0.005). Maximal (SUV_{max}) and mean (SUV_{mean}) ^{18}F-FDG uptake in the classical BAT regions did not differ between South Asian and Caucasian subjects. However, total BAT volume was markedly lower in South Asians (-34%, P<0.05), as was total BAT activity (-38%, P<0.05). In addition, cold exposure resulted in higher shiver temperature in South Asians (+22%, P<0.01), while cold-induced NST was lower in South Asians, both indicative of a lower BAT function than white Caucasians. Taken the subjects together, total BAT activity correlated positively with basal REE (R=0.42; P<0.05).

Conclusions: Healthy South Asian adolescents have lower REE, BAT volume and total BAT activity as well as lower NST and cold-induced FFA release compared to matched white Caucasians. This might underlie their high susceptibility to develop metabolic disturbances, such as obesity and type 2 diabetes.

Abstract-ID: 281

RESULTS OF REGISTER OF PATIENTS WITH CUSHING'S SYNDROME IN THE REPUBLIC OF UZBEKISTAN

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Aim of the study: analysis of Register data on diagnosis, complications, and results of different methods of therapy in patients with Cushing's syndrome (CS).

Materials and Methods. According to the Register, there are 178 patients with CS in Uzbekistan: 121 women (64.4 %, age 31,8±2,5 years), 55 men (29.3%, age 29±0,5), 12 children and adolescents (6.4%, age 13,4±2,5, range 1.8 to 17 years). The average age of the disease onset is 27.2 years (range 3-59 years) with a predominance of women - 2:1. ACTH-dependent CS - in 84.9%, ectopic ACTH syndrome in 0.5%. ACTH independent CS – 14.5%. Analysis of complications at diagnosis in patients with ACTH-dependent CS revealed carbohydrate metabolism disorders (CMD) in 41.8%, osteopenia and osteoporosis in 68.9%, cardiovascular complications in 80.4%, reproductive disorders in 68.4%. Analysis of complications at diagnosis in patients with ACTH-independent CS showed: CMD in 65%, osteopenia and osteoporosis in 80%, cardiovascular complications in 95%, reproductive disorders 75%.

Analysis of patients condition after different methods of treatment showed the large percentage of remissions after TSAE -90.6%, after combined therapy -80%, after adrenalectomy -78.3% and after drug therapy -51.5%. Patients with ACTH-independent CS undergone surgery, and all are in remission. Of all patients with CS 67.4% are in remission, 7% had relapse, 17% didn't achieve remission, and there is no information about 8.4% of patients.

Conclusions. The results of the Register of patients with CS in the Republic showed that there are 178 patients with endogenous CS registered with significant predominance of patients with ACTH-dependent CS (85.4%).

The frequency and severity of complications prevale significantly in individuals with ACTH independent CS, suggesting more aggressive course of this syndrome.

According to the Register, higher frequency of remission was achieved after TSAE (90.6%), confirming TSAE to be the treatment of choice for CS.

ORAL PRESENTATION 3

Abstract-ID: 384

ASSOCIATION OF SPLICING VARIANTS OF THE SOMATOSTATIN AND GHRELIN SYSTEMS WITH THE EVOLUTION AND AGRESSIVENESS OF HUMAN NEUROENDORINE TUMORS

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Introduction: Somatostatin/cortistatin, ghrelin and their receptors (ssts and GHRs, respectively) comprise complex, pleiotropic regulatory systems involved in the regulation of a plethora of overlapping pathophysiological functions. Interestingly, recently discovered splicing variants of some components of these systems (truncated receptors sst5TMD4, sst5TMD5, GHSR1b or In1-ghrelin variant) have been associated with development and progression of some endocrine-related cancer. Objective: To determine, for the first time, the presence and possible pathological implications of somatostatin/cortistatin/ghrelin systems, specially their splicing variants, in human neuroendocrine tumors (NETs).

Methodology: 26 patients with NETs were prospectively and retrospectively studied. 72 samples from primary and metastatic tissues (30 normal and 42 tumors) and clinical data were obtained. Expression of sst1-5, sst5TDM4, sst5TDM5, ghrelin, In1-ghrelin, GHS-R1a, GHS-R1b, Ghrelin O-Acyl Transferase (GOAT; the enzyme that acylates ghrelin) and angiogenesis markers [angiopoietin (Ang)-1 y 2, Tie2 and VEGF] were determined by quantitative real-time PCR. *In vitro* studies were used to analyze the role of these splicing variants in aggressiveness of NET cell lines (BON-1 and QGP-1).

Results: Expression of sst1-3, sst5TDM4, sst5TDM5, In1-ghrelin, GOAT, GHS-R1a and GHS-R1b were elevated in tumor samples compared to normal, control tissues. Moreover, sst5TMD4 expression in metastatic lymph tissues was higher than in primary tumor tissues within patients, and was positively correlated with Ang1, Ang2, Tie2 and VEGF expression. Additionally, expression levels of In1-ghrelin, GOAT, and GHS-R1b were positively correlated in tumor, but not in normal samples, and were higher in patients with progressive disease compared to patients with stable disease or cured. Finally, *in vitro* studies confirmed the involvement of sst5TMD4 and In1-ghrelin in increasing aggressiveness markers (e.g. proliferation and/or migration, etc.) of NET cells.

Conclusions: Various components of the somatostatin/cortistatin/ghrelin regulatory systems, including novel splicing variants, are overexpressed in NETs. Overexpression of sst5TMD4 in metastatic lymph tissue compared with primary tumor, together with its correlation with the expression of the angiogenic markers suggests a role for this truncated receptor in aggressiveness of NETs. Likewise, overexpression of In1-ghrelin and GHSR1b, and their correlation with worst progression of patients suggests the potential implication of these splicing variants in the clinical outcome of NET patients. Altogether, these data suggest an association between the dysregulation of spliced variants within the somatostatin/cortistatin/ghrelin systems and the progression of NETs, which could help for the development of molecular targets with prognostic and/or therapeutic value.

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Abstract-ID: 535

ANTI-TUMOR EFFICACY OF SOMATOSTATIN ANALOGUES (SSAS) IN PATIENTS WITH NEUROENDOCRINE TUMOURS (NETS) ACCORDING TO KI-67 SCORE: A MULTICENTRIC STUDY FROM ELIOS (EDUCATIONAL LEARNING INVESTIGATIONAL OBSERVATIONAL STUDY)

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Introduction: Somatostatin analogues (SSAs) have been demonstrated to have antiproliferative effects in neuroendocrine tumours (NETs). However, responsiveness of NETs to these compounds is variable. The 2010 WHO NET classification provides a grading score which can be helpful to predict tumour response to SSA.

Objective: To evaluate the efficacy of long-acting SSA in NET pts according to Ki-67 score.

Materials and Methods: An observational Italian multicentric study has been designed to collect data on pts with gastro-entero-pancreatic or thoracic NETs who were under treatment with SSA. The observational data have been collected through an e-CRF and stored in a centralized computer database. Both retrospective data of pts in treatment with SSA from 2005 and prospective data of pts treated with SSA from March 2012 to June 2013 were included. Ki-67 score was immunohistochemically evaluated in tumour samples and gradued according to WHO classification of NETs (G1= ki-67 score 0-2%, G2= ki-67 score 3-20%, G3= ki-67 score >20%).

Results: Among 350 pts with a histological diagnosis of gastro-entero-pancreatic or thoracic NET or NET with unknown primary, 136 treated with octreotide LAR or lanreotide autogel were included. An objective tumour response was observed in 10%, stability in 52% and progression in 38%. Objective tumor response was significantly higher in G1 - G2 than G3 NETs ($p<0.01$), while not significantly different between G1 and G2. However, clinical benefit (including both objective response and stability) was significantly higher in G1 than G2 ($p<0.05$), as well as in GEP than in either thoracic or unknown primary NETs ($p<0.05$). Ki-67 score significantly impacted on PFS (median PFS in NETs with Ki-67 >5% 31 mths vs Ki-67 ≤5% 89 mths, $p<0.001$).

Conclusion: Therapy with SSAs is a remarkable antiproliferative therapeutic option in well differentiated low/intermediate-proliferating NETs, not only G1 but also in G2 type. GEP-NETs with Ki-67 ≤5% seems to be the best responders to SSA.

Abstract-ID: 410

EXPRESSION AND ROLE OF RSUME IN ANGIOGENIC FACTOR PRODUCTION IN HUMAN PANCREATIC NEUROENDOCRINE TUMORS

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The (patho-)physiological functions of RSUME, a small RWD-containing sumoylation enhancer protein, are still largely unknown. As the pancreas was reported to represent one of the mammalian organs with the highest RSUME production level, the expression of this protein was comparatively studied in normal pancreas and in some types of pancreatic neuroendocrine tumors. RSUME was strongly expressed in normal pancreas, in particular in β-cells, was reduced in the insulinomas and nearly absent in the hormone-inactive panNETs suggesting a role of RSUME in the tumorigenesis of panNETs. To identify the potential role of RSUME on angiogenesis, RSUME was stably silenced by shRNA in BON1 pancreatic neuroendocrine tumor cells and the influence of this protein on angiogenic factor(s) production has been tested. RSUME itself was up regulated by hypoxia and was involved in hypoxia-induced production of HIF-1α and VEGF-A, which was strongly impaired in $BON1^{RSUME\text{-}KD}$ cells. However, HIF-1α level was strongly reduced when RSUME is silenced, whereas VEGF-A decreased only by 30% indicating the induction of a mechanism to compensate the reduction of HIF-1α-driven VEGF-A production. When searching for such a compensatory pathway the pro-angiogenic and VEGF-A stimulating cytokine IL-8 was identified as a putative candidate. The production of pro-angiogenic acting IL-8 was strongly enhanced in $BON1^{RSUME\text{-}KD}$ cells because the knockdown of RSUME was associated with an increased production of the transcription factor NF-κB, a potent stimulator of IL-8. The findings show the complexity of RSUME action in balancing angiogenic factor production in the microenvironment of panNETs. Future studies are needed to identify the consequences of RSUME down regulation for the development of human panNETs.

Featured Poster Presentation

Abstract-ID: 449

ADRENAL INSUFFICIENCY IN CORTICOSTEROIDS USE: SYSTEMATIC REVIEW AND META-ANALYSIS.

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Objective: We aimed to estimate pooled percentages of patients with adrenal insufficiency after treatment with corticosteroids for various conditions in a meta-analysis. Secondly, we aimed to stratify the results by route of administration, disease, treatment dose and duration.

Design: Systematic review and meta-analysis of studies reporting the percentage of patients with adrenal insufficiency after use of corticosteroids. Percentages were pooled in a random effect logistic regression, or in a fixed logistic regression if the number of studies was <5. Pooled percentages were reported with 95% confidence intervals (CI). Risk of bias assessment was performed for all included studies.

Data sources: We searched seven electronic databases (PubMed, MEDLINE, EMBASE, COCHRANE, CENTRAL, Web of Science and CINAHL/Academic Search Premier) in February 2014 to identify potentially relevant studies.

Eligibility criteria for selecting studies: Original articles, testing adult corticosteroid users for adrenal insufficiency, were eligible.

Results: We included 74 articles in this meta-analysis with a total of 3753 participants. Stratified by administration form, percentages of adrenal insufficiency ranged from 4.2% (95% CI: 0.5-28.9) (nasal) to 52.2% (95% CI: 40.5-63.6) (intra-articular). Stratified by disease, percentages ranged from 6.8% (95% CI: 3.8-12.0) (asthma with inhalation corticosteroids only) to 60.0% (95% CI: 38.0-78.6) (haematological malignancies). The percentage adrenal insufficiency varied according to dose from 8.9% (95% CI: 3.4-21.4) (low dose) to 32.5% (95% CI: 18.7-49.1) (high dose), and according to treatment duration from 4.2% (95% CI: 1.4-12.3) (<28 days) to 35.9% (95% CI: 26.9-45.9) (>1 year).

Conclusions: These analyses show that in corticosteroid users there is no administration form, disease, dose group or treatment duration for which adrenal insufficiency can certainly be excluded. Therefore, the threshold to test corticosteroid users for adrenal insufficiency should be low.

Abstract-ID: 389

ROLE OF LEPTIN AND GHRELIN IN STRESS-RELATED PSYCHOPATHOLOGICAL SYMPTOMS IN FEMALE PATIENTS

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Background: Chronic stress could induce hormonal imbalance and affect negatively food intake as well as mood. It's been found that some peripheral hormones as leptin and ghrelin could also influence mood and anxiety.

Aim: The aim of our study was to investigate the relationship between leptin, ghrelin and severity of stress-related psychopathological symptoms of anxiety and depression in female patients with weight changes.

Patients and Methods: 60 patients and 20 healthy age-matched controls were clinically examinated. Body composition was determined by a bioelectrical impedance analyzer. Hamilton Rating scales for Anxiety (HAM-A), Depression (HAM-D) and stress test were administered. Fasting plasma desacylghrelin, leptin, 24 hour urine cortisol were measured.

Results: In the patient group 22 had lost weight (BMI kg/m^2 16,94±3,4). 38 had gained weight (BMI kg/m^2 31,54±6,5) and had significantly higher anxiety scores (14,5±5,3) and leptin levels (101,06 ±39,7 ng/ml), lower ghrelin (166,9±73,9 pg/ml) and cortisol levels (78,63±47,6 nmol/24h) compared with the weight lost group and the controls. They also had higher stress test scores (11,56±4,0) than the controls (9±3,29; p<0,05). There was weak inverse correlation between levels of ghrelin and anxiety (p<0,05; r=-0,25), which became insignificant after controlling for fat mass. Partial correlation between HAM-A scores and leptin levels controlled for the effects of fat mass % was significant (p<0,05, r=0,27).

Conclusion: The relationship between leptin and anxiety was more convincing than that for ghrelin in females with weight changes. The females with weight gain had more aberrations than the reduced weight group.

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Abstract-ID: 175

RECONSTRUCTION OF NEURONAL DEATH BY USING STEM CELL THERAPY FOLLOWING HYPOXIC–ISCHEMIC BRAIN DAMAGE IN THE RAT

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Introduction: hypoxic–ischemic (HI) is one of most important injuries in the human neonate at birth and stem cell therapy is one of the hopeful perspectives for treatment against this injury.

Methods: The possible therapeutic potential of human umbilical cord blood stem cells (HUCBSCs) was evaluated in 7 days rats subjected to the right common carotid occlusion, a model of neonatal hypoxic ischemic (HI) brain damage. Seven days after HI, rats received either saline solution or 4×105 HUCB cells intravenously. After two weeks, rats were assessed using two motor tests. Subsequently, rats were killed for histologic and immunohistochemical analyses. Animals who did not receive any injection or surgeries were used as a control group.

Results: Immunohistochemical evaluations revealed HUCB cells located in rat brain and behavioral assessment also shown that a significant improvement in group that received HCBSCs.

Conclusion: Intravenous transplantation can be a future line in treatment of infants with hypoxic who are exposed to irreversible damages. These results show that treatment by HCBSCs in young hypoxic–ischemic brain injury is a feasible and efficacious method for cell therapy with potential for clinical use.

Key words: Neuronal death, Stem cell, Hypoxic-ischemic, Rat.

Abstract-ID: 240

CLINICAL APPLICATION OF SPECT-CT IMAGING IN PATIENTS WITH THYROID PATHOLOGY

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Nuclear medicine techniques are well established in various thyroid diseases. Intensity of different tracers' uptake such as ^{131}I, ^{99m}Tc-pertechnetate, ^{99m}Tc-MIBI/Tetrofosmin, ^{111}In/^{99m}Tc-somatostatin analogues in thyrocytes depends on the physiological distribution of applied radionuclides, metabolic activity, vascularisation, oxygen consumption and tumor's receptor status.

- Fusion SPECT-CT images allow to make comparison of SPECT with CT data:
  - ➢ exact topography and size of each nodule
  - ➢ to identify morphological patterns that have occured in the "hot" or "cold" scintigraphic spots:

    solid, cystic or complex; microcalcifications or capsulation, hyperplastic benign tissue; advanced malignant neoplasm. These data are used by surgeons to select the most dominant nodules for FNA or biopsy.
- Malignant neoplasms of the thyroid found may be epithelial or non-epithelial. The epitelial tumors arise either from follicular cells or from parafollicular C cells.

Medullary thyroid cancer (MTC) is neuroendocrine tumor that accounts for 5-10% of all thyroid malignancies. This kind of tumors does not uptake ^{131}I. Loco-regional lymph node and distatnt metastases are found very often in patients with MTC of less than 1 cm. There is not good MTC response to systemic chemotherapy or to external been radiotherapy. Radical thyroidectomy is the main method of therapy. So early diagnosis and correct N/M-staging are extremely important for the management of MTC.

Some somatostatin receptors are expressed in MTC. SPECT-CT with ^{111}In/^{99m}Tc labeled pentetreotide is very useful for precise topographic localization of metastatic foci with abnormal tracer uptake and differentiation from physiological activity. SPECT-CT imaging should be performed for re-staging of MTC with increased level of calcitonin to establish disease extension

In conclusion: SPECT-CT imaging depicts precise location and the type of morphological changes that have occured in the thyroid parenchyma.

Abstract-ID: 52

GENE EXPRESSION PROFILING IN HUMAN ACTH-SECRETING PITUITARY TUMORS

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Introduction. ACTH-secreting pituitary adenomas present considerable variability both in terms of clinical presentation, responses to endocrine testing, surgical outcomes and efficacy of medical therapy. Heterogeneity is evident also at molecular level with variable responses to known modulators of ACTH secretion *in vitro* (Pecori Giraldi et al J. Neuroendocr. 2011) as well as diversity in receptor, transcription factor and miRNA expression. Microarray analysis provides a powerful means to evaluate the expression pattern of thousands of genes and has yielded interesting results in several endocrine tumors, such adrenal carcinoma and thyroid neoplasia. **Aim** of this study is to evaluate transcriptome expression pattern in archival human ACTH-secreting adenomas paraffin sections and verify whether gene profiles are associated with clinical variables.

Methods. Forty-six human ACTH-secreting pituitary adenoma formalin-fixed paraffin-embedded specimens were cut into 20 µm thick sections and RNA extracted using Recover All Total Nucleic Acid Isolation Kit (Invitrogen, Carlsbad CA, US). One normal pituitary tissue block was used as control. Real-Time PCR with house-keeping *RPL13A* gene attested to the efficacy of RNA recovery. RNA (300 ng) was hybridized to Human HT-12V4 expression bead Chip (approx 29000 transcripts) and analyzed with the WG-DASL-HT assay (Illumina, San Diego CA, US). Results were processed with Genome Studio software.

Results. Hybridization yielded informative data in 41 pituitary adenoma specimens. *POMC* was clearly overexpressed in all corticotrope adenomas attesting to validity of microarray analysis. Clustering analysis revealed several different clusters, all clearly distinct from the normal pituitary gene expression profile with 4 adenomas forming a clearly separate expression cluster.

Conclusion. Microarray analysis on archival pathology specimens proved a valid and informative technique for the study of Cushing's disease molecular features. Human ACTH-secreting adenomas appear to present several, distinct gene expression profiles.

Abstract-ID: 350

A FAMILY WITH FAMILIAL ISOLATED PITUITARY ADENOMA (FIPA) AND PARAGANGLIOMA

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Familial isolated pituitary adenoma (FIPA) is a term used to describe the presence of pituitary tumors in two or more related members of one family in the absence of MEN1 or Carney complex and represents approximately 5% of all pituitary tumors. There are a few case reports of pituitary adenoma and paraganglioma or pheochromocytoma, many of these associated with mutations in the *SDHx* genes. We report a family with two female relatives affected with pituitary adenomas. The proband was diagnosed with somatotroph/lactotroph adenoma at the age of 28 years. Her daughter was found to have a lactotroph adenoma at 24 years of age and her son died at 19 years of age of paraganglioma, 6 months after his initial diagnosis. The granddaughter presented to our clinic at the age of 6 years with suspicion of Cushing's disease but this was ruled out at this stage and simple obesity was diagnosed. Biochemical investigations of the proband, her daughter and granddaughter were negative for MEN1 and there was no clinical evidence of Carney complex. The proband was negative for *AIP* and *MEN1* mutation. Genes associated with paraganglioma or pheochromocytoma (*SDHB, SDHC, SDHD, SDHAF2, TMEM127, VHL, RET, MAX, NF1*) were negative, while SDHA screening is ongoing. The 6 year old granddaughter, the only living unaffected member of this family, is planned to undergo preventive screening procedures every 6 months. Further genetic studies are required in complex families as this one.

Abstract-ID: 93

ALTERATIONS IN DIURNAL RHYTHMICITY IN PATIENTS TREATED FOR NONFUNCTIONING PITUITARY MACROADENOMA; A CONTROLLED STUDY AND LITERATURE REVIEW

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Context: Patients treated for nonfunctioning pituitary macroadenoma (NFMA) frequently have fatigue and alterations in sleep characteristics and sleep-wake rhythmicity. Since NFMA often compress the optic chiasm, these complaints might be related to dysfunction of the adjacent suprachiasmatic nucleus (SCN).

Objective: To explore whether indirect indices of SCN functioning are altered in the long-term after surgery for NFMA.

Methods: We studied 17 NFMA patients in long-term remission after transsphenoidal surgery, receiving adequate and stable hormone replacement for hypopituitarism, and 17 controls matched for age, gender, and BMI. Indirect indices of SCN function were assessed from ambulatory 24-hour recordings of skin and core body temperature, blood pressure, and salivary melatonin levels. Altered melatonin secretion was defined as absent evening rise, considerable irregularity, or daytime values >3 pg/ml. We additionally studied 8 patients treated for craniopharyngioma.

Results: Distal-proximal skin temperature gradient did not differ between NFMA and controls, but proximal skin temperature was decreased during daytime (P=0.006). Core body temperature and non-dipping of blood pressure did not differ, whereas melatonin secretion was often altered in NFMA (OR 5.3, 95%CI 0.9–30.6). One or more abnormal parameters (≥2.0 SD score of controls) were observed during nighttime in twelve and during daytime in seven NFMA patients. Similar patterns were observed in craniopharyngioma patients.

Conclusion: The majority of patients previously treated for NMFA showed signs of altered diurnal rhythms in skin temperature and/or melatonin secretion. These observations suggest that suprasellar tumors may persistently affect diurnal regulation of physiological rhythms, possibly through effects on the SCN.

Abstract-ID: 308

EVALUATION OF DIAGNOSTIC TEST USING THE SYNTHETIC ANALOGUE OF LH-RH (BUSERELINE) IN THE DIFFERENTIAL DIAGNOSIS OF RETARDED PUBERTY IN ADOLESCENTS

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Background: Because of episodic secretion of gonadotropins (LH,FSH), basal levels of these hormones can not objectively be assessed to differentiate delayed puberty in males.

Objective and hypotheses: To assess the efficacy of the gonadotropin-releasing hormone(GnRH) agonist(as spray) in diagnosing of delayed puberty in males.

Method: Prepubertal males(n=18;age range 13.3-18.5 years)were studied; buserelin 0,15 (spray) microg was administered intranasally, with blood sampling at 0;1 and 4 hours for serum luteinizing hormone(LH) and follicle-stimulating hormone(FSH).In 7/19 males had testicular volume (more than 8 ml) consistent with a normal hypothalamic-pituitary-gonadal axis.In 12/19 males testicular volume were less than 4 ml suggesting HH (hypogonadotropic hypogonadism) or CDGP(constitutional delay of growth and puberty).

Results: Stimulated serum LH response to buserelin was lower in males

with HH (mean±under the mean for HH,at 1 hour 3.6±1.2 U/l; 4 hours 3.0±1.8U/l compared with a normal HPG axis 9.4±1.8 U/l at 1 hour;4 hours 15.9±0.9 U/l; P<0.0001). Stimulated serum FSH response was 10.0±2.2U/l at 1 hour and 16.1±2.3 U/l. at 4 hours in males with normal HPG axis and 4.4±0.8 at 1 hour and 3.9±0.6 at 4 hour in males with HH. There are no significant difference in basal levels of LH, FSH in both groups (2.6±0.22, /3.6± 0.9 for healthy males compared with HH 1.3±0.1/3.2±0.33).

Conclusion: The buserelin (in a spray form) stimulation test may be helpfull in patients with delayed puberty to assess HPG axis.

ORAL PRESENTATION 4: "Say it with a tweet" – THE ENEA YOUNGSTERS

Abstract-ID: 446

GLUCOCORTICOIDS DIFFERENTIALLY MODULATE BETA ARRESTIN 1 AND BETA ARRESTIN 2 EXPRESSION IN CORTICOTROPH TUMOR CELLS

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Backgroud: Pituitary directed treatment for Cushing's Disease (CD) is mainly represented by G-protein coupled receptor (GPCR) targeting drugs such as somatostatin analogs (pasireotide) and dopamine agonists (cabergoline). Like most GPCRs, both somatostatin and dopamine receptors are known to be regulated by beta-arrestins (β-arrs). Recently β-arr1 and β-arr2 were demonstrated to be differentially regulated by glucocorticoids in non-neuroendocrine tumor cell lines. The primary aim of our study was to confirm these findings in corticotroph tumor cells.

Material and Methods: AtT20 cells were used as model for corticotroph tumor cells. Cells were exposed to dexametasone (Dex, 10nM) at different time points. β-arr1 and β-arr2 mRNA, as well as protein expression was evaluated by qRT-PCR and Western Blotting, respectively. The receptor antagonist RU486 was used to antagonize the effect of Dex.

Results: Dex treatment resulted in time dependent increase in β-arr1 mRNA expression (+76% at 72h, p<0.0001) and in β-arr2 mRNA decrease (-26% at 72h, p<0.001). After 72h Dex exposure, the same modulation of β-arrs was observed at protein level. Noteworthy, Dex-mediated modulation of β-arrs was completely abolished by co-treatment with RU486 (100nM). Moreover, Dex withdrawal, followed by 72h wash out, resulted in β-arrs levels back to control values, demonstrating the reversibility of Dex action.

Interestingly, in tumor samples of a patient which underwent adenomectomy twice, during different phases of glucorticoid exposure (mild first, than severe hypercortisolism), we detected an increase in β-arr1 and a decrease in β-arr2 levels in the severe hypercortisolism state compared with the mild one.

Conclusion: Glucocorticoids result in an inverse modulation of both β-arrs in corticotroph tumor cells. This finding can help to better understand the variable response to GPCR ligands (both drugs and endogenous peptides) of patients with corticotroph tumors.

Abstract-ID: 119

PATIENTS WITH ADRENAL INSUFFICIENCY HATE THEIR MEDICATION: CONCERNS AND STRONGER BELIEFS ABOUT THE NECESSITY OF HYDROCORTISONE INTAKE ARE ASSOCIATED WITH MORE NEGATIVE ILLNESS PERCEPTIONS

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Context: Patients with adrenal insufficiency (AI) require daily and lifelong hydrocortisone substitution with risks of under- and over-replacement, the necessity to adjust the dose in stressful situations, and a lack of clinical and biochemical parameters to assess optimal dosing. The spectrum of medication beliefs in patients with AI is currently unknown.

Objective: To examine the possible association between illness perceptions and medication beliefs about HC in patients with AI.

Design and subjects: Cross-sectional evaluation of illness perceptions and medication beliefs in 107 patients with primary AI (n=49), secondary AI following treatment of Cushing's syndrome (n=29) or treatment of non-functioning pituitary adenoma (n=29). The Illness Perception Questionnaire-Revised and the Beliefs about Medicines Questionnaire were used for the assessment.

Results: Stronger beliefs about the necessity of HC and stronger concerns about the adverse effects of HC were associated with attribution of more symptoms to AI, to the perception of AI being more cyclical, to the perception of more negative consequences of AI, and to the presence of stronger emotional representations (all P<0.05). Furthermore, stronger beliefs about the necessity of HC intake were associated with feelings of less personal control over AI (P<0.05). Stronger concerns about the adverse effects of HC were associated with lower perceived treatment control and lower illness coherence (both P<0.05). In addition, patients with Cushing's syndrome reported stronger beliefs regarding the necessity of taking HC, compared with patients with Addison's disease (P=0.039) or NFA (P<0.001).

Conclusion: Specific beliefs about the necessity of hydrocortisone replacement and concerns about its adverse effects were strongly associated with more negative illness perceptions. These specific beliefs differed depending on the etiology of AI. These results need to be taken into account in the treatment of patients with AI, and may serve to enable the development of psychosocial education /self-management programs aiming at improving QoL.

Abstract-ID: 152

CIRCADIAN RHYTHM MODULATES BODY FAT MASS THROUGH BROWN ADIPOSE TISSUE ACTIVITY

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Background: Disturbed circadian rhythms are associated with the development of obesity in humans and rodents. Recently, we showed that obesity in mice is induced faster by continuous light, which disturbs the circadian rhythm, than by high fat diet feeding. Brown adipose tissue (BAT) recently emerged as an important player in energy expenditure by its high capacity to take up and combust triglycerides (TG). Interestingly, BAT detectability in humans is inversely correlated to day light exposure,

supporting a role for the circadian clock in BAT function.

Aim: The aim of this study was to evaluate the effect of prolonged light exposure on BAT activity.

Methods and results: Male C57Bl/6J mice on chow diet were exposed to 12h (i.e. regular), 16h or 24h light for 5 weeks. Prolonged light exposure increased adiposity without increasing food intake, suggesting reduction in energy expenditure. Kinetic studies with glycerol tri[^{3}H]oleate labeled TG-rich lipoprotein-mimicking particles showed a light exposure-dependent selective reduction in the uptake of radiolabel by BAT. Compared to the 12h light exposed group, the uptake of TG by BAT was decreased in mice exposed to 16h light (-25%; $p<0.05$) or 24h light (-49%; $p<0.02$), while TG uptake by other organs was not affected. In fact, the light exposure negatively correlated with TG uptake ($r^2=0.32$; $p<0.01$). The TG uptake by BAT correlated with the content of tyrosine hydroxylase, which is the rate-limiting enzyme in the production of noradrenalin ($r^2=0.17$; $p=0.056$). Light exposure inversely correlated with phosphorylation of thermogenic proteins in BAT, as well as expression of the key thermogenic gene UCP1 ($\beta=-0.28$; $r^2=0.28$; $p<0.01$).

Conclusion: This study provides novel evidence that prolonged light exposure increases body fat mass through decreased BAT activity related to decreased sympathetic outflow to BAT. We anticipate that disturbed BAT activity mediates the association between disturbed circadian rhythm and obesity associated diseases.

Abstract-ID: 97

GROWTH HORMONE INDUCES CHEMORESISTANCE IN HUMAN ENDOMETRIAL CANCER CELL LINES INVOLVING ERK 1/2 AND PKCDELTA.

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Background: Surgery is the main therapeutic option for advanced endometrial cancer; however, when disease relapses, chemotherapy is the only option. Chemoresistance is a very common phenomenon in these tumors. We previously demonstrated that GH protects breast cancer cells towards the cytotoxic effects of doxorubicin, inducing chemoresistance. Recent evidences show that endometrial cancer cells secrete GH, stimulating their own growth in an autocrine fashion.

Aim: to evaluate whether GH may impact on sensitivity of HEC1A and AN3CA endometrial cancer cell lines to Doxorubicin (D) and Cisplatin (C) and to investigate the possible implicated mechanisms.

Methods: Two endometrial cancer cell lines were used to carry out this study: the HEC-1A cell line, expressing the estrogen receptor (ER), and the AN3CA cell line, which does not express ER. To evaluate cell viability we performed ATPlite assay and to assess apoptosis activation we performed a Caspase 3-7 activity assay. To evaluate protein expression, we performed Western Blot analysis.

Results: GH protected endometrial cancer cells from D- and C-induced apoptosis. In addition, GH reduced D- and C-induced ERK 1/2 phosphorylation and PKCδ expression, both involved in chemotherapic-dependent apoptosis. These effects were reduced by Pegvisomant, a GH receptor antagonist.

Conclusion: GH promotes resistance to apoptosis induced by chemotherapeutic drugs by modulating the apoptotic pathway, inhibiting ERK1/2 phosphorylation and PKCδ expression. These findings support the hypothesis that blocking GH receptor may be viewed as a potential new therapeutic approach to overcome chemoresistance in endometrial cancer.

Abstract-ID: 313

NEUROENDOCRINE ASPECTS OF CUTANEOUS MELANOMA: EXPRESSION OF SOMATOSTATIN RECEPTORS AND EFFECTS OF PASIREOTIDE ON MELANOMA CELL LINES VIABILITY, PROLIFERATION AND CELL CYCLE

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Cutaneous malignant melanoma (CMM) is a highly aggressive skin cancer. CMM incidence continues to increase. Melanocytes originate from neural crest and the mRNA expression of somatostatin receptors (SSTRs) has been demonstrated in CMM, suggesting the presence of neuroendocrine features in this tumor. This study aimed to characterize the expression of SSTRs and to assess the *in vitro* effect of the somatostatin (SST) analog pasireotide on viability, proliferation and cell cycle in human melanoma cell lines. SSTRs expression was assessed in 4 human melanoma cell lines: A375, HMCB, COLO38 and M14. SSTRs were evaluated by RT-qPCR and SSTR1, SSTR2 and SSTR5 protein expression was confirmed by immunocytochemistry (ICC). Cell viability and proliferation were assessed by MTT and DNA assay, respectively. Cells were treated daily with serial doses of pasireotide for 72 hours. Cell cycle was investigated by FACS. Melanoma cell lines express SSTRs mRNA and protein. SSTR2 mRNA was the most expressed, followed by SSTR1, SSTR3 and SSTR5. ICC showed a predominant cytoplasmic localization for SSTRs. Pasireotide significantly inhibited viability (41% and 44% $p<0.001$ in 10^{-7}M vs control, for A375 and M14 cells, respectively) and proliferation (20.57% and 21.02% $p<0.05$ in 10^{-6}M *vs* control, for A375 and M14 cells, respectively). FACS results showed that pasireotide blocked the cell cycle in G0/G1 phase. *In vitro* response to pasireotide was associated with strong SSTR5 staining in CMM. In conclusion, this is the first study describing the protein expression of SSTRs in CMM cell lines, suggesting that CMM presents neuroendocrine features. The strong protein expression of SSTR5 in the cell lines responsive to pasireotide indicates that this particular pattern of SSTRs expression could be predictive of responsiveness to pasireotide in CMM. These data suggest that SST analogs, radiolabeled/chemotherapeutic-conjugated SST analogs and SSTRs scintigraphy might be useful in the clinical management of patients with CMM.

Abstract-ID: 395

QOL IN ACROMEGALY: DEPRESSION AND ANXIETY, BUT NOT BIOCHEMICAL CONTROL, ARE PROMISING MODIFIABLE VARIABLES FOR TARGETING REDUCED QOL

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Background: Remission criteria for acromegaly focus on biochemical control. However, patient-reported therapy outcomes (quality of life; QoL) often remain reduced despite biochemical control.

Objective: The aim of this study is to identify modifiable factors that influence QoL in acromegalic patients in order to plan complex interventions that address an amelioration of QoL apart from normalizing the biomarkers GH/IGF-1. For the model, we performed 3 steps: 1) theoretical operationalization of a biomarker/QoL model, 2) literature review and 3) statistical analyses in our dataset for relevant variable identification.

Design/Patients: Acromegalic patients treated at the Max-Planck Institute of Psychiatry and the Ludwigs-Maximilians-University, Med. Klinik IV Munich (n=81) were selected for cross-sectional analysis. Clinical data including neuropsychiatric aspects were obtained through patients' interviews and

clinical examination additionally using standardized questionnaires (such as the Beck's Depression Inventory for depressive symptoms, the State-Trait Anxiety Inventory for anxiety, and the disease-specific scale QoL instrument AcroQoL).

Results: The mean age of acromegalic patients was 54.67 years. Out of 81 patients, 56 patients had a macro-adenoma while 49 patients were biochemically controlled. Out of all predictors, we identified 9 factors as most relevant predicting QoL in acromegaly: age, gender, disease duration, tumor size, comorbidities, baseline GH/IGF-1 levels, treatment type, biochemical control and psychopathology. Out of those, disease duration, tumor size, arthralgia, depression and anxiety were all significantly associated with a reduced QoL while depression and anxiety were the most significant and also modifiable predictors (depression: $p<0.001$, $\Delta R^2=0.214$; anxiety: $p<0.001$, $\Delta R^2=0.124$). Data showed biochemical control not to be associated with QoL ($p=0.867$).

Conclusion: Biochemical control is not associated with perceived QoL in acromegaly, whereas depression and anxiety seem to be among the most relevant modifiable factors associated with reduced QoL in acromegaly. Hence, treatment of depression and anxiety might serve as a starting-point for future interventions in acromegaly therapy.

Abstract-ID: 385

QOL IN CUSHING'S DISEASE: DEPRESSION AND ANXIETY, BUT NOT BIOCHEMICAL CONTROL, ARE PROMISING MODIFIABLE VARIABLES FOR TARGETING REDUCED QOL

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BACKGROUND: Remission criteria for Cushing´s disease (CD) focus on biochemical control. However, patient-related therapy outcomes as measured by disease-specific quality of life (CushingQoL) often remain reduced despite normalization of biomarkers (24-hour urinary free cortisol and serum cortisol during low-dose dexamethasone suppression test).

OBJECTIVE: The aim of this study was to identify modifiable factors that influence QoL in patients with CD, in order to plan complex interventions that address an amelioration of QoL, apart from normalizing the biochemical parameters. For the model, we performed 3 steps: 1) theoretical operationalization of a biomarker/QoL model, 2) literature review, and 3) statistical analyses in our data set for relevant variable identification.

DESIGN/PATIENTS: 50 Patients with CD treated at the Max-Planck-Institute for Psychiatry and the Ludwig-Maximilians-University, Med. Klinik IV in Munich were selected for cross-sectional analysis. Clinical data including neuropsychiatric aspects were obtained through patients' interviews and clinical examination additionally using standardized questionnaires (such as the Beck's Depression Inventory for depressive symptoms, the State-Trait Anxiety Inventory for anxiety, and the disease-specific scale QoL instrument CushingQoL).

RESULTS: Mean age was 50 years, 20 patients were biochemically controlled. We identified 7 relevant factors for predicting QoL in Cushing´s disease: age, gender, treatment type, tumor size, hormonal levels (cortisol), comorbidity, biochemical control, disease duration and psychopathology. Interestingly, in our model only neuropsychiatric aspects like depression ($p<0.001$, $\Delta R^2=0.284$) and anxiety ($p<0.001$, $\Delta R^2=0.232$) predicted CushingQoL performance. Biochemical control was not associated with CushingQoL performance ($p=0.068$).

CONCLUSION: Biochemical control and comorbidities are not associated with perceived QoL in CD. However, modifiable factors such as neuropsychiatric symptoms (depression and anxiety) seem to play a key role in reduced QoL, highlighting new diagnostic and therapeutical possibilities for interventions.

Abstract-ID: 198

EXTRA-PITUITARY NEOPLASMS IN AIP MUTATION POSITIVE INDIVIDUALS: FINDINGS IN A LARGE COHORT OF FAMILIAL ISOLATED PITUITARY ADENOMA (FIPA) AND YOUNG-ONSET SPORADIC PITUITARY ADENOMA PATIENTS

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Introduction: In contrast to other syndromes with familial pituitary adenomas, individuals with germline *AIP* mutations (*AIP*muts) develop isolated pituitary adenomas. The presence of extra-pituitary neoplasms has never been assessed in a large cohort of *AIP*mut positive individuals.

Methods: We studied 290 *AIP*mut positive individuals: 144 pituitary adenoma patients (110 FIPA patients/34 *simplex* cases) and 146 unaffected *AIP*mut positive subjects (128 from FIPA families/8 related to *simplex* patients).

Results: We found 10 cases of 8 different extra-pituitary neoplasms in 9 subjects. GH excess patients represented 44.4% (4/9) of them, the rest were *AIP*mut positive carriers with no pituitary adenoma. We found a GIST and a meningioma in 2 *AIP*mut acromegalic siblings. LOH for *AIP* was found in the pituitary tumour but not in the meningioma. A GIST was also identified in an acromegalic male from a different FIPA family. In another family, 3 siblings with no pituitary adenoma were affected with other tumours: breast cancer in 2 females (*p53* and *BRCA1/2* mutations negative in one of them) and osteosarcoma and colon carcinoma in a male. In 2 more FIPA families, an *AIP*mut positive carrier died of spinal ependymoma and a gigantism patient harboured non-Hodgkin's lymphoma. An *AIP*mut carrier related to a *simplex* patient had a history of glioma.

Discussion: We have identified extra-pituitary neoplasms in 3.1% of the *AIP*mut positive individuals studied, which is higher than the general prevalence of neoplasms for the general population[1]. An increased risk of malignancy within unselected pituitary adenoma patients has been reported before; however, it was interesting to also find neoplasms within *AIP*mut positive individuals with no pituitary adenoma. Further genetic analyses are needed to study a possible increased risk of extra-pituitary tumours in families with with *AIP*mut-related pituitary adenoma.

1. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. 2012.

ORAL PRESENTATION 5

Abstract-ID: 527

THE COUPLED DEXAMETHASONE-DESMOPRESSIN TEST, A USEFUL ADDITIONAL TOOL TO ADAPT FOLLOW-UP TO THE RISK OF POSTOPERATIVE RECURRENCE IN CUSHING'S DISEASE

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Context: Predicting the outcome of patients operated on for Cushing's disease (CD) is a challenging task.

Objective: Our objective was to assess the accuracy of the coupled dexamethasone desmopressin test (CDDT) as a predictor of post-surgical outcome of CD.

Design and setting: Our study was a retrospective bicenter study.

Patients: Sixty-seven patients with initial remission and a minimal follow-up greater than 18 months were included.

Interventions: Follow-up included three months followed by yearly 24-h urinary free cortisol, ACTH and cortisol plasmatic levels, a low-dose dexamethasone suppression test (LDDST), desmopressin test and the CDDT.

Main Outcome Measures: After CDDT, the ACTH ratio (ACTHr) was defined as (peak ACTH – base ACTH)/base ACTH and cortisol ratio (Cortisolr) as (peak cortisol – base cortisol)/base cortisol. Basal values were observed after the LDDST. A receiver operator characteristics curve defined ACTHr and Cortisolr, providing the best sensitivity and specificity associated with recurrence.

Results: Eleven patients presented recurrence. The patient's median follow-up was 52 months (range, 18-180). ACTHr and Cortisolr were superior or equal to 0.5 in all patients with recurrence (100% sensitivity, 75% specificity). The test was positive in 10/11 recurring patients 6 to76 months before classical markers of hypercortisolism. Six patients presented recurrence despite a 0800 h postsurgical cortisol level below 50 nmol/L. All of this patients presented CDDT positivity within three years after surgery. The CDDT was highly reproducible, as the same response was observed every year in 91% of the patients.

Conclusions: CDDT is an early reliable predictor of recurrence of CD and is of major interest in the first three years after surgery for tailoring an optimal surveillance scheme.

Abstract-ID: 515

PERIOPERATIVE THROMBOPROPHYLAXIS IN CUSHING'S DISEASE: WHAT WE DID AND WHAT WE ARE DOING.

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Purpose: Cushing's disease (CD) is associated with increased risk of thrombotic events particularly in post-operative period. No guidelines are available on management of patients with CD submitted to pituitary transsphenoidal surgery (TSS). The aim of this study was to evaluate the alterations of coagulation indexes induced by hypercortisolism and compare the effectiveness of different prophylaxis procedures on prevention of post-surgical thrombotic events in CD.

Methods: We retrospectively collected data of 78 patients (60 females/18 males, mean age 43.2 ± 14.1 years) submitted to TSS between 2001 and 2012; haemostatic, hormonal and anthropometric parameters were recorded. Patients were divided into 2 groups according to perioperative management. Group A (34 patients) received fractionated heparin for a maximum of 14 days whereas patients of group B (44 patients) were treated without early glucocorticoid substitutive therapy, with subcutaneous enoxaparin 4000-8000 U/daily (according to the weight) for 30 days plus graduated elastic stocking until mobilization and early ambulation.

Results: The entire cohort of patients showed a significant increased in both clotting and anti-coagulant factors with respect to normal range. The two groups were comparable for age, BMI, ACTH, urinary free cortisol levels, outcome of surgery and main clotting parameters. Surgical procedure did not change over the time. Three venous thrombotic events (VTE, 2 associated with pulmonary embolism) were recorded only in group A, none in B (p=0.079). No hemorrhagic events were reported.

Conclusions: Provoked thrombotic events represents a major problem in the management of CD after surgery, regardless of its outcome. Patients with CD presented elevation of clotting factors and impaired fibrinolytic capacity, and despite the anticoagulant system activation, showed tendency to thrombotic complication. The combination regimen proposed in this paper provided excellent prophylaxis against VTE in the post-operative setting of patients with CD. Due to rarity of disease, a multicenter study would be advisable in order to collect a greater number of thrombotic events.

Abstract-ID: 508

PATIENT REPORTED OUT-COME IN POSTTRAUMATIC PITUITARY DEFICIENCY

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Background: Posttraumatic pituitary hormone deficiencies are often described. Questioning the impact of these predominantly marginal and often irreproducible deficiencies, the objective was to describe patient reported outcome in a national a-priori unselected cohort of patients with traumatic brain injury (TBI), in relation to deficiency upon pituitary assessment.

Patients: We included 463 adult patients hospitalized ≥ 24h, with more than subtle TBI as indicated by loss of consciousness, amnesia, or cranial/cerebral imaging abnormalities. They underwent pituitary assessment 2.5 years (range 1.0 - 4.4) postTBI. Deficiencies were defined according to local assay and test specific cut-offs from healthy controls. Sufficient and deficient patients had similar trauma characteristics (e.g. Glasgow coma scale score, coma and amnesia duration, cranial and intracranial damage).

Measurements: Quality of life questionnaires (SF36, EQ5D, and QoLAGHDA) and the Multidimensional Fatigue Inventory (MFI-20) were completed in conjunction to pituitary assessment.

Results: Patients had worse questionnaire scores compared to matched healthy individuals (p<0.0001). Patients with pituitary deficiencies (n=83) had increased physical fatigue (MFI-20, p=0.03), worse SF36 physical component score (p=0.03), and physical function (p=0.006) relative to patients with intact pituitary function. Gender, age and waist circumference explained 14-21% of the variation in physical fatigue-, function and the summary physical component score in healthy controls. Adjustment for these covariates removed the relationship between pituitary deficiency and questionnaire scores for all but physical function (β -2.5; p=0.03).

Only patients with untreated gonadal deficiency (n=26) had worse SF36 physical component score (p=0.02), physical and social functioning (p=0.004 and p=0.05, respectively), and increased physical fatigue (MFI-20; p=0.05)

compared to eugonadal patients. Patients with growth hormone deficiency (n=27) had decreased overall health perception on EQ5D (p=0.03).

P-Testosterone in male patients remained related to worse physical component score, bodily pain and general health perception (β 0.12- 0.24, $p<0.05$; R^2 0.09-0.13), and physical fatigue (MFI-20; β -0.11, p=0.02; R^2 =0.06) after adjustment for age, waist, opioid and antiepileptic drug treatment. Use of opioids was the main determinant for SF36 scores, whereas age was the main determinant for MFI-20 scores.

Conclusion: Posttraumatic pituitary deficiency and male hypogonadism in particular independently predicted worsened patient reported outcome including increased fatigue. Whether this relation is causal or due to confounding by one of the various influencing conditions affecting plasma testosterone remains unanswered.

Abstract-ID: 506

IS CLINICAL PRACTICE REFLECTIVE OF ACROMEGALY TREATMENT GUIDELINES? RESULTS FROM A SURVEY OF TREATING PHYSICIANS IN 45 COUNTRIES

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Introduction: Current acromegaly treatment guidelines recommend GH<1.0µg/L and IGF-1≤ULN to reduce morbidity and normalize mortality. Recent studies suggest many patients remain inadequately controlled, despite several available treatments. In collaboration with Novartis, ENEA conducted a survey on the perceived definition of biochemical control and real-world treatment decision making.

Methods: A 19-question multiple-choice online survey was sent to ENEA members in November 2013, and to attendees of an international pituitary meeting in Stockholm, Sweden in October 2013 (N=629).

Results: 179 respondents (28.5% of recipients) (Europe, n=118) from 45 countries (European, n=23/45) completed the survey; 120 considered themselves pituitary specialists. All respondents treated ≥1 patient with acromegaly; 114 treated >10/year (mean, 27/year). 58% of all respondents' patients were on medical therapy. Of those patients, 61% were considered biochemically controlled (range, 0–100%). 74% of all respondents measure both GH and IGF-1 to determine biochemical control. 56% consider it acceptable for a patient to have IGF-1>ULN; reasons include levels within assay error range (61%), no symptoms (35%), normal GH (28%). 32% of respondents consider IGF-1≥1.3xULN as the threshold for taking action; 18% wait until IGF-1≥1.5xULN. 51% of all respondents base treatment decision on signs/symptoms if biochemical markers are slightly elevated. 58% of all respondents reported barriers to changing medical therapy in patients with inadequate biochemical control; most prevalent were increased cost (53%) and reimbursement issues (49%), with 29% responding that IGF-1 assay variability is a barrier.

Conclusions: Although guidelines recommend control of both GH and IGF-1, 56% of responding physicians consider it acceptable for a patient to have IGF-1>ULN, and 18% consider IGF-1≥1.5xULN acceptable. Although this lack of urgency to treat may reflect challenges in clinical practice, it suggests many patients remain on the same treatment despite being inadequately controlled, which may impact on long-term patient outcomes, as well as disease management cost.

Abstract-ID: 339

COOPERATIVE EFFECT OF THE HORMONE 5-HYDROXYTRYPTAMINE (SEROTONIN) AND ENDOTHELIN-1 ON CONTRACTILE BEHAVIOUR OF ISOLATED HUMAN MESENTERIC ARTERIES: NEW INSIGHT

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Serotonin (5-hydroxytryptamine, 5-HT) has been shown to regulate an impressive number of physiological and pathophysiological processes in living organisms while it serves as a neurotransmitter (for example in brain) or as a hormone throughout the body (in gastrointestinal and cardiovascular systems). Despite the intensive investigation, the mechanisms of the serotonin actions remain unclear. Therefore, the present study examined the complex interaction between endothelin-1 and serotonin systems during an isometric contraction of artery isolated from human mesentery. Contractile responses of the artery preparations were registered using the precise method of myography of small artery by Mulvany-Halpern wire myograph. Segments of human mesenteric artery (1-2 mm outer diameter) with intact endothelium and perivascular nerves suspended in modified physiological salt solution were normalized, contracted by noradrenaline (1 µM and 10 µM), 42 mM KCl, ET-1 (1 nM) and five increasing concentrations of 5-hydroxytryptamine (100 nM to 10 µM). The results showed that 5-HT augmented the ET-1-contraction in dose-dependent manner (*n*=6; maximal tension registered at 1 µM 5-HT=260.7±52%). In other experiments, ω-agatoxin IVA (AGA IVA), a specific inhibitor of P/Q-type neuronal voltage-operated Ca^{2+} channels was added on the plateau of ET-1-contraction and 15 min before the application of 5-HT in a concentration relatively selective for P-type channels (50 nM). It was found that ω-agatoxin IVA did not influence significantly ET-1-evoked contraction and also did not alter 5-HT-contraction suggesting no, or a minimal role of these voltage-gated channels in ET-1- and 5-HT-signalings in human mesenteric artery *in vitro*. In conclusion, this is the first study in the literature investigating the role of P/Q-type neuronal voltage-operated Ca^{2+} channels in endothelin-1-serotonin contractions in human mesenteric artery. Moreover, the present experiments and scientific results highlight new aspects of endothelin-1-serotonin crosstalk in cardiovascular system. The obtained results could be aimed at the development of adequate disease treatments.

Abstract-ID: 158

RESTING-STATE FUNCTIONAL CONNECTIVITY OF THE NEUROCIRCUITRY OF STRESS IN PATIENTS WITH REMISSION OF CUSHING'S DISEASE

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Background: Patients with Cushing's disease represent a unique model for examining effects of prolonged exposure to high levels of endogenous cortisol on brain structure and function in humans as well as for examining the relation between these effects and psychiatric symptomatology. This study aims to investigate the differences in resting-state functional connectivity (RSFC) with the neurocircuitry of stress in patients with long-term remission of Cushing's disease compared to healthy controls.

Methods: RSFC with the neurocircruitry of stress was compared between

patients in remission of Cushing's disease (n = 24) and matched healthy controls (n = 24), using probabilistic independent component analysis to extract the neurocircuitry of stress and a dual regression method to compare groups. Psychological and cognitive functioning were assessed with validated questionnaires and clinical severity was assessed using the Cushing's syndrom Severity Index (CSI).

Results: Dual Regression analyses revealed increased RSFC between the neurocircuitry of stress and the subgenual subregion of the anterior cingulate cortex (ACC) in patients with remission of Cushing's disease ($p < 0.05$, corrected). The strength of the functional connectivity between these regions could not be associated to depression symptom severity, apathy scores or CSI scores in the patient group.

Conclusion: Patients with remission of Cushing's disease show differences in RSFC between the neurocircuitry of stress and the subgenual ACC long after the correction of hypercortisolism. This could be an indication that hypercortisolism causes persisting changes in brain function, which could potentially explain the psychiatric symptoms that are reported by the patients long after correction of the hypercortisolism.

Abstract-ID: 470

A SINGLE-CENTER, OPEN-LABEL, PHASE II, PROOF-OF-CONCEPT STUDY WITH PASIREOTIDE LAR IN PATIENTS WITH PROGRESSIVE MEDULLARY THYROID CANCER (MTC) AND THE COMBINATION WITH RAD001 UPON PROGRESSION

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Background: MTC is a slowly growing well-differentiated neuroendocrine tumor which is often uncured after surgery. Pasireotide (SOM230), a multi-receptor targeted somatostatin analogue, is a promising therapy for MTC, due to its high-binding affinity for somatostatin receptor $(sst)_{1,2,3,5}$.

Objective: The objective of this study is to evaluate the effectiveness of pasireotide long-acting release (LAR) in MTC pts with metastatic or unresectable disease. Everolimus in combination with pasireotide LAR is also evaluated in those MTC pts who progress under monotherapy.

Patients and Methods: Trial enrollment started in February 2012 and was completed in June 2014 (study registration no. NCT01625520). As a whole, 23 MTC pts were screened and 19 of them were enrolled. All pts enrolled started therapy with pasireotide LAR 60 mg/m. At now, a 6-month evaluation was available in 15/19 pts. Primary endpoint was progression-free survival (PFS).

Results: The median PFS and median overall survival were not reached. At 6-mth CT scan, target tumor lesions were stable in 13/15 pts and progressive in 2/15. These two pts received everolimus in combination with pasireotide. FDG-PET SUVmax decreased in 10/15 pts in MTC lesions which were positive before therapy. Calcitonin serum concentrations significantly decreased in 12 pts, were stable in 5, increased in 1 and not evaluable in 1 other. All pts who had bone and bowel symptoms at baseline experienced clinical response. Grade ≥2 adverse events were diarrhea in 1 and hyperglycemia in 7, which was managed with hypoglycemic diet and/or oral hypoglycemic drugs.

Conclusions: This is the first experience on the use of pasireotide (SOM230) in pts with MTC. Pasireotide LAR seems to be active and well tolerated, preventing tumour progression and maintaining quality of life. It could represent an additional treatment option for patients with slowly growing MTC.

Abstract-ID: 214

CRANIOPHARYNGIOMA: 13 YEARS OF MULTIDISCIPLINARY MANAGEMENT IN SEVILLE (SPAIN)

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Craniopharyngiomas (CP) are rare, locally aggressive tumors derived from embryonic remnants of the craniopharyngeal duct, with an incidence in Spain of 0.5-2 cases/million inhabitants/year. Our hospital is a Reference Center in the treatment and follow-up of this disease for both children and adults.

Objective: To describe the main features of patients diagnosed with CP admitted to our center between years 2000-2013.

Material and Methods: Descriptive retrospective study. We performed a systematic search in our clinical database, including all patients with postoperative diagnosis of CP between years 2000-2013.

Results: Total sample: n=58; n=20 (54.2%) children, n=38 (45.8%) adults; n=30 males (62.5% children, 50% adults); age at diagnosis (Median) 7 years (children), 43 yr (adults). Main neurological manifestations at diagnosis: visual impairment (66.7% children, 75% adults), headache (50% children, 70.6% adults), intracranial hypertension (50% children, 33.3% adults); main endocrine abnormalities at diagnosis: diabetes insipidus (50% children, 16.7% adults), menstrual disorders and growth impairment. The preferred surgical approach was an open technique. Postoperative sequelae: 97.9% of total patients (100% children, 96.7% adults), mainly panhypopituitarism (92.3% children, 89.3% adults), diabetes insipidus (81.8% children, 76.9% adults) and obesity/polyphagia (71.4 % children, 40% adults), visual impairment (72.7% children, 63.6% adults), epilepsy (37.5% children, 25% adults), hydrocephalus (30% children, 30.8% adults), CSF leakage (45.5% children, 10.5% adults), and psychiatric disorders (80% children, 26.3% adults). 47.7% of total cases required external adjuvant treatment, mainly radiotherapy (100% conventional radiotherapy in children; 67% stereotactic vs. 33% conventional in adults). Disease relapse rate: 46.7% (69.2% children, 37.9% adults) approximately 2 years after initial surgery. Mortality rate: 20% (n=12).

Conclusions: We observe high rates of morbidity and mortality, in concordance with currently available evidence about CP. These findings support the need of a multidisciplinary approach to this disease in order to minimize the consequences of both CP and its treatment.

ORAL PRESENTATION 6

Abstract-ID: 215

LACK OF THE ARYL HYDROCARBON RECEPTOR INTERACTING PROTEIN (AIP) GENE MUTATION IN YOUNG TURKISH PATIENTS WITH SPORADIC PROLACTINOMAS.

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INTRODUCTION: The *AIP* gene mutations predispose to pituitary adenoma in FIPAs and less often in sporadic cases. Recently, *AIP* gene mutations related to sporadic pituitary tumors have been increasingly reported in young patients. Especially, male gender is associated with a higher rate of aggressive and treatment-resistant macroprolactinomas.

OBJECTIVE: We aimed to examine the *AIP* gene mutations in young Turkish patients with sporadic prolactinomas and to correlate clinical features of pituitary tumors with these mutations, if they exist.

METHODS: The study population comprised 15 patients (age ≤30 yr) with sporadic prolactinomas without hypercalcemia and/or MEN1-associated lesions. All patients received dopamine agonist (BRC/CAB) therapy. Mean follow-up duration (months) was 69 for men and 79 for women.The entire coding sequence of the AIP gene was screened for germline mutations.

RESULT: Fifteen patients were included (5M/10F),mean age was 27yr (15-30). Fourteen tumors were macroadenomas (93%; 5M/9F), half of them invaded local structures (50%; 4M/3F) and 2 were giant adenomas (1M/1F). Mean PRL level was 1921 ng/ml in men,1679 ng/ml in women (130-4800), mean maximum tumor diameter was 28mm (8.0-45.0 mm). Normalization of PRL occurred in nine cases (87%; maximum CAB dose 2 mg/wk and BRC dose 17.5 mg/day). Five patients (2M/3F; 3 BRC, 2 both BRC and CAB) developed resistance to therapy. Three patients were switched to CAB,and surgery was performed in patients resistant to both drugs. Long-term control was achieved in 8 of 13 patients. The mean tumor shrinkage was 52% (35-78%) in 9 patients. Four invasive macroadenomas (2M/2F) disappeared during follow-up, and only two of them were managed without medication.

CONCLUSION: The *AIP* is not a candidate gene predisposing risk for young men and women with sporadic macroprolactinomas, and we observed positive response to medical therapy in AIP sequencing-negative young patients with macroprolactinoma. Further studies are required in this regard.

Abstract-ID: 245

THE ROLE OF MGMT AND MSH6 EXPRESSION IN TEMOZOLOMIDE TREATMENT OF FUNCTIONING PITUITARY ADENOMAS

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Background: Temozolomide (TMZ), an alkylating agent, was published as a possible alternative treatment for recurrent pituitary adenomas. However, some adenomas with low O-6-methylguanine-DNA methyltransferase (MGMT), a marker found to correlate with response to TMZ, were still unresponsive to chemotherapy. Previous studies reported that a positive expression of MSH6 might correlate with response to TMZ.

Methods: We investigated MGMT and MSH6 status in 231 functioning pituitary adenomas to determine if they serve as prognostic parameters. The patients found were classified as recurrent (group 1) or in remission (group 2). The expression of MIB-1, MGMT and MSH6 were evaluated. For evaluation independent-samples t-test as well as two-factorial ANOVA was applied.

Results: 79 patients in group 1 (recurrent), 152 in the group 2 (remission) were identified. 24/79 (30%) in group 1 and 26/152 (17%) in group 2 showed a negative MGMT expression (<10%). A positive expression of MSH6 (>10%) was found in 28/79 (35%) in group 1 and 56/152 (37%) in group 2. A combined expression of low MGMT and high MSH6 was found in 8/79 (10%) in group 1 and 8/152 (5%) in group 2. Combining both groups MIB-1 was 4.2 in patients with low MGMT/high MSH6 compared to patients with high MGMT/lowMSH6 2.6 (p value 0.07). In group 1 MIB-1 was 2.4% in MSH6 negative and 4.3% in MSH6 positive samples (p-value 0.01).

Conclusion: TMZ, a possible alternative therapy, does not induce a successful response to therapy in every treated case. The findings of this study suggest that MSH6 may have important roles in prediction biological behavior and serves as a possible decision support for TMZ therapy.

Abstract-ID: 108

MARKERS OF PROLIFERATION AS PROGNOSTIC FACTORS IN PITUITARY TUMOURS

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Introduction: We investigated Ki-67, TOPO 2A (topoisomerase 2 alpha), AIP (Aryl Hydrocarbon Receptor-Interacting Protein) and VEGF (Vascular Endothelial Growth Factor) as potential pathological markers to predict the aggressiveness of pituitary adenomas.

Material and Methods: Ki-67, TOPO 2A, AIP and VEGF indices were determined by immunochemistry in specimens from neurosurgically removed somatotropinomas. Histopathological material was examined from 31 patients with pituitary macroadenoma (20 females and 11 males, mean age 43.3 ± 14.3 yrs.) who underwent pituitary surgery. The mean value of maximum diameters of tumours in MRI was 22.84 ± 21.23 mm. Relations between staining indices and clinical symptoms, tumour features, and MR imaging, were analysed. In all studied adenomas GH expression was confirmed by immunostaining. Local invasiveness, defined as sella turcica destruction, cavernous sinus penetration, optic chiasm compression, was observed in 18/31 patients (58,1%).

Results: Expression of Ki-67, TOPO 2A, AIP and VEGF was revealed only in cells of pituitary tumours and was present in 77.4%, 87.1%, 83.8%, and 87.1% of 31 cases, respectively. The median values of Ki-67, TOPO 2A, AIP and cytoplasmic VEGF indices were 1.23% [IQR=2.17], 1.5% [IQR=1.6], 21.16% [IQR=19.76] and 16.64% [IQR=16.41], respectively. Ki-67, TOPO 2A, AIP and VEGF indices did not correlate with patient age nor gender (p>0.05). Values of Ki-67 and of TOPO 2A indices correlated with tumour size (for Ki-67: r=0.42, p=0.025; for TOPO 2A: r=0.53, p=0.003). No correlation between AIP or VEGF expression with tumour size was found. In invasive, as compared with non-invasive somatotropinomas, significantly higher indices were found only for TOPO 2A (median values: 1.96% [IQR=1.9] vs 1.04% [IQR=1.4], p=0.034).

Conclusions: While Ki-67, TOPO 2A, AIP and VEGF were expressed in most of the investigated pituitary tumours, only Ki-67 and TOPO 2A expression was related to tumour size. However, only TOPO 2A expression correlated with tumour invasiveness.

Abstract-ID: 242

MOSCOW REGION ACROREGISTRY UPDATE 2014

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We updated Moscow region Acroregistry. Till 2014 180 patients have been

registered in Moscow region (25,7 cases on 1 mln people): 32 men, 148 women, M:F ratio 1:4.6. Median age of patients 55 y.o. (from 20 to 82 years). Median duration from the onset of first symptoms to diagnosis of acromegaly was 6 years (from 2 up to 25 years). Macroadenomas 78%, microadenomas 22%.

The most frequent complaints were sweating (90% patients), headache (87.2%), muscle weakness and decreased exercise tolerance (87.2%), acrial changes (87%), swelling of the face and limbs (84.1%), arthralgia (72%). Hypertension was observed in 64.7% of cases (1-2-3 stage of hypertension in 53.5 - 32.1 - 14.2% of patients, accordingly). Patients complained of sleep snoring in 51.4% of cases, however, during cardiorespiratory monitoring sleep breathing disorders were revealed in 80% of patients (moderate in 46% and severe in 34% of cases). Severity of SBD was associated with patients' age, IGF-1 levels, acromegaly duration and gravity of hypertension. Glucose metabolism disorders were found in 75.4% of patients: prediabetes in 25.8% and overt diabetes in 52.6% (OGTT was performed in all patients with normoglycemia). In women of reproductive age menstrual and/or reproductive disturbances were observed in 89% of cases (including 34% of amenorrhea, 34% of opsomenorrhea, and high prevalence of leymomyoma, adenomyosis). Thyroid disorders were found in 78% of patients, predominantly nodular goiter (46.7%) and diffuse goiter (14.3%); thyroid cancer was identified in 9.5% of patients. Endoscopic investigation showed high prevalence of gastroduodenitis (100% of patients), esophagitis (23.9%), incompetence of cardia (35.8%), stomach polyps (30.4%). It was noticed high rate of Helicobacter pylori contamination (78%). Colonic pathology was found in 86.5% of patients including colonic diverticula (30%), dolichocolon (28.4%), colonic polyps (52.7%).

Comparing to the first data obtained from Moscow region acroregistry in 2005-2007, high rate of comorbidities (such as sleep breathing disorders, menstrual dysfunction, glucose metabolism disorders, thyroid cancer, gastro/colonic pathology) was found in our cohort of patients during dynamic investigation. Monitoring of the patients with acromegaly should be active and multimodal.

Abstract-ID: 216

SCREENING OF ACROMEGALY IN PATIENTS WITH SLEEP APNEA SYMPTOMS

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Acromegaly is a rare disease that usually takes years of symptoms before the diagnosis. The estimated prevalence of 40-125 cpm could be much higher according to screening studies. Acromegaly symptoms are non-specific but acral enlargement is almost universally present at diagnosis. We aimed at investigating the prevalence of acromegaly in a population of patients with symptoms of sleep apnea and acral enlargement.

Methods: multicenter Spanish study involving 15 Hospital sleep referral units. Patients who were seen in first visit for hoarseness or suspected sleep apnea were recruited. Symptoms of acral enlargement (increase in ring or shoe size, enlargement of the tongue, lips or jaw, paresthesiae or carpal tunnel and widening of tooth spaces) were collected. Patients were also inquired about other acromegaly symptoms including headaches, hoarse voice, arthralgia, diabetes, hypertension, fatigue, excessive sweating, menstrual disturbances or erectile dysfunction. Only in patients with at least one acral enlargement symptom, a serum IGF-1 was measured; if elevated, it was repeated and if confirmed, an OGTT was performed. We present preliminary data.

Results: from 1153 patients included in the study, three cases of acromegaly were diagnosed. Complete data on 644 patients (76% men and 24% women) were analysed. Mean age was 56 ± 12 years and mean BMI 30 ± 4 kg/m2. SAHS was confirmed in 95,5%. Thirty six percent had at least one symptom of acral enlargement (paresthesiae 24%, increase in ring size 19% and increase in shoe size 11%). Eighty four percent had at least one of the "other acromegaly symptoms" and 44% had three or more.

Conclusion: In a population of patients with sleep apnea symptoms and acral enlargement, we found an acromegaly prevalence of 2,6 cases per 1000. It is important that sleep specialists beware of the disease and recognize its symptoms in order to perform an early diagnosis.

Abstract-ID: 244

ASYMMETRIC DIMETHYLARGININE LEVELS IN ADULTS WITH GROWTH HORMONE DEFICIENCY ARE NOT ASSOCIATED WITH TRADITIONAL CARDIOVASCULAR RISK FACTORS

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Background: Asymmetric dimethylarginine (ADMA) has been established as a biochemical marker of endothelial dysfunction (ED) in numerous conditions related to increased cardiovascular risk, including growth hormone deficiency (GHD). Few studies, however, have examined the relationship between increased ADMA levels and other factors affecting endothelial function and atherogenesis in acquired hyposomatotropism.

Objective: To investigate the association of serum ADMA concentrations in adult GHD patients with age, gender, onset and severity of GHD, anthropometric and biochemical cardiovascular risk factors.

Patients and methods: Serum ADMA levels were determined by an ELISA assay (Human ADMA ELISA kit, PromoKine, Heidelberg, Germany) in 84 patients (46 males and 38 females, aged 44.8±15.5 years) with childhood-onset (n=30) and adult-onset (n=54) GHD. Hyposomatotropism was diagnosed according to the Endocrine Society Clinical Practice Guideline recommendations from 2011.

Results: ADMA was increased in GHD patients, irrespective of their age (p=0.480), gender (p=0.830), onset of GHD (p=0.302) and serum IGF-1 concentrations (p=0.795). The difference between ADMA in patients with and without metabolic syndrome (p=0.671) or hypertension (p=0.116) failed to reach statistical significance. Comparing ADMA levels and the values of some anthropometric (waist circumference, waist/hip ratio, BMI, percent body fat, visceral fat area) and biochemical (cholesterol, HDL, LDL, triglycerides, plasma glucose, uric acid, HOMA) risk factors, no correlation was found.

Conclusion: The lack of association between the increased ADMA concentrations and the anthropometric and biochemical parameters analyzed in this study indicated that ED in GHD patients could not be attributed simply to their adverse metabolic profile.

Abstract-ID: 112

THERAPEUTIC OPTIONS AND OUTCOME OF PATIENTS WITH CUSHING'S DISEASE AFTER FAILURE OF INITIAL TRANSSPHENOID SURGERY

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Transsphenoidal surgery (TSS) is the first option in the management of patients with Cushing's disease (CD). However, it does not always lead to

cure of hypercortisolism. Data concentrating on the outcome of patients that failed initial TSS is scarce. The aim of this retrospective study was to analyze and present the therapeutic options and their efficacy to control hypercortisolism in patients with CD that failed initial TSS.

The study included 96 patients with CD (age 43.2 ± 1.3 years; 83 women and 13 men). All patients underwent TSS. Post surgery, 42 patients (43.8 %) were considered cured, 27 patients (28.1 %) presented with remission and, 27 patients (28.1 %) had persistent disease (defined as morning cortisol levels < 1.8, between 1.8-10 and > 10 µg /dl respectively). Seven patients who were initially cured and 11 patients with remission relapsed in the following 57.4 ± 12.1 months. Eighteen patients who failed the initial TSS underwent a second TSS, which led to apparent cure 1 (5%) and to remission 6 patients (33.3 %); 11 patients (61.1 %) failed the second TSS. Forty-five patients with disease recurrence (N=18) or persistence (N=27) underwent pituitary irradiation (N=23) and/or bilateral adrenalectomy (N=9) and/or treatment with steroidogenesis inhibitors (N=18). Long term follow up was obtained in 41 of the 45 patients. At their latest follow up (111.1 ± 10.8 months from diagnosis) 34 of the 41 patients (82.9 %) achieved control of cortisol excess (defined as daily average cortisol <10 mg/dl and/or normal 24-hrs urine cortisol.

These results demonstrate that a second transsphenoidal surgery is effective only in a limited proportion of patients. Further interventions applied to patients who failed the first or even second transsphenoidal surgery improve hypercortisolism in a substantial proportion of patients. However, several patients still remained uncontrolled requiring modified and/or additional therapeutic manipulations.

Abstract-ID: 114

FETAL AND GESTATIONAL OUTCOME IN PATIENTS WITH PITUITARY ADENOMAS

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Introduction: Pregnancies are becoming reported in an increased rate in patients with pituitary adenomas.

Materials and Methods: 60 patients with pituitary adenomas from 8 centers in Turkey were included, but 51 patients with 62 pregnancies (43 prolactinoma, 13 acromegaly, 1 GH and PRL secreting adenoma, 5 non-functional adenoma) were reported since others had ongoing pregnancies.

Results: All patients with hormone secreting adenomas had active disease during conception except one acromegaly. 42 patients were on medical treatment during conception. 7 patients were given bromocriptine and 2 were given cabergoline during gestation. Clinical signs of compression were reported in 5 patients; 2 with prolactinoma; 1 with visual field loss (managed with bromocriptine), 1 with pituitary apoplexy on cabergoline (managed conservatively) and 1 acromegaly with ptosis (diagnosed during pregnancy and operated on at the end of 1st trimester). 85% of pregnancies resulted in live births and 11% of live births were associated with congenital malformations (3 girls had labial fusions, 2 babies had microcephalies and 1 baby had cranial sinostosis, microcephaly and microophtalmia). 8% of pregnancies resulted in abortus (3 prolactinoma patients 2 of them were on cabergoline during conception, 1 acromegaly on cabergoline, octreotide and pegvisomant and 1 NFPA associated with lupus) and 6.4% resulted in still births (1 corpus callosum agenesis from mother with prolactinoma on bromocriptine during conception, 1 severe IUGR from mother with prolactinoma who received antibiotics during periconceptional period, 1 neural tube defect from mother with prolactinoma used cabergoline during conception and bromocriptine during gestation and 1 gestational hypertension in a diabetic, acromegalic patient).

Conclusion: Symptomatic tumor growth during gestation can be seen in patients with pituitary adenomas. Periconceptional use of drugs for prolactinoma and acromegaly is common and more data regarding safety of medical treatment is warranted.

ORAL PRESENTATION 7

Abstract-ID: 220

PREDICTIVE VALUE OF SOME GROWTH FACTORS AND CYTOKINES IN PITUITARY ADENOMAS

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In spite of the intensive research on the pathogenesis of pituitary tumors focusing on growth factors, receptors, cytokines, signal transduction and cell cycle regulation there remains a great deal of controversy. The aim of our work was to estimate the predictive value of some markers for malignant potential of pituitary tumors.

Material and methods: 50 patients with pituitary tumors (36 somatotropinomas, 7 prolactinomas, 5 corticotropinomas and 2 nonsecreting; mean age 43.16+/-11.4 /17-73 y, 19 males and 31 females), matched by sex and age with 42 controls (mean age 41.88+/-10.96,19 males and 23 females). All patients underwent neurosurgery. Levels of the epidermal growth factor receptor (EGFR), IL-6, fibroblast growth factor (FGF19), transforming growth factor beta (TGFß) in sera of patients and controls were measured by ELISA. Immunohistochemistry for P53 and MIB1i was performed in all tumors. The results were analyzed by age, sex, type of tumor, hormonal secretion, tumor size, invasion, expansion, remission and surgical intervention. Results: EGFR levels were significantly higher in pituitary tumors (especially somatotropinomas) compared to healthy controls /p=0.0001/ and p53 negative subjects /p=0.016/. There was no significant correlation with invasion, expansion, recurrence and tumor size. IL-6 levels were significantly higher in non recurrent, non invasive and p53 negative tumors and negatively correlated with tumor size (r=-0.36). There were no correlations of FGF19 and TGFß with the tumor characteristics and the other studied parameters. Conclusion: Recently, there have been exciting data still under research that IL-6 underlies the slow proliferation rate and benign nature of pituitary tumors which is supported by our results. Further analyses are required for defining the potential of EGFR as a marker of tumor aggressiveness.

Abstract-ID: 424

A RISK ASSESSMENT MODEL FOR VENOUS THROMBOEMBOLISM IN PATIENTS WITH CUSHING'S SYNDROME

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Introduction: Cushing's syndrome (CS) is associated with elevated incidence of venous thromboembolism (VTE), contributing at least in part to morbidity and mortality. The aim of this study was to develop a simple risk assessment

model (CS-VTEs) for the identification of CS patients with high VTE risk in whom to adopt adequate thromboprophylaxis.

Materials and methods: In a consecutive cohort of 176 CS patients from two Italian Centres we retrospectively considered clinical, hormonal and coagulation data to quantify the degree of hypercortisolism and to evaluate the VTE risk. All CS patients had active disease based on specific clinical and hormonal criteria. We administered a questionnaire to collect information on additional risk factors and used a forward-stepwise logistic multivariate regression analysis to select major independent risk factors to compute the score.

Results: Among CS patients (mean age 48.2±13.9 years, F:M =4:1), 20 (11.3%) developed a thromboembolic event. CS patients with VTE were older than those without VTE (59.8±12.4 vs 46.8±13.5 years, p<0.001). Previous cardiovascular events (p=0.033), infections and periods of reduced mobility (both p<0.001) were significantly more frequent in the VTE group compared with the no VTE one. Midnight plasma cortisol was higher in the VTE group (p=0.038) and Partial Thromboplastin Time (PTT) was shorter (p=0.002). Six independent risk factors for VTE emerged from our analysis: age ≥ 69 years [2 points], reduced mobility for at least 3 days [2 points], acute severe infections [1 point], previous CV events [1 point], midnight plasma cortisol level > 3.15 times upper normal value [1 point] and shortened PTT [1 point]. The CS-VTEs score results from the sum of points of present risk factors. In patients with CS-VTEs less than 2 we observed no VTE risk (0 %), for those with CS-VTEs=2 mild risk (10%), while a relevant risk emerged for CS-VTEs=3 (46%) and very high risk for CS-VTEs ≥4 (85%). Considering predictive into clinical setting a score value ≥3, the 94% of patients have been correctly predicted by the model with a sensitivity 85% and a specificity 95%, with Positive Predictive Value=68% and Negative Predictive Value=98%.

Conclusions: Our study underlines the frequency of VTE in CS and how this complication results from the additive effect of different factors with synergistic action. CS-VTEs may be a simple tool to recognize multiple situations with high risk of VTE that could be prevented by an adequate thromboprophylaxis.

Abstract-ID: 262

THE GENDER DIFFERENCE IN THE GROWTH OF PROLACTIN TUMORS IS RELATED TO ESTROGEN RECEPTOR ESR1: CLINICAL, PATHOLOGICAL AND MOLECULAR ARGUMENTS IN A COHORT OF 89 PATIENTS.

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Context: A gender difference in progression of prolactin (PRL) tumors has been disputed for years.

Objective: To compare tumor characteristics and postoperative clinical course between males and females, and correlate data to estrogen receptor α (ESR1) expression status.

Design: we selected a series of 89 patients (59 women and 30 men) operated of a PRL tumor and followed for at least 5 years. Tumors were classified according to their size, invasion and proliferation characteristics into 5 grades. The ESR1 expression was detected by immunohistochemistry (IHC) in 81 cases and a score (0-12) established taking into account the percentage of positive cells and the intensity level. Molecular analyses were performed on fragments from 30 frozen tumors (10 women and 20 men).

Results: there was a significant preponderance of high grade tumors among males and the surgical cure rate was lower in men (23%) than in women (71%). Patients resistant to medical treatment were mainly men (7/8) and 6 of them (5 men) showed tumor progression despite postoperative medical treatment leading to multiple therapies including radiotherapy (n = 6) and temozolomide (n = 2). Three male patients eventually died from their tumor. For ESR1, a good correlation was found between protein expression detected by IHC and mRNA levels. The median score for ESR1 expression was 1 in men (range, 0-8) and 8 in women (range, 0-12) (p<0.0001). In both sexes, tumors with lower ESR1 expression (score: 0-5) had significantly higher proliferative activity. All DA-resistant tumors and all grade 2b (invasive and proliferative) tumors (10 men and 4 women) where characterized by low ESR1 expression. Expression level of miR-18a, a microRNA that directly target ESR1 was negatively correlated with ESR1 expression.

Conclusions: PRL tumors in men are characterized by lower ESR1 expression which is related to greater proliferative potential and resistance to treatment.

Abstract-ID: 418

CHANGES OF PLASMA RENIN ACTIVITY AND PLASMA ADRENALINE CONCENTRATION DURING NEURONAL NITRIC OXIDE SYNTHASE INHIBITION IN SPONTANEOUSLY HYPERTENSIVE RATS

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This study investigate participation of nitric oxide (NO), produced by neuronal nitric oxide synthase (nNOS) in the regulation of plasma adrenalin level as well as in plasma renin activity (PRA) in conscious spontaneously hypertensive rats (SHR).

Materials and Methods: Experiments were carried out on four experimental groups (n=10) each: normotensive Wistar rats (WR); SHR; WR with nNOS inhibition and SHR with nNOS inhibition. The SHR groups consisted of animals in which systolic arterial pressure (SAP) was more than 180 mmHg. One day before experiments under general anaesthesia (Nembutal 35 mg/kg, i.p.), in femoral artery for blood pressure registration and vein for application of selective nNOS inhibitor 7-Nitroindazole (7-NI) in dose 2 mg/kg/h, catheters were inserted. Experiments were carried out in conscious rats. The arterial blood pressure was registered directly by a blood pressure transducer Gould Statham P23ID, connected to data acquisition system Biopac MP100WS during 40 min long control period and 20 min after 7-NI application for 40 min. The blood needed for determination of PRA (RIA) and plasma adrenaline concentration (ELISA) was taken from femoral artery catheter.

Results: SAP in SHR was higher in comparison to WR: 185.1±3.5 and 133.8±1.6 mmHg, (p<0.01). 7-NI did not change SAP in both WR and SHR: 134.8±2.1 and 184.1±3.4 mmHg. PRA did not differ between WR and SHR: 12.1±1.97 and 11.17±1.46 ng/ml/h. 7-NI decreased PRA in WR to 2.62±0.43, (p< 0.01) as well as in SHR to 5.76±1.12 ng/ml/h, (p< 0.05). Decrease of PRA was more pronounce in WR (78.4%) in comparison to SHR (48.7%). The plasma adrenaline concentration in SHR was higher as compare to WR: 8.76±0.95 and 4.19 ±0.53 ng/ml, (p<0.01). 7-NI increased plasma concentration of adrenaline in WR to 8.81±1.12 ng/ml, as well as in SHR, to 26.63±4.87 ng/ml, (p<0.001). The increase in SHR was significantly higher, (by 204 %) in comparison to WR (by 110%).

Conclusions: Our results displayed that NO produced by nNOS, inhibit adrenaline release and stimulate renin-angiotensin system in both normotensive and spontaneously hypertensive rats. The greater effect of NO, produced by nNOS on adrenaline release in SHR may be a result of changed interaction with increased sympathetic nerve activity in SHR that is the other important factor in regulation of adrenalin release. Attenuated action of NO, produced by nNOS on regulation of PRA in SHR is due to impaired nNOS function in the juxtaglomerular apparatus, established in SHR.

Key words: adrenaline, PRA, nNOS, SHR

Abstract-ID: 280

DISTURBED SLEEP-WAKE RHYTHMICITY IN PATIENTS PREVIOUSLY TREATED FOR NONFUNCTIONING PITUITARY MACROADENOMAS

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Context and objective: In a small pilot study in patients treated for nonfunctioning pituitary macroadenoma (NFMA), we observed alterations in polysomnographic sleep characteristics, actigraphic sleep-wake rhythmicity, and subjective fatigue, daytime somnolence, and low sleep quality. We aimed to confirm the actigraphic data in a larger scale cohort of NFMA patients, powered to address risk factors for altered rhythmicity, including the effects of hydrocortisone use.

Methods: Sleep-wake rhythmicity in treated NFMA patients was measured using 7 days of actigraphy, and subjective sleep quality and quality of life with validated questionnaires. To assess the influence of hydrocortisone dependency, we additionally studied Addison's disease (AD) patients. Results were compared to matched healthy controls.

Results: We included 69 NFMA patients in long-term remission after transsphenoidal surgery that received adequate replacement therapy for hypopituitarism, 21 AD patients, and 58 controls. NFMA patients reported severely impaired quality of life, sleep quality, and increased daytime sleepiness. The day-night dichotomy of activity was fragmented, with decreased daytime activity and a tendency for increased nighttime activity. Pre-operative visual field defects (VFD) were associated with this fragmentation, and vasopressin deficiency with decreased sleep efficiency, independent of age, hypopituitarism, or radiotherapy. AD patients showed similar decreases in daytime functioning, but normal subjective and objective sleep, and no daytime sleepiness.

Conclusion: NFMA patients suffer from altered sleep-wake rhythmicity. Hydrocortisone dependency may explain part of the decreased daytime functioning, but the independent influence of VFD and the differences between AD and NFMA patients point towards dysfunction of the adjacent suprachiasmatic nucleus.

Abstract-ID: 370

MEN1 AND PITUITARY ADENOMAS IN CHILDREN AND YOUNG ADULTS

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Introduction: Pituitary adenomas in young population are rare, and their prevalence varies in literature. The prevalence of multiple endocrine neoplasia type 1 (MEN1) and clinical predictors of mutations in MEN1 gene in these patients are still unknown.

Materials & Methods: We analyzed 74 consecutive patients (52 females, 22 males) with pituitary tumors under the age of 35 (mean 24, range 10-35) treated in one Centre from 2003-2013. Diagnosis of MEN1 was established according to current diagnostic criteria. We used direct DNA sequencing and multiplex ligation-dependent probe amplification for detection of mutations and large deletions of MEN1 gene.

Results: Twenty four patients (32.4%) were diagnosed with MEN1. Germline mutation was detected in nineteen patients (79%), and large deletion was found in one patient (4.1%). Among those with pituitary tumor only, MEN1 was diagnosed in four patients (7.3%). MEN1 patients were older than non-MEN1 ($p<0.05$). Fifteen patients (78.9%) with germline mutations presented with at least two MEN1 components. Pituitary adenomas were associated with primary hyperparathyroidism (70.8%), neuroendocrine (37.5%) and adrenal tumors (12.5%). Majority of patients were diagnosed with macroadenoma and secretory tumors, irrespective of MEN1 status. Prolactinoma was the most frequent (43.3%). However, nonfunctioning adenoma was more prevalent in MEN1 than non-MEN1 patients (35% vs. 11.1% respectively, $p<0.05$). After adjusting for age and sex, MEN1 phenotype was the strongest predictor of germline mutation.

Conclusion: MEN1 phenotype but not the age of young patients with pituitary adenoma is the predictor of mutation in MEN1 gene. The youngest patients with pituitary adenoma are not at the highest risk for MEN1 mutation.

Abstract-ID: 365

CAVERNOUS AND INFERIOR PETROSAL SINUS SAMPLING IN THE PREOPERATIVE EVALUATION OF ACTH-DEPENDENT CUSHING'S SYNDROME.

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Purpose: Though inferior petrosal sinus sampling (IPSS) is considered the gold standard test for the differential diagnosis of ACTH-dependent Cushing's syndrome, false-negative results have been reported in 1-10% cases. Anomalous venous drainage and hypoplastic petrosal sinuses are mentioned among the causes of unsuccessful IPS catheterization. Cavernous sinus sampling (CSS) was suggested as a diagnostic tool in a complex ACTH-dependent Cushing's syndrome cases.

Aim: To study the role of cavernous sinus sampling in differential diagnosis of ACTH-dependent Cushing's syndrome.

Materials and methods: Four patients with ACTH-dependent Cushing's syndrome were included. According to pituitary MRI data in two cases microadenomas 3mm and 4mm were revealed, in one case structure heterogeneity was found and in one case no changes were detected. In all patients CSS and IPSS were performed and ACTH and prolactin levels were measured in plasma samples. All patients underwent transsphenoidal endoscopic surgery.

Results: ACTH CS/P ratio was more than 2 suggesting the pituitary source in 100%. Baseline prolactin CS/P and IPS/P ratio ipsilateral to the dominant ACTH CS/P ratio side was more than 1,8 in all patients. As for the IPSS, in two cases ACTH IPS/P ratio was more than 2, supporting the data of CS. But in two cases ACTH IPS/P ratio was less than 2 (0,42-0,75) indicating the ectopic ACTH syndrome, these data contradicted CSS results. During the surgery pituitary microadenomas were found in all patients, ACTH secretion was approved by immunnohistochemistry, all patients became eucortisolemic after the operation. The lateralization of adenoma was correctly predicted by CSS in 3cases.

Conclusion: According to our experience, CSS has a higher accuracy than IPSS in differential diagnosis of eutopic and ectopic ACTH production. CSS could be recommended for diagnostic purposes in complex cases of ACTH-dependent Cushing's syndrome, also it might be helpful for the localization of ACTH-secreting microadenomas within pituitary.

Abstract-ID: 448

HYPOTHALAMIC-PITUITARY-OVARIAN AXIS REACTIVATION BY KISSPEPTIN-10 IN HYPERPROLACTINEMIC WOMEN WITH CHRONIC HYPOGONADOTROPIC AMENORRHEA.

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Background: Hyperprolactinemia-induced hypogonadotropic anovulation (PRL-HA) is a major cause of amenorrhea secondary to hypothalamic GnRH deficiency. In hyperprolactinemic mice we recently demonstrated that hypothalamic kisspeptin expression was diminished and that kisspeptin administration restored hypothalamic GnRH release, gonadotropin secretion, and ovarian cyclicity (J Clin Invest 2012), suggesting that kisspeptin neurons play a major role in PRL-HA.

Aim: To study the effect of kisspeptin-10 administration on gonadotropic-

ovarian axis in women with PRL-HA.

Patients: Two hyperprolactinemic women (34,39 yrs-old) with cabergoline resistant microadenomas (<6 mm) and serum prolactin respectively at 95 and 98 ng/mL (ULN <20) with chronic (> 6 months) secondary amenorrhea related to PRL-HA.

Protocol: Blood sampling every 10 min for 12 h during 2 consecutive days to measure LH, FSH and free alpha-subunit (FAS) pulsatilities and serum Estradiol (E2) and inhibin B (IB) levels. Vehicle or kisspeptin-10 (1.5 µg/kg/h) were infused intravenously each day for 12 hours.

Results: Kisspeptin-10 induced a significant increase in pulsatile secretion of the two gonadotropin, and FAS with a dramatic rise in their amplitude. A rapid and very significant increase, in mean LH, FSH, but also in E2, IB circulating levels ocurred. See below (Mean ± SD):

Woman 1

	LH (IU/L)	FSH (IU/L)	E2 (pg/mL)	IB (pg/mL)
vehicle	5.3±2.9	3.6±0.3	19.1±4.8	19.2±5.0
kiss-10	54±22****	12.1±4.3****	50.2±21***	53±19***

Woman 2

	LH (IU/L)	FSH (IU/L)	E2 (pg/mL)	IB (pg/mL)
vehicle	1.2±0.4	5.5±1.0	14±2.0	17±2.9
kiss-10	6.1±2.9***	13±3.1****	28±3.3**	27±2.2*

FAS secretion changes will also be detailed.

Conclusion: We demonstrate here for the first time, that kisspeptin administration can dramatically stimulate short term gonadotropin secretion in women with PRL-HA. This exploratory study suggests that kisspeptin could be an alternative therapeutical approach to restore ovulation and fertility in hyperprolactinemic women resistant to dopamine agonists.

ORAL PRESENTATION 8

Abstract-ID: 423

CORRELATION BETWEEN INTRAOCULAR PRESSURE AND PLASMA AND SALIVARY CORTISOL VALUES IN PATIENTS WITH CUSHING'S SYNDROME

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Introduction: Ocular hypertension is frequent in patients under corticosteroid therapy but can also be a complication of endogenous hypercortisolism (Cushing's syndrome, CS). The aim of this study was to verify the prevalence of ocular hypertension in a group of patients with CS and to evaluate possible correlations between intraocular pressure (IOP) values and hormonal parameters of hypercortisolism.

Materials and methods: 22 adult patients with active CS underwent ophthalmic examination including fundus photography, applanation tonometry and visual field testing. IOP values were corrected according to corneal thickness, measured by ultrasound pachymetry. We also collected, for all patients, clinical and hormonal data at the time of ophthalmic evaluation.

Results: Among CS patients (mean age 43.86±13.02 years, F:M =3.7:1), 18 had ACTH-dependent CS (15 of pituitary and 3 of ectopic origin) and 4 ACTH-independent CS. Mean IOP value was 18.9±5.2 mmHg. We found ocular hypertension (IOP > 21 mmHg) in 5 patients (22.7%), of which 3 males (corresponding to 50% of male population examined). Patients with ocular hypertension were younger (mean age 32±10.3 vs 47.3±11.8 years, p=0.016) and presented higher 23:00 h plasma (p=0.0001) and salivary (p=0.011) cortisol values than patients with normal IOP. Disease duration, BMI, prevalence of arterial hypertension and diabetes did not significantly differ between the two groups. We found a significant positive correlation between IOP values on one hand and 08:00 h salivary cortisol (p=0.04), 23:00 h plasma cortisol (p=0.001) and 23:00 h salivary cortisol (p<0.0001) on the other hand. No significant correlation emerged between IOP values and 08:00 h plasma cortisol, urinary free cortisol and ACTH.

Conclusions: Our study shows a considerable prevalence of ocular hypertension among patients with CS, especially at a young age, and underlines the importance of ophthalmic evaluation including tonometry in these patients. We confirmed also in endogenous hypercortisolim a data already reported for normal and glaucomatous subjects without CS, that is the correlation between IOP and cortisol values. 23:00 h salivary cortisol, which is representative of free cortisol fraction and of loss of circadian rhythm, seems to be the most significant parameter associated to IOP.

Abstract-ID: 455

HIGH PREVALENCE OF AUTOIMMUNE THYROID DISEASES IN WOMEN WITH PROLACTINOMAS: SHOULD THE ROUTINE SCREENING FOR THYROID DYSFUNCTION BE INTRODUCED IN THESE PATIENTS?

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Background: Our retrospective studies revealed significantly higher prevalence of autoimmune thyroid diseases (AITD) in prolactinoma patients compared to general population: data supporting the experimental evidence for the potent immunomodulatory action of prolactin. Women of reproductive age represent the vast majority of all prolactinoma patients which raises some important questions regarding the screening for AITD and follow-up before and during pregnancy.

The aim of this prospective cross-sectional "case-control" study was to assess the frequency of newly diagnosed AITD in female patients with prolactinomas compared to sex- and age matched controls.

Materials and methods: The study population consisted of 154 consecutive patients in a single tertiary referral centre and 106 control subjects. All study participants underwent physical, ultrasonographic and laboratory examination (including measurement of serum TSH and FT4 levels as well as autoantibodies to thyroglobulin, thyroid peroxidase and TSH-receptor).

Results: AITD were three times more frequent in patients than in healthy controls (29.9% vs. 10.4%; p=0.0002). Similarly, we found subclinical hypothyroidism in 9.7% of patients versus 2.8% of healthy controls (p=0.044). Autoimmune hyperthyroidism was observed in 1.3% of all patients and none of the control subjects.

Conclusions: Patients with prolactinomas seem to develop more frequently AITD and predominantly autoimmune subclinical hypothyroidism in comparison to general population. The immunomodulatory impact of hyperprolactinemia on both humural and cell-mediated immune responses may be suggested as an additional factor in the pathogenesis of AITD in genetically predisposed subjects. Based on these results we recommend routine screening for AITD (measurement of TSH, thyroid peroxydase antibodies and thyroid ultrasound examination) in all patients diagnosed with prolactinoma. More frequent control is needed in young women with prolactinomas as maternal thyroid dysfunction may be associated with adverse obstetric and fetal outcomes.

Abstract-ID: 467

EFFECTIVENESS OF PASIREOTIDE TREATMENT IN PATIENTS WITH CUSHING'S DISEASE: A NATIONAL EXPERIENCE BASED ON CLINICAL PRACTICE

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A recent phase III clinical trial has demonstrated that the treatment with the somatostatin analogue pasireotide normalizes cortisol secretion in 15-28% of patients with Cushing's disease (CD). No data are presently available on the outcome of pasireotide treatment when used in the daily clinical practice. The aim of the current study was to evaluate the effectiveness of 6-months pasireotide treatment on clinical and hormonal profiles in a group of CD patients with mild to moderate disease. Twenty-seven patients with CD unsuccessfully treated by surgery and with persistently increased urinary cortisol (UC) levels started treatment with pasireotide at the dose of 600 mg bid. UC, plasma ACTH and serum cortisol levels were measured every three months together with clinical and metabolic parameters. Three patients discontinued pasireotide treatment after 2-4 weeks for gastrointestinal disturbances (2), or death (1, unrelated to the drug); among the remaining 24 patients, 15 with mild (12) or moderate (3) UC increase reached 6-months follow-up, and were considered for the study. After 6-months pasireotide treatment, UC levels were normalized or nearly normalized in 10 out of 15 (67.7%) patients. A significant decrease of UC (p=0.01) and a trend to a significant decrease in plasma ACTH levels was demonstrated in the entire cohort of CD patients. The decrease of UC levels was accompanied by a significant decrease in weight (p=0.002) and body mass index (p=0.005) and a trend to a significant decrease in waist circumference (p=0.09). Fasting plasma glucose (p=0.004) and glycosylated haemoglobin (p=0.004) levels increased significantly. Hyperglycaemia or deterioration of diabetes was documented in 41% whereas gastrointestinal disturbances, mainly diarrhoea, were documented in 30% of patients during the period of pasireotide treatment. In conclusion, the use of pasireotide in the management of mild or moderate CD during clinical practice induces normalization of UC in nearly 70% of patients, with consequent improvement in the clinical picture but with occurrence or deterioration of diabetes, or gastrointestinal disturbances in 30-40% of cases. These results confirmed the usefulness of pasireotide in controlling CD especially in patients with mild disease.

Abstract-ID: 445

PASIREOTIDE LAR CAN MAINTAIN BIOCHEMICAL CONTROL IN PATIENTS WITH ACROMEGALY: RESULTS FROM THE EXTENSION OF A RANDOMIZED PHASE III STUDY (PAOLA)

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Background: The core 24-week PAOLA study demonstrated that pasireotide LAR 40 and 60 mg provides superior efficacy over continued treatment with octreotide LAR/lanreotide Autogel in patients with inadequately controlled acromegaly; biochemical control (defined as GH levels <2.5 µg/L *and* normal IGF-1) was achieved in 15.4% and 20.0% versus 0% of patients, respectively. This preliminary analysis (data cut-off 3 June 2013) from an extension study of PAOLA further assesses the efficacy/safety of pasireotide LAR.

Methods: The extension started following a 4-week bridging phase, during which time patients completing the core continued receiving the same treatment. Patients who received pasireotide LAR 40 and 60 mg and had biochemical control at week 24 of the core study continued on double-blind pasireotide LAR at the same dose; those who were not biochemically controlled received open-label pasireotide LAR 60 mg. Patients receiving octreotide LAR/lanreotide Autogel who were not biochemically controlled at week 24 of the core study were switched to open-label pasireotide LAR 40 mg (crossover group). Efficacy endpoints included the proportion of patients with: biochemical control; normal IGF-1; GH <2.5µg/L at week 28 of the extension study. Safety and tolerability was also assessed.

Results: 181/198 patients completed the core; 173 entered the extension (pasireotide LAR 40 mg, n=57; 60 mg, n=54; crossover, n=62). Of patients with available data at week 28 of the extension study, 18.4% (9/49) and 33.3% (15/45) in the pasireotide LAR 40 mg and 60 mg groups achieved biochemical control, respectively; 32.7% (16/49) and 37.8% (17/45) achieved normal IGF-1 levels; 38.8% (19/49) and 46.7% (21/45) had GH levels <2.5 µg/L. Of patients in the crossover group, 20.0% (10/50) had biochemical control, 24.0% (12/50) achieved normal IGF-1 levels and 42.0% (21/50) had GH levels <2.5 µg/L at week 28 of the extension study. The overall safety profile of pasireotide LAR in the extension study was similar to the core; hyperglycemia, diabetes mellitus, cholelithiasis and diarrhea were the most common adverse events.

Conclusions: Pasireotide LAR can maintain biochemical control in patients with acromegaly who are inadequately controlled by first-generation somatostatin analogues. Pasireotide LAR may therefore provide a viable, long-term treatment option for patients with acromegaly.

Abstract-ID: 494

NEUROPROTECTIVE EFFECT OF BOSWELLIA SERRATA AND ITS ACTIVE CONSTITUENT ACETYL 11-KETO BETA BOSWELLIC ACID AGAINST ISCHEMIA-INDUCED CYTOTOXICITY

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Introduction: Neurons are especially sensitive to oxidative stress due to having relatively low levels of endogenous antioxidants and high rate of oxidative metabolic activity. Increased levels of reactive oxygen species (ROS) damage cellular macromolecules and are considered as important inducer of apoptosis in ischemia condition. *Boswellia serrata* and its active constituent, 3-acetyl-11-keto-β-boswellic acid (AKBA) have displayed a broad spectrum of pharmacological properties such as antioxidant, anti-ischemic, anticonvulsant and anti-nociceptive activities. The present work was carried out to investigate if they have protective effect against oxygen, glucose and serum deprivation (OGSD)-induced cytotoxicity in PC12 neuron like cells.

Methods: The cells were pretreated with different concentrations of *B. serrata* extract (1-400 µg/mL) or AKBA (0.5-40 µg/mL) for 2, and then subjected to the OGSD for 6 h. Cell viability was quantitated by

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) assay. Intracellular ROS and lipid peroxidation were determined by spectrofluorimetry. The extent of DNA damages were determined using single cell gel electrophoresis assay.

Results: Exposure PC12 cells to OGSD condition leads to significant decrease in cell viability. The *B. serrata* at concentrations of 3-12.5 µg/ml and AKBA at concentration of 1 µg/ml significantly increased the cell viability ($P < 0.05$) as compared with untreated cells. The OGSD Also significantly increased the percent of DNA fragmentation ($P < 0.001$) and a significant decrease in DNA damage was seen following treatment with both *B. serrata* and AKBA. The lipid peroxidation and generation of intracellular ROS were significantly increased ($P < 0.001$) after OGSD insult. Incubation with *B. serrata* and AKBA significantly decreased the OGSD-induced lipid peroxidation and ROS accumulation ($P < 0.001$).

Conclusion: The experimental results suggest that *B. serrata* and its active constituent AKBA protect neurons against ischemia condition via antioxidant mechanisms. Our findings might raise the possibility of potential therapeutic application of *B. seratta* for managing cerebral ischemic and neurodegenerative disorders.

Abstract-ID: 530

ROLE OF FILAMIN-A IN SOMATOSTATIN RECEPTOR 2 (SST2) SIGNALING AND EXPRESSION IN GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOR CELLS

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Somatostatin receptor type 2 (SST2) is the main target of pharmacological therapy for GEP-NETs. A subset of patients is resistant to somatostatin analogs (SSa), although the molecular mechanisms responsible for resistance to SSa are poorly understood. Several studies identified specific protein-protein interactions as determinant in the regulation of receptor anchoring and signaling. Filamin A (FLNA) is a ubiquitous cytoskeleton protein with scaffolding properties, involved in the intracellular signaling and trafficking of different receptors.

Since SST2 was recently demonstrated to associate with FLNA, the aim of this study was to investigate the role of FLNA in SST2 expression and signaling in human GEP-NETs and in QGP1 GEP-NET cell line. We studied FLNA and SST2 expression in GEP-NETs by Western blotting (N=8) and by immunohistochemistry (N=20) and we found highly variable expression of FLNA in GEP-NETs, without correlation with SST2 levels and clinical phenotype. FLNA gene silencing did not induce any significant change in SST2 total levels in QGP1 cells. On the contrary, the reduction in cyclin D1 levels (-55±12%, $p<0.05$ vs basal) and ERK1/2 phosphorylation (-63±9% $p<0.05$ vs basal) induced by the selective SST2 agonist (BIM23120) was abolished in cells transfected with siRNA FLNA. Similarly, BIM23120 inhibited forskolin-stimulated cAMP accumulation in cells transfected with negative control siRNA and this effect was abrogated in FLNA silenced cells. Moreover, FLNA knockdown reduced SST2 expression after agonist exposure (-35±5%, $p<0.05$ vs basal). Finally, preliminary data showed that BIM23120 promoted cell adhesion in QGP1 cells, this stimulatory effect being abolished in FLNA silenced cells.

These results suggest that FLNA might be implicated in SST2 signaling and stabilization in GEP-NET cells. In contrast, FLNA does not seem to be necessary for receptor expression.

Abstract-ID: 543

THE STIMULATION OF MUSCARINIC ACETYLCHOLINE RECEPTORS INHIBITS DIFFERENTIATION OF MOUSE INDUCED PLURIPOTENT STEM CELLS TO NEURAL PROGENITOR CELLS

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Introduction: The present study examined whether stimulation with musucarinic acetylcholine (mAch) receptors affects proliferation or differentiation into NPCs of mouse iPS cells.

Materials and Methods: Mouse iPS cells were cultured under feeder-free conditions in the presence of leukemia inhibitory factor (LIF). The cells were treated by carbachol (a mAch receptor agonist; 0.1 ~ 10 µM) for 48 h. Proliferation of mouse iPS cells was examined by MTT assay. Mouse iPS cell differentiation was initiated by embryoid body (EB) formation under LIF-free condition. The EBs were pretreated by atropine (a mAch receptor antagonist; 0.1 ~ 10 µM) and stimulated with all trans retinoic acid (ATRA; 1 µM) and/or carbachol (0.1 ~ 10 µM) for 4 days and then transferred to fibronectin-coated dishes. The differentiation potential into NPCs was evaluated by Nestin expression using immunofluorescence staining and western blot analysis.

Results: Treatment with carbachol did not affect the proliferation of mouse iPS cells. On the other hand, treatment with carbachol (10 µM) significantly inhibited ATRA-induced Nestin expression in the differentiated cells. Pretreatment with atropine (10 µM) significantly blocked the inhibitory effect of carbachol.

Conclusion: These results suggest that the stimulation of mAch receptors inhibits the differentiation of mouse iPS cells to NPCs.

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Abstract-ID: 148

EARLY ENDOCRINE ALTERATIONS REFLECT PROLONGED STRESS AND PROBABLY PREDICT ONE-YEAR FUNCTIONAL OUTCOME IN PATIENTS WITH SEVERE BRAIN INJURY

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Context: Pituitary hormone alterations in the early recovery phase after brain injury may have implications for patient's long-term functional recovery. It is not yet clear whether such hormonal alterations reflect damage to the hypothalamo-pituitary region, or represent stress response and adaptation to acute illness following brain injuries.

Objective: To assess the pattern and prevalence of pituitary hormone alterations three months after severe brain injury with relation to functional outcome at one-year follow-up.

Design: Prospective study.

Setting: Tertiary university referral center.

Participants: Patients admitted to neurorehabilitation after severe traumatic (N=111) and non-traumatic (N=52) brain injury.

Main outcome measures: Functioning and ability, as measured by Functional Independence Measure and Glasgow Outcome Scale-Extended at one-year follow-up and their relationship to endocrine alterations measured 3.3 months (median) after the initial injury.

Results: At 3 months, increased stress hormones (i.e. 30 min. stimulated

cortisol, prolactin and/or IGF-I) and/or suppressed gonadal- or thyroid hormones were recorded in 68% and 32% of the patients, respectively. At one year, lower functioning level (Functional Independence Measure) and lower capability for normal life activities (Glasgow Outcome Scale-Extended) were related to both increased stress hormones ($p \leq 0.01$) and reduced gonadal and/or thyroid hormones ($p \leq 0.01$) measured at 3 months.

Conclusion: The present study suggests that brain injury-related endocrine alterations mimicking secondary hypogonadism and hypothyroidism most probably reflect prolonged stress response in the early period after severe brain injury, rather than pituitary insufficiency per se. Elevated stress hormones and reduced gonadal and thyroid hormones probably reflect more severe disease states, and probably predict one-year functional outcome.

POSTER CLINICAL PITUITARY

Abstract-ID: 65

RELATION OF ACROQOL SCORES WITH DEPRESSION, ANXIETY, BALANCE AND FEAR OF FALLING MEASURES IN ACROMEGALIC PATIENTS

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Introduction: The aim of this study is to evaluate the relation between quality of life (QoL), psychological status, balance and fear of falling in acromegalic patients.

Methods: Fifty-one acromegalic patients (mean age 49.3 years and mean disease duration 6.6 years) were enrolled in the study. Beck depression scale (BDS) and Beck anxiety scale (BAS) were used to evaluate psychological status. Berg balance scale (BBS), one-leg stance test (OLST) and 50 meters walking test were used to evaluate balance and falls efficacy scale-international (FES-I) was used to evaluate fear of falling. AcroQoL, a disease specific QoL questionnaire for acromegaly with physical and psychological dimensions, was used to evaluate QoL. Spearman correlation analyses were done among these tests.

Results: AcroQoL total score was negatively correlated with BDS, BAS and FES-I scores and positively correlated with BBS score and OLST. AcroQoL physical score was negatively correlated with BDS, BAS, and FES-I scores and positively correlated with BBS score and OLST. AcroQoL psychological score was negatively correlated with BDS, BAS and FES-I scores. Univariate analysis revealed that the presence of hypopituitarism ($p = 0.002$) and visual field defects ($p = 0.027$) independently affect AcroQoL total score. Regression analysis showed that only BDS and BAS scores were related with AcroQoL total score. AcroQoL scores, BDS, BAS, BBS, OLST 50 meters walking test and FES-I scores did not differ between remitted and un-remitted patients (all p's > 0.05).

Discussion: QoL in acromegaly is correlated with psychological status, presence of balance disturbances and fear of falling. This correlation is evident in total AcroQoL score and scores of AcroQoL dimensions . However, only presence of depression or anxiety was found to independently affect QoL. Remission status did not affect QoL, balance and fear of falling.

Abstract-ID: 115

TWO PITUITARY ADENOMAS IN THE SAME FAMILY

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Pituitary adenomas occur with a prevalence of approximately 1:1000 in the developed world. The clinical condition of familial isolated pituitary adenomas (FIPA) encompasses the familial occurrence of isolated pituitary adenomas outside of the setting of syndromic conditions like multiple endocrine neoplasia type 1 and Carney complex. FIPA families comprise approximately 2% of pituitary adenomas. Here we present two brothers with pituitary adenomas and different clinical presentations.

CASE 1: 52 years old male patient was admitted to emergency unit with symptoms of sight loss, fatigue, urinary incontinence. The laboratory data revealed secondary adrenal insufficiency, secondary hypothyroidism, hypogonadotropic hypogonadism. IGF-1: 43 ng/ml (87-238), GH level at 75 g OGTT: 0.207 ng/ml, Prolactin: 6.5 ng/ml (2.1-17.7), FT4: 0.62 ng/dl (0.88-1.72), TSH: 0.22 uIU/ml (0.35-5.5), Cortisole: 0.85 µg/dl (4.6-22.8), ACTH: <1 pg/ml (7.2-63.3). 3x4,5x5 cm solid pituitary mass invading cavernous sinuses bilaterally was demonstrated at pituitary imaging. There was also compression of optic nerve. First he was treated with surgery, but cyberknife was also applied for the residual adenoma.

CASE 2: His 50 years old brother was noticed to have acromegalic symptoms when he came to visit his brother. IGF-1: 517 ng/ml (94-252), GH level at 75 g OGTT: 1.96 ng/ml, Prolactin: 5.9 ng/ml (2.1-17. Pituitary adenoma (3-4 mm) was detected at the pituitary MRI on the left side. Somatostatin analogue treatment was initiated because he refused to have surgery. Clinical screening for signs and symptoms of multiple endocrine neoplasia 1 or Carney complex are negative for both of the patients.

Early diagnosis of pituitary tumors while they are smaller may help increase cure rates. When considered together, familial forms of pituitary tumors account for approximately 5% of tumors that occur in everyday practice. This reinforces the importance of including a detailed family history in the assessment of all patients with pituitary tumors.

Abstract-ID: 121

"THE FREQUENCY OF DIABETES INSIPIDUS IN CHILDREN AND ADOLESCENTS OF THE REPUBLIC OF UZBEKISTAN"

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Aim. To study the epidemiological data of the cases of diabetes insipidus in children and adolescents of the Republic of Uzbekistan (RUz).

Materials and methods. We evaluated retrospective data of 235 children and teenagers with diabetes insipidus (DI) from all regions of RUZ, which were treated in regional endocrinology ambulances during 2012-2013 years. The average age of patients were from 2 to 18 years old.

All patients were evaluated for hormones levels (GH, LH, FSH, prolactin, cortisole, free thyroxine, etc.), visual fields, pituitary MRI, urine tests, etc.

Results. The frequency of DI was different in regions of RUz: Andijan region – 15 (6,4%) patients, Bukhara region – 22 (9,4%), Djizakh region – 19 (8,0%), Fergana region – 30 (12, 8%), Kashkadarya region -23 (9,8%), Khorezm region – 17 (7,2%), Navoiy region -2 (0,8%), Namangan region -37(15,7%), Samarkand region -16 (6,8%), Surkhandarya region - 17(7,2%), Syrdarya region -6 (2,5%), Tashkent region – 10 (4,2%), Tashkent-city -11 (4,7%), the Republic of Karakalpakstan – 10 (4,2%).

Conclusions. 1) More cases of patients with DI were diagnosted in Namangan region – 37 (15,7%) and in Fergana region – 30 (12, 8%), which characterized most of frequency of iodine deficiency in RUz too, 2) The first complication of DI in children and adolescents is delay of growth – 153 cases (65,1%)

Abstract-ID: 127

FREQUENCY AND SIGNS OF MACROPROLACTINEMIA

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According to guidelines on diagnosis and treatment of hyperprolactinemia (2011) patients without symptoms should be assessed for macroprolactin. We analyzed clinical data, total and monomeric prolactin levels of 85 patients (75 female, 10 male) who had been investigated in our Endocrinology Department during 2008-2012: NonTumor hyperprolactinemia (NT, n=34), MIcroadenomas (MI, n=36), MAcroadenomas (MA, n=15). Patients' age was 33.5 [28; 42] y.o. and did not differ between subgroups. Median prolactin levels were in NT 1716 (1150; 2700), MI 2974 [1190; 3665], and MA 3546 [1312; 48209] mMU/l ($p=0.04$). Prevalence of macroprolactin in serum (>40%) was found in 17/34 (50%) patients with NT (2 men/15 women), 9/36 (25%) patients with MI (1 men/8 women), and none in MA. In patients with or without macroprolactinemia total prolactin levels were 2165 [1179; 3832] and 1629

[1184; 1976] mMU/l (NS), monomeric prolactin levels were 1600 [900; 3100] and 363 [256; 571] mMU/l (p<0.001), and relative amount of monomeric prolactin was 86 [78; 90] and 20.5 [10; 24] % accordingly. Among patients with macroprolactinemia normal levels of monomeric prolactin were found in 10/17 patients with NT (6 asymptomatic) and 4/9 patients with MI (4 asymptomatic). However, asymptomatic cases were also observed in patients with elevated monomeric prolactin levels with or without macroprolactinemia, and patients with normal monomeric prolactin levels had symptoms due to problems not related to hyperprolactinemia.

Thus, in our cohort of patients macroprolactinemia was found in women and men with non tumoral hyperprolactinemia (50% of cases) and microadenomas (25% of cases). There was not obvious correlation between symptoms and macroprolactinemia. To avoid misunderstanding we suggest assessing for macroprolactin in all patients with non tumoral hyperprolactinemia and microadenomas regardless of symptoms.

Abstract-ID: 136

THE VALUE OF SERUM IGF-1 LEVEL IN THE DIAGNOSIS OF GROWTH HORMONE DEFICIENCY

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Introduction: Insulin tolerance test (ITT) has been accepted to be the gold-standard test for the diagnosis of growth hormone deficiency (GHD). Our aim was to retrospectively assess the value of serum insulin like growth factor-1 (IGF-1) level for the diagnosis of GHD in patients with pituitary disorders.

Methods: 205 patients, in whom ITT was performed, were enrolled in this retrospective study. Demographic data, basal hormone levels, and ITT results were evaluated. Biochemical hypoglycemia (plasma glucose level ≤ 40 mg/dl) was achieved in all patients. A peak GH value of <3,00 µg/L for ITT was accepted as GHD.

Results: The mean age of patients was 48.8 ± 14.2 years. Underlying causes of pituitary disorders are shown in Table-1. 180 out of 205 (87.8%) patients had GHD according to ITT, while 25 (12.2%) patients had sufficient GH responses. A serum IGF-1 level less than 117 ng/ml was found to be 100 % specific in the detection of GHD. All of the patients, in whom IGF-1 value was below '117 ng/ml', had blunted responses to ITT.

Conclusions: According to the results found in the present study, in patients with pituitary disorders, a serum IGF-1 level < 117 ng/ml strongly suggests the diagnosis of GHD.

Table-1: The distribution of patients according to the underlying pituitary disorders.

Underlying Disorder	Number (%) of patients
Pituitary Adenoma & Related Treatments	95 (46.4 %)
Sheehan's Syndrome	54 (26.3 %)
Congenital Hypopituitarism	17 (8.3 %)
Primary Empty Sella	16 (7.8 %)
Head Trauma	13 (6.3 %)
Rathke Cleft Cyst	7 (3.4 %)
Subarachnoid hemorrhage	2 (1,0 %)
Meningitis	1 (0.5 %)
Total	205 (100%)

Abstract-ID: 143

MULTISYSTEM MORBIDITY IN PATIENTS WITH BENIGN ENDOGENOUS CUSHING'S SYNDROME BEFORE AND AFTER DIAGNOSIS AND TREATMENT

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Chronic exposure to glucocorticoid excess is associated with increased multisystem morbidity and mortality. Our study aimed to elucidate morbidity in patients with endogenous Cushing's syndrome of benign origin before and after treatment of hypercorticism.

Patients and methods: Fifty seven patients (48F/9M) mean age 48.9 ± 33.2 years, diagnosed with benign endogenous Cushing's syndrome of pituitary and adrenal origin were included in the study. Patients' electronic case histories were analyzed for a period 2007-2014. Cushing's disease was diagnosed in 41 patient (33F/8M), adrenal cortisol secreting adenoma in 16 (15F/1M); median follow-up period was 7.3 years (range 1-29 years).

Results: Prevalence of arterial hypertension was 87 %, diabetes and glucose intolerance 53%, osteoporosis 35%, osteopenia 20%, vertebral fractures 20%, hyperlipidemia 47%, obesity 42%, cholelithiasis 42%, thyroid disorders 45%, neoplasia 29% (malignancy 11%), psychiatric disturbances 20%, infections 58%. Cardio- and cerebrovascular complications were present in 49% and more than 2 cardiovascular risk factors in 70% of patients. Significant improvement in control of arterial hypertension was achieved in 50%, metabolic control in 30%, obesity in 20% and hyperlipidemia in 10% of patients after treatment of hypercorticism. Severe osteoporosis with fractures was especially pronounced in male patients and improved significantly with the use of potent bisphospnonates and control of hypercorticism. Menstrual irregularities were present in 30% of female patients, in the reproductive period, and normalized in 15% after treatment of hypercorticism. Complications after surgery were observed in 26% and reactivation of autoimmune disorders in 5% of patients after treatment of hypercorticism.

Conclusions: Increased multisystem morbidity is present in patients with Cushing's syndrome years before diagnosis and persists with mild attenuation after biochemical cure during the follow-up period.

Abstract-ID: 147

COMPARATIVE ANALYSIS OF CLINICAL AND HORMONAL STUDIES IN PATIENTS WITH NEUROENDOCRINE ACTH-PRODUCING TUMOURS

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In this work the problem of neuroendocrine tumours (NET) accompanied by clinical symptoms of hypercortisolism caused by excessive secretion of adrenocorticotropic hormone (ACTH) by tumour cells is presented. In most cases (85%) the tumour was located in the pituitary gland (Cushing's disease, CD) and in 15% of the cases it was located outside the pituitary gland (ectopic ACTH secretion, ACTH-EC). In this study the comparative analysis of clinical and hormonal characteristics of pituitary tumours (corticotropinomas) in Cushing's disease (CD) and non-pituitary ACTH-secreting NET (ACTH-EC) was performed. 46 patients with CD and 38 patients with ACTH-EC were enrolled in the study. The extent of clinical manifestations, NET localization and hormone activity were assessed by means of clinical, laboratory, and instrumental methods.

The results of the study show that clinical manifestations of CD and ACTH-EC are very similar. ectopic ACTH secretion closely resemble each other. Hormonal studies revealed the markedly elevated ACTH level in patients with ACTH-EC in contrast to CD. When petrosal sinuses were catheterized

secretion of ACTH was enhanced in CD patients 3-5 minutes after desmopressin stimulation but did't change in patients with ACTH-EC.

The histological structure of all corticotropinomas suggests their benign origin while NET of non-pituitary localization have a different morphological structure, extent of malignancy, invasiveness and metastatic properties. The highest cell proliferation potential (Ki-67) was discovered in NET of the patients with ectopic ACTH secretion as compared to corticotropinomas.

Abstract-ID: 154

FROM DEPRESSION TO CUSHING SYNDROME:AN ATYPICAL PRESENTATION OF A CUSHING DISEASE

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A 17 year-old girl was initially evaluated in September 2011 due to weight gain, oligoamenorrhea, acne vulgaris. Also she had physical findings suggesting hypercortisolism as hair loss, striae. At this time, she was diagnosed with major depressive episode without psicotic features according to the DSM-IV criteria. Antidepressant therapy were started (Sertralin 50mg/day, gradually increased 100mg/day). Laboratorial evaluation confirmed cushing syndrome. But pituitary MRI and adrenal glands MRI were normal. It was thought she was in major depression with a disturbed hypothalamic-pituitary-adrenal (HPA) axis leading to a Cushing-like habitus.

Clinical and laboratorial hypercortisolism persisted and a medical therapy with ketoconazole was initiated in progressive doses up to, 800mg/day. Because of positive family history recurrent major depression with psicotic features maintenance antidepressant therapy was continued for 18 months (Fluoxetine 20mg/day, Bupropion 150-300mg/day, Aripiprazol 5 mg/day).

Two years later, she had gained 4-5 kg and developed symptoms and signs of hypercortisolism:central obesity, moon face, hirsutism, hair loss and violaceous striae again.

Initially, her plasma ACTH levels increased from 30.1pg/ml to 74.7pg/ml after ketoconazole therapy. Later laboratorial evaluation and radiological imaging tests were repeated

At this moment, MRI showed a pituitary adenoma measuring 4*3mm, near to left cavernous sinus. Corticotropin-releasing-hormone-stimulated IPSS was performed. A diagnosis of Cushing's disease (Cushing's syndrome as a result of a pituitary adrenocorticotropic hormone-secreting tumor) was made. She underwent transsphenoidal surgery. The pituitary tumor was removed in March 2014, and she was followed subsequent hydrocortisone treatment. Depression may accompany Cushing's syndrome from whatever cause (pituitary, adrenal, or ectopic adrenocorticotropic hormone-secreting tumor or hyperplasia, or exogenous administration of glucocorticoids) and hypercortisolemia is prevalent in major depression.

This case highlights many difficulties in the diagnosis of cushing syndrome especially if it is with an atypical presentation as major depression.

Abstract-ID: 194

TOTAL PLASMA AND SALIVARY CORTISOL AND ITS METABOLITES RESPONSE IN HYPOTHALAMIC-PITUITARY-ADRENAL AXIS TESTS

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Total plasma and salivary cortisol and its metabolites response in hypothalamic-pituitary-adrenal axis tests

The aim of the study was a detailed analysis and a comparison of hypothalamic-pituitary-adrenal axis(HPA) tests and cortisol and its metabolites during these tests analyzed by LCMS/MS and current immunoassays. This procedure might enable to design new diagnosis algorithms of hypocorticalism and normal levels for salivary cortisol estimation for early diagnostic of patients with HPA disorder as well as to give us a possibility to reveal adrenal disorder in patients on estrogen therapy or with altered levels of cortisol-binding proteins whose HPA evaluation is always problematic.

20 healthy volunteers (age 38±10yr(mean ±SD), BMI24.5±2.7 kg/cm2) were examined by high (250 µg), low dose(1 µg) and 10 µg Synacthen test and insulin test(ITT) and 20 patients with adrenal insufficiency(age 42±8 yr(mean ±SD), BMI26.5±3.7 kg/cm2). The study was approved by the local Ethical Committee.

We evaluated serum cortisol, serum cortisone, salivary cortisol, steroids in Δ4 pathway, other steroids and their polar conjugates in Δ4 and Δ5 pathway: reduced 5alpha/beta-metabolites of cortisol during dynamic tests by LCMS-MS and serum cortisol and basal levels of cortisol binding globulin, aldosterone and ACTH, respectively.

All healthy volunteers reached the normal response of cortisol (>500nmol/L) in all tests. The levels of cortisol metabolites were significantly lower in 1 µg Synacthen test comparing to remaining tests.The levels of salivary cortisol were significantly higher 45±10,5 nmol/L in the 250 µg and ITT compared to low and 10 µg Synacthen test, 32±2,5nmol/L. Cortisol levels were significantly lower after stimulation in these test.

Four different hypothalamic-pituitary-adrenal axis tests gave similar response of cortisol and its metabolites in healthy volunteers compared to patients. These results may contribute to better understanding the pathophysiology of changes HPA axis disorders. The study was supported by grant No.NT11 277-6 of the IGA MZCR.

Abstract-ID: 200

A CASE OF PROLACTINOMA RESISTANT TO DOPAMIN AGONISTS

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Introduction: Dopamine agonists are usually effective in the treatment of prolactinomas, which represent the most common type of pituitary adenomas.Dopamine agonist resistance is an infrequent phenomenon. Resistance to dopamine agonists is defined as failure to normalise or reduce PRL levels or tumour size by ≥50. Management of prolactinoma resistant to dopamine agonists include changing to another dopamine agonist and increasing the dose of the drug as long as there is continued response to the dose increases and no adverse effects with higher doses.Transsphenoidal surgery is also an option.Herein we present a patient with prolactinoma resistance to dopamin agonist.

Case report: A 32 year old women was referred to our institution with a history of headache, secondary amenorrhea and galactorrhea for one year. Laboratory evaluation showed prolactin level of 118 ng\ml(normal range 4.8 to 23.3 ng/mL) and pituitary MRI showed a 15x14x18 mm macroadenoma. There was no sellar enlargement or extrasellar extension. All other causes of hyperprolactinaemia were excluded.Firstly, the patient was treated with cabergoline during the three months, the dose of cabergoline was progressively increased from 1 mg\ week to 3 mg\week and her prolactin level did not decreased.Secondly her regimen was switched to bromocriptine 5mg\day for three months, prolactin concentration did not decreased. Lastly cabergoline was increased from 3 mg\week to 7.5 mg\week. Prolactin levels remained unchanged with incremental doses of cabergoline up to 6 mg\week and bromocriptine up to 5 mg\day.Treatment with cabergoline 7.5 mg\week dropped prolactin levels from 119 to 78 ng\ml. After one year MRI scan showed 10×10×6 mm pituitary adenom and symptoms of prolactinoma persisted despite escalating doses of cabergoline up to 7.5 mg weekly.Transsphenoidal excision of the macroadenoma was suggested, which she has refused before.

Conclusions: In conclusion, we describe a patient with a prolactinoma resistant to dopamine agonists and transspenhenoidal surgery is an option.

Abstract-ID: 224

ACROMEGALY AND PREGNANCY – TWO CASE REPORTS

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[1]Chlo

The occurrence of a pregnancy in a woman with acromegaly is infrequent. The maternal growth hormone excess does not seem to be harmefull for maternal and foetal outcomes but diabetes mellitus and hypertension, if present, are. In the last years 2 cases were followed by a multidisciplinary team in our institution.

A 34 years old lady presented headache enlargement of hands and feet. She had amenorrhea and had type 2 diabetes insulin treated. She had a pituitary adenoma with supraselar extension and was submitted to transfenoidal surgery with partial remission. Immunostaining was positive for PRL/GH. She started lanreotide 120mg each 2 months and bromocriptine 10 mg/day. IGF1 levels progressively decline and glycemic control improved under antidiabetic drugs. She has able to stop insulin, amenorrhea persists. Six years after she had menses once and she experienced weight gain. She was a 5th month pregnancy. Medical therapy was stopped, pregnancy was uneventful and she delivered a full term healthy baby, 4 years old now.

A 23 years old lady presented headache enlargement of hands and feet. She had regular menses and border-line high IGF1 and GH nadir on the OGTT was 0,3ng/ml. She had a pituitary adenoma with supraselar extension and was submitted to transfenoidal surgery. Immunostaining was positive for PRL/GH. IGF1 and GH were then elevated. She started lanreotide 120mg each 2 months and bromocriptine 10 mg/day. IGF1 levels progressively decline. Three years after surgery she desired to conceive. Lanreotide and bromocriptine were stopped. A pregnancy was confirmed 6 months later. It was uneventful with a full term healthy baby. Now, 2 years after acromegaly remain controlled under the same medical treatments

These cases illustrate successful outcomes of pregnancy in 2 patients with acromegaly with different severity managed conservatively.

Abstract-ID: 228

HISTOLOGICAL AND IMMUNOHISTOCHEMICAL CHARACTERISTICS OF CORTICOTROPINOMAS IN PATIENTS WITH REMISSION AND THE ABSENCE OF CUSHING`S DISEASE REMISSION AFTER NEUROSURGICAL TREATMENT

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The study includes 46 patients with Cushing`s disease (CD) divided into two groups: 31 (67.4 %) patients with remission (1st group) and 15 (32.6%) without remission (2nd group) observed on average for 4 years. We present histological and immunohistochemical study (with antibodies to pituitary hormones , Ki-67, CD31, VEGF, 1-5 subtypes of somatostatin receptors (SR) and 2 subtype of dopamine receptors DR2) in the removed corticotropinomas.

The majority of corticotropinomas from both groups were basophilic with secondary changes: mitosis, necrosis, hemorrhage, stromal edema, angiomatosis and pituitary hyperplasia without significant difference in the said groups. 51.6% of tumors (1st group) and 40.0%of adenomas (2nd group) were monohormonal with ACTH immunoexpression, bihormonal were 32.2% and 33.3% , polihormonal were 16.1% and 26.7% respectively. Expression of CD31 (p=0.3) and VEGF (p=0.7) in tumors from both groups. Median of Ki-67 labeling index was 0.13% in adenomas of the 1st group and 0.16 % in tumors of the 2nd group. Expression of 1-5 subtypes of SR in corticotropinomas of the 1st group, n=12: 1st subtype – 7, 2nd subtype – 2, 3rd – 7, 4th subtype – 6, 5th subtype – 3; in corticotropinomas of the 2nd group: 1st subtype – 5, 2nd subtype – 4, 3rd – 4, 4th subtype – 3, 5th subtype – 3. Expression of DR2 in corticotropinomas of the 1st group: 3, in corticotropinomas of the 2nd group – 3. Co-expression of SR and DR2 - in 3 adenomas from the both groups.

Thus, the majority of corticotropnomas from the both groups were basophilic with secondary changes. More than half corticotropinomas from the both groups expressed ACTH and other tropic pituitary hormones, CD31 and VEGF expression didn`t differed between the 2 groups. Ki-67 was significantly higher in corticotropnomas (2nd group). Immunoexpression or co-expression of SR and DR2 allows administration of somatostatin analogues and dopamine agonists for patients from the 2nd group.

Abstract-ID: 229

SANDOSTATIN IN TREATMENT OF ACROMEGALY AFTER RADIOTHERAPY

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Aim: to study complications in patients with acromegaly receiving sandostatin after radiotherapy.

Materials and methods: we examined 16 patients with disease duration 8.5±4.2 years (age 41.5±5.6 years) receiving distant gamma-therapy in total dose 60Gy. The patients divided into two groups: 8 patients receiving sandostatin in dose of 0.5 mg thrice a day and symptomatic therapy for 2 months were included into the 1st group, other 8 patients received only symptomatic therapy. To establish the disease activity we examined diurnal GH secretion at 8.00, 11.00, 13.00, 15.00 and 18.00

Results and discussion: at first examination (6 months after radiotherapy) GH diurnal secretion showed the presence of active acromegaly. Average daily GH level was 58.6 ± 8.2 and 49.8 ± 9.3 mIU/L in two groups of patients, respectively. 98% patients of the 1st group had endocrine-metabolic disorders, 85% had cardiovascular disorders, 80% had neuromuscular-skeletal-joint complications, 42% had respiratory disorders, 25% had neoplasms. In the 2nd group endocrine-metabolic disorders were found in all patients, 80% and 30% had cardio-vascular and respiratory complications, respectively, neuromuscular-skeletal-joint disorders and neoplasms were found in 85% and 20%, respectively. Two months later the repeated examination of the 1st group showed that average daily GH level was 5.6±1.2 mIU/L, remaining high in the 2nd group (26.6 ±8.5 mIU/L). In the 1st group, decrease in the incidence of endocrine-metabolic (78%), cardiovascular (45%) and respiratory (15%) disorders observed. In the 2nd group the incidence of endocrine-metabolic disorders preserved (100%), cardio-vascular (90%) and respiratory (40%) disorders tended to increase.

Conclusions: sandostatin and its analogues are the first line drugs in treatment of acromegaly. Post-radiotherapy use of sandostatin as the part of combined therapy of acromegaly reducing both process activity and complications is the evidence for its efficacy.

Abstract-ID: 259

EXPANDED ENDOSCOPIC ENDONASAL TRANS-SPHENOIDAL APPROACH VERSUS MICROSCOPIC ACCESS IN HYPOTHALAMIC-PITUITARY TUMORS: RESULTS IN A REFERENCE CENTER

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Introduction: The Pituitary-Hypothalamic Tumors Unit from Virgen del Rocío and Virgen Macarena University Hospital is a multidisciplinary group including endocrinologists, neurosurgeons and radiologists. This unit evaluates the indication of neurosurgery in selected cases on a regular basis. Recently, the expanded endoscopic endonasal trans-sphenoidal approach (EEETS) has been added to the portfolio of services.

Aim: To compare the results of EEETS versus microscopic access (MIC) in hypothalamic-pituitary tumors in our center.

Material and methods: Descriptive-retrospective study, including all patients who underwent surgical removal of hypothalamic-pituitary tumors in our center throughout the year 2013.

Results: MIC (n=19). Mean age 51.1 years, 8 females/11 males. Tumor size: <10 mm (n=5), 10-25 mm (n=9), 25-40 mm (n=4), ≥40 mm (n=1). Sinus invasion (n=6). Hormonal secretion profile: n=4 Cushing, n=1 acromegaly. Endocrine impairments: pre-surgical n=6, post-surgical n=11. Post-surgical complications n=4 (1 abscess, 2 CSF leakage, 1 cacosmia). Mean length of hospital stay 10.21 days (Median 6, maximum 5, minimum 32). Early postoperative MRI (n=10): n=4 tumor persistence. Biochemical outcome: 3 Cushing meeting curation criteria; 1 Cushing and 1 acromegaly with persistent disease.

EEETS (n=20). Mean age 49.9 years, 8 females/12 males. Tumor size: <10 mm (n=3), 10-25 mm (n=5), 25-40 mm (n=7), ≥40 mm (n=5). Sinus invasion (n=12). Hormonal secretion profile: 4 prolactinomas, 2 Cushing. Other: 1 meningioma, 1 bone dysplasia. Endocrine impairments: pre-surgical 13, post-surgical 7. Post-surgical complications 2 (1 CSF leakage, 1 cacosmia). Mean length of hospital stay 11.05 days, (Median 9, maximum 5, minimum 27). Postoperative MRI (n=10): n=6 tumor persistence. Biochemical outcome: 2 prolactinomas and 2 Cushing meeting curation criteria, 2 prolactinomas with persistent disease.

Conclusions: EEETS, as MIC, is a safe option and elective in our series for pituitary adenomas over 25mm and cavernous sinus invasiveness.

Abstract-ID: 264

GONADAL DYSFUNCTION IN WOMEN OF REPRODUCTIVE AGE WITH ACROMEGALY

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According to Moscow regional registry of patients with acromegaly, 75% of patients are female, median age 59 [50;66] y.o. However, 64% of women had onset of acromegaly at reproductive age (<45 y.o.). We retrospectively analyzed data of 75 women who experienced first symptoms of acromegaly at age 34 [25; 39] y.o., macroadenomas in 66 cases (88%) and microadenomas in 9 cases (12%). Initially GH levels were 22.8 [10.5;49] ng/ml, IGF levels 2.52 [2.27;3.13] times above upper normal limits. Menstrual disturbances (MD) were observed in 88% of patients and were one of the first symptoms of acromegaly in 36% of cases. Patients were younger with MD than without MD – 28 [23;32] and 36.5 [30;40.5] y.o. respectively (p<0.001); median time before diagnosis of acromegaly was shorter in patients with than without MD – 4 [2; 6] y. and 8 [5;18] y. respectively (p=0.006). MD included: amenorrhea (34%), opsomenorrhea (34%), menorrhagies (15%), and acyclic bleeding (17%). Hyperprolactinemia was observed in 38/75 (50.6%) women including 27 (36%) cases with MD and 11 (14.6%) cases without MD. Elevated prolactin levels were found in most patients with amenorrhea. Low gonadotropin levels were found in 53.3% women and were associated with MD. Initial GH and IGF-1 levels did not differ in women with or without MD, with or without hyperprolactinemia. Hyperandrogenemia was not common in our patients (2 cases, 2.7%).

After treatment of acromegaly menstrual cycle restoration was observed in 56% women with previous MD and menstrual dysfunction was found in 22.7% women with previous normal cycle.

Thus, gonadal dysfunction was very common in women with acromegaly onset at reproductive age. Main causes of menstrual disturbances were hyperprolactinemia and hypogonadotropic hypogonadism. Acromegalic women with gonadal dysfunction were younger and were diagnosed earlier than patients with normal cycle. Treatment of acromegaly had different impact on menstrual function

Abstract-ID: 270

PREVALENCE OF HYPERTENSION IN PATIENTS WITH ACTIVE ACROMEGALY AND SLEEP APNEA.

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Purpose: To assess the prevalence of hypertension in acromegaly patients with and without sleep apnea (SA).

Methods: Fifty patients (12 men, 38 women), mean age 54,2±12,4 (27-81) years, mean BMI 30,8±4 (19,9-44,3) kg/m2 with active acromegaly were included. Median estimated acromegaly duration was 7,84±6,4 (1-30) years. All patients underwent full polysomnography. Blood pressure was estimated during the first clinic visit (office blood pressure) in all patients and twenty-four-hour blood pressure monitoring was performed in 32 cases.

Results: Out of 50 patients, 40 (80%) had obstructive SA. Ten (20%) patients did not have SA, their mean apnea/hypopnea index (AHI) was 2,3±1,8 (1-4)/h. Twelve patients had mild SA, mean AHI 9±3,4(5-14)/h. 28 patients had moderate-to-severe SA, AHI 40,8±24,4(15-92)/h. Among 10 patients without SA 3(30%) had systolic office blood pressure ≥140 mmHg and 2(20%) had diastolic office blood pressure ≥90 mmHg. Fifteen (53,6%) of 28 patients with moderate-to-severe SA had systolic office blood pressure ≥140 mmHg and 18 (64,3%) had diastolic office blood pressure ≥90 mmHg. The prevalence of office diastolic hypertension was significantly higher in patients with moderate-to-severe SA ($\chi 2$=4,16; p=0,042). 24-h blood pressure monitoring was done in 9 patients with normal AHI, and in 15 patients with moderate-to-severe AHI. According to twenty-four-hour blood pressure monitoring only 24-h diastolic blood pressure and daytime diastolic blood pressure were significantly higher in SA group: 85,3±10,3 (74-100,2) vs 75,6±8,9 (64-87,9) mmHg (p=0,014) and 89,1±11 (76,2-105,6) vs 72±7,3 (72-91,1) mmHg (p=0,013), respectively. No correlation was proved among metanephrine excretion and AHI or blood pressure level.

Conclusions: Hypertension is more frequent in acromegalic patients with moderate-to-severe SA. 24-h diastolic blood pressure and daytime diastolic blood pressure were significantly higher in moderate-to-severe SA group. Mechanisms of diastolic hypertension development in daytime are needed to be elucidated.

Abstract-ID: 288

SCREENING FOR SOX2 AND SOX3 MUTATIONS IN BULGARIAN PATIENTS WITH CONGENITAL HYPOSOMATOTROPISM: FIRST RESULTS

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Background: Pituitary transcription factors (TF) play a critical role in its embryological development. The most common cause of congenital combined pituitary hormone deficiency (CPHD) is mutations in the PROP1 gene, followed by PIT1 mutation. Bulgarian pituitary TF study showed an

allele frequency of PROP1 mutations in 12.2% and no confirmed PIT1 mutations.

The TFs SOX2 and SOX3 are expressed early in the embryological development. They are essential for the development of structures like neural system, pituitary gland, eyes, ears, esophagus, gonads. The most common clinical manifestations of SOX2 mutations are eye abnormalities (anophthalmia/microphthalmia, coloboma, nistagm, refractive errors) and hypopituitarism. SOX3 is known with its X-linked inheritance. Over- and underdosage of SOX3 has been implicated in the etiology of hypopituitarism. Because of the prevalence of male patients among the Bulgarian CPHD cohort, the TF SOX3 was considered as a candidate gene.

Objective and hypotheses: To implement a mutational screening for SOX2 and SOX3 as a diagnostic tool in congenital CPHD and to assess the overall allele frequency in Bulgarian hyposomatotropic patients.

Patients: 23 patients, aged (x±SD) 14.7±12.0, median 9.7 years, 14 females (14.7±12.3, median 12.0 years), 9 males (15.8±9.8, median 14.0 years).

Methods: Inclusion criteria: obligate congenital GH deficiency; additional criteria: CPHD, ophthalmologic abnormalities; pathologic findings on hypothalamo-pitutary region MRI; phenotype characterization based on: auxology, bone age, hormonal tests (GH, TSH, fT4, PrI, LH, FSH, T, E2 by Delfia®, IGF1&BP3, cortisol by ELISA); Molecular genetic analysis by direct sequencing of the SOX2 and SOX3 genes.

Results: No mutations in SOX2 or SOX3 gene were verified in the selected patients.

Conclusions: Mutations in SOX2 and SOX3 are a rare cause of hypopituitarism. For a precise etiological diagnosis, patients with complex phenotype including pituitary and extrapituitary manifestations should undergo whole genome sequencing.

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Abstract-ID: 291

LAUNCHING A MUTATIONAL SCREENING STRATEGY, USING CANDIDATE GENE APPROACH, FOR PATIENTS WITH CONGENITAL COMBINED PITUITARY HORMONE DEFICIENCY (CPHD) IN BULGARIA (2002-2013)

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If the differentiation pathway of neuroendocrine cells of the pituitary gland, involving a cascade of transcription factors, is altered, it predominantly leads to CPHD rather than to isolated hormone deficiency.

Objective: To systematically build a mutational screening panel establishing the etiology of patients with congenital CPHD in Bulgaria.

Methods: A group of 103 patients with confirmed hyposomatotropism was characterized based on phenotype (auxology, bone age, hormonal tests for GH, TSH, fT4, PrI, LH, FSH, T, E2, IGF1, BP3, Cortisol); PROP1, POU1F1 mutational screening strategy included enzyme restriction, SSCP, and direct sequencing, while the POU1F1, HESX1, SOX2 and SOX3 coding regions were directly sequenced.

Results: All 103 patients were screened for PROP1 mutations, based on *obligatory* criteria- Growth failure due to GH deficiency; *additional criteria*- at least one other pituitary hormone deficiency. For the mutational screening in POU1F1, HESX1, SOX2 and SOX3 patients were selected based on a negative screening of PROP1 and phenotypes typically associated with anomalies caused by mutations in these genes. 49 patients were analysed for mutations in POU1F1. HESX1 mutational study was done on 16 patients, 23 patients were analysed for SOX3 and 22 for SOX2.

Two mutations (150 delA-allele frequency of 0.063 and 296-302 delAG-allele frequency of 0.014) in PROP1 were confirmed in 8 patients with. No other mutations were found in the remaining four genes.

Conclusions: CPHD caused by mutations in POU1F1, HESX1, SOX2 or SOX3 genes, is relatively rare in comparison to PROP1 mutations in the studied Bulgarian patients. 92% of them were not diagnosed with this panel. Therefore, future strategy for molecular diagnostic of CPHD has to prioritize analysis of PROP1 gene, broaden the phenotype of the studied group and the number of TFs involved in pituitary development.

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Abstract-ID: 296

CHANGES OF GH AXIS AFTER TRANSSPHENOIDAL ADENOMECTOMY IN CURED PATIENTS WITH FUNCTIONING PITUITARY ADENOMA

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Objective: Impaired GH secretion usually accompanied in cured patients with functioning pituitary adenoma after transsphenoidal adenomectomy (TSA). Although surgery itself could induce the GH deficiencies, preoperatively over-secretion of pituitary hormones might influence on the secretory function of GH axis after TSA. However, there had been no studies about the role of over-secreted hormone from functioning pituitary adenoma on GH axis after achieving biochemical remission

Research Design and Methods: From the cohorts of Severance Hospital Pituitary Tumor Clinic, GH axis had been evaluated in cured patients after TSA. GHD was defined when the peak serum GH level was less than 3.0 ng/mL in insulin tolerance tests (ITT) which were conducted before TSA and at least 2 times at 1.5 years intervals after TSA.

Results: Three hundred and sixty five patients had been followed up for 8.36±4.21 years and the axis of GH had been evaluated 2.81±1.51 times with ITT for 5.52±6.62 years. The enrolled patients were consisted of 253 in GH secreting pituitary adenoma, 28 in Cushing disease, 73 in prolactinoma, and 11 in TSH secreting pituitary adenoma. The frequency of preoperative GHDs was significantly higher in patients with Cushing disease (21/28; 75.0%) than subjects with prolactinoma and TSH secreting pituitary adenoma (26/73; 35.6%, and 3/11; 27.3%, respectively) ($P < 0.001$). After TSA, newly developed GHDs were diagnosed in 25/253 (9.9%) in GH secreting pituitary adenoma, 2/28 (7.1%) in Cushing disease, and none in both prolactinoma and TSH secreting pituitary adenoma. Among the patients with GHD before TSA, the recovery rates of GH axis were 6/21 (28.6%) in Cushing disease, 16/26 (61.5%) in prolactinoma, and 2/3 (66.7%) in TSH secreting pituitary adenoma.

Conclusions: These data provide the first clinical evidence that differentiating evaluations for GHD should be applied in patients with functioning pituitary adenoma according to species of over-secreting pituitary hormones.

Abstract-ID: 304

THE EFFECT OF DOPAMINE AGONIST THERAPY ON PREGNANCY AND LACTATION

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Although prolactinoma predominantly occurred in young women of reproductive age, there are limited data about the effect of pregnancy and lactation on prolactinoma. We evaluated the safety of dopamine agonists including bromocriptine and cabergoline in early pregnancy and the effect of lactation in women with prolactinoma. Among prolactinoma patients taking dopamine agonists, subjects who experienced pregnancies were analyzed. Sellar MRI and serum prolactin levels were performed before and after pregnancy and lactation. Among 65 pregnancies in total 50 patients, 64 (98.5 %) spontaneous pregnancies occurred in 49 patients and only one pregnancy was made by *in vitro* fertilization. Live births were in 55 (84.6 %), while spontaneous abortions occurred in 10 (15.4%). Twenty-

two and thirty three patients were treated with cabergoline and bromocriptine at the time of conception, respectively. Of all, breast-feeding was performed in 38 pregnancies. Mean duration of lactation was 4.8 ± 4.4 months. Among those 38, 16 patients had done MRI follow-up after the lactation. There were decreased adenoma sizes in 9 patients, no changes in 5 patients, while increased only in two patients. We compared clinical parameters between increase and decrease/no change in adenoma size after lactation. There were no differences in any parameters between these two groups. In conclusion, dopamine agonists, not only bromocriptine but cabergoline, did not grow the adverse pregnancy outcome in women with prolactinoma. In addition, breast-feeding did not induce tumor growth, so it would be safe in patients with prolactinoma. Further studies with large population are needed.

Abstract-ID: 312

SEVERE FLAVOR IMPAIRMENT IN PATIENTS WITH KALLMANN SYNDROME

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Kallmann Syndrome (KS) is defined by the association between congenital hypogonadism and anosmia. Despite the well-recognized olfactory impairment, patients with KS surprisingly report flavor integrity. The current study aimed at assessing flavor function in 20 patients with KS, as compared to 20 patients with acquired anosmia (AA) and 50 healthy controls. All participants were prior invited to self-determine their smell and flavor abilities by means of a 10-grade arbitrary scale. They were submitted to the standardized sniffing olfactory test (TDI). Flavor test has been developed by dilution of a series of 21 natural aromatic extracts in aqueous solutions, orally administered at room temperature, in order to restrain physical biases (aspect, texture, temperature). Each subject was invited to identify the correct compound by choosing one of five alternative items. The final score was calculated as the sum of correct answers (from 0 to 21). Demographic characteristics of the sample population were similar except for age (AA patients being older, p=0.013). Self-assessment revealed decreased smell perception in KS and AA compared to controls (p<0.001 for both). In contrast, flavor perception was lower in AA than in KS (p=0.006) and controls (p=0.002), but not different between KS and controls. TDI revealed anosmia for both KS and AA and normosmia for all controls. Flavor test scores were not different between KS (5.4±1.4) and AA (6.4±1.9), but dramatically lower in KS and in AA as compared to controls (16.7±1.9, p<0.0001 for both). Flavor test had high rates of reliability and reproducibility among controls and patients, and positively correlated with all items of TDI score (r=0.89, p<0.0001). This is the first report showing flavor impairment in KS. The quantification of flavor disability shows similarity to AA. This contrasts with what generally evidenced in routinely clinics, since KS patients, contrarily to AA, do not complain flavor inability, perhaps owing to the congenital nature of sensorineural injury. Flavor deficiency has to be accounted in the burden of the complications in KS, because of the relatively high impact on physical and mental health, and in order to prevent life-threatening accidents.

Abstract-ID: 317

MORPHOLOGICAL, BIOCHEMICAL AND RADIOLOGICAL FEATURES OF NONFUNCTIONING PITUITARY ADENOMAS (NFPA)

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Objective: To present morphological, biochemical and radiological features of nonfunctioning pituitary adenomas (NFPA):

Methods: 33 pituitary adenomas excised surgically from patients who had an extensive clinical and hormonal workup were immunostained to reveal pituitary hormones, ki-67, and chromogranin A (CgA). Serum Cg A concentration was determined before and after surgical treatment by ELISA. All patients underwent MRI, adenomas with extension of more than 40 mm were regarded as "giant".

Results: NFPA were equally prevalent in men and women - M: F = 16:17,mean age of patients was 51.09 years (21-73). Giant adenomas were detected in 13 cases. Parasellar growth was seen in 12 cases (S = D). Of the 33 NFPA, 19 were gonadotrophic tumors, 6 were null cell adenomas, immunopositivity for ACTH was detected in 5 cases, for STH in 2 and for PL in 1 cases. The median level of Ki-67 was 2.65% (0.2-7%). The CgA immunopositivity was found in 81.8 %, being more frequent in gonadotropinomas and null cell adenomas. The average serum CgA concentration before operation was 65,45 ng/ml (N), with elevated levels in 4 patients, after operation - 76,4 ng/ml and elevated in 6 patients. Positive correlation was detected between the size of adenomas (giant adenomas) and retro- and infrasellar growth (p = 0,001 and p = 0,037 respectively), but not for parasellar growth. There were no correlations between serum levels of CgA and CgA expression in studied tissues.

Conclusions: Our work shows that a majority of NFPA are truly secreting adenomas with significant numbers comprising potentially hazardous cortico- and somatotropinomas. CgA has a high expression in most of the NFPA, but its serum levels were not much different from the controls and did not correlate with tumor removal/volume reduction after surgical treatment so cannot be used as a biochemical tumor marker.

Abstract-ID: 319

ROLE OF IMUNOCHISTOCHEMICAL ANALYSIS IN THE SURGICAL TREATMENT OF HORMONE-SECRETING PITUITARY ADENOMAS

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Subject and Aim:Pituitary adenomas (PA) show a broad clinicomorphological spectrum. The proliferation activity, evaluated by MIB-1 labeling index (LI) and p53 expression have been pointed as predictive markers for invasiveness and progression. The aim of this study was to evaluate the proliferation rate and p53 expression and to look for any relationships with the clinical behavior and follow-up results in a series of Bulgarian patients with pituitary adenomas

Material and Methods: A total of 433 patients with pituitary adenomas (81- hormone-secreting, 352 - non-functioning) who were operated on and followed up for a period of 5 years, were included. The surgical procedure that was used was an endoscopically assisted endonasal transsphenoidal adenomectomy. The MIB-1 LI and p53 expressions were determined by immunohistochemistry (n=93) and correlated with various clinical and tumor variables.

Results: A visibly total resection was achieved in 93,1% of cases. Full clinical remission in terms of resolution of the hormone hypersecretion at the end

of the 5 year follow-up period was achieved in 79,1% of cases. Incomplete clinical remission was achieved in 20,9% of cases. The whole group of PA showed a low proliferation rate with evident variations in a small number of cases (MIB-1 LI - 0.50±0.56, from 0.1 to 3.30). MIB-1 LI correlated with tumor size (p=0.012) and was positively related with male gender (p=0.23) and partial surgical resection (p=0.036). We found no significant differences regarding the age, functional activity, invasion (n=33), expansion (n=37) and tumor recurrences (7 cases). Only 10 cases (10.8%) showed a focal, nuclear p53 immunoreactivity. The p53 positive tumors had higher proliferation rate (p=0.0001) but no relationship with the other clinical and tumor variables. Among all cases there was only 1 case with higher MIB-1 LI (3.3 %), positive p53 expression and tumor recurrence after surgery.

Conclusion: Our results show that most pituitary adenomas have a low proliferation rate and lack of p53 expression, as well no relationship with tumor invasion or postsurgical progression.

Key words: pituitary adenomas, transsphenoidal surgery, imunochistochemical analysis

Abstract-ID: 351

MARKERS OF EARLY ATHEROSCLEROSIS, INFLAMMATION AND OXIDATIVE STRESS IN PATIENTS WITH ACROMEGALY

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Cardiovascular disease is the most important cause of mortality and morbidity in patients with acromegaly. In the literature, there is controversial data regarding the development of atherosclerosis in patients with acromegaly. Oxidative stress and inflammation pathways are important in the pathogenesis of atherosclerosis. We aimed to investigate the role of oxidative stress, inflammation and cardiovascular risk factors in the pathogenesis of subclinical atherosclerosis in acromegaly. This study included patients diagnosed with acromegaly attending Endocrinology and Metabolism Department. Thirty-nine patients with acromegaly enrolled and patients were classified into two groups; active and controlled acromegaly. Control group matched by gender, age, body mass index, presence of hypertension, diabetes mellitus, hyperlipidemia. Flow mediated dilatation (FMD), carotid intima media thickness (CIMT) and epicardial fat thickness (EFT) were measured as subclinical atherosclerotic parameters and serum levels of oxidative stress parameters, high mobility group box 1 protein (HMGB1), high sensitive CRP (hs CRP), vascular cellular adhesion molecule-1(VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin were evaluated. Significantly decreased FMD and increased CIMT and EFT were found in patients with acromegaly compared to control group (p< 0,05, p< 0,05, p< 0,001, respectively). We found a negative correlation between EFT and FMD (r= -0,24, p= 0,038), and positive correlation between CIMT and EFT (r= 0,37, p < 0,01). Hs CRP levels were found to be decreased in acromegaly patients (p< 0,05). There were no significant difference for serum levels of oxidative stres parameters, HMGB1, VCAM-1, ICAM-1 and E-selectin compared to control group (p> 0,05). Our results indicate that subclinical atherosclerosis measured with FMD, CIMT and EFT may exist in patients with acromegaly.

Abstract-ID: 354

PERSISTENCE OF MOOD DISORDERS IN PATIENTS WITH CUSHING'S SYNDROME IN REMISSION

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Context: Mood disorders might persist in Cushing's syndrome patients (CS) after correction of hypercortisolism.

Objective: To assess depressive symptoms and negative affect long-term after remission of CS and to evaluate whether these are associated with salivary cortisol.

Methods: Thirty-five CS patients [32 F; mean age (±SD), 52±13 years; mean BMI (±SD), 29±6 Kg/m^2] and 35 gender-, age-, and BMI-matched controls were included. Mean (±SD) duration of CS remission was 98±88 months. Beck Depression Inventory (BDI), Positive Affect Negative Affect Scale (PANAS), State Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS) and EuroQoL were completed to evaluate depressive symptoms, affect, anxiety, stress perception and quality of life, respectively. Salivary cortisol was collected twice a day (at 8 a.m. and 11 p.m.) on two consecutive days and measured by an enzyme immunoassay (Salimetrics ®).

Results: Total scores of BDI, PANAS and PSS were significantly higher in CS patients as compared with those in control subjects (BDI, 10(0-36) vs. 3(0-30); PANAS, 6.31±14.55 vs. 18.09±13.82; PSS, 25.63±10.17 vs. 18.77±9.51; p<0.01 for all comparisons). Scoring of both affective and somatic symptoms, as measured by BDI, was significantly worse in CS patients than controls (affective, 5(0-29) vs. 1(0-17); somatic, 5(0-10) vs. 2(0-13); p<0.01 for both comparisons). CS patients showed more negative affect and less positive affect than controls, as assessed by PANAS (negative affect, 20±9.6 vs. 15.3±6.5, p<0.05; positive affect, 72.5±8.54 vs. 33.4±9.3, p<0.001). Both state and trait anxiety of STAI scores were significantly higher in CS patients than controls (state, 22.97±13.51 vs. 13.2±8.83; trait, 26.46±14.02 vs. 16.66±11.42, p<0.01).

CS patients showed greater impairment of quality of life than controls (EuroQoL, 71.91±17.71 vs. 82.73±14.49, p<0.05). EuroQoL was correlated with the scoring of BDI, PANAS, STAI and PSS scores (p<0.001 for all correlations), and when these variables were included in a linear regression model, positive affect and somatic symptoms still predicted quality of life (positive affect, β=0.295, R=0.674; somatic symptoms β=-0.515 R=0.718; p<0.001 for both factors).

Salivary cortisol at midnight was significantly higher in CS patients than controls (4.22±3.21 mmol/L vs. 2.6±2.35 mmol/L; p<0.05), whereas morning salivary cortisol was significantly lower (9.29±4.9 mmol/L vs. 13.82±7.02 mmol/L; p<0.01). No correlation was found between salivary cortisol levels and mood alterations.

Conclusions: Mood disorders, including impaired stress perception and negative affect, persist long-term after remission of CS, and negatively impact on quality of life.

Abstract-ID: 357

5W1H (WHAT, WHO, WHEN, WHERE, WHY, HOW) FOR ACROMEGALY

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Objective: To evaluate the initial complaints, detailed history and surgical procedures prior to the first diagnosis in acromegalic patients.

Method: Three hundred and thirteen out of 490 acromegaly patients who were under follow-up at University of Istanbul, Cerrahpasa Medical Faculty, Endocrinology and Metabolism outpatient clinic between 1998 and 2014 were included. Patients were asked via phone call or face to face interviews about their initial complaints, the physician they were admitted to first, the interval from onset of symptoms to diagnosis, and the previous surgeries. The surgery types and the possible relation of the surgery with acromegaly were evaluated.

Results: This study included 313 participants; 181women and 132 men. The mean age was 48.8±12.0 years. Twenty one of them were dead. The frequent complaints of the patients were acral growth of hands and feet (32.6%), headache (26.2%), visual defects (9.3%), menstrual irregularities (8%), and coarsened facial features (7%). The first physician the patients were admitted to was as follows; internist (29.4%), neurosurgeon (11.8%), neurologist (11.2%), ophthalmologist (8%), and ear nose throat specialist (6.1%).

Initial diagnosis was made by an endocrinologist (55%), neurosurgeon (23%), internist (13.7%), neurologist (2.9%).The mean diagnosis delay time was 38.3 ± 41.7 months.

Almost half of the patients had undergone an operation prior to diagnosis (45.7%). In total, 33.3% of the surgeries were related to acromegaly complaints. The most common operations were as follows; head and throat surgery (12.8%), nose surgery (9.3%), thyroidectomy (6.4%), carpal tunnel surgery (4.8%).

Conclusion: Acromegaly patients were mostly referred to internists because of co-morbidities, to ear nose throat specialist for deformities and to neurosurgeons due to the mass effect symptoms, Most frequently they had undergone head and neck surgery prior to diagnosis. Therefore, it is important that medical staff be aware of the clinical aspects of acromegaly which causes such prominent physical changes.

Abstract-ID: 363

MANAGEMENT CHALLENGES AND FOLLOW-UP OF A PATIENT DIAGNOSED WITH CUSHING DISEASE IN 2008

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The patient presented aged 5.8 years in 2008 after 8 month history of rapid weight gain (15kg) and decreased growth velocity (1cm/1.5yr). He developed hypertrichosis, progressive fatigue, reduced muscle strength and a round plethoric face. He had pubic hair but was pre-pubertal with testicular volumes 2ml. Investigations showed sustained elevation of urinary free cortisol (1476 mcg/24h, NR 28.5-213.7) and morning cortisol levels of 1158 nmol/l with detectable ACTH (16.9 pg/ml), consistent with ACTH-dependent Cushing's syndrome. CRH test showed increased peak cortisol and ACTH; Dexamethasone did not suppress serum cortisol. MRI of the pituitary and adrenals were normal.

The child was referred to Barts Health Trust. IPSS confirmed central and left lateralised ACTH production, indicative of a left-sided pituitary corticotroph adenoma. In 2009, selective transsphenoidal adenomectomy and second-line pituitary radiotherapy failed to cure him. Ketoconazole treatment was instituted until December 2011 when cortisol levels normalized. In 2013 symptoms returned; in July biochemical assessment confirmed relapse of Cushing's disease. The pituitary MR showed a 2 mm tumour at the side of the initial operation but little residual pituitary tissue therefore he was not a good candidate for repeat transsphenoidal pituitary surgery. Four months later, off treatment, cortisol levels reached life-threatening morning values (1274 nmol/l). However, suppressed 0900h ACTH levels (<5 ng/l) suggested autonomous adrenal cortisol production in addition to relapse of the pituitary adenoma. CRH test showed a 206% rise in cortisol from baseline without ACTH response. Adrenal MRI scan was normal. Metyrapone therapy was commenced and a month later both adrenal glands were removed endoscopically. The histology demonstrated normal tissue. Adrenal replacement therapy was commenced post-operatively. The patient resumed his normal life, continued to lose weight and his puberty is progressing fast. This patient demonstrates the prolonged and difficult disease course in children who are not cured after the initial surgery.

Abstract-ID: 397

MARKEDLY ELEVATED ASYMMETRIC DIMETHYLARGININE LEVELS IN ADULT PATIENTS WITH GROWTH HORMONE DEFICIENCY

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Background: Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase, is established as a reliable biochemical marker of endothelial dysfunction (ED). The latter is a common feature of numerous conditions predisposing to cardiovascular diseases, such as growth hormone deficiency (GHD) in adults.

Objective: To investigate ED in hyposomatotropism by determining ADMA concentrations in GHD patients, healthy controls and subjects with essential hypertension (EH).

Patients and methods: The study included 84 adults with GHD (childhood-onset GHD: n=30, adult-onset GHD: n=54), 18 patients with essential hypertension and 18 healthy subjects. ADMA levels were determined by ELISA method and GHD was diagnosed according to the Endocrine Society Clinical Practice Guideline recommendations from 2011.

Results: ADMA concentrations in adults with GHD were almost twice higher than in controls (0.79±0.19 μmol/l vs. 0.43±0.05 μmol/l, p <0.0001). The levels remained elevated even in the subjects without metabolic syndrome (n=59, ADMA: 0.78±0.20 μmol/l, p <0.0001) and with normal blood pressure (n=63, ADMA: 0.77±0.19 μmol/l, p <0.0001). Furthermore, GHD patients had significantly increased ADMA concentrations in comparison with EH subjects (0.48±0.07 μmol/l, p <0.0001) as well, despite their similar metabolic profile (comparable values of BMI, cholesterol, HDL, triglycerides and plasma glucose in both groups).

Conclusion: Adults with hyposomatotropism demonstrated pronounced ED, which was even more severe than in the patients with EH. The increase of ADMA levels, however, could not be explained by some traditional risk factors of ED, considering their comparable values in GHD and EH subjects. These results suggested that ADMA could be regarded as an independent cardiovascular risk factor in hyposomatotropism. Apparently, ED in adult GHD has complex etiology and its pathogenesis remains unclear, considering the heterogenic phenotype of the patients.

Abstract-ID: 400

AROMATASE ENZYME EXPRESSION IN ACROMEGALY AND ITS POSSIBLE RELATION WITH PROGNOSIS

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Introduction: Aromatase is an enzyme of the cytochrome P450 family that converts androgen to estrogen. Aromatase expression has been demonstrated in pituitary gland of rats and humans also recently in human prolactinomas. The regulatory function of testosterone on growth hormone (GH) axis has been demonstrated in several studies after conversion to estrogen by local aromatization in pituitary. Therefore we aimed to demonstrate aromatase expression in GH secreting adenoma of the pituitary gland and its effect on tumor behavior. Also comparison of aromatase expression between GH adenoma, prolactinoma, nonfunctional adenoma and normal pituitary gland was secondary goal of the study.

Material and method: 38 patients with acromegaly, 26 patients with prolactinoma and 31 patients with nonfunctional pituitary adenoma were included in the study. Eleven normal pituitary samples obtained from autopsies were included as controls. Aromatase and Estrogen Receptor-alpha (ERα) were evaluated by Immunohistochemical method, demographic, preoperative and postoperative clinical features of the patients were noted.

Results: Aromatase immunreactivity was seen variable degrees in all cases in study including controls. Aromatase expression in patients with acromegaly were significantly higher than patients with prolactinoma, nonfunctional adenoma and controls (p=0,04. p=0,01 and p<0,001 respectively). Conversely, ER-alpha expression were higher in controls than acromegaly and nonfunctional adenoma groups (p<0,001 for both groups) but not different from prolactinoma group. Taken together the two functional adenoma groups; prolactinoma and acromegaly, aromatase expression was negatively correlated with ER-alpha (p=0,02, r=-0,34). The Ki-67 immunohistochemical results were negatively correlated with aromatase expression (p=0,03, r=-0,27) while positively correlated with ER expression (p<0,01, r=0,48).

Discussion: Compatible with the growing evidence about testosterone effect on pituitary functions, aromatase expression was shown highly in GH secreting pituitary adenoma concerning local aromatization. The possible role of local aromatization was currently suggested in prolactinoma tissues by two studies. The first one have demonstrated higher aromatase expression in prolactinoma then normal pituitary tissues while the other study have shown aromatase expression in female prolactinomas. In our study, aromatase enzyme was expressed in all pituitary tissues including autopsy samples. It was highest in patients with acromegaly among adenoma groups. Taken together two functional adenoma groups aromatase expression was negatively correlated with Ki-67 score also in patients with complete postoperative remission aromatase expression was higher. Therefore aromatase expression may be a good prognostic marker of mainly GH secreting pituitary adenomas also aromatase inhibitors may be an option in the treatment of acromegaly in the future.

Abstract-ID: 416

HYPOPITUITARISM IN NON FUNCTIONING PITUITARY ADENOMAS: A RETROSPECTIVE ANALYSIS OF 218 PATIENTS WITH FOCUS ON THE PREVALENCE OF ISOLATED HYPOADRENALISM

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Introduction*:* Non functioning pituitary adenomas (NFPA) account for about 40% of all pituitary tumors. One or more anteropituitary deficiencies are present at diagnosis in 60-80% of NFPA and, classically, GH secretion is firstly lost while ACTH secretion is expected to disappear at last. The aim of our study was to evaluate the incidence and the order of appearance of pituitary deficiencies in a large series of patients with NFPA.

Materials and methods: We retrospectively analyzed the data of 218 NFPA (59% females, 59% macroadenomas, average age at diagnosis: 50.2±17 years) followed at our center from 1990 to 2013. At diagnosis all patients underwent a complete evaluation of basal anteropituitary function and provocative tests for hypotalamic-pituitary-adrenal axis.

Results*:* 45% of patients (59% of macroadenomas, 26% of microadenomas) presented at least one anteropituitary deficiency (30.7% hypogonadism, 19.7% GH deficiency, 25.2% hypoadrenalism and 13.8% hypothyroidism). In particular, 22% of patients had an isolated deficiency (23% in micro and 22% in macro), 30% multiple deficiencies (2% in micro, 22% in macro) and 9% panhypopitutiarism (15% in macro). Isolated deficiencies were represented by hypogonadism in 11.5% of patients (8% in micro, 14% in macro), hypoadrenalism in 10% (14% in micro, 7% in macro) and GH deficiency in 1% (1% in micro, 1% in macro).

Conclusions*:* About 25% of patients with microadenoma had at least one anterior pituitary hormonal deficiency at diagnosis. The presence of patients with isolated hypoadrenalism suggests that the order of appearance of hypopituitarism does not always follow the one expected. In particular, given the relative high prevalence of isolated hypoadrenalism even in microadenomas, we suggest the full assessment of basal and dynamic anterior pituitary function in all patients with NFPA regardless of tumor size.

Abstract-ID: 417

BIOCHEMICAL CONTROL OF ACROMEGALY IN AUSTRIA: EVALUATION OF 607 CASES FROM THE AUSTRIAN ACROMEGALY REGISTER

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The Austrian Acromegaly Register is an initiative of the Austrian Society

for Endocrinology and Metabolism, formally established in 2005 and financially supported by Novartis. This database aims to provide epidemiological data on diagnosis, treatment, long-term co-morbidities and mortality of patients with acromegaly in Austria. Here we report descriptives and evaluate the biochemical control of acromegaly in patients included in this national register.

The database includes 607 patients (46% females) diagnosed with acromegaly between 1956 and 2012 in twelve centers. Mean age at diagnosis was 46.7 years for females (range 17-83) and 44.1 years for males (range 9-85). Mean treatment period is 10.7 years (range 0-50 years), the total number of patient-years is 6470. At diagnosis, 20% of tumors were microadenomas (22% in females, 18% in males), 27% were intrasellar macroadenomas and 53% were macroadenomas with extrasellar extension (50% in females, 58% in males). Younger age at diagnosis of acromegaly was associated with larger tumour size (P=0.001). At the last follow-up visit 86% of patients had undergone at least one surgical intervention, 22% of patients were treated by radiotherapy, and 44% of patients were on medical therapy. First-line medical therapy was reported in 11.4% of patients.

Data on biochemical control were collected in 474 patients with acromegaly, who were last visited between 2003 and 2013. Disease control was evaluated by GH less than 1.0 ng/ml during an OGTT and/or normal age- and gender-specific IGF-1. These outcome data were available for 418 patients. At the last visit, 69,1% of the patients were biochemically controlled. Female gender was a significant predictor of biochemical control (P=0.011), as 74% of females but only 63% of males showed normal IGF-1 or GH response during OGTT. Pituitary surgery was significantly associated with normalized GH/IGF-1 (P<0.001), 308 out of the 474 patients with known outcome had only one surgery, and one single operation managed to cure the disease in 42,5% of the cases. In addition, 71% of patients who had undergone radiotherapy had normal GH/IGF-1. Among patients who were biochemically controlled, only 26.6% were on continuous medical therapy. 62% of patients receiving medical therapy presented normalized GH/IGF-1.

In summary, data from the Austrian Acromegaly Register reveal a strong incidence of macroadenomas (80%) and biochemical control in 69.1% of patients who last attended participating centers during the last 10 years.

Abstract-ID: 422

FACTORS ASSOCIATED WITH RISK OF FRACTURES IN PATIENTS WITH CUSHING'S SYNDROME

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Introduction: Cushing's syndrome is a well recognized cause of bone loss, mainly at trabecular site, with consequent higher risk of non-traumatic fractures, both symptomatic and asymptomatic. The aim of this study was to investigate the prevalence and the possible risk factors associated with fractures in a population of patients with CS.

Materials and methods: We retrospectively studied 51 adult patients with active CS, evaluated at diagnosis. All patients underwent a comprehensive assessment including: clinical history; physical examination; hormonal tests; metabolic screening; evaluation of carotid intima-media thickness (IMT) and prevalence of atherosclerotic plaques by echo color Doppler ultrasonography; study of bone metabolism and of lumbar and femoral bone mineral density by DEXA; spine x-ray examination to assess vertebral fractures.

Results: Among CS patients (mean age 49±13 years, 34 females and 17 males, F:M=2:1), 42 had ACTH-dependent CS (37 of pituitary and 5 of ectopic origin) and 9 ACTH-independent CS. The prevalence of spontaneous fractures was 29/51 (57%) in all patients, 15/34 (44%) among women and 14/17 (88%) among men. 23 patients had vertebral fractures, 11 peripheral fractures, 5 both kind of fractures. No difference was found between fractured and non-fractured patients in terms of age, BMI, cortisol levels, parameters of mineral metabolism, glucose tolerance and lipid profile. Fractured patients presented lower lumbar T-score values (p=0.047), higher waist circumference (p=0.036), higher waist-to-hip ratio (WHR, p=0.028) and higher common carotid IMT (p=0,019) compared with non fractured ones. At logistic regression analysis, the variables significantly related to fractures were male sex, duration of disease, the presence of calcified carotid plaques, lumbar T-score and Z-score.

Conclusions: Our study shows a high prevalence of non-traumatic fractures in patients with CS, with men more frequently affected than women. We also found an association between fractures and some cardiovascular risk parameters (WHR, carotid IMT and prevalence of carotid plaques) in CS patients, which seems to be independent from the common effect of age on bone damage and atherosclerosis.

Abstract-ID: 426

STUDY DESIGN OF A RANDOMIZED, OPEN-LABEL, PHASE IV STUDY FOR MANAGEMENT OF PASIREOTIDE-INDUCED HYPERGLYCEMIA IN PATIENTS WITH CUSHING'S DISEASE OR ACROMEGALY

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INTRODUCTION: Hyperglycemia was a frequently observed adverse event in pasireotide clinical studies. Data from healthy-volunteer studies indicate that it occurs due to decreased insulin and incretin hormone secretion. Study objective: to evaluate efficacy of incretin-based therapies versus insulin added to metformin or other background oral anti-diabetic agents in patients with pasireotide-induced hyperglycemia.

METHODS: Patients: Adult patients with Cushing's disease (CD) or acromegaly who are pasireotide naïve will start treatment with pasireotide s.c or pasireotide LAR, respectively; those previously treated with pasireotide are eligible if they have elevated fasting plasma glucose (FPG)>ULN or diabetes at screening. Patients with diabetes receiving anti-diabetic agents other than incretin based therapies can enroll. **Design**: Phase IV, multi-center, randomized, open-label. Target enrollment ~133 patients. Previously normo-glycemic patients who develop diabetes will start metformin. If uncontrolled on stable, maximum tolerated dose of metformin for up to 8 weeks, patients will be randomized (1:1) to either incretin-based therapy (sitagliptin followed by liraglutide) or insulin for ~16 weeks. Maximum duration of core phase: 32 weeks. Patients receiving insulin at study entry will enter non-randomized observational arm. **Endpoints**: Primary endpoint: change in HbA_{1c} from randomization to ~16 weeks in incretin-based therapy versus insulin arm. Secondary endpoints: At core end-of-phase, change from baseline in HbA_{1c} and FPG by treatment group; proportion of patients with ≤0.3% HbA_{1c} increase from baseline per randomized arm; change in HbA_{1c} and FPG from randomization over time per randomized arm; proportion of patients requiring anti-diabetic rescue therapy with insulin in incretin-based therapy arm; safety.

CONCLUSIONS: Results will provide basis for optimal management of pasireotide-induced hyperglycemia in patients with acromegaly and CD, including those with diabetes at the start of pasireotide treatment.

Abstract-ID: 427

BODY IMAGE PERCEPTION MIGHT CONTRIBUTE TO LATE DIAGNOSIS IN ACROMEGALY

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Objective: Acromegaly, a state of growth hormone excess, is a disfiguring disorder, characterized by numerous bone and soft-tissue deformities. We hypothesized that body image perception in acromegalic patients might contribute to the late disease diagnosis.

Design: In a cross-sectional study, we investigated the body image in 81 patients with acromegaly and contrasted them to a clinical control group of 60 patients with non-functioning pituitary adenomas (NFPA) and to age-matched norm values for the applied questionnaires FKB-20 (Fragebogen zum Körperbild) and the FBeK (Fragebogen zur Beurteilung des eigenen Körpers).

Results: When compared to age-matched norm values, but not against NFPA, acromegalic patients showed significantly higher mean values in the negative body image scale (22.73±7.54 vs. 19.1±6.4; p=0.000) and significantly lower mean values in the vital body dynamics scale (27.98±7.45 vs. 31.80±7.3; p=0.000) of the FKB-20 questionnaire. Additionally, patients with acromegaly presented with an unfavorable body image compared to norm values, but again not against NFPA, showing significantly higher mean values in 3 of the 4 FBeK scales (16.96±2.09 vs. 6.79±2.5; p=0.000 for accentuation of the body/sensitivity; 21.17±2.20 vs. 3.36±2.77; p=0.000 for insecurity/concerns and 9.84±1.29 vs. 1.77±1.43; p=0.000 for bodily-sexual misfeelings).

In a subgroup of patients (n=39) with available frontal and side photographs of the faces, we grouped patients into subjects with mild (n=14), moderate (n=19), and severe acromegaly (n=6) by expert opinion. We could not detect any significant correlations between disease severity and unfavorable body image. However, multiple regression analyses associating disturbed body image with factors e.g. time between symptom onset and diagnosis, disease duration and biochemical control are to be performed.

Conclusions: Although patients with acromegaly suffer from a disturbed body image perception compared to healthy control values, there are no differences in body image perception compared to NFPA patients or between acromegalic patients with severe or mild disease, despite considerable objective disfigurements. This lack of bodily self-perception might have an impact on late diagnosis of the disease through late initiation of medical advice seeking.

Abstract-ID: 440

EPIDEMIOLOGICAL CHARACTERISTICS OF PATIENTS WITH PITUITARY TUMORS IN BULGARIAN POPULATION

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Background: A national database of patients with endocrine tumors has been recently created in the Clinical Centre of Endocrinology, Medical University-Sofia, with common efforts of the leading endocrinological centres in our country. To date, medical records of all visits of 2530 patients with pituitary tumors have been entered in this database.

The aim of the present study was to report the main demographic and clinical characteristics of Bulgarian patients with different hormone producing and non-functioning pituitary adenomas (NFPA).

Results: Patients with prolactinomas (n=908; 9% men, 91% women) represented more than one third of all patients in the database. Mean age in females was 32,8 ± 9,3 years and males were slightly older – 40 ± 14,4 years. A total number of 742 patients with acromegaly were registered. Women were twice as much as men, 465 (62,66%) vs. 277 (37,33%) respectively. Mean age at diagnosis was similar between sexes: 43,68 ± 11,67 in females and 43,40 ± 12,58 in males. In our database we included 395 cases with Cushing's disease (CD). The mean age of diagnosis was 37 ± 12 years. Similarly to patients with prolactinomas and acromegaly, CD was diagnosed more often among women (87% vs 17% in men). The database also included 484 patients with NFPA with similar female predominance - 391 (80,8 %) women vs. 93 (19,2 %) men. Mean age was 36,5 ± 14 years in females and 43 ± 18,2 years in males. Records of only one female patient with TSH-secreting adenoma were entered in the database.

Conclusion: As the majority of non functioning microadenomas remain undiagnosed the database provides information about the clinically relevant pituitary tumors – hormone secreting, invasive and aggressive. Thus it represents a useful tool for further research on improving their diagnostics and management.

Abstract-ID: 443

HOW AGE AND THE METABOLIC SYNDROME AFFECTED SALIVARY CORTISOL RHYTHM IN A COMMUNITY SAMPLE

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Objective: Measurement of cortisol levels in saliva is an index of free hormone. How salivary cortisol rhythm is affected by age, gender, the metabolic syndrome and estrogen-progestin therapy was evaluated in healthy adults.

Subjects and Methods: One hundred twenty volunteers recruited from the staff and family members of Endocrinology Unit were instructed to collect 7 salivary samples: the first at the time they woke up (F^0) and six

more ($F^{1.5}$, F^{5}, F^{6}, F^{10}, $F^{11.5}$, and F^{14}) over the next 14 hours. Each volunteer also underwent a complete physical evaluation, and a comprehensive medical history was taken. Salivary cortisol was measured using a radioimmunometric assay. Daily cortisol secretion was evaluated computing the Area Under the Curve ($AUC^{F0àF14}$), the F^{14}/F^{0} ratio was calculated as marker of cortisol rhythm.

Results: F^{14} levels were higher in the subjects over 60 than in those falling in the 40-59 and 20-39 age brackets (3.2 vs 2 vs 1.5 ng/mL, p <0.001), in the hypertensive volunteers (2.8 vs 1.7 ng/mL, p <0.05) and in those with the metabolic syndrome (3.2 vs 1.7 ng/mL, p <0.01), with elevated F^{14}/F^{0} ratio (0.45 vs 0.27, p <0.01). According to univariate analyses, the most important factor affecting the F^{14} value was age (p <0.001). $AUC^{F0àF14}$ was not influenced by gender, age, the metabolic syndrome or estrogen-progestin therapy.

Conclusions: While it does not affect the daily cortisol rate, late-night salivary cortisol levels were found to be increased in the subjects over 60 and in those with the metabolic syndrome.

Abstract-ID: 452

GIANT GH-SECRETING ADENOMAS; A LARGE COHORT OF RARE PITUITARY TUMORS

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Patients with acromegaly usually harbor macroadenomas. Most of these tumors measure between 10-30 mm in maximal diameter. Our study objective was to characterize the rarely encountered giant (adenoma size ≥ 40 mm) GH-secreting pituitary tumors.

We have identified 27 patients (9 men, 18 females) with giant adenomas among 642 subjects (4%) with acromegaly in our records. Mean age at diagnosis was 34.2±11.4 years (range, 16-67 years). Mean adenoma size at presentation was 49.4±10 mm (range, 40-80 mm). 24/27 adenomas showed cavernous sinus involvement and 25/27 had suprasellar extension. Twenty-two out of 27 had significant visual fields damage. Mean baseline IGF-1 was 3.7 x ULN. Eight patients presented with PRL- and one with TSH-co-secretion, but GH was the dominant hormone in all cases. All patients beside one underwent pituitary surgery (24 had transsphenoidal and six transcranial procedures; seven had 2-3 procedures), however none achieved hormonal remission post-operatively. Among the 21 subjects with pre-operative visual disturbances, nine patients recovered post-operatively, eleven improved their vision, and one had no change. Radiotherapy was given to nine patients (Radiosurgery in 2); only one achieved GH/IGF-1 control. Medical treatment with somatostatin analogs (Octreotide-LAR, n=26; Lanreotide-Autogel, n=4) was given to all patients after surgical failure. Remission was noticed in seven, five were partially controlled (IGF-1< 1.5 x ULN; 4/5 when combined with cabergoline), and 14 did not respond (one was lost to F/U). Five patients were treated with pegvisomant, either alone (n=3), or in combination with Octreotide; Remission was achieved in two, good response was noticed in two, and one showed poor response. Currently, after a mean F/U of 9.6 years, ten patients are in biochemical remission, six are partially controlled, and 10 are uncontrolled. This was acquired after exposure to multiple treatment modalities (mean, 3.6 modalities / patient).

Conclusions Giant GH-cell adenomas are rarely diagnosed. These patients usually harbor invasive macroadenomas, resistant to surgery, and respond poorly to medical treatment. Aggressive multimodal therapy is critical in the management of giant GH-adenomas, enhancing the chance for disease control and biochemical remission.

Abstract-ID: 454

IMPAIRMENT OF GLUCOSE METABOLISM IN PATIENTS WITH CUSHING'S DISEASE BEFORE AND AFTER TRANSSPHENOIDAL ADENOMECTOMY

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Introduction: Diabetes is considered to be a common complication of chronic exposure of glucocorticoid excess and it plays an important role in contributing to morbidity and death in patients with Cushing's disease (CD).

Aim: To assessed frequency of glucose disturbances (GluD) in CD-patients at initially and 12 months postoperatively.

Material and methods: 29 female patients (39.5 ± 1.4 y.o., BMI 33.6± 6.5 kg/m^2) with CD examined for GluD before and 12 months postoperatively. Oral glucose tolerance test was performed to patients without previously diagnosed GluD.

Results. I. Before treatment of CD 23 (79.3%) patients had GluD: 17 had diabetes mellitus (DM) (6-previously diagnosed, 11 - first established at the time of diagnosis of CD) and 6- impaired glucose tolerance (IGT). Patients with IGT were on diet, 13 patients with DM were on oral hypoglycemic medications and 4 on combination therapy (insulin and metformin). Patients with DM and patients without DM did not differ from each other on the levels of UFC, morning plasma cortisol and cortisol after LDDST. No significant correlations were found between fasting glucose or HbA1c (before prescribing antidiabetic medication) and UFC, morning plasma cortisol or cortisol after LDDST. Patients on oral medications and combined therapy did not differ in morning plasma cortisol or cortisol after LDDST or UFC.

II. After transsphenoidal adenomectomy for CD DM remained in 9 of 17 patients with previous DM: 6-with DM diagnosed before CD (3 has hypercortisolism persistence), 3 – in whom DM was first established at the time of diagnosis of CD (1 with hypercortisolism persistence). In 8 of 17 patients DM disappeared. IGT persisted in 1 patient with cured CD. 7 DM-patients receive peroral antidiabetic medications and 2- insulin+ metformin.

In patients with persisted DM plasma cortisol level after LDDST (at the moment of diagnosis) was significantly lower than in patients with regression of DM (415,0 ± 224,3 and 678,5 ± 300,7 nmol/L respectively, p=0.02), with significant negative correlation between the level of fasting blood glucose and plasma cortisol after LDDST (r= -0,5, p=0.03). There was no any difference between IGT-patients and normal glucose methabolism-patients.

Conclusion: Before CD-treatment DM observed in 17 (58.6%) patients and IGT in 6 (20.7%). There were no patients with impaired fasting glucose. One year postoperatively diabetes remains in 9 patients, 3 of them has persistence of hypercortisolism. Also 1 patient with persistence of hypercortisolism doesn't have GluD. IGT remain in 1 patient.

Abstract-ID: 456

PREDICTORS AND INCIDENCE OF TUMORS OF THE GASTROINTESTINAL TRACT AND THYROID GLAND IN PATIENTS WITH ACROMEGALY.

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Objective: To investigate the incidence and predictors of tumors of the thyroid gland and gastrointestinal tract in patients with acromegaly.

Design, setting, and participant: The study included 113 patients with acromegaly (51yr of age [43-59]): 68 patients as the prospective group and 45 patients of retrospective group from 125 medical records. Patients were underwent ultrasound of thyroid gland, nodules biopsy and cytology, also esophagogastroduodenoscopy and colonoscopy with histological examination

of biopsy specimens. Additionally there were defined serum levels of IGF-1, GH, insulin, 25-OH-D. Statistical analysis was performed using Statistica 7.0. Comparison of quantitative traits was performed using the Manna-Whitney comparison of qualitative attributes using the Pearson chi-squared.

Results: The tumors of the pharynx and stomach were identified in 14.4 % of patients, in 37.14 % of cases - neoplasms of intestine, usually benign polyps (adenomatous, hyperplastic), 1 case – mucinous carcinoma of the stomach, 2 cases of colon adenocarcinoma, 1 - tubulovillous adenoma. In 26.17 % - nodular goiter with normal thyroid volume, at 22.42 % - diffuse thyroid enlargement. 29.9% of patients have a mixed form of goiter, in 9.3 % of cases diagnosed with papillary thyroid cancer. Combined pathology was identified in 4 patients: in 2 patients –both gastric and colon tumors, in 2 patients - gastric cancer and cancer of the thyroid gland. Neoplasms of the gastrointestinal tract were prevalent more significantly in patients older than 45 years (p = 0.035). At the same time depending of frequency of thyroid cancer by age have not been identified (p = 0,54). There were found no correlation between rate of gastrointestinal tumors (p = 0,21); thyroid cancer (p = 0,54) and disease activity (the level of IGF -1); insulin levels as a possible predictor of development of tumors (p = 0,2/p = 0,29); 25-OH-D, as a marker of tissue apoptosis (p = 0.74/p = 0,55).

Conclusions: There is a high incidence of gastrointestinal tumors and thyroid cancer in patients with acromegaly. Neoplasms of the gastrointestinal tract dominated by benign polyps, the most frequently detected in patients older than 45 years. There were revealed no correlation with the studied biochemical markers at this period of the study.

Abstract-ID: 463

CUSHING`S DISEASE: REVERSIBILITY OF GLUCOSE HOMEOSTASIS ALTERATIONS AND IMPROVEMENT IN ANTHROPOMETRIC PARAMETERS, FOLLOWING A SUCCESSFUL TRANSSPHENOIDAL SURGERY – PRELIMINARY REPORT

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Background: Cortisol excess in Cushing's disease (CD) leads to metabolic complications and increased cardiovascular risk.

Aim: The aim of this study was to assess the reversibility of glucose homeostasis alterations and dynamics of inflammatory and coagulation parameters after the successful transsphenoidal surgery (TSS) for CD.

Study population and methods: The group consisted of 17 patients with CD (14 females and 3 males; age:40.6±14.8) operated on by the same neurosurgeon according to the same surgical protocol. Anthropometric parameters, glucose and insulin levels during an oral glucose tolerance test (OGTT), HbA1c, hsCRP, fibrinogen, and D-dimers were assessed prior to, and 3 months after TSS. HOMA-IR, QUICKI, and Matsuda indices were calculated. Patients previously diagnosed with diabetes were assessed exclusively for fasting glucose and HbA1c.

Results: Three patients (17.7%) had been diagnosed with diabetes prior to CD confirmation. Four patients (23.5%) were diagnosed with diabetes based on OGTT results prior to surgery. Eight patients (47.1%) were diagnosed with impaired glucose tolerance. Three months after the surgery BMI decreased significantly (32.94±7.3 kg/m^2 vs 31.67±6.96 kg/m^2, p<0.001). Additionally, reduction in waist (115.9±17.9cm vs 110.7±17.8cm, p<0.001) and hip (111.9±16.3cm vs 106.8±14.4cm, p<0.001) circumference was observed. A significant decrease in OGTT parameters was confirmed: fasting blood glucose (96.2mg/dL±15 vs 85.4mg/dL±13.1, p<0.05), mean blood glucose (161.4mg/dL±32.7 vs 121.4mg/dL±24.8, p<0.001), 120-minute blood glucose (160mg/dL±47.5 vs 138.3 mg/dL±40.1, p<0.05) and 90-minute insulin (187.3µIU/mL±112.1 vs 119.7±96.8, p<0.05). The Matsuda index and QUICKI improved significantly (2.1±1.3 vs 3.9±2.6, p<0.01 and 0.31±0.02 vs 0.33±0.03 p<0.05, respectively). No differences were observed with regards to mean and fasting insulin levels, HbA1c, HOMA-IR, hsCRP, D-dimers and fibrinogen.

Conclusions: Three months following successful surgical treatment of CD significant improvements in BMI, waist and hip circumference as well as a decrease in fasting and mean OGTT glucose levels could already be seen. The Matsuda index, which is based on mean OGTT glucose and insulin levels, might be the most sensitive out of IR indices in the early postoperative period. To demonstrate differences in insulin levels during OGTT, and improvement in inflammatory and coagulation parameters, a longer follow-up may be required.

Abstract-ID: 478

CUSHING`S DISEASE: GLUCOSE HOMEOSTASIS ALTERATIONS, BODY COMPOSITION AND ANTHROPOMETRIC ASSESSEMENT.

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Introduction: Cortisol excess in Cushing's disease (CD) can lead to pre-diabetes and diabetes, unfavorable changes in body composition, overweight, obesity and arterial hypertension.

Aims: 1 Prospective evaluation of the frequency of glucose homeostasis alterations, anthropometric parameters, body fat content and indices of insulin resistance (IR) in patients with CD. 2 Analysis of the impact of family history of type 2 diabetes (T2D) on the anthropometry in CD.

Material and methods: The study group included 32 consecutive patients with CD (25 women and 7 men, aged 42.8 ± 16.45) hospitalized in 2012 and 2013. Anthropometric parameters: waist and hip circumferences, body mass index (BMI) and body fat content were recorded. Glucose and insulin levels during an oral glucose tolerance test (OGTT) were assessed. HOMA-IR, QUICKI and Matsuda indices were calculated. Patients previously diagnosed with diabetes were examined exclusively for fasting glucose and HbA1c.

Results: Ten patients (31.3%) had diabetes, another 15 (46.9 %) had impaired glucose tolerance. Hypertension was confirmed in 25 patients (78.1%). Mean total fat content was 35.38±11.21kg, whereas the trunk fat was 17.9±5.52kg. Mean BMI was 31.03±6.67kg/m^2. Obesity was confirmed in 16 patients (50%) and overweight in 12 (37.5%) . In patients with hypertension total and trunk fat were higher than in the normotensive group (37.73±11.3kg vs. 27±6.12kg, p<0.05 and 19.29±5.15kg vs.12.93±3.79kg, p<0.05, respectively). Positive family history of T2D was found in 13 patients (in 7 cases mother had T2D, in 3 patients father, and in 3 cases both parents). Positive history of maternal T2D was associated with a higher BMI (35.44±8.1kg/m^2 vs. 27.51±7.8kg/m^2, p<0.05), greater waist and hip circumference (119.7±22.53cm vs.104.66±11.81cm, p<0.05 and 118.25±17.83cm vs.103.16±9.74cm, p<0.05, respectively) compared to those without T2D in the family history. The Matsuda index was higher in patients without concomitant glucose homeostasis alterations than in patients with pre-diabetes (3.54±1.35 vs 1.98±0.94, p<0.05). It was not observed with regards to HOMA-IR and QUICKI (3.14±1.02 vs. 5.82±5.16, p=0.23 and 0.33±0.02 vs. 0.31±0.03, p=0.14).

Conclusions: 1.The glucose homeostasis alterations were observed in almost 80% of patients with CD. 2.In CD, similarly to the general population, there is an association between the presence of arterial hypertension and body fat content. 3.The presence of T2D in the mother may be associated with a higher risk of obesity in patients with CD. 4.Matsuda index contrary to HOMA-IR and QUICKI may be a more sensitive marker of IR in the pathogenesis of glucose homeostasis alterations in CD.

Abstract-ID: 487

CAPABILITIES AND LIMITATIONS OF TRANSSPHENOIDAL SURGERY IN PITUITARY ADENOMAS

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Subject and Aim: To perform a detailed analysis of surgical results in patients with pituitary adenomas, abiding contemporary internationally accepted criteria for remission/persistence/recurrence. Capabilities and limitations of TSS are analyzed and options for managing recurrence are discussed.

Material and Methods: We present personal data from a sizable clinical material of 671 cases with pituitary adenomas, operated on by the senior author during the last 15 years: 251 growth hormone secreting, 143 with M. Cushing, 101 with prolactinomas and 176 with non-functioning adenomas. We determined the factors, responsible for the early and late postoperative outcome as well as the role of additional medical and radiation treatment.

Results: The endocrinological cure rate at last follow-up was 74.9% for acromegaly; factors, determining unfavorable results were tumor basal GH and IGF-levels, size and invasiveness (twice as higher risk of recurrence). In patients with M. Cushing, early endocrinological remission was observed in 84.8%. The cumulative risk probability for living without relapse was 81.8%±8.9% at 5th postoperative year and nearly 70% at 11th postoperative year. In selected cases with prolactinomas, surgery offers an effective radical alternative to medical treatment - in intrasellar tumors and Prl<200ng/ml remission rate of was 85.2%, whereas in extrasellar prolactinomas and preoperative Prl>200 ng/ml remission rate dropped to 23.1%.

Conclusion: Contemporary TSS is the initial treatment of choice for most intrasellar adenomas, non-invasive macroadenomas and in compressive symptoms, but successful long-term control of the disease still remains a challenge. Successful surgical treatment long-term management still remains a challenge, necessitating prolonged biochemical&clinical surveillance of treated patients

The effectiveness of surgical management of pituitary adenomas undoubtedly depends on organizational issues (specialized large volume pituitary centers, devoted neurosurgeons with sufficient expertise in pituitary surgery, multidisciplinary team work), as well as on adoption of innovative intra-operative technologies.

Abstract-ID: 491

RUSSIAN REGISTRY OF PATIENTS WITH TUMORS OF THE HYPOTHALAMIC-PITUITARY REGION (OGGO): APRIL 2014 UPDATE

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Introduction: The Russian Registry of patients with tumors of the hypothalamic-pituitary region (OGGO) is a national registry founded in 2004 by Russian Society of Endocrinology and Endocrinology Research Centre as a patient registry for acromegaly; in 2006 it was expanded to collect information on all lesions of the hypothalamic-pituitary region. In 2010 the first fully electronic version and in 2013 a new upgraded electronic online version were implemented. At this point the Registry is actively supported by 32 out of 85 regions of Russia, representing about 1/3 of population.

Materials and Methods: There are overall 5794 patients registered in the OGGO from 2004 to 2014.

Results: The largest part of registered patients constitutes patients with acromegaly (51%), followed by patients with prolactinomas (25%), inactive pituitary tumors (9%), Cushing's disease (8%), mixed secretion pituitary tumors (3%) and other tumors (3%). Among 2943 patients with acromegaly 72% are women. Peak incidence is between the ages of 40-50 years. 1% of patients have got first (highest) degree of disability, 18% - second degree and 13% - third degree. 57% of acromegalic patients do not have updated disease status, only 6% of patients have remission, 7% partial remission and 30% are in the active state of the disease. Surgery was performed in 33.1% of patients, 17% received radiation therapy and 49% - drug therapy (octreotide long acting – 28%, lanreotide long acting – 2.6%, bromocriptine – 24%, cabergoline – 5.6%, with about 9% of patients receiving combination therapy of dopamine agonists and somatostatin analogs). Among 457 patients with Cushing's disease 85% are women. Peak incidence is between the ages of 20-30 years. Two percent of patients have got first (highest) degree of disability, 22% - second degree and 12% - third degree, 27% don't have any established degree of disability, and 33% - no data. Seventy percent of patients with Cushing's disease are in remission. Surgery was performed in 60% of patients, 31% received radiation therapy and 15.5% - underwent total adrenalectomy. Drug therapy is received by 27% of patients, mainly consisting of ketokonazole > 90%, bromocriptine - 44%, cabergoline - 8%, long acting somatostatin analogs <4%.

Conclusions: Our database show low implementation of surgical and specific drug treatment among acromegalic patients. As for Cushing's disease the definitive remission rate of 70% is quite promising as soon as medical treatment choices are still limited.

Abstract-ID: 524

OBSERVATION OF INSULIN SECRETION IN ACROMEGALIC PATIENTS AFTER USING EITHER OCTREOTIDE LAR OR PASIREOTIDE LAR - A PRELIMINARY REPORT

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Objectives: This study was designed to observe the difference of changes in insulin secretion of acromegalic patients treated with either octreotide LAR or pasireotide LAR.

Methods: This study was performed with acromegalic patients who had been originally enrolled in a global study comparing the effect of octreotide LAR (OCT) and pasireotide LAR (PAS). After randomization to either octreotide LAR (n=3) or pasireotide LAR group (n=3), all patients underwent a 75 g oral glucose tolerance test every three months for 12 months in octreotide LAR group and for 24 months in pasireotide LAR group, which measured insulin and C-peptide at 0 and 30 minutes. Insulin and C-peptide, calculated in AUC (area under curve), were compared between two groups.

Results: Baseline insulin levels demonstrated differences with borderline significance between OCT and PAS group (AUC: 512.0±74.4 vs 1751.0±1174.4 min•uU/mL, P = 0.05). However, those in OCT group decreased to the levels analogous to PAS group after the first injection of octreotide LAR, which maintained similarly for the rest of 24 weeks. C-peptide also showed similar trend despite the lack of statistical significance.

Conclusion: Suppression of insulin secretion was greater in OCT group than PAS group, especially after three months of the treatment initiation. Since then, interestingly, both groups showed similar insulin and C-peptide levels during the study period.Please copy and paste the text here into this template, then store it on your computer for upload

Abstract-ID: 526

ANOMALIES OF HPA AXIS IN PATIENTS TREATED WITH MEGESTROL ACETATE

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Incidentally discovered secondary adrenal insufficiency is rare. Besides hypopituitarism, administration of substances with glucocorticoid-like activity should be sought. Megestrol acetate is a synthetic progestin used as an antineoplastic agent in the treatment of breast, endometrial and prostate cancers and as an appetite stimulant in cancer or AIDS-induced cachexia. It acts also as a weak agonist of the glucocorticoid receptor. We present the anomalies of the hypothalamic-pituitary-adrenal (HPA) axis recorded in two women treated with megestrol acetate for uterine cancer.

Case 1. A 65 year-old woman with operated and irradiated endometrial cancer presented for low cortisol and ACTH levels incidentally discovered at an evaluation for thyroid nodules. The patient was currently treated with megestrol acetate 160 mg/day and had no clinical signs of adrenal or pituitary insufficiency. She had a stable BMI 30 kg/sqm, mild hypertension and a multinodular goiter with subclinical hyperthyroidism. Serum biochemistry and PRL were normal, FSH 41.5 mIU/mL (normal menopausal level), 8 a.m. plasma cortisol was 1.6 µg/dL (normal, 6.7-22.6), ACTH 2.4 pg/mL (normal, 3-66)]. Serum cortisol level was normally stimulated (27 µg/dL) after 1 mg i.m. depot cosyntropin test. A cranial MRI was normal. Because the patient was asymptomatic no hydrocortisone replacement therapy was recommended. One month after megestrol withdrawal serum cortisol returned to normal levels.

Case 2. A 33 year-old women with operated and irradiated endometrial cancer, treated with chemotherapy and currently with megestrol acetate 160 mg/day, presented for a recently diagnosed prolactinoma. The clinical examination revealed only a recently acquired obesity (20 kg in 1 year, BMI 35 kg/sqm). Cranial MRI showed a 12/6/7.5 mm pituitary adenoma, serum PRL was 268 ng/mL (normal, 6 – 29.9). Thyroid function, IGF-1 were normal, FSH was low for the patient's menopausal status (9.8 mIU/mL), estradiol 35 pg/mL (normal). 8 a.m. plasma cortisol and ACTH levels were low [cortisol 0.2 µg/dL, ACTH 2.8 pg/mL. Serum cortisol was insufficiently stimulated at 4h (1.4 µg/dL) and 24h (8.2 µg/dL) after i.m. depot cosyntropin test. Seven days after Megestrol withdrawal, albeit the patient being asymptomatic, morning and ACTH-stimulated cortisol remained low (0.55 µg/dL, and 9.04 µg/dL at 24h, respectively). Hydrocortisone replacement was recommended.

Conclusion. Besides progesterone activity and inhibition of gonadotropin secretion, megestrol acetate may have glucocorticoid-like activity, occasionally inducing Cushing's syndrome or new-onset diabetes mellitus. Adrenal insufficiency has also been described during high-dose or prolonged treatment or after drug cessation, as in our cases, and its treatment should be individualized.

Abstract-ID: 531

IS THERE ANY GENDER DIFFERENCE IN EPIDEMIOLOGY, CLINICAL PRESENTATION AND CO-MORBIDITIES OF NON-FUNCTIONING PITUITARY TUMORS? A PROSPECTIVE SURVEY OF A NATIONAL REFERRAL CENTER

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The aim of the current survey is to evaluate the presence of gender differences based on anthropometric, clinical, biochemical and instrumental characteristics of patients newly diagnosed with non functioning pituitary tumors on a three years period in a national referral center in Italy.

Patients and methods: In this study we included the 91 patients with non functioning tumor (39 men, mean age 51.0 ± 16.7 years; 52 women, mean age 40.9 ± 17.1 years)

Results: The non-functioning pituitary lesions diagnosed in the center of Molecular and Clinical Endocrinology "Federico II" of Naples since January 2010, represent the 37.8% of all pituitary lesions .Rathke's pouch cysts were 4.3 % and were exclusively female. *P*ituitary lesions (>1 cm) were significantly more frequent in male gender than in female one (74.3% vs. 36.5%, $\chi 2$ = 11,317, p = 0.0001). There was no significant difference in males and females as to the presence of headache (66% *vs*. 50%, $\chi 2$ = 1,893, p = 0,169) or visual disturbances(49% *vs*. 34%, $\chi 2$ = 1.299, p = 0,254), although more in males than in females. Hypopituitarism was more frequent in the male than female gender (50% vs 20.5%, $\chi 2$ = 7,068, p = 0.008). In particular the male gender showed two degrees (≥ 3hormonal deficit) of hypopituitarism more frequently than the female gender while there were no gender differences in one degree (1-2hormonal deficit). No difference was found regarding the prevalence of diabetes insipidus between male and female gender. Secondary hypothyroidism and secondary hypocortisolism were more frequent in the male gender than in the female gender, while there was no gender difference regarding the presence of GH and gonadotroph deficiency.

No differences were found about dose of L-tiroxine and acetate cortisone between male and female patients.

Conclusions: In conclusion, in this study tumor size and hypopituitarism in patients with pituitary non-functioning lesions, were more frequent in male gender than in female one. However, the present study reported the data of a short time of observation in a national referral center. More time of observation and more patients are needed to confirm these results.

Abstract-ID: 533

THE PRELIMINARY RESULTS OF PSYCHOLOGICAL PROFILES IN PATIENTS WITH ACROMEGALY

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Introduction: In recent years, the quality of life (QoL) has become a fundamental concept in terms of the health-disease continuum. In 1999, Webb developed a questionnaire to examine the perception of quality of life in acromegaly (AcroQoL). According to the latest consensus concerning the diagnosis, treatment and monitoring of acromegaly, AcroQoL questionnaire should be used to assess the success of treatment.

Objective: The aim of this study was to create the psychological profiles of patients with acromegaly and assess these profiles in correlation with the activity of disease. We also compared these results to the patients with non-functioning pituitary adenomas.

Methods: Forty one acromegalic patients and thirty one with non-functioning pituitary adenomas treated at Department of Endocrinology, Diabetology and Isotope Therapy, Medical University, Wroclaw were selected for a cross-sectional analysis. Psychological aspects were obtained through the patients' interviews using standardized questionnaires, including the quality of life (AcroQoL and WHOQoL), psychiatric morbidity (General Health Questionnaire-28) and acceptance of illness (AIS). Patients with acromegaly were also divided into three subgroups accordingly to minimal GH concentration during the OGTT and IGF-1 concentration: surgical cured acromegaly group, well-controlled acromegalic group and active acromegaly group.

Results: The mean age of acromegalic patients was 52.31 ± 14.81, and mean duration of illness since diagnosis of 8.71 ± 8.69 years. The non-functioning adenoma group had mean age 46.88 ± 15.29. Acromegaly was diagnosed considerably later compared to diagnose of non-functioning adenoma. The average AcroQoL score was 55.38 ± 16.33, with the mean physical dimension score of 53.05 ± 20.70 and mean psychological dimension of 56.72 ± 15.73. Age, quality of life and acceptance of illness were not associated factors in acromegaly versus non-functioning adenomas comparison.

Headache was not a significant predictor of quality of life, acceptance of the disease and prevalence of psychopathological symptoms as measured by the GHQ-28. Patients with decreased libido have significantly lower scores in the environment domain in WHOQoL regardless of diagnosis.

Conclusion: Results of the study indicated that patients with pituitary adenomas may have psychological, social and cognitive functioning problems. The coexistence of mental disease may have impact on the quality of life, as well as on the acceptance of illness. There is no difference in psychosocial perspective between patients with acromegaly and non-functioning adenomas in the study group.

Abstract-ID: 541

STUDY DESIGN OF A PHASE IIIB MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE EFFICACY AND SAFETY OF PASIREOTIDE IN PATIENTS WITH ACROMEGALY INADEQUATELY CONTROLLED WITH FIRST-GENERATION SOMATOSTATIN ANALOGUES

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INTRODUCTION: Study SOM230C2402 compared double-blind pasireotide long-acting release (LAR) 40mg and 60mg, separately, with open-label first-generation somatostatin analogs (SSAs) octreotide-LAR or lanreotide Autogel (ATG) in patients with inadequately-controlled acromegaly after at least 6mo of treatment with high doses of the latter. This study demonstrated superior efficacy of pasireotide-LAR 40mg and 60mg versus continued treatment with first-generation SSAs (active control) in providing biochemical control (mean growth hormone levels [GH] <2.5µg/L and normal insulin-like growth factor-1 [IGF-1]). No patient in the active control group achieved either biochemical control or normal IGF-I. An earlier treatment change (within <6mo) to pasireotide-LAR might be beneficial for inadequately controlled patients. Objective: To assess efficacy of pasireotide-LAR in patients with inadequately-controlled acromegaly after at least 3mo of treatment with maximal approved doses (MADs) of first-generation SSAs.

METHODS: Patients: Adults with inadequately-controlled acromegaly (mean GH≥1.0µg/L and sex- and age-adjusted IGF-1≥1.3xULN) after at least 3-mo of MADs of octreotide-LAR (30/40mg) or lanreotide-ATG (120mg); target enrollment~112. **Design:** Phase IIIb, international, multicenter, open-label, single-arm study. Patients at study entry will receive pasireotide-LAR 40mg/28d. Patients remaining uncontrolled at wk12 will have the dose of pasireotide-LAR increased to 60mg/28d at wk16; controlled patients will be maintained on 40mg/28d or their dose increased to 60mg/28d should biochemical control lost during the study. Patients remaining uncontrolled during the extension phase will be allowed to receive concomitant treatment with medications used to manage acromegaly as per investigator's judgment (exploratory purposes). **Endpoints:** Primary: Proportion of patients with GH<1µg/L and IGF-1<ULN at wk36. Key secondary: Proportion of patients who achieved GH<1µg/L and IGF-1<ULN at wk36 among patients having 1) GH level between 1-2.5µg/L and 2) GH>2.5µg/L at screening. Change in mean GH and standardized IGF-1 from study baseline to wk36. Secondary: Proportion of patients achieving GH<1µg/L and IGF-1<ULN at wk12 and 24 (overall and by GH level at screening); GH<1µg/L (overall and by GH level at screening) and IGF-1<ULN at wk12, 24 and 36; tumor volume reduction >20% from baseline to wk36; changes in tumor volume from baseline to wk36; safety and health-related quality of life.

CONCLUSIONS: This study will assess the efficacy and safety of pasireotide-LAR in patients with inadequately controlled acromegaly after at least 3-mo treatment with MAD of first-generation SSAs. Based on the new criteria for biochemical control, the study will also evaluate pasireotide-LAR in patients with baseline GH between 1-2.5µg/L; a new patient population that was not studied in SOM230C2402.

Abstract-ID: 542

THE GENDER RELATED DIFFERENCES IN EVOLUTION AND PROGNOSIS OF DOPAMINE AGONISTS RESISTANT PROLACTINOMAS.

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Retrospective study was designed to learn the gender related differences in evolution and prognosis of dopamine agonists resistant prolactinomas.

Material and methods: A total of 197 patients with prolactinomas (87% female and 13% male), the mean age 36 ± 12 years, were examined using generally accepted laboratory and instrumental criteria of the disease. Prolactinomas were classified as micro or macroadenomas (separation point – 10 mm in maximal diameter)

Phenomenon of dopamine agonist resistance was defined as uncontrolled hyperprolactinemia and/or failure of tumor size reduction by at least 50% in patients on cabergoline first-line therapy ≥ 1mg per week.

Results: Microprolactinomas were detected in 79% in women and 37% in men, macroprolactinomas - in 21% and 67% respectively.

First-line cabergoline therapy achieved prolactin normalization, tumor shrinkage and restoration of reproductive disorders in 183 cases (90% female and 95% male).

Among the 15 resistant prolactinoma patients, 13 were female (10%) and 2 were male (5%). The mean age at diagnosis was 31±7 years. Significant gender-related differences were noticed

In women 9 cases (69%) were presented by microprolactinomas, while in men all cases were macroadenomas. In men leading clinical symptoms at the time of diagnosis were neurological disorders (100% of resistant men), while the main clinical symptoms in resistant women were represented by hopogonadotropic hypogonadism - irregular menstrual cycles (73%), galactorrhea (59%) and infertility (51%).

According to the generally accepted indications, surgery was performed to 30% of patients with resistant forms. Among 5 patients (4 women and 1 men who underwent surgery), 60% exhibited long-term normalization of prolactin levels without added medications.

Conclusions: Thus, the clinical cases of prolactinomas in women are characterized by a predominance of microprolactinomas, higher incidence of resistance to dopamine agonists than men. In men prolactinomas have a higher potency for growth; they are often diagnosed at the stage of large adenomas, accompanied by neurological symptoms that require surgical treatment in 30% via to 10% in women.

Abstract-ID: 548

THE FOLLOW-UP OF ACROMEGALY PATIENTS PERFORMED SURGERY AND GAMMA KNIFE

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Aim: This study aimed to evaluate the laboratory findings and treatment results of 230 acromegalic patients, followed at Marmara University Faculty of Medicine, Endocrinology Outpatient clinics between the years of 2000-2013.

Material-Methods: Normal IGF-1 levels, GH during OGTT being <0.4 ng / ml or random GH being <1.0 ng / mL were taken as remission criteria of acromegaly. Patients were assessed in 3 groups according to clinical situation. Uncontrolled group had high GH and IGF-1 levels, controlled group had normal GH and IGF-1 levels under medical treatment , remission group had normal GH and IGF-1 levels without any medical treatment. Patients were also classified into 4 groups acoording to treatment they

got; patients who had surgery and gamma knife, patients who had only gamma knife, patients who had only surgery and patients followed with medical treatment.

Results: Mean age of the patients was 49.6 ± 12.6 years, and mean follow-up time was 7.6 ± 6.4 years. The mean tumor size was 17.5 ± 8.7 mm. The remission rate was 30.5% in patients with microadenomas and was 13.5% of patients with macroadenomas. Tumor size at diagnosis was significantly correlated with disease remission rate (p = 0.0077). Patients who had only gamma knife treatment had a shorter duration of disease and lower GH levels. In the multivariate analysis with remission state as an dependent risk factor and age, sex, disease duration, and other hormone deficiencies and GH levels as independent ones, the r^2 of the system was found to be 17.8. (p:<0.0001).

Conclusions: Surgery has an important role in the treatment of GH secreting adenomas. A successful surgery is associated with long term improvement, especially in microadenomas. Gamma knife treatment in the early stages in patients with postoperative residual tumors increases the rate of remission .

	Remissionion	Controlled with medical treatment	Uncontrolled	P
	N: 48	N:116	N: 66	
Age (year)	**47.93± 10.87**	**53± 12.67**	**45.18 ± 12.75**	0.0002
Gender F/M	28/20	53/63	35/31	
Time of disease (year)	**7.3 ± 7.2**	**8.61± 6.33**	**6.5 ± 5.6**	0.0882
GH (ng/ml)	0.52 ± 0.50	**1.02± 0.96**	**4.0± 4.0**	<0.0001
Tumor size (mm)	**16.65 ± 11.7**	**16.44± 7.5**	**21.30 ± 10.6**	0.0077
Gamma knife + Surgery (%)	**%27**	**%48.3**	**%42.5**	NS
Surgery(%)	**%68.8**	**%38**	**%51.5**	NS
Gamma knife (%)	**%4.2**	**%7.7**	**%4.5**	NS
Medical treatment (%)	**%0**	**%6**	**%1.5**	NS
Panhypopituitarism (%)	**%18.8**	**%3.5**	**%12**	NS

Abstract-ID: 553

IMPACT OF SURGERY AND RADIOTHERAPY TO INDUCE ADRENAL INSUFFICIENCY IN ACROMEGALY

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Background and aim: Adrenal Insufficiency (AI) in acromegaly could be related to the presence pf pituitary adenoma, as well as induced by available treatments (neurosurgery, medical treatment or radiotherapy).

Aims: Our goals were to assess: (a) the prevalence and the incidence of AI in a cohort of acromegalic patients followed in the same Tertiary Care single-centre; (b) the role of neurosurgery, medical treatment or radiotherapy in AI development.

Materials and Methods: We retrospectively studied 87 patients, in regular follow-up at our Endocrinology Unit, with a mean follow-up of 13 years (from 1 to 57 years). It was considered as AI either basal morning serum below 138 nmol/L or inadequate cortisol response to low dose ACTH test (cortisol response below 440 nmol/L). The basal serum cortisol and the ACTH test were performed at diagnosis and 3-6 months after surgery, then, the serum cortisol was performed every 12 months after the beginning of each treatment.

Results: In our patients we observed 19 cases of AI (22%). Considering treatment, in our cohort 62 patients underwent at least one surgery (71%), 15 underwent radiotherapy (18%) and 59 assumed medical therapy (68%): 49 were taking medical somatostatin analogs (56%, 15 in primary medical therapy), 20 pegvisomant (23%, 7 patients in monotherapy) and 4 cabergoline (16%, 3 in monotherapy). It was found no difference between patients with or without AI in duration of acromegaly, controlled or uncontrolled GH and IGF-1 levels, medical treatment with somatostatin analogues or pegvisomant. Frequency of AI was 26% in operated patients (16 out of 62, p: 0.09), 56% in patients who underwent radiotherapy (8 out of 15, p<0.01) and 6% (1 out of 17) in patients in primary medical treatment. Interestingly, the patients with AI presented higher to develop other pituitary deficiencies as TSH (10 out of 18, p<0.01), GH (6 out of 18, p<0.01) and LH-FH (10 out of 18, p<0.01).

Conclusions: Medical treatment and duration of acromegaly are not related to AI development, and in our series surgery is related to AI but further studies are needed to establish its role. On the contrary, radiotherapy play a role in ACTH-secreting cells. Endocrinologists must bear in mind that AI is related to other anterior pituitary deficiencies.

Abstract-ID: 554

TEMOZOLOMIDE AND PASIREOTIDE TREATMENT IN AGGRESSIVE PITUITARY ADENOMA: CLINICAL ACTIVITY AND GENETIC EVALUATION IN A THIRD CARE CENTRE

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Background: Aggressive pituitary adenoma (PA) are a clinical challenge for endocrinologists and neuro-surgeons due to their locally invasive nature or resistance to standard treatment (surgery, medical treatment or radiotherapy). Recently, two pituitary-directed drug have been proposed for PA: temozolomide (TMZ) for aggressive PA, and pasireotide for ACTH-secreting PA. We present the local multidisciplinary team (made up with endocrinologists, neuro-surgeons, neuro-radiologists, oncologists, otolaryngologists and pathologists) experience of TMZ and pasireotide treatment in aggressive PAs, looking at radiological shrinkage and genetic pattern (isocitrate dehydrogenase-IDH; BRAF and RAS; 6 methylguanine DNA methyltransferase-MGMT).

Materials and methods: We observed 5 patients with aggressive pituitary adenoma: 4 with non secreting (one GH-silent and 2 ACTH-silent) and one ACTH secreting PA; during observation period, the GH-silent and one ACTH-silent PA developed GH and ACTH secretion, respectively. TMZ was administrated orally (5 patients) at 150-200mg/m^2 daily for 5 days every 28 days, pasireotide was administered 600-900µg bid subcutaneously in 2 patients. We evaluated the MRI at baseline and during TMZ use. We analyzed MGMT methylation and IDH, BRAF and kRAS mutations.

Results: All patients had evidence of radiological progression of PA at the time of last magnetic resonance before TMZ treatment. One patient discontinued TMZ after 3 months of therapy due to growth of GH secreting PA, 2 patients not manifested radiological shrinkage after 6 months of therapy (one ACTH silent and one non-secreting), whereas 2 patients continued TMZ achieving radiological and clinical response; TMZ treatment was well tolerated, only 1 patients developed a grade 2 thrombocytopenia. Pasireotide was administered in 2 ACTH secreting PAs (in one combined in one subject combined with TMZ) and was effective in reducing hypercortisolism in both cases, without worsening of metabolic control or other adverse events. None of the described patients developed hypopituitarism during TMZ or pasireotide treatment. We found no genetic alterations in adenoma tissue.

Conclusions: TMZ and pasireotide treatment may represent an important therapeutic tool in aggressive, in monotherapy or combined.

Abstract-ID: 555

LONG TERM RESULTS IN THE TREATMENT OF CUSHING´S DISEASE : 20 YEARS EXPERIENCE IN A TERTIARY REFERRAL CENTER.

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Long term results in the treatment of Cushing´s disease : 20 years experience in a tertiary referral center.

Introduction: The diagnosis and management of Cushing´s disease is ever a challenging problem in clinical endocrinology. Transsphenoidal surgery (TTSS) represents the treatment of choice for Cushing´s disease, but even under the best circumstances remission rates range from 42 to 86 %.

Subjects and methods: Between 1993 and 2013, 107 patients were evaluated with diagnosis of hypercortisolism. 88 of them had Cushing´s disease, 76 women and 12 males, mean age 39.9 ±12.8 years(range 6-67). The diagnosis was based documenting at least two elevated Urinary Free Cortisol (UFC). Pituitary dependence was established measuring ACTH concentrations and by Magnetic Resonance Imaging (MRI) with evidence of a pituitary adenoma, or a history of prior transsphenoidal adenoma resection with positive histological evidence of a ACTH stainning adenoma. Sixty-six patients underwent transsphenoidal surgery by three skilled neurosurgeons of our center. In ten other patients surgery was performed outside. Of patients who underwent surgery 33 had microadenomas (43.2%), 20 were macroadenomas (26.3%) and 11 (10.3%) were non conclusive. Twelve MRI (11.2%) were negative for adenomas. In those cases we did not perform IPPS procedure because there is not sufficient expertise in our center. Five patients had bilateral adrenalectomy and two of those developed Nelson´s syndrome.

Results: In our population there was statistically significant female prepondarance. Clinical and biochemical remission was achieved in 20 of 66 patients (30%). 12 of 33 microadenomas (36%) had remission and 8 of 20 macroadenomas (40%). Those who had been operated in non expert centers experienced higher persistence rate. Histological examination revealed 37 positive ACTH immnunostaining and seventeen of these achieved remission. 7 patients experienced recurrence (35%) after TSS and 3 underwent a second surgery. Mean time until relapse was 28.4±26.00 months. Death occurred in 7 out of 88 patients and main causes were complications of bronchopneumonia, cardiovascular disease and pulmonary thromboembolism.

Conclusions: our remission rate in the surgical treatment of Cushing´s disease is low but there are similar results reported in more experienced centers. After surgical failure normalization of hypercortisolism would require association of other forms of therapies as radiotherapy or pharmacological therapy. New drugs are promising treatment options when cortisol values indicate persistent tumor.

The authors declare that there is no conflict of interest that could be perceived as prejudicing the imparciality of the research project.

Abstract-ID: 563

CARDIOVASCULAR AND METABOLICS RISKS ASSOCIATED WITH HYPOPITUITARISM AFTER FRACTIONATED STEREOTACTIC RADIOTHERAPY IN NON FUNCTIONING PITUITARY MACROADENOMAS

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Introduction: Pituitary adenomas represent 10 to 20% of all primary brain tumors. Stereotactic Fractionated Radiotherapy (SFR), is indicated as second line treatment. The most common associated morbidity is hypopituitarism and is related to an excess standardized mortality ratio of 1.2 - 2.2 years and a higher incidence of cardiovascular and metabolic events.

Objective: to evaluate the prevalence of metabolic events and cardiovascular risk in patients treated with SFR for non functioning pituitary macroadenomas (NFPMA).

Methods: Retrospective study, patients treated with SRF for NFPMA were searched from neuroendocrinology database from 2003 to 2013. Hormonal disturbances, metabolic parameters (glucose, triglycerides, total colesterol, HDL, LDL), and cardiovascular risk were evaluated before and after SRS. Time of following: 1 to 8 years. X^2 y Framingham risk score were determinated in statystical analysis.

Results: 164/238 patients (68.9%) developed hypopituitarism after SRS. Male: 87/164 (53%); female: 77/164 (47%). Mean radiation dose: 58.6 Gy (50-75.6). Prevalence of metabolic disturbances in patients with hypopituitarism: hypertriglyceridemia 55/70 (78.57%), hypercholesterolemia 21/68 (61.76%), impaired fasting glucose 10/74 (13.5%), diabetes 19/74 (25.6%), hypertension 17/65 (26.15%), metabolic syndrome 33/48 (68.74%), obesity/overweight 25/66 (37.8%), 34/66 (51.5%). Hypopituitarism was associated with increase in metabolic risk (HR 3.9, p = 0.04). There were no deads related to cerebrovascular or cardiovascular disease.

Conclusions: In our poblation we found an increase in risk of metabolic syndrome in radiated patient who developed hypopituitarism compared with patients with hormonal axis preserved. We didnt find an increase in other metabolic alterations, 90% of our patients had obesity/overweight before SRS and relative risk was significantly increased in association with hypopituitarism.

Abstract-ID: 573

THE ROLE OF HYPOTHALAMIC GONADOTROPIN- RELEASING HORMONE IN THE HYPERANDROGENIC DYSFUNCTION OF OVARIES.

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The hyperandrogenic disfunction of ovaries is the more frequent form of the polycystic ovaries syndrome (PCOS). The etiology and pathogenesis of hyperandrogenism in this syndrome is a matter of dispute.

It is known that secretion of the androgens or estrogens by the gonads is depending on respectively tonic or cyclic secretion of hypothalamic Gonadotropin-Releasing Hormon (Gn-Rh).

The goal of our research was to establish the role of the hypothalamic Gn-Rh in the hyperandrogenic disfunction of ovaries

The study represents the clinical and paraclinical data of 62 patients with hyperandrogenic disfunction of ovaries.The test with i/v 100 mcg of GH-RH was performed in 20 of them. The dosage of LH, FSH, PRL, testosterone, estradiol and progesterone was made at 0, 30, 60, 90 and 120 minute of the test We observed a correlation between clinical forms and the levels of LH and FSH (basal and stimulated by GN-RH).The GN-RH did not stimulate the secretion of PRL . Testosteron did not increase after introduction of

GN-RH, despite the significant increase of LH. The changes of estradiol and progesterone were not significant.

We observed a unexpected ovulatory effect after a single i/v dose of GN-RH, even in the patients with amenorea.

We concluded that GN-RH may be useful in diagnostics and treatment of hyperandrogenic disfunction of ovaries. A inssuficiency of hypotalamic secretion of Gn –Rh or lac of its cyclicity may be a cause of this disorder.

Abstract-ID: 578

USE OF TEMOZOLOMIDE IN THE TREATMENT OF AGGRESSIVE PITUITARY TUMORS – REPORT OF TWO CASES

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Introduction: In recent years temozolomide (TMZ) has been proposed as a therapeutic option in aggressive pituitary tumors and pituitary carcinoma. We report two patients with aggressive pituitary adenoma in whom TMZ was applied.

Case reports: First patient is a 21 year old female with a giant somatotroph adenoma with suprasellar extension, invading cavernous sinuses and cavum Meckeli. Despite three operations, conventional radiotherapy, and high doses of octreotide and cabergoline, tumor continued to grow and was biochemically active. Patient suffered treatment resistant headaches. Therefore the therapy with TMZ was initiated (dose-dense 21/28-day regimen, at a dose level of 75 mg/m^2). Biochemical remission was observed three months after starting TMZ and one year after radiotherapy. During the follow-up of 6 months, tumor volume reduced about 30% and headaches markedly improved.

Second patient is a 64 year old female with macrocorticotropinoma. She was first operated four years ago when tumor was 15 mm in diameter. Operation led to disease remission with no residual adenoma. Tumor histology was consistent with atypical adenoma. After two years, rapid tumor regrowth was observed as well as biochemical and clinical signs of hypercortisolism, together with visual field defects and occuloparesis. Tumor diameter rapidly increased to 3 cm, invading local structures. Despite reoperation, quite large tumor remnant and severe hypercortisolism persisted. Treatment with ketoconazole was started. Histology of the second operation was consistent with atypical adenoma (Ki 67 20%, p 53 <5%, no mitosis). No distant metastases were found. Because of the rapid growth of tumor remnant and high value of proliferation marker, we decided not to wait for the effect of radiotherapy, but we applied concomitant chemoradiotherapy (daily radiotherapy fractions of 180 cGy combined with TMZ at a dose of 75 mg/ m^2 per day). One week after initiation of the therapy, visual field improved. Biochemical remission was observed after two weeks of TMZ treatment and ketoconasole was taken off.

Conclusion: Although limited by short follow-up period, our results suggest that TMZ might be a good therapeutic option for aggressive pituitary tumors. For the reliable assessment of TMZ efficacy randomized controlled trials are needed.

Abstract-ID: 579

ECHOCARDIOGRAPHIC EVALUATION OF PATIENTS WITH CLINICALLY NONFUNCTIONING PITUITARY ADENOMAS USING CABERGOLINE

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OBJECTIVE: Cabergoline has been found to be associated with increased risk of cardiac valve regurgitation in Parkinson's disease, whereas several retrospective analyses failed to detect a similar relation in hyperprolactinemic patients. The current study aimed at investigating cardiac valve disease before and after 12 months of continuous treatment with cabergoline only in patients with nonfunctional pituitary adenomas.

SUBJECTS AND METHODS: 35 patients (19 men and 18 women, aged 51.7 ± 12.5 years) with clinically nonfunctional pituitary adenomas underwent transsphenoidal surgery and who had evidence of tumor rest after six months of surgery, started treatment with cabergoline aiming to control the rest of the tumor and / or reduction of tumor rest. All patients received a dose of 3.5 mg per week (182 mg / year - generally greater than the cumulative dose used for the treatment of prolactinomas) and all patients underwent a complete trans-thoracic echocardiographic examination before starting treatment with cabergoline and after 12 months use of cabergoline. Valve regurgitation was assessed according to the American Society of Echocardiography.

RESULTS: The prevalence of trace mitral, aortic, pulmonic, and tricuspid regurgitations was 22,85%, 5,71%, 8,57% and 48,57% respectively. After 12 months, no change in the prevalence of trace mitral (P=0.68) and pulmonic (P=0.79) regurgitations and of mild aortic (P=0.90) and tricuspid alterations (P=0.79) regurgitations was found when compared with baseline. The prolactin levels were below the limit of detection in all patients.

CONCLUSION:

CAB does not increase the risk of significant cardiac valve alterations in nonfunctional pituitary adenomas after the first 12 months of treatment, even if used in larger doses than those commonly used in the treatment of prolactinomas.

Abstract-ID: 580

CABERGOLINE IN PATIENTS WITH RESIDUAL TUMOUR AFTER TRANSPHENOIDAL SURGERY BY CLINICALLY NONFUNCTIONING PITUITARY ADENOMAS

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Introduction: Clinically Nonfunctioning Pituitary Adenomas (NFPA) are approximately 30% of all pituitary tumors. The treatment of choice is surgical resection. Although surgery can relieve symptoms related tumor compression, complete surgical resection is not frequent and radiotherapy is required in many cases. The role of dopamine agonists have not yet been well established in NFPA and better designed studies are lacking to prove its effectiveness.

Objective: To evaluate the useful of cabergoline in patients with NFPA who had evident residual tumor after transsphenoidal (TS) surgery in reducing and /or maintain a stable tumor rest.

Methods: We compared two groups of NFPA patients who presented residual tumor in a MRI performed six months after surgery: 65 patients treated by cabergoline - 3.5mg/week (A) and 60 patients followed without cabergoline (B). No patients were treated by irradiation before or during the follow-up. All patients were evaluated every 6 months with MRI for 12 months. Change of tumor volume bigger than 15% were considering significant. Statistical analysis was performed using the statistical program SOFA.

Results: The MRI in group A showed stabilization of residual tumor in 71,64% (48/65) and tumor reduction in 20,89% (14/65) of patients, while tumor progression was observed in 7,46% (5/67). In group B, stabilization was observed at 78.68% (48/61), reduction in 4,91% (3/61) and growth in 16.39% (10/61) of patients. Statistical difference between groups A and B was obtained regarding tumor reduction (20,89% vs. 4,91%, $p < 0.01$) and tumor progression (7,46% vs. 16,39%, $p = 0.02$) with no difference in the stabilization of residual tumor ($p = 0.4$).

Conclusions: Cabergoline, after TS surgery, was useful in reducing or stabling residual tumor in significant number of NFPA patients in a 12 months follow up.

POSTER CLINICAL GASTROINTESTINAL NETS

Abstract-ID: 237

SPECT-CT IMAGING OF NEUROENDOCRINE TUMORS (NETS) WITH Γ-EMITTED RADIOPHARMACEUTICALS

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Neuroendocrine tumors (NETs) are heterogeneous group of neoplasms produced peptides and amines which act as hormones or as neurotransmitters throughout the body. Functional imaging procedure applying somatostatin-receptor imaging (mainly SSTR2 and SSTR5) using $^{111}In/^{99m}Tc$ – labeled somatostatin analogues are used to select essential information for staging, assessing SSTR status and making decision on the most appropriate therapy regiments. Recently, new hybrid SPECT-CT γ-cameras have become available. The addition of CT images enables the addition of exact localization to the tracer uptake in lesions. Anatomical cross-sectional CT data increase certainty of standard nuclear medicine approaches because of their excellent spatial resolution.

The aim of this study is to present advantages of hybrid SPECT-CT images of NETs.

SPECT-CT somatostatin-receptor scintigraphy with $^{111}In/^{99m}Tc$-labelled pentetreotide improve topography of hot "spots" with abnormal uptake and provide differential diagnosis of malignant from benign foci and physiological uptake.

Diagnosis of primary NETs: To depict the most appropriate suspicious malignant lesion for correct biopsy

To discover primary tumor in cases with metastatic lesions from tumor with unknown origin.

To establish SSTR expression in order to predict an individual response to therapy

Staging of malignant diseases: Pre-treatment correct N/M-staging of NETs

Follow-up of patients after the treatment: For monitoring of treatment response – complete, partial, stable or progressive disease

For differential diagnosis of pathological lesions from physiological uptake especially in the regions below the diaphragm.

For early determination of recurrence or re-staging of NETs.

For precise topography of metastatic foci in patients with disease extension.

In conclusion: SPECT-CT systems can reduce false positive results and can improve specificity and accuracy of somatostatin-receptor imaging of NETs.

Abstract-ID: 305

STUDY ON THE FREQUENCY, LOCATION AND MORPHOLOGICAL CHARACTERISTICS OF NEUROENDOCRINE TUMORS OPERATED ON AT UNIVERSITY HOSPITAL „DR. G. STRANSKI" - PLEVEN FOR A TIME PERIOD OF 5 YEARS.

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Introduction: The incidence of neuroendocrine tumors (NETs) is increasing annually with 5.8%. The morbidity in the U.S. is 2.5 to 5.0 / 100 000 patients and ranks second in GIT malignancy after colorectal cancer. The localization is mainly in the small intestine, the rectum, the appendix, and less in the colon, stomach and pancreas. There are no characteristic symptoms for NETs, they lack specific and accurate methods for early detection. They present with unusual and unpredictable biological behavior and at the time of diagnosis 50% of patients are with metastases.

Matherials: Retrospective study covering 5 years period. Patients operated on in surgical clinics of the University Hospital "Dr. Georgi Stranski" Pleven are examined.

Results and discussion: Morphological types of tumors, organ localization and the ratio of our results assigned to those of the country are presented. The emergence of mixed tumors composed of neuroendocrine tumors and adenocarcinomas is noteworthy. We have found secondary neuroendocrine tumor of the breast in one patient. The overall incidence of neuroendocrine tumors is increasing and the incidence of NETs diagnosed within the University Hospital "Dr. Georgi Stranski" - Pleven is higher than the average for the country.

Conclusion: Despite significant advances in modern medicine, the diagnosis NETs is made with a delay of 3 to 7 years after the first symptoms. Morphological verification done after primary surgery involves complex multidisciplinary behavior, including drug, interventional and surgical methods.

Abstract-ID: 323

A CASE OF MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

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Multiple endocrine neoplasia is a rare disorder, presenting as familial, but also as sporadic cases. It is caused by a germ-line tumor suppressor gene deffect.

We report a 62-year old woman diagnosed at the age of 52 with multiple parathyroid hyperplasia. The subject had no family history of endocrine disease. One year later a microprolactinoma and a right adrenal incidentaloma were found as well as a not-well defined pancreatic lesion that did not show on the contrast-enhanced CT. Five parathyroids were removed and prolactin levels were controlled with dopaminergic therapy. Follow up abdominal US did not reveal any change in the findings for 9 years. A CT done in December 2013 revealed a lesion 106/61/52 mm in the pancreatic head with signs of extrapancreatic involvment, a new lesion in left adrenal and multiple abdominal lymph nodes up to 45 mm in diameter. A SPECT-CT with 99mTc-Tectrotide demonstrated intense uptake of the radiomarker by the lesions in the pancreas, left adrenal and mesenteric lymph nodes. Immunohistochemistry of endoscopic gastric mucosal biopsy proved cellular hyperplasia and disseminated highly-differentiated neuroendocrine tumours (1 mm in diameter) in lamina propria staining for synaptophysin and chromogranin. Serum Chromogranin A was 683 ng/ml (<100), 5-hidroxyindolacetic acid - 448.48 mcmol/24h (13.1-52.6) and Gastrin - 23 748.0 pg/ml (<108).

Conclusion: The patient had a typical presentation of MEN1, posing however a therapeutic challenge due to the aggressive course of the gastrinoma.

POSTER CLINICAL CASE REPORTS

Abstract-ID: 58

MISDIAGNOSING OF CUSHING'S SYNDROME (CS)

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Introduction: We describe a case, that was originally considered as polycystic ovary syndrome (PCOS), in conjunction with neurological symptoms, and the patient was under the supervision of a neurologist. Later, as a result of thorough research she was diagnosed as ACTH-dependent CS.

Case Description: Our patient, 19 years old young girl, since 15, she has noted menstrual irregularities, weight gain and hirsutism. Patient was under the supervision of a neurologist because of frequent headache, high blood pressure, pain and weakness in the legs, difficulty in walking and climbing the stairs for myopathy. For a long time (3y) the patient took hormonal contraceptives, without any effect. Thereafter during an objective

examination, the patient was noted to have moon face, excess body weight, hirsutism and striae. In a laboratory tests, the level of cortisol was 953,26ng/ml(norm 50-250ng/ml), Progesterone-0.26ng/ml(norm 2-25ng/ml), LH-10.25ME/ml(0.8-10.5ME/ml), FSH-7.99ME/ml(3-12ME/ml), Estradiol-145.3pg/ml(70-250pg/ml), Testosterone-0.15pmol/ml(0.2-0.8pmol/ml), ACTH-69,7ng/ml(<50ng/ml). MRI showed the presence of pituitary microadenoma. The patient was diagnosed with ACTH-dependent CS, and recommended pituitary surgery. After TM surgery within 1 month there was a decrease in body weight, normalization of blood pressure and MC, pain in the legs and general weakness were also decreased. The diagnosis of myopathy was not confirmed.

Discussion: This case clearly demonstrates the widespread errors in diagnosis of CS. Our patient has come a long way from the time of the first symptoms of the disease before a correct diagnosis, being undergone of gynecological and neurological treatment.

Conclusion: Cushing's syndrome requires a more careful approach in the diagnosis and differential diagnosis.

Abstract-ID: 75

HYPEROSTOSIS FRONTALIS INTERNA IN A MAN WITH MACROPROLACTINOMA

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Hyperostosis frontalis interna is characterized by thickening of lamina interna of the frontal bone. It is considered a benign condition that causes compression and atrophy of the underlying brain structures and also headaches. Although the etiology of the condition is not clear, it has been related to some metabolic and hormonal disturbances. The frequency of hyperostosis frontalis interna is considered 12.5% and is usually found in post-menopausal women but rarely- in men (women: men ratio = 10 : 1). The relation with androgen deficiency has been discussed. Our case-report presents a 32 year old male that has a macroadenoma of the pituitary gland- with hyperprolactinemia and hypogonadism. Thickening of lamina interna of the frontal bone was described as an incidental finding on his MRT imaging.

Abstract-ID: 80

A CASE OF EXOGENOUS STEROID-INDUCED KAPOSI'S SARCOMA DEVELOPED AFTER CURE OF ENDOGENOUS HYPERCORTISOLISM.

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Kaposi's sarcoma is a malignant vascular tumor caused by human herpesvirus 8 (HHV-8) infection associated with immunosupression. Kaposi's sarcoma commonly has seen in acquired immunodeficiency syndrome (AIDS) patients. The occurrence of Kaposi's sarcoma associated with Cushinig's syndrome is rare. A few cases of Kaposi's sarcoma associated with the chronic use of systemic steroid have been reported, but Kaposi's sarcoma that was developed in endogenous Cushinig's syndrome is a rare case. The authors report a very unusual case of Kaposi's sarcoma associated with steroid replacement therapy after surgical treatment for Cushinig's syndrome caused by adrenal adenoma.

A 70-year-old man presented with a left adrenal mass. Cortisol-secreting adrenal adenoma was confirmed by the results of low and high dose dexamethasone suppression tests and serum ACTH level. The patient underwent laparoscopic left adrenalectomy. After surgery, his cortisol level was remarkably decreased. At discharge, he was prescribed oral prednisolone (15mg/day) to prevent adrenal insufficiency. Six weeks later, he presented to emergency department with symptoms of acute adrenal insufficiency such as hypotension, hypoglycemia and fever. He was treated with intravenous hydrocortisone, but swelling and numerous raised nonblanching purple plaques on lower extremities were newly detected. The biopsy findings in skin lesion were compatible with Kaposi's sarcoma, but anti-HIV antibodies were negative. As systemic steroid therapy was suspected to be the cause of Kaposi's sarcoma, steroid had been tapered. After withdrawal of steroid therapy, the skin lesions regressed completely leaving residual hyperpigmentation.

In conclusion, we describe a case of systemic corticosteroid therapy-induced Kaposi's sarcoma that was developed after cure of endogenous hypercortisolism. It is presumed that endogenous and exogenous steroids have different effects on the development of Kaposi's sarcoma.

Abstract-ID: 176

A CASE REPORT OF ACROMEGALY ASSOCIATED WITH PRIMARY ALDOSTERONISM

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We describe a patient with a rare combination of acromegaly and primary aldosteronism. A 37 year-old female patient was diagnosed with acromegaly on the basis of typical clinical, hormonal and image characteristics. She presented also with one of the most common co-morbidities – arterial hypertension. The patient has been regularly followed-up and after three surgical interventions, irradiation and adjuvant treatment with a dopamine agonist, acromegaly was finally controlled in 2008 (20 years after diagnosis). Arterial hypertension however, remained a therapeutic problem even after prescription of four antihypertensive drugs. She had normal biochemical parameters, except for low potassium levels 3.2 (3.5-5.6) mmol/l. This raised the suspicion of primary hyperaldosteronism, confirmed by a high aldosterone to plasma rennin activity ratio, high aldosterone level after a Captopril challenge test and visualization of a 35 mm left adrenal nodule on a CT scan. After an operation, the patient recovered from hypokalemia and antihypertensive therapy was reduced to a small dose of a Ca blocker. Co-morbid arterial hypertension is common in acromegaly, though it is rare for this to be caused by Conn's adenoma. The association of Conn's adenoma with acromegaly has been interpreted in two lines: as a component of multiple endocrine neoplasia type (MEN1) syndrome or as a direct mitogenic effect of hyperactivated GH-IGF1 axis.

Abstract-ID: 197

SHEEHAN SYNDROME: CLINICAL CASE

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Introduction: Sheehan syndrome is a rare complication of postpartum hemorrhage. Women with Sheehan syndrome have varying degrees of hypopituitarism, ranging from panhypopituitarism to only selective pituitary deficiencies.

Case presentation: A 29-years-old female presented to the hospital with complaints of marked weakness, dizziness, fatigue, loss of appetite, nausea, feeling of coldness, headaches, shortness of breath, cessation of periods after childbirth for the past 8 years, pain during intercourse, frequent urination and burning sensation when passing urine. The patient considers herself sick since 2001, after the childbirth as a result of her second pregnancy. She noted full term delivery, twins, unassisted home birth. Delivery was difficult, and assessment of bleeding degree is complicated. In the postpartum period she noted the absence of breast milk and periods, a progressive deterioration of health and the appearance of the above complaints. Physical examination was remarkable for temperature reduction, feeling severe weakness in the upright position, BP-70/50 mmHg, dense swelling of the feet and lower legs, absent of axillary hair, atrophic mammary glands. Laboratory findings demonstrated hypochromic anemia, hypoglycemia, low level of free thyroxine, LH, FSH, estradiol, urine free cortisol. Brain MRI shows empty sella. She was admitted with a Sheehan syndrome. Medical management consisted of hydrocortisone orally 30 mg/day, Thyroxine 50 mcg/day, estradiol+dydrogesterone (2mg +10mg) with significant improvement.

Discussion: Although Sheehan syndrome is uncommon in developed countries as a result of improved obstetric care, it is a frequent cause of hypopituitarism in the rest of the world. The clinical features of hypopituitarism are often subtle and years may pass before the diagnosis is made following the inciting delivery. History of postpartum hemorrhage, lactation failure and cessation of periods are important clues to the diagnosis. Early diagnosis and appropriate treatment are necessary to reduce the morbidity and mortality among obstetrical patients.

Abstract-ID: 212

ASSOCIATION OF ACROMEGALY AND COLITIS ULCEROSA: THE AFFECT OF OCT-LAR AS A FIRST LINE THERAPY

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INTRODUCTION: Acromegaly with colitis ulcerosa (CU) has not been reported in literature thus far. Ulcerative colitis is an inflammatory disease restricted to colon. Both diseases are characterized with risk of colorectal neoplasia. Somatostatin analogues (SSAs) administered in acromegaly patients who refuse/unsuitable for surgery, control GH/IGF-1 excess, induce tumor shrinkage, improve acromegaly symptoms. Long-acting somatostatin (Octreotide-LAR) ameliorate the inflammation in experimental colitis. The aim of this case is to evaluate the efficacy of Octreotide-LAR (OCT-LAR) vs surgery as a first line treatment.

CASE: 58-year-old woman with CU was referred to Endocrinology with suspicion of Acromegaly due to typical features, such as progressive thickening of hands and feet, uncontrolled diabetes and hypertension over 7 years. She was taking oral sulfasalazine and mesalazine, insulin, antihypertensive drugs. Blood pressure was 140/90 mmHg. Laboratory showed iron deficiency anemia (hemoglobin: 10.5 g/dL), elevated plasma levels of blood sugar (191 mg/dl), GH (8.14 ng/ml), IGF-I (562 ng/ml; normal 81-225). Serum PRL, fT4, TSH, basal cortisol levels were normal. Pituitary MRI indicated invasive cystic macroadenoma (15x15 mm). She did not accept surgery and OCT-LAR (30 mg, every 28 days) was initiated. Serum IGF-I was normal (91 ng/ml) by the 12th month of treatment. The tumour size decreased at the end of 12 months, disappeared at 24 months. Anemia recovered spontaneously. Insulin was converted to metformin, blood pressure decreased to normal. With OCT-LAR treatment, her shoe size decreased, bloody stool and diarrhea disappeared, she felt better. Colonoscopy didn't show inflammatory signs. Clinical improvement in both diseases was attained with OCT-LAR.

CONCLUSIONS: As a complete response to surgery in GH-secreting macroadenomas can be difficult, Octreotide-LAR can be considered as a primary therapy for acromegaly patients especially with comorbidities such as inflammatory bowel disease. SSAs might have beneficial effects on the inflammatory bowel disease, however, further studies are required.

Abstract-ID: 213

CANDIDA ESOPHAGITIS IN A PATIENT WITH CUSHING'S DISEASE: A RARE FINDING

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Introduction: Hypercortisolemia induces a state of immunocompromision that predisposes the patient to various bacterial, viral, fungal, and parasitic infections. In the literature, 42% of non-treated Cushing's patients develop opportunistic infections,but Candida oesophagitis is very rare. We hereby present a patient with Cushing's disease and Candida esophagitis.

Case: 36-year-old woman with symptoms of weight gain, hypertension and secondary amenorrhea was referred to Endocrinology for further investigation of hypercortisolemia. Her history was unremarkable until 3 years ago. Physical examination revealed typical Cushingoid habitus with congestive heart failure; hypertension(160/90mmHg),pretibial edema,truncal obesity, purplish abdominal striae, nuchal gibbus, acne and hyperpigmented macules on her back consistent with fungal infection.Laboratory revealed hyperglycemia (250 mg/dl), hypokalemia (2.5 mEq/l), iron deficiency anemia (Hb: 9 g/dl). Basal serum cortisol was high (49 µg/dl). After treating her heart failure and hypokalemia, failure of cortisol suppressions after 1 mg, 2 mg and 8 mg dexamethasone administrations (48 µg/dl, 29 µg/dl and 35 µg/dl, respectively) with high ACTH levels (133-160 pg/ml) were suggestive of ACTH dependent Cushing's syndrome. During the clinical course, hemoglobin level gradually decreased to 6 g/dl with symptoms of anemia. Two units of erythrocyte suspensions were transfused as a result of bleeding hemorrhoids. She also developed substernal odynophagia. Endoscopy revealed whitish plaques scattered throughout the esophageal mucosa consistent with Candida esophagitis. Colonoscopy was unremarkable other than internal hemoroids. Her symptoms improved immensely with oral Fluconazole 200 mg twice daily. Cortisol also decreased (29 µg/dl) with Flucanazole therapy. Sella MRI showed a lesion of 6 mm in the pituitary gland, and inferior petrosal sinus sampling was consistent with a pituitary adenoma.

Conclusion: When patients with endogenous hypercortisolism and a fungal skin infection develop dysphagia or substernal odynophagia, although rare, Candida esophagitis should be suspected. After endoscopic confirmation, prompt control of the fungal infection, as well as cortisol overproduction, should be initiated.

Abstract-ID: 217

SECONDARY AMENORRHOEA CAUSED BY HYDROCEPHALUS: A CASE REPORT

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Endocrine dysfunctions, among which amenorrhoea, although recognized for many years, are not common manifestations of chronic hydrocephalus. The patient was 27-year old woman admitted to our hospital in December 2010 for evaluation of secondary amenorrhoea. Reported menarche was at the age of 13, followed by regular periods next 12 years, oligomenorrheic periods next 2 years and absence of menstrual bleeding 6 months prior to admission. She complained of progressive headache and light dizziness, especially in the morning. Clinically, her BMI was within normal range and there were no signs of anosmia and galactorrhea. Endocrinological evaluation showed normal thyroid function, normal levels of cortisol, IGF-I, prolactin and androgens but low to normal estradiol, follicle stimulating hormone (FSH) and luteinizing hormone (LH). Magnetic resonance imaging (MRI) of endocranium revealed severe ventriculomegaly involving the lateral and third ventricles, cerebral aqueductal stenosis and herniation of third ventricle into sella. The visual field was normal and there were no signs of neurological deficit. In addition to clinical symptoms, findings on MRI scan fulfilled the criteria for diagnosis of long-standing overt ventriculomegaly in adults (LOVA). In March 2012 our patient underwent endoscopic third ventriculocisternostomy and 6 months later she experienced spontaneous menstruation followed by regular periods. Initial endocrinological evaluation 18 months after the surgery showed normal levels of previously low hormones – estradiol, FSH and LH. Further endocrinological testing is underway. To date, less than thirty cases of patients with hydrocephalus and amenorrhea, primary and secondary, have been published in the literature. This case and other reported indicate that surgical intervention for hydrocephalus resolves amenorrhea, presumed by the correction of increased intracranial pressure and restoration of LH pulsatility.

Abstract-ID: 261

PANCREATIC VIPOMA VISUALIZED BY GA-68 SOMATOSTATIN RECEPTOR PET/CT

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Introduction: Neuroendocrine tumors (NRTs) are considered a rare tumor entity, but the incidence has been increasing over the past years. Most NETs present somatostatin receptor (sstr) type 2 expression, which can be utilized for diagnostic or therapeutic purposes. Pancreatic NETs derive from hormone producing cells in the pancreas and can be divided into functional and non-functional tumors. VIP secreting NETs occur at a very low incidence of 1 per 10 millions. They can be found in pancreas, adrenals, neuroganglia, liver, colon or the lungs.

Aim: We report the case of a 74-year-old woman who presented with persistent watery diarrhea at our department of internal medicine in 12/2013. Medical history revealed DM II, osteoporosis, lactose intolerance and bioptically proven lymphocytic colitis. Weight loss of 16 kg had occurred in the course of past 6 months. Laboratory revealed marked hypokalemia, hyponatremia and hypercalcemia. Serum VIP was elevated 10 times at 682 pg/ml. As a NET was taken into consideration tumor screening was initiated. MRI showed enlarged lymph nodes (3cm) located between the pancreatic tail - where a small intra-parenchymal leasion was also suspected - and the spleen. F18-DOPA-PET/CT was definitely positive for the lymph node metastases, whereas the pancreatic lesion in question presented only scarce tracer uptake. Ga-68-DOTA-NOC clearly visualized the primary tumor in the pancreatic tail as well as the regional lymph node metastases. Operation took place in 3/2014, histology showed a G1 NET of the pancreas with regional lymph node metastases. After a final control examination in our hospital in 4/2014 our patient was in a good clinical condition and without diarrhea.

Conclusion: Ga-68 SSTR PET/CT can be helpful to detect (metastatic) VIPoma.

Abstract-ID: 326

COEXISTENCE OF ACROMEGALY AND END STAGE RENAL DİSEASE: WHICH PROCEDURE SHOULD BE THE FIRST? TRANSSHENOIDAL SURGERY OR RENAL TRANSPLANTATION?

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Introduction: Coexistence of acromegaly and end stage renal disease is rare in the literature. We herein present a 33 year-old female patient who has been newly initiated on a hemodialysis programme due to rapidly progressive crescentric glomerulonephritis and was referred to our endocrinology department with typical acromegalic features. In her detailed history, she experienced headache, increase in shoe size and oligomenorrhea for the last 6 months. Serum IGF-1 levels and 75-g oral glucose load results confirmed diagnosis of acromegaly. Sella MRI revealed 12x10 mm pituitary macroadenoma. Primary medical therapy with Lanreotid was preferred due to end stage renal disease and possible complications of transsphenoidal surgery. After six months of treatment with Lanreotid 60 mg (every four weeks) with no adverse events, a successful renal transplantation was performed from a living donor. Lanreotide dosage was gradually increased to 120 mg (every four weeks) as the renal functions recovered. One year after transplantation, transsphenoidal adenomectomy was performed due to persisting high serum IGF-1 levels and clinical findings. acromegaly clinic. Pathology revealed a pituitary adenoma with positive immun staining for GH and Prolactin. Three months later IGF-1 level was 386 ng/ml (NR: 107-246) and Lanretotide was planned 60 mg every four weeks.

Conclusion: GH hypersecretion causes increased glomerular filtration rate, glomerular hypertrophy and tubular defect which can exacerbate ongoing renal dysfunction. As there is a possibility of new onset diabetes insipidus after pituitary surgery which may result with tubular damage and further deterioration of renal functions, it may be a reasonable approach to treat renal disease before pituitary surgery.

Abstract-ID: 331

CASE OF A DIFFUSE FORM OF NESIDIOBLASTOSIS AND ADENOMA OF THE PANCREAS IN MIDDLE-AGE

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Case of a diffuse form of nesidioblastosis and adenoma of the pancreas in middle-age

Introduction: The most common reason for hypoglycemia among newborns is nesidioblastosis (1: 50 000). Whereas insulinoma is the most frequent cause among adults (3-10: 1 000 000) annually. We represent a rare case of diffuse form of nesidioblastosis combined with insulinoma in middle-aged woman.

Case report: 47 - year-old woman with BMI>30, was hospitalized in the University Hospital with complaints of neck pain, emotional lability, nervousness, episodes of palpitations, trembling, starvation. Sometimes loss of consciousness, with blood glucose levels- 1.7 to 2.4 mmol/L. Hypoglycemia is treated by glucose solutions. Clinical, laboratory and imaging diagnostics was conducted. An accent was put on biochemical and hormonal tests: 72- hours fasting test, plasma glucose profile for 24 – hours, immunoreactive insulin. Blood sugar level average 3.5 mmol / L and inadequate rates of insulin for those of blood sugar was indicated. CT and scintigraphy showed suspected for insulinoma formation with noradrenaline receptors in the body of the pancreas. Hemi pancreatectomy specimen was recived for pathologic evaluation. Result shows diffuse acinar cell hyperplasia with b-cell hypertrophy and atypism – islet cell tumor and a small insulinoma. Despite of the surgical treatment and standard conservative treatment with Diazoxide, hypoglycemia and complaints persisted. After discussion by the specialized committee - endorinologist , pathologist and abdominal surgeon, it is decided that the reason for hypoglycemia, despite the removal of insulinoma , is a diffuse form of nesidioblastosis.

Conclusion: In elderly patients who have no detectable insulinoma as a cause of hyperinsulinemic hypoglycemia, it is established diffuse form of nesidioblastosis as in newborns. The removal of 90% of the pancreas is the only alternative for the curative treatment of this disease.

Abstract-ID: 345

THREE CASES OF BRAIN TUMORS PRESENTING WITH PRECOCIOUS PUBERTY

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Precocious puberty is defined as the development of secondary sexual characteristics (breast/genital development Tanner stage II) before the age of 8 years for girls and 9 years for boys. It is shown to be secondary to an underlying condition in 10% of the girls and 90% of the boys. Among the known causes of precocious puberty are a variety of brain lesions. We report three patients with brain tumors in the area of the optic chiasm and central precocious puberty as a presenting feature who were all diagnosed in the last 4 years. In two of the patients (a 12 year old boy and a 14 years old girl) the precocious puberty was not recognized until headaches and visual disturbances prompted investigations at 12 years and 10 years respectively. The third patient, a boy, was diagnosed with precocious puberty at the age of 6, but no further investigations were made until 6 months later, when supratentorial tumor was found on MRI. Two of the patients had optic nerve glioma (pilocytic astrocytoma) and underwent

partial tumor resection. The third patient was suspected of having germinoma and was planned for surgical treatment. This case series underlines the importance of not neglecting central precocious puberty, especially in boys, as a presenting sign of tumors in the hypothalamo-pituitary region and the required full investigation from the start.

Abstract-ID: 358

A CASE OF FAMILIAL MEDULLARY CARCINOMA OF THE THYROID

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The medullary carcinoma of the thyroid (MCT) is a parafollicular cell tumor, more aggressive than other thyroid carcinomas; extending locally or invading lymph nodes and blood vessels, with lung, liver, and other metastases. Eighty percent of MCT cases are sporadic and 20% are familial. The familial syndromes are associated with *RET* protooncogene mutations, most commonly in exons 10,11 and 16. We describe the case of a 24-years-old man and his 18-years-old sister with positive familial history for MEN2A and thyroid carcinomas. Their father had been diagnosed with MEN2A- MTC and pheochromocytoma, positive for a Cys634-Tyr (exon11) *RET* protooncogene mutation. Their grandmother had been operated for thyroid carcinoma in the 80's and had died at the age of 69. Their uncle had been diagnosed with thyroid carcinoma considered as unresectable because of local invasion with pulmonary and bone metastases; he had died at the age of 49. In the male patient thyroid ultrasound found a 4/4/5mm hypoechoic nodule in the right lobe with a calcification. The lab tests revealed an elevated calcitonin level - 4.4 pmol/l (<1.4 pmol/l) and a *RET* protooncogene mutation - p.Cys634Tyr (exon11). The FNA biopsy revealed a colloid nodule. The patient was referred for surgery and total thyroidectomy was performed. In the female patient thyroid ultrasound described a 3/6/7mm hypoechoic nodule in the right lobe. Elevetated serum calcitonin was found - 6.4 pmol/l as well as the same *RET* protooncogene mutation. The FNA biopsy revealed parafollicular cell hyperplasia. Near total thyroidectomy was performed. In both patients the histological diagnosis confirmed the presence of MCT. The screening tests for other endocrine disturbances with regards of MEN 2A were negative in both patients. This case report underlines the importance of a complex endocrinological investigation in case of familial thyroid nodules and carcinomas or rare endocrine tumors.

Abstract-ID: 450

CASE REPORT: LONG-TERM BIOCHEMICAL CONTROL OF ACROMEGALY WITH PASIREOTIDE

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Introduction: Acromegaly is a disease caused by growth hormone excess mostly due to a pituitary adenoma. In spite of progress in surgical and pharmacological management, it is still difficult to achieve biochemical remission in a significant proportion of patients. We report here a 35 year old patient with gigantism and acromegaly in whom multi-modal therapy failed and therapy with pasireotide was begun in 2004. Thus, he has received pasireotide for 10 years now, the longest time span of pasireotide treatment in acromegalic patients reported to date.

Methods: The patient was diagnosed with pituitary gigantism in 1997 (at age 19) and surgery performed the same year. Due to persisting growth hormone excess radiotherapy with Gamma knife was done in 1999, but to no avail. A macroadenoma extending to the parasellar region on the left side still persists to this day. Medical treatment with octreotide did not achieve biochemical control. Therapy with pasireotide s.c. was initiated in July 2004 within the phase II clinical trial CSOM230B2201 and switched to pasireotide LAR in August 2006 (CSOM230C2110).

Results: Before start of pasireotide the patient's IGF-I levels were approximately twofold elevated under treatment with octreotide. As of start of therapy with pasireotide IGF-I levels have significantly dropped and have further decreased after start of pasireotide LAR below the upper limit of normal (ULN) and remained there stably throughout the study.

Baseline GH levels were > 5 ng/ml before therapy and decreased to values between 2-4 ng/ml after start of pasireotide s.c. and further decreased to values 1-2 ng/ml soon after pasireotide LAR was started and have remained at this level ever since. An impaired fasting glucose with HbA1c of 6.2% prior to therapy remained stable. However, as of late 2007 fasting glucose increased and in 2008 antidiabetic therapy was started with repaglinide and sitagliptine added in late 2011. In 2013 the patient discontinued repaglinide therapy which resulted in a slight increase in HbA1c. Throughout the study no changes on sellar imaging were detected.

Conclusion: Pasireotide LAR is an effective drug in the treatment of acromegaly, especially in patients in whom other treatment options including octreotide/lanreotide fail. Biochemical control of the disease can be sustained over a long period of time with pasireotide.

Abstract-ID: 460

METASTSIS FROM RENAL CELL CARCINOMA TO THE PITUITARY GLAND

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Metastases to the pituitary gland are an uncommon complication of malignancy. Pituitary metastasis from renal cell carcinoma is unusual medical condition. Herein, we present a 68-years old, male patient with a history of renal cell carcinoma with progressive visual disturbance. Endocrinological examination revealed normal pituitary function without diabetes insipidus. Computed tomography and magnetic resonance imaging showed an intrasellar mass with parasellar extension. The initial radiological diagnosis was invasive pituitary macroadenoma. The tumor was decompressed via the transsphenoidal route followed by Cyberknife therapy with visual impovement. Histological examination revealed metastatic renal cell carcinoma. Combined treatment using decompressive surgery and stereotactic radiotherapy may result in better outcomes. Our case illustrates that metastatic pituitary lesions can mimic typical symptoms of pituitary macroadenoma and moreover diabetes insipidus, a common sign of pituitary metastases, can be absent.

Abstract-ID: 489

CASE PRESENTATION OF ANTIBIOTIC-RESPONSIVE HYPOPHISITIS

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A 24-year old woman experienced a sudden onset of acute headache irradiating to the brows, eyes, worsening during walking and changing body position. NSAIDs and spasmolytics did not offer any substantial relief. MRI showed an enlargement of the *sellar turcica*; enlargement of the pituitary gland with suprasellar extension with additional inhomogeneous mass 12.5*15.7*19.3 mm; well-defined neurohypophisis; enlarged, shortened and deviated left pituitary stalk; partially compromised optic chiasm. A week before the symptom's onset the patient recalls purulent nasal discharge without hyperthermia. Hormonal analysis did not show any disturbances: TSH – 1.9 mcU/ml (0.4-4.0), fT4 – 15.9 nmol/k (10-24), PRL – 630 mIU/ml (67-726), FSH – 3.6 mIU/l (1.8-11.3), Lh 8.6 mIU/l (1.5-14.4), GH – 21.8 mIU/l (<10), IGF-1- 216 hg/ml (142-250), GH during OGTT – less than 0.3 mIu/l. Ophthalmology examination - no visual fields abnormalities, venous stasis of the optic

discs. The patient was treated with celecoxib 200 mg twice a day and moxifloxacin 100 mg once a day for 7 days with complete resolution of symptoms occurred on the third day of this treatment. MRI at 6 and 12 months from the resolution of symptoms showed nearly normal pituitary appearance with dimensions of 7*18*12 mm, normal pituitary stalk, 4*8*6 mm hypointense zone on T2 and mildly hyperintense on T1-weighted images, with decreased contrast enhancement (residual structures of Rathke's pouch). Thus, this case was regarded as a possible spread of the bacterial infection from the nasal cavity to the pituitary with consequent inflammation and subsequent resolution after antibacterial treatment.

Abstract-ID: 520

A CASE OF SUCCESSFUL PREGNANCY IN AN ACTIVE ACROMEGALIC PATIENT

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Pregnancy is rather rare in acromegaly because of hyperandrogenemia, hyperprolactinemia and impairment of gonadotropin-secretion due to tumor mass effect. Few data are available on pregnancy outcomes in women with acromegaly.

Here, we report a case of successful pregnancy in an active acromegalic patient who was underwent to surgery and on octreotide LAR treatment with stable residual tumor.

A 36-year-old female patient presented with headache and enlargement of hands and feet. She was examined for suspected acromegaly. Her mean basal GH level was 34.7ng/ mL, and decreased to 20.8ng/mL during an oral glucose tolerance test with elevated IGF-1 levels (838ng/mL). Pituitary magnetic resonance imaging (MRI) reported an adenoma measuring 10 mm in diameter on left lateral pituitary gland.

The patient underwent adenomectomy by the transsphenoidal approach with the diagnosis of acromegaly. After surgery basal GH and IGF-1 levels remained elevated 6 ng/mL and 250 ng/mL, respectively. Thus, octreotide LAR was started at an initial dose of 20 mg every 28 days.

After 3 months therapy basal levels of GH and IGF-1 decreased to 5 ng/mL and 250 ng/mL, respectively, and ovulatory menstrual cycles resumed. Tumor size was 5x2 mm on MRI.

Twelve months later, octreotide was discontinued due to pregnancy, and octreotide LAR was withdrawn at 4 weeks of pregnancy. GH was 6.93ng/mL and IGF-1 579 ng/mL. Although GH and an IGF-I were slightly above to the normal levels, she remained asymptomatic during pregnancy. Likewise, pregnancy period was uneventful and the patient remained without arterial hypertension or glucose abnormalities.

Normal vaginal delivery took place at 41 weeks. The newborn was healthy with normal weight and length. Four weeks after delivery GH and IGF-1 levels were 6.6 and 837 ng/mL respectively. Repeated MRI after delivery showed no increase in residual adenoma.

We present a case of uneventful pregnancy in an active acromegalic patient who was undergone to surgery and on octreotide LAR treatment.

Abstract-ID: 540

ACROMEGALY WITH NO PITUITARY ADENOMA AND NO EVIDENCE OF ECTOPIC SOURCE: A CASE REPORT

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Introduction: Growth hormone (GH) secreting pituitary adenomas are the cause of acromegaly in over 99% of patients. Most of these tumors are large and almost always visible on sellar magnetic resonance imaging (MRI). Acromegaly secondary to a very small pituitary microadenoma not visualized on pituitary MRI is rare.

Case Report: 69 year-old woman, with a past history of hypertension, type 2 diabetes *mellitus*, mixed dyslipidemia and obstructive sleep apnea syndrome. She was referred to the Endocrinology outpatient department due to generalized and disabling arthralgias, headache and poorly controlled diabetes. On examination, the blood pressure was 130/70mmHg and she had frontal bony prominence and acral enlargement. Laboratory tests suggested acromegaly (GH 1,48ng/mL, insulin-like growth factor 1 – IGF-1 – 461ng/mL), which was confirmed by the oral glucose tolerance test. Prolactin and the other pituitary axis were normal. Sellar MRIs (with a 3.0 T magnet) did not reveal a pituitary lesion. To rule out an ectopic source of GH or growth hormone releasing hormone, a body computed tomography and an octreoscan were perfomed, but no tumour was detected. The echocardiogram was normal, the abdominal ultrasound revealed liver steatosis and the colonoscopy showed sigmoid diverticulosis and a sigmoid polyp, which was excised. Once the thyroid gland appeared to be enlarged and had a nodular consistency on palpation, a thyroid ultrasound was performed and confirmed its enlargement and the presence of multiple nodules, the biggest one with 18mm (histology: colloid goiter). The patient started treatment with a long-acting somatostatin analog once a month, with IGF-1 normalization. Four years later, she is biochemically controlled and without therapy adverse effects. The tumour remains undetected.

Conclusion: This case report suggests that acromegaly complications not related to pituitary stalk and optic chiasm compression are independent of the tumour size. Actually, though the tumour remains undetected, our patient presents multiple co morbidities related to the disease. Currently, there is no consensus for the treatment of patients with acromegaly and negative pituitary imaging. Although in other series surgical exploration identified microadenomas not diagnosed on MRI, medical treatment remains an option and it is less invasive and achieves a good biochemical control, as it is illustrated by our case report.

Abstract-ID: 551

A CASE OF ACROMEGALY: SEEING BEYOND THE OBVIOUS

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Introduction: Acromegaly is a rare chronic disorder due to growth hormone (GH) hypersecretion and elevated levels of insulin-like growth factor-1 (IGF-1). An early diagnosis is crucial to prevent the complications and morbidity of the disease.

Case Report: A 40 year old woman was referred to the Endocrinology outpatient department due to obesity (BMC 40, 4 kg/m^2). She also had mixed dyslipidemia and impaired glucose tolerance, for which she was being treated with metformin and simvastatin, and a history of headaches, which had become more frequent and intense in the last months. She was taking multiple painkillers for the headaches with weak improvement. In her medical history we can highlight a tonsillectomy for tonsillar hypertrophy four years before and a surgery to a carpal tunnel syndrome of the right hand three years before. On examination, she had a normal blood pressure and did not have clinical features of any endocrinopathy.

Laboratory tests, including pituitary axis evaluation, and a MRI were ordered. The results were suggestive of acromegaly (GH 3, 81 ng/mL, IGF-1 898 ng/mL), which was confirmed by the oral glucose tolerance test. Prolactin was also elevated (73, 1 ng/mL) and there was no evidence of hypopituitarism. The MRI showed a sellar macroadenoma (13, 9mm x 8, 5mm x 12, 1mm) with necrosis of the central nucleus. No deviation, invasion, or compression of the surrounding structures was detected. An echocardiogram was performed, which was normal, and the patient refused colonoscopy. She was medicated with octreotide 20 mg once a month and she was proposed to surgery. Before the surgery and after 3 injections of octreotide there was a significant decrease of IGF-1 (378 ng/ml) and normalization of prolactin. A transsphenoidal excision of the pituitary mass was made, which was complicated by the development of insipid diabetes. After the surgery she was medicated with nasal desmopressin and prednisolone 5 mg and keeps the monthly somatostatin analogue injection. There was total resolution of the headaches and normalization of glucose metabolism. Four months after the surgery the IGF-1 value is normal (248 ng/mL) as well as GH (1, 32 ng/mL) and the patient lost 5 Kilograms.

Conclusion: This case aims to illustrate that the diagnosis of acromegaly can be a challenge, especially when suggestive physical features are not evident. Acromegaly should be considered as a differential diagnosis when several clinical problems that could be explained by this disease coexist.

POSTER CLINICAL ADRENAL

Abstract-ID: 72

"THE FREQUENCY OF ARTERIAL HYPERTENSION IN CHILDREN AND TEENAGERS WITH HYPERCORTICOIDISM ON THE BASE OF RETROSPECTIVE ANALYSIS"

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Aim – to study the frequency of arterial hypertension in children and teenagers with hypercorticoidism on the base of retrospective analysis

Material and methods: We evaluated retrospective data of 39 children and teenagers with hypercorticoidism, which were treated in 3 departments (pediatric, neuroendocrinology and endocrine surgery) of the Center of Endocrinology during 1999 - 2011 years. The average age of boys (19 patients) was 16,05, girls (20 patients) 16,15 years. Control group constituted by 20 healthy children and teenagers with same average age.

All patients were evaluated for hormones levels (ACTH, GH, LH, FSH, testosterone, prolactin, cortisole, free thyroxine, etc.), visual fields, pituitary MRI, CT of adrenals, etc.

Results and discussion: We established, that among patients with hypercorticoidism more often found cases of Cushing Disease (CD) – 26 (66,6%), but others more rare: Cushing syndrome (CS)– 4 (10,2%), yuvenile dispituitarism (YD) – 7 (17,9%), obesity with disorder of ACTH/cortisol rhythm secretion – 1 (2,5%), and yatrogenic hypercorticoidism - 1 (2,5%).

Among patients with CS 1 patient has corticosteroma, 3 patients have adrenal hyperplasia. The average ACTH level was 34,4 pg\ml, cortisole 1156 nmol/l.

There are 15 patients from 39 have arterial hypertension (38,5%): 6 patients with CD, 4 – with CS, 5 – with YD.

Conclusions. 1) There are 39 children and teenagers with hypercorticoidism were treated in 3 departments during 1999-2011 years; 2) There are 15 patients from 39 chldren and teenagers with hypercorticoidism have arterial hypertension (38,5%): 6 patients with CD, 4 – with CS, 5 – with YD.

Abstract-ID: 195

AN ADRENOLEUKODYSTROPHY PATIENT WITH ADULT ONSET ADRENAL INSUFFICIENCY

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X- linked adrenoleukodystrophy (X-ALD) is a peroxisomal neurodegenerative disorder with a very broad clinical spectrum ranging from the most severe chidhood cerebral form to late-onset adrenomyeloneuropathy. Approximately 50 % of patients with the genetic defect of X-ALD develop the inflammatory cerebral form at some time in their life. Virtually all males develop some type of neurological abnormality during their life span. 20 % of male X-ALD patients have primary adrenocortical insufficiency without clinical or MRI evidence of neurological involvement. Such patients are classified as ''Addison only'' phenotype of X-ALD. These patients are are identified by screening patients with plasma saturated very long chain fatty acids (VLCFA). 23 years old male patient was admitted to emergency unit with symptoms of fatigue, vertigo, nausea, vomiting which were continuing more than two months. He was diagnosed as X-ALD 7 years ago, but he was not treated. There was also darkening of the skin especially over the lips in the last five years. Physical examination revealed hypotension, tachycardia,hyperpigmentation of the skin, buccal mucosa and gingiva. Low sodium levels and low cortisol levels were discovered during ACTH stimulation test. His clinical status recovered immediately with metilprednisolone treatment. It can be concluded that some X-ALD patients can have adrenal insufficiency symptoms without neurological findings in adulthood. Careful monitoring and appropriate adrenal hormone replacement therapy can prevent morbidity and mortality associated with overt adrenal insufficiency.

Abstract-ID: 236

CHARACTERISTICS OF CARBOHYDRATE DISTURBANCES IN PATIENTS WITH CUSHING'S DISEASE AND CORTICOSTEROMAS

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The important implications of glucocorticoids in intermediary metabolism is a well established fact, but the data concerning characteristics of carbohydrate disturbances in different forms of Cushing's syndrome vary among studies. Our aim was to characterize the carbohydrate disturbances in the two main forms of the syndrome – Cushing's disease and corticosteromas.

Materials and methods: A retrospective study was performed on 357 patients - 256 with Cushing's disease (mean age 35.21±10.99 ys) and 101 with corticosteromas (mean age 37.77±12.20 ys). In addition, 30 patients with Cushing's disease and 14 with corticosteromas, and 55 healthy volunteers were included in a case-controlled study. Body mass index (BMI), glucose and insulin during an oral glucose tolerance test (oGTT), and HbA_{1c} were analyzed.

RESULTS: IN THE RETROSPECTIVE STUDY DIABETES WAS OBSERVED IN 36.7% OF PATIENTS WITH CUSHING'S DISEASE AND IN 27.8% OF THOSE WITH CORTICOSTEROMAS, AND IMPAIRED GLUCOSE TOLERANCE IN 16.0% AND 15.8%, RESPECTIVELY, THE DIFFERENCES BEING NON-SIGNIFICANT. IN THE PATIENTS WITH CUSHING'S DISEASE AS COMPARED TO THOSE WITH CORTICOSTEROMAS THE DISEASE DURATION WAS LONGER (4.98±4.35 VS. 2.68±2.99 YS, P<0.001), AND BOTH BODY WEIGHT AND BMI WERE HIGHER (83.00±17.19 VS. 78.22±17.34 KG, P<0.05, RESPECTIVELY 31.74±6.05 VS. 29.74±6.75 KG/M^2, P<0.001). IN THE PROSPECTIVE STUDY FASTING GLUCOSE AND HBA_{1C} DID NOT DIFFER SIGNIFICANTLY BETWEEN PATIENTS WITH BOTH FORMS OF CUSHING'S SYNDROME AND HEALTHY VOLUNTEERS BUT ALL OTHER PARAMETERS OF GLUCOSE AND INSULIN DURING THE OGTT WERE SIGNIFICANTLY HIGHER IN THE PATIENTS. NO CORRELATION BETWEEN PLASMA CORTISOL AND INSULIN LEVELS WAS FOUND. THE DURATION OF THE DISEASE CORRELATED POSITIVELY WITH THE AUC_{INS}. CARBOHYDRATE DISTURBANCES WERE NOT ASSOCIATED WITH FAMILY HISTORY OF DIABETES IN BOTH FORMS OF THE SYNDROME.

Conclusion: We found similar metabolic complications in Cushing's disease and corticosteromas but in the latter some physiological regulatory interrelationships were still preserved due mainly to the shorter duration of the disease.

Abstract-ID: 249

SUBCLINICAL PHAEOCHROMOCYTOMA: THE SURGEONS POINT OF VIEW – A SINGLE-INSTITUTION EXPERIENCE.

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BACKGROUND: Phaeochromocytoma is a rare neuroendocrine tumor. Autopsy studies indicate that relatively large numbers of these tumors remain undiagnosed during life. This may reflect non-specific signs and symptoms and low medical alertness or it may reflect a silent clinical presentation of the subclinical phaeochromocytoma. We report our institution experience with silent phaeochromocytomas - their preoperative characteristics, intraoperative management and postoperative complications.

MATERIAL AND METHODS: A total of 104 patients underwent operation

for phaeochromocytoma between 1980 and 2010 in our department. Eleven of them had no clinical symptoms. We describe and analyze retrospectively: criteria for diagnosis and surgery, length of hospital stay, intra and postoperative complications.

RESULTS: In total, 11 of the 104 patent operated in our department had no clinical symptoms. From the classical triad (headache, palpitation and diaphoresis) only five of those patients had occasional palpitation when they felt severe anger, which is rather unspecific. When we analyzed the data of these patients we found a longer operative time (p = 0.04), more intraoperative complications (p = 0.02), higher estimated blood loss and larger transfusion requirement. Postoperative complications however showed no statistical significance.

Conclusion: Phaeochromocytoma can have variable presentation. Patients with silent pheochromocytoma scheduled for surgery should be closely evaluated and medically treated preoperatively to ensure an excellent outcome.

Key Words: subclinical pheochromocytoma, intraoperative management, postoperative complications

Abstract-ID: 328

ADRENAL MEDULLA RESPONSE TO PHYSICAL EXERTION IN PATIENTS WITH PRIMARY ADRENAL FAILURE

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Many patients with primary adrenal insufficiency (Addison's disease) take extra doses of hydrocortisone in response to physical and psychological stress, but the effect of such stress-doses have never been studied under controlled conditions. In this double blind cross-over trial we tested the effect of an extra dose of hydrocortisone(HC) on cardiorespiratory parameters and levels of catecholamines and glucose in response to a maximal incremental exercise test determining the maximal aerobic capacity ($V0_2$max). Two hours after morning medication 10 women with AD and 10 healthy female controls matched for age and body fat were included and assigned to receive either an additional 10 mg of hydrocortisone (HC) or placebo (P) one hour prior to testing. The normal exercise-induced increase in cortisol was not observed in AD patients, but levels of cortisol increased 2-3 fold after extra dose of HC. V02max and duration of exercise were significantly lower in women with AD, and did not improve by stress-dosed HC. Fasting and exercise-induced blood glucose, growth hormone, insulin, lactate and free fatty acids did not differ between AD women and controls. NA response to exercise was also similar, but the A response was significantly different and flattened in patients. We conclude that women with AD had reduced physical capacity and did not benefit from additional HC during high-intensity exercise. Stress dosing in this setting does not seem to be justified.

Abstract-ID: 537

SALIVARY VS. SERUM CORTISOL IN ACTH TEST

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Salivary cortisol constitutes a free fraction of serum cortisol. Monitoring salivary cortisol may be a promising alternative method for assessing serum cortisol levels in some clinical situations. We aimed to compare the reliability of measuring salivary vs. serum cortisol to assess ACTH levels. 84 subjects with clinical suspicion of adrenocortical insufficiency underwent an ACTH test. Patients were divided into two groups, based on peak serum cortisol. The reference group had a peak serum cortisol over 500 nmo/l (n=76; mean age 64; 60 males, 16 females). The hypocortical group had an abnormal response with peak serum cortisol ≤ 500 nmol/l (n=8; mean age 61.4; 6 males, 2 females). A dose of 250 mcg of tetracosactide was administered intravenously. Blood and saliva samples were taken prior to administrating the dose, and then again at 30 and 60 minutes after. Median serum cortisol in the reference group was 445; 766 and 902 nmo/L at 0, 30 and 60 minutes, respectively. In the hypocortical group, median serum cortisol was 256; 394 and 453 nmol/L at 0, 30 and 60 minutes, respectively. Median salivary cortisol levels were 19.02, 40.02 and 62.1 nmol/L in the reference group, and 9.60, 14.08 and 13.28 nmol/L in the hypocortical group. These results suggest good correlation between serum and salivary cortisol concentrations during the ACTH test (r= 0,773, n=272, p<0.0001). The percentage of variability as an expression of discriminating power, explained by the repeated measures ANOVA model, was significantly (p=0.021) higher for serum cortisol (R^2=93.4%) compared to salivary cortisol (R^2=89.3%). Our findings show good correlation between salivary and serum cortisol concentrations during the ACTH test. Statistical analysis showed a stronger discriminating power of serum cortisol, with a higher percentage of variability for serum compared to salivary cortisol. Our findings provide evidence that serum cortisol in compare to the salivary cortisol is slightly, but statistically significantly more appropriate marker of adrenocortical reserve in ACTH test. The study was supported by grant No. NT 11277-6 of IGA MZC

POSTER BASIC METABOLISM

Abstract-ID: 230

TARGETING THE GLUCOCORTICOID RECEPTOR TO PREVENT DIET INDUCED OBESITY

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Background: Excessive glucocorticoids are associated with the metabolic syndrome, as is evidenced by the extreme case of Cushing's disease. Accordingly, antagonism of the glucocorticoid receptor (GR) by means of mifepristone (RU486) markedly lowers obesity in men and mice. However, RU486 also shows affinity for the progesterone receptor. Therefore, various selective GR modulators were developed, which have both antagonistic and agonistic effects on the GR. This study aims to unravel metabolic effects of GR modulation in mice.

Methods and results: 10-week old C57Bl/6J mice were fed a high fat diet for 3 weeks and treated with the selective GR modulators Cort 118335 (C118), Cort 108297 (C108), dexamethasone (Dex, a classic GR agonist), RU486 (a classic GR antagonist) or vehicle. All compounds reduced body weight gain and fat mass, accompanied by increased fat oxidation (up to +20% by C108) as measured by fully automated metabolic cages. Lean mass was also reduced by Dex (-13%), and to a lesser extent by C118 (-8.5%), C108 (-7.9%), and RU486 (-3.7%). Thymus weight was strongly reduced by Dex (-77%) and C108 (-71%) with more modest inhibition by RU (-48%) and C118 (-46%). C108, but not the other compounds, increased plasma free fatty acid levels. RU486 and C118 improved glucose tolerance tested via ivGTT and lowered basal plasma glucose levels. Dex increased brown adipose tissue (BAT) weight and increased uptake of radioactive labelled triglyceride particles in BAT.

Conclusion: GR modulation results in reduction of diet-induced obesity development and improved glucose metabolism. Further studies should elucidate the underlying mechanisms. Selective modulation of the GR

results in tissue-specific agonism or antagonism and may be a promising target for combating obesity and related disorders.

Abstract-ID: 316

ACROMEGALY TREATMENT AND CARBOHYDRATE METABOLISM DISTURBANCES

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Background: In acromegaly, carbohydrate metabolism disorders (CMD) are frequently observed. We aimed to assess the differences in insulin secretion and sensitivity depending on stage of acromegaly and type of treatment.

Design: 85 patients with acromegaly (59 women; age 55 [interquartile range, IQR 47-60] yrs); 44 were newly-diagnosed (NA group), 22 treated with somatostatin analogues (SSA group) and 19 after transsphenoïdal surgery (TSS group). All underwent an OGTT, with measurement of plasma insulin and blood glucose in the fasting state and every 30 minutes for 2 hours after oral administration of 75 g glucose. CMD (impaired glucose tolerance, impaired fasting glucose, diabetes mellitus) were diagnosed according to WHO recommendations. We used the Matsuda index and HOMA-IR to estimate insulin sensitivity.

Results: Mean age (50-54.5 yrs) and mean BMI (29.1-29.9 kg/m2) were comparable between the 3 groups. Z-score IGF1 was similar between the SSA and TSS groups (3.2 [2.3-3.9] vs. and 3.5 [2.7-6.4]), but severely elevated in NA patients (p=0.0001). In the SSA group, prevalence of CMD was 86%, whereas it was 59% in the NA group and 37% in TSS group. NA patients were mainly insulin-resistant, with high fasting plasma insulin (FPI) (91 [51-192] pmol/l, high HOMA-IR (3.6 [1.7-7.8]) and low Matsuda index 7.1[2.7-9.1]. TSS patients had normal FPI (66 [IQR 25-98] pmol/l), and normal HOMA-IR and Matsuda index for their BMI, while SSA patients were mainly insulin-deficient, with FPI 23 (14-63) pmol/l, decline of the first phase of insulin secretion, HOMA-IR 1.3 (0.6-2.9) and Matsuda index 7.1 (2.7-10.1).

Conclusion: Hyperinsulinaemia compensates the high level of insulin resistance in NA patients. In SSA patients, suppression of insulin secretion, particularly its first phase, leads to increasing of percentage of DM patients in this group. After TSS, insulin resistance decreases and insulin secretion is restored, that leads to normalization of carbohydrate metabolism.

Abstract-ID: 408

EFFECT OF THE COMBINED PHARMACOTHERAPY WITH ALPHA- LIPOIC ACID AND BENFOTIAMIN, PYRIDOXINE AND CYANCOBALAMINE ON THE POSTURAL STABILITY OF PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHY

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Background: Diabetic peripheral neuropathy (DPN) is one of the most common complications which occurs in 50-70% of patients with Type 2 diabetes mellitus and . The disease usually affects peripheral nerves and leads to the tingling, pain, loss of sensation in the legs and postural instability. There are researches about the effect of Alpha- Llipoic Acid (ALA) on the reduction of pain and improvement of neuropathic deficits.

Patients and Methods: Sixty patients with good glycaemic control took part in this investigation. The two schemes of treatment were applied: the first- with 600 mg ALA and the second – combined therapy (ALA, benfotiamin, pyridoxine and cyancobalamine together). The postural stability was evaluated using static posturography under two visual conditions (eyes open and eyes closed) on stable and soft surfaces. The investigations were made on the first and 60th day after the drug therapy.

Results: No patient under therapy with deterioration. Improvements of mean sway velocities during stance with closed eyes on two supports for two therapeutic treatments were observed. The best effect was observed for decreasing the amplitudes of postural sways during stance on stable support with open eyes. The patients with combined therapy showed considerably better improvements than patients group treated with ALA only.

Conclusion: Treatment with combined therapy (ALA, benfotiamin, pyridoxine and cyancobalamine together) showed stabilizing effect on the quiet upright stance, that leads to improvement of the quality of life of patients with type 2 DPN.

Keywords: Alpha- Llipoic Acid, Diabetic peripheral neuropathy, Postural sway, Static posturography

Abstract-ID: 469

THE "HUNGER HORMONE" GHRELIN AND ITS MODULATORY EFFECT ON URINARY BLADDER

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Ghrelin is a 28 amino acid hunger-stimulating peptide hormone that is produced mainly by P/D cells lining the fundus of the human stomach and epsilin cells of the pancreas. Ghrelin levels have been found to increase in children with anorexia nervosa and decrease in children who are obese, suggesting that ghrelin is a good marker of nutritional status. It is shown that before eating ghrelin levels go up highly, which signals hunger to the brain. For about three hours after the meal ghrelin levels go down. Ghrelin is unique for its post-translational modification of O-n-octanoylation at serine 3 through the enzyme ghrelin O-acyltransferase, which enables ghrelin to activate the ghrelin receptor. The unique ghrelin system may be the most important player compared to the other hindgut hormones participating in the "entero-insular axis". The effects of the peptide ghrelin on various organs and systems are not well established however it is known that it affects the performance of smooth muscle. The aim of the present study was to investigate the influence of ghrelin alone as in combination with angiotensin II (Ang II) on the contractile activity of urinary bladder smooth muscle strips from rat detrusor. The receptors for ghrelin described in the literature are associated with activation of phospholipase C and increase in intracellular calcium. Therefore, the application of ghrelin on muscle strips of urinary bladder would lead to the occurrence of tonic contractions. We found no statistically significant changes in contractile activity after application of ghrelin alone as compared to the spontaneous activity. The effects of ghrelin were displayed when it was applied in combination with other peptides. For example, 30 min after ghrelin application, the administration of Ang II did not lead to the typical tonic contractions occurring when only Ang II was administrated. The amplitude of the Ang II stimulated contractions was reduced from 1.90 ± 0.20 g to 0.78 ± 0.09 g in the presence of ghrelin ($n = 21$, $P < 0.05$). Based on these results we can assume that the urinary bladder possesses receptors for ghrelin, which are different from those in the digestive tract, with respect to the kind of intracellular signalling mechanism to which they are coupled.

Abstract-ID: 495

GINGIVAL STIMULATION: AN IMPORTANT METABOLIC REGULATOR?

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Objective: The aim of this study was to determine if there was a relationship between tooth brushing and the levels of leptin, ghrelin, insulin and glucose, which are important participants of energy homeostasis.

Materials and Methods: The present study included 15 male subjects with

a mean age of 23-31 years, who were final year medical students or research assistants at Ondokuz Mayis University Faculty of Medicine. The participants did not have any systemic diseases, smoke, and receive periodontal treatment during the previous six months. They brushed their teeth regularly and had a BMI of 19- 29 kg/m^2. Blood samples were taken from the subjects, who did not brush their teeth for one day, after 12-hour long overnight fasting, and before standard breakfast 0, and at 30-60-120-180 minutes after breakfast. After tooth brushing following dinner and a 12-hour long overnight fasting, blood sample were taken before standard breakfast 0 and after following tooth brushing without using toothpaste, at 30-60-120-180 minutes. Ghrelin, leptin, glucose, and insulin levels were measured from the blood samples.

Results: A significant reduction was found in all leptin levels measured at 0, 30, 60, 120, and 180 minutes after tooth brushing ($p < 0.05$). The ghrelin levels also declined at these time points. There was a statistically significant reduction at 0, 30, and 120 ($p < 0.05$). Additionally, the AUC leptin and ghrelin values, were statistically significantly lower after tooth brushing ($p < 0.05$). Despite the reduced insulin levels at 120 and 180 minutes after tooth brushing ($p < 0.05$), no significant change was observed in the glucose levels.

Conclusion: The present study established a reduction in the secretion of ghrelin, leptin, and insulin, which are involved in appetite and energy homeostasis, upon gingival stimulation by tooth brushing in non-obese young adult men. Further understanding of the nutrition physiology and disorders will be obtained with similar studies to be conducted in slim and obese individuals.

Abstract-ID: 564

NUCLEAR ERA AND PPARΓ: RECEPTOR- AND LIGAND-BASED ANALYSIS

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Introduction. The nuclear receptors (NRs) are involved in the control of a wide range of physiologically significant processes. The estrogen receptor alpha (ERα) and the peroxisome proliferator-activated receptor gamma (PPARγ) are important targets for drugs to treat many human diseases and also for chemicals with potential toxic effects on the living organisms. A number of 3D-ligand complexes of these NRs are resolved providing useful data to reveal essential structural and functional characteristics of the receptors and their ligands.

Methodology. In this study a detailed analysis of the human ERα and PPARγ ligand complexes is performed. The available 3D complexes of these receptors were extracted from the Protein Data Bank. The molecular modelling software MOE was used to: (i) analyse binding pockets of the complexes, (ii) identify ligand pharmacophores and (iii) calculate ligand structural descriptors to differentiate between agonists and antagonists.

Results and Discussion. The pocket residues were analysed and the key protein-ligand interactions were identified in the extracted ERα and PPARγ complexes. Activity data of the ligands were collected from various databases and, when possible, used for compounds' ranking according to their effects. The protein structures of each NR were superposed and the aligned ligands in their bioactive conformations were extracted and stored for further analysis. Based on these conformations pharmacophore models of both receptors were proposed outlining differences in the space arrangement of hydrogen bonding and hydrophobic features between agonists and antagonists of ERα. Differences in the site location between the full and partial agonists of PPARγ were recorded. The ERα pharmacophore models outlined the shape and hydrophilic properties of the ligands as key molecular descriptors to differentiate between agonistic and antagonistic effects. In correspondence with the pharmacophore models, classification models to predict the ligand effects were obtained based on shape and polarity structural descriptors. The results show that the successful prediction of the ligand effect should combine pharmacophore, shape, and polarity descriptors. The models can be used for screening compounds which binding to ERα and PPARγ could be a molecular initiating event for dysregulation of activity of ERα and PPARγ.

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Abstract-ID: 574

INVESTIGATION OF KETAMINE-INDUCED ENDOCRINE MODIFICATIONS USING C. ELEGANS AS A MODEL

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C. elegans is a genetically tractable model organism which is widely used to investigate human metabolic regulation. The key components of human metabolism are conserved in *C. elegans*. With its conserved genome and signalling pathways, *C. elegans* serves as a valuable platform to understand endocrine aspects of human biology and medicine.

Ketamine is used as an anaesthetic and anti-depressant drug despite its neurotoxic effects. Ketamine is reported to modulate steroid hormone levels and is implicated in down regulation of ERK/MAPK signalling. In this study, worms were exposed to different doses of ketamine in a time-dependent manner. While temporary exposure to ketamine starting from embryonic stage to mid-larval stage did not show an obvious phenotype, continuous exposure to ketamine from late larval stage to adult hood at which oogenesis and vulval development takes place, resulted in decreased brood size and reduced growth. Interestingly, exposure to ketamine at late larval stage induced defective vulval development which in *C. elegans* is regulated by ERK/MAPK signalling pathway. Neuromuscular effect of ketamine is well documented however to our knowledge this is the first time where ketamine is shown to act in a different cell type. With these preliminary findings, we embarked on investigation of a link between ketamine-induced steroidogenesis and ERK/MAPK pathway. By exploiting the highly conserved *C. elegans* system, the molecular mechanism by which ketamine acts to induce endocrine changes will be enlightened.

POSTER BASIC HYPOTHALAMUS PITUITARY

Abstract-ID: 92

SPATIAL AND TEMPORAL EXPRESSION OF IMMUNOGLOBULIN SUPERFAMILY MEMBER 1 (IGSF1) IN THE RAT

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Loss-of-function of immunoglobulin superfamily, member 1 (*IGSF1*) results in an X-linked syndrome of central hypothyroidism and macroorchidism, and in some prolactin deficiency, GH deficiency, delayed puberty, or increased body mass index and fat percentage. IGSF1's functional role in development and disease is unknown; therefore, we investigated the spatial and temporal expression of IGSF1.

In the adult brain, high levels of IGSF1 immunoreactivity were observed in various areas, including the hypothalamus. In the adult pituitary gland, IGSF1 is present in the Pit1-cell lineage comprising GH, TSH, and PRL-producing cells, but not in gonadotrophs and corticotrophs. In the adult testis, IGSF1 is present in the cytoplasm of Sertoli cells (during stages XIII to VI of the seminiferous epithelium) and Leydig cells. In adult females,

IGSF1 is expressed at relatively low levels in the ovary at oviduct. IGSF1 is strongly expressed in hepatocytes of the fetal liver, but decreases rapidly to background levels immediately after birth. In all cases, specificity of IGSF1 protein expression was corroborated by *in situ* hybridization and real-time PCR for the *Igsf1* mRNA.

The results of this study represent the first comprehensive overview of the organ specific expression profile of IGSF1. The expression pattern in the pituitary gland suggests a local role of IGSF1 in the autocrine or paracrine regulation of secretion of TSH, GH, and prolactin. In contrast, IGSF1 is not expressed in the gonadotrophs, indicating that the delayed puberty and macroorchidism in these patients is not likely caused by pituitary dysfunction, but rather by a local defect in the testis. This is consistent with our observations that IGSF1 is expressed in Sertoli cells (the number of which determines testicular size) and Leydig cells (which produce testosterone). The results of our study provide a framework that will facilitate future research on IGSF1 function in relevant cells and tissues.

Abstract-ID: 188

PRETREATMENT WITH AT-101 ENHANCES CYTOTOXIC AND APOPTOTIC EFFECT OF SOM-230 IN MOUSE CORTICOTROPH ADENOMA CELLS

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Introduction

Pasireotide (SOM230) which is a somatostatin analog has been used in Cushing disease. AT-101, an -(-) enantiomer of gossypol, is a potent anticancer agent. It was shown that AT-101 induced apoptosis and decreased ACTH level in mouse corticotroph adenoma cell line in a previous study. We examined whether pretreatment with AT-101 would result in enhancement of SOM230 mediated cytotoxicity.

Material-Method: Mouse AtT-20 coritcotroph adenoma cells were treated with AT-101, SOM230 alone and as sequentially. AtT-20 cells were exposed to increasing concentrations of AT-101 (0.5-20 μM) and of SOM230 (5-60 μM) alone. For sequential treatment, AtT-20 cells were pretreated with changing concentration of AT-101 in 2.5-10 μM and then treated with SOM230 in 5-20 μM doses. Combination index was used to evaluate synergism. If CI is below 1, it points out synergism and if CI is below 0.5, it is called as strong synergism.

Results: IC50 value of AT-101 was calculated as 10.7 μM and IC50 of SOM230 was 28 μM at 24 hour. Treatment of corticotroph adenoma cells with low dose of AT-101, that is 2.5 μM, and sequential treatment with low dose, 5 μM of SOM230 indicated strong synergism (CI=0,271). Sequential treatment wih 10 μM AT-101 and 5 μM SOM230 resulted in strong synergism (CI=0,171). 10 μM AT-101 and 5 μM SOM230 showed 52.8%and 7.4% decreases in viability of AtT-20 cells, respecitvely, but the sequential treatment with AT-101 and SOM230 resulted in 92% decrease in viability ($p<0.05$). It has been shown that10 μM AT-101 and 5 μM SOM230 caused 60% and 33.5% increase in caspase 3/7 activity, respectively. Sequential treatment with AT1-101 and SOM230 increased caspase 3/7 activity by 73.5%.

Conclusion: The sequential treatment of AT-101 followed by SOM-230 resulted in significant synergistic cytotoxicity anad apoptosis. Combination therapy at low doses may provide efficacy with less side effects.

Abstract-ID: 207

AMENORRHEA DUE TO AN EPIDERMOID CYST

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Introduction: Epidermoid tumours represent 0.5 to 1.5 % of all brain tumours, usually located in the cerebellopontine angle followed by the parasellar region. The diagnosis is directly related to its location

Case Report: A 41-year-old woman came to the clinic complaining of amenorrhea and loss of visual field from 1 year ago.She had a son at 40-years-old with regular menses for 5 months after delivery and then, she developed amenorrhea until she was seen

She underwent an MRI where a cystic suprasellar mass of 18 x 14 mm was observed. It was hypointense on T1 and hyperintense on T2, with a ring enhancement after administering contrast. It displaced the stalk and the optic chiasm forwards, touched the hypothalamus and the anterior recess partially, obliterating the third ventricle without hydrocephaly. It was evaluated as a probable craniopharyngioma or Rathke's cleft cyst. Laboratory tests showed normal pituitary function, which led to the diagnosis of the amenorrhea as hypothalamic. The test of visual field showed a bitemporal quadrantanopsia. Surgery was performed through a right craniotomy with subtotal excision of the cystic mass located in the anterior third of the third ventricle. The anatomical pathology report was consistent with epidermoid cyst. After surgery she had diabetes insipidus and adrenal insufficiency. The menses returned, the visual field improved and tumor remains of 9x7mm on MRI control were observed. At the 3 year follow-up, she has diabetes insipidus treated with 120mcg minurin flash twice a day, adrenal insufficiency treated with hydrocortisone 10mg twice a day, a small peripheral temporal scotoma in the left eye with no change in size of the tumoral remains

Conclusion: 1. To consider epidermoid tumours in the differential diagnosis of cystic suprasellar tumours 2. A rapid diagnosis is determined by its location and associated symptoms

Abstract-ID: 263

HETEROGENITY OF GENETIC BASIS OF HYPOGONADOTROPIC HYPOGONADISM

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Hypogonadotropic hypogonadism (HH) is a disorder characterized by delayed or absent pubertal development due to pathology of the hypothalamic-pituitary-gonadal axis. HH may be both congenital or sporadic, isolated or combined with other types of pituitary defficiencies. Congenital isolated HH can be associated with anosmia/hyposmia (Kallmann syndrome) and with normal olfaction (normosmic isolated HH). By now, over 65% of cases of HH remain without a definite genetic cause and further research is required to obtain a genetic component in the pathogenesis of specific cases of disorder.

In our study of we measure candidate genes expression in the blood of 4 patients (3 females and 1 male) with isolated HH. RNA was extracted from peripheral blood and real time RT-PCR was conducted. Candidate genes expressed in leukocytes were included in investigation: *FGFR1*, *PROK2/PROKR2* control migration of the GnRH neurons from their embryonic origin to the hypothalamus; *GNRH1/GNRHR* contribute to the biological action of GnRH.

Different patterns of altered genes expression was found in 3 cases. In one case high level of the GNRHR gene expression, reduction of the *FGFR1* expression and low level of the *PROKR2* expression were found. In one other case the increased *FGFR1* and low *PROK2* expression were observed.

In the third case reduction of both *GNRH* and *PROK2/PROKR2* genes expression was obtained.

From these preliminary results, we can conclude that different gene interaction can be a cause of the disease in each case. Probably, there is a significant variability in genetic basis of isolated hypogonadotropic hypogonadism.

Abstract-ID: 278

LACK OF CIN85 CAUSES IMPAIRMENT OF MATERNAL BEHAVIOUR

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Cbl-interacting protein of 85 kDa (CIN85) is a scaffold/multi-adaptor protein implicated in the regulation of receptor endocytosis, cell division and the cellular cytoskeleton. Recently, we reported that mice deficient of CIN85 expression show hyperactive phenotypes. As a molecular explanation of this phenotype, the absence of striatal CIN85 causes decreased dopamine receptor endocytosis in striatal neurons in response to dopamine stimulation. We show here another phenotype besides the hyperactivity of CIN85 knockout (KO) mice that of maternal neglect to the newborns. Even though there is no difference in the number of live births from CIN85 KO homozygote, heterozygote and wild-type mothers, respectively, almost all pups born to CIN85 KO homozygote mothers have died within two days of birth. Moreover, despite of the fact that no defect in the mammary glands of CIN85 KO mother mice was found, milk was not detected in the stomachs of most pups. Importantly, when measuring the plasma levels of prolactin (PRL), we detected significantly decreased PRL levels in CIN85 KO mice compared to heterozygote and wild-type mice. PRL injection in CIN85 KO mice could however partially rescue the defect in maternal behavior. Our findings indicate a loss of CIN85 function leads to a neglect–like behavior due to aberrant dopamine-PRL signaling.

Abstract-ID: 413

ROLE OF IGF1-(CA)19 PROMOTER MICROSATELLITE IN THE CLINICAL PRESENTATION OF ACROMEGALY

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Background: A highly polymorphic Cytosine-Adenosine (CA) repeat sequence microsatellite has been identified in the promoter region of IGF1 gene. Several studies investigated the relationship between IGF1-$(CA)_n$ polymorphism and IGF1 levels, with conflicting results. Aim of this study was to investigate the influence of this polymorphism on clinical and biochemical characteristics of acromegalic patients.

Methods: Eighty-eight acromegalic patients and 104 normal subjects were included in the study. Blood DNA was extracted and analyzed by microsatellite technique using capillary electrophoresis. Patients and controls were subdivided in 19/19 (homozygous for the $(CA)_{19}$ allele), 19/X (heterozygous for the $(CA)_{19}$ allele) and X/X (any other genotype).

Results: The genotype frequency was significantly different between patients and controls, the proportion of 19/19 being lower (28.4% vs 50.0%) and 19/X and X/X higher in acromegalic patients than in controls (P = 0.004). There were no significant differences in age, gender, basal and nadir GH, IGF1-SDS, tumor size, metabolic parameters, outcome, and treatment among the three groups. The different frequency of genotypes in acromegalic patients vs controls, as well as the lack of relationship between IGF1-$(CA)_n$ polymorphism and clinical and biochemical data in acromegalic patients, was confirmed by using an additional alternative genotyping considering $(CA)_{19}$ and $(CA)_{20}$ homozygotes and heterozygotes vs alleles with more than 19/20 repeats or less.

Conclusions: Our results indicate that IGF-$(CA)_n$ alleles did not have a clear impact in determining clinical, biochemical and outcome pattern in acromegaly. The possible role of IGF1 polymorphism on susceptibility to acromegaly remains to be investigated.

Abstract-ID: 503

BYL719, A SPECIFIC INHIBITOR OF THE PI3K, CONTROLS PITUITARY TUMOUR GROWTH THROUGH A DIRECT EFFECT ON TUMOUR POTENTIALIZED BY TUMOUR MICROENVIRONNEMENT MODULATION.

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Background: Fifteen percent of the pituitary tumours, resistant to conventional treatment, (combining surgery, medical treatment and radiotherapy) are classified as aggressive. Alkylating drugs have been efficient in some rare cases, so there is a real need for new therapies. As in many types of tumours, it has been demonstrated that the PI3K/AKT/mTOR pathway is overexpressed in pituitary tumours.

Objective: To study the effect of BYL719, a specific inhibitor of the catalytic subunit p110α of PI3K, as potential therapy for aggressive pituitary tumours.
Design: BYL719 effect was evaluated in vitro on two different pituitary cell lines (GH3 and AtT20) at different concentrations (10 to 250nM) and in vivo in a rat model of pituitary tumours (SMtTW3) at 30mg/kg/day (n=11) or vehicle (n=11) for 4 weeks. In vitro,cell viability was accessed using a CCK8 assay and Propidium Iodide Staining by flow cytometry. Flow cytometry was also used to evaluate the cell cycle and apoptosis (Annexin V). Westernblot of AKTp/AKT, mTORp/mTOR, p27, and Rbp were performed to evaluate the PI3K/AKT/mTOR activity and PARP/PARPcleaved to measure apoptosis.

Results: *in vitro* BYL719treatment did not affect cell viability or cell cycle of both cell lines. *In vivo*, BYL719 treatment was well tolerated and reduced drastically the tumour growth and the plasma prolactin (PRL) concentration. One rat died in each group. Final tumour weight in vivo was statistically different between BYL719 (11.3±1.7g) and control (30.4±2.2g) groups (P<0.001). PRL secretion was also significantly lower in BYL719 (8 736 ± 2084 µg/L) compare to control group (41 360ug/l ± 12410) (p<0.001). The antitumoral effect was associated with a decrease of mitosis number (37.7±8.5 vs 105.3±15.2 P<0.001), a decrease of AKT/AKTp, mTOR/mTORp, and rb an increase of p27, however these differences were not statistically significant, and an increased of PARPcleaved (P<0.05).

Preliminary results demonstrated a reduction of VEGF and an increase of GSK3 expression in the tumours treated with BYL719 compare to control group suggesting that tumour microenvironement was implicated in tumour growth reduction. Moreover, SMtTW3 primary cultures were not affected by BYL719 treatment excluding a cell specific effect.

Conclusion: The discrepancy between in vitro and in vivo results, suggested that, in addition to the modulation of the PI3K/AKT/mTOR, antitumoral effect of BYL719 may be potentialized by a modulation of the tumour microenvironment. Further experimentations will be required, but its efficiency in vivo is promising for the treatment of aggressive pituitary tumours.

Abstract-ID: 513

INTERRELATIONS OF SERUM GALANIN-LIKE PEPTIDE AND PROLACTIN LEVELS IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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Background: Galanin-like peptide (GALP) is a 60 amino acid neuropeptide. GALP-expressing neurons are limited, and are mainly found in the arcuate nucleus of the hypothalamus (ARC) and the posterior pituitary. GALP-positive neurons in the ARC project to several brain regions where they appear to make contact with multiple neuromodulators.

Pituitary prolactin secretion is regulated by endocrine neurons in the hypothalamus, the most important ones being the neurons of the ARC, which secrete dopamine to act on the D2 receptors of lactotrophs, causing inhibition of prolactin secretion.

Aim: To estimate whether there is a relationship between GALP and serum prolactin levels in women with polycystic ovary syndrome (PCOS).

P**atients and methods**: The study included 42 women with PCOS according to the recent ESHRE-ASRM criteria. Serum levels of TSH, FT4, LH, FSH, Estradiol, Testosterone, SHBG, prolactin, fasting glucose and insulin were measured at follicular phase of the menstrual cycle. Serum GALP levels were determined by the quantitative sandwich enzyme immunoassay (ELISA) technique. Free androgen index (FAI), homeostasis model assessment of insulin resistance (HOMA-IR) and body mass index (BMI) were calculated.

Statistical analyses were performed using SPSS Ver. 16.0. The data are presented as mean±SE or as frequency with percentages. A P-value less than 0.05 was considered as statistically significant.

Results: The patients were at average age 25.17±0.77. There were significant negative correlations between GALP and prolactin (R= -0.524; P<0.001) and between prolactin and FT4 (R= -0.375; P<0.031) and a significant positive correlation between GALP and FT4 (R=0.470; P<0.004).

Conclusion: Our study indicates that GALP plays a role as a regulator of prolactin levels.

Key words: prolactin, galanin-like peptide, PCOS

Abstract-ID: 552

IDENTIFICATION AND CHARACTERIZATION OF PITUITARY ADENOMA STEM-LIKE CELLS IN HUMAN NON FUNCTIONING PITUITARY ADENOMAS

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Several studies support the existence of multipotent stem/progenitor cells in the adult pituitary, but their role in pituitary tumorigenesis is still on debate. Aim of this study was to identify and characterize stem-like cells in non functioning pituitary adenomas (NFPAs). To this purpose primary cell cultures from 32 NFPAs were grown in culture conditions that favored stem cell growth and non adherent round cell clusters (pituispheres) were found in about 2/3 of NFPAs tested (21/32). The expression of stem cell markers and genes involved in pituitary development was evaluated by FACS analysis, reverse transcription-PCR and immunofluorescence. RT-PCR analysis revealed the expression of stem cell markers Sox2, Oct4, Nanog and Egr1, transcription factors involved in gonadotroph differentiation (DAX1, SF1) and the glycoprotein hormone alpha subunit (alphaGSU), consistent with gonadotroph lineage derivation of most NFPAs. Immunofluorescence analysis revealed that pituispheres co-express Sox2 with the pituitary embryonic factor Prop1, E-cadherin, and nestin. Moreover, tumor pituispheres expressed dopamine (DA) receptor 2 (DRD2), that was able to induce antimitotic effects in a subset of NFPAs (57 % reduction of cell proliferation, p<0.05 vs bas). Finally, preliminary data obtained in normal autoptic pituitary by immunofluorescence analysis showed a small proportion of cells positive for Sox2, supporting the existence of stem/progenitor cells in the human adult pituitary

In conclusion, our data demonstrate the existence in a good proportion of NFPAs of progenitor/stem-like cells that grow in suspension as spheres, express stem cell-associated markers and pituitary embryonic factors and maintain responsiveness to dopaminergic drugs.

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