

The pathogenic role of MMP-9 in migraine: a pilot study with sulodexite

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Migraine is the manifestation of a sensitivity of neurovascular reactions to certain stimuli or to cyclic changes in the central nervous system (Lance 1993) and matrix metalloproteinases (MMP) and their inhibitors are discussed to be involved in this pathophysiologic mechanism. Many studies have already demonstrated that an increased MMP activity is tightly associated with migraine (Bernecker 2011), at least with the chronic form. More in detail, the MMP-9 levels in migraineurs are significantly higher than those in controls (Imamura 2008), particularly in patients affected by the form without aura, and Moskowitz in 2004 demonstrated that Cortical Spreading Depression alters blood–brain barrier permeability by activating brain MMPs, particularly MMP-9, that are finally involved in the disruption of blood–brain barrier (Martins Oliveira et al. 2009) and subsequent parenchymal damage (Shibata 2012). Sulodexite is a substance usually effective in the therapy of dizziness: on the basis of its demonstrated role in the inhibition of circulating levels of MMP-9, in the present pilot-study we have used sulodexite as a prophylactic treatment for 10 patients affected by severe migraine, with and without aura, in order to analyze a clinical improvement caused by the reduction of MMP-9 plasma levels.

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Tension type like headache and bilateral tinnitus symptomatic to intracranial dural arteriovenous fistulas: unusual case report

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Bilateral tinnitus is a common pathology among elderly population (10–30 %) and is usually benign [Delgado], contrary to pulsatile tinnitus (4 %) due to more serious conditions [Kim]. Also the tension type headache is frequent in elderly population (44.5 %), occurring for the first time in old age between 17 and 43 % of subjects; only in the 2.2 % headache is related to brain serious event. Dural arteriovenous fistulas are rare vascular anomalies that account for 10–15 % of all cerebrovascular malformations whose neurological symptoms are closely related to intracranial bleeding or to intracranial hypertension [Kirsch].

A 78 year old man came to our observation by reporting 1 year history of daily recurring frontal-occipital moderate constrictive headache and constant no pulsatile bilateral tinnitus. From 5 months he developed an extrapyramidal hypertonic syndrome and moderate cognitive impairment. Basal CT scan showed lacunar ischaemic lesions. He was admitted to our hospital for severe headache; an urgent brain CT scan showed two intracerebral hemorrhages in left hemisphere.

The neurological examination revealed diffuse pyramidal signs and right retroauricular 6/6 bruit was audible. Ocular funduscopy examination showed no papilledema. Brain MRI with contrast showed multiple intraparenchymal venous ectasias, right sinus and sagittal sinus, two hemorrhagic lesions in the left parietal near vascular ectasias. These findings are compatible with diagnosis of DAVFs bleeding. Conventional cerebral angiography revealed two DAVFs, the first near to right transverse sigmoid sinus and the second near to torcular. The patient was transferred in neuroradiology department to perform endovascular treatment. The patient died 2 days later for a massive intracerebral hemorrhage complication.

The our patient presented chronic tension like headache and no pulsatile bilateral tinnitus as the first and unusual clinical manifestations of DAVFs. The clinical diagnosis of DAVFs was complex and misunderstood, this disorder remains still unfamiliar and must be considered in presence of new headache.

Efficacy and reproducibility of response of greater occipital nerve blocks in chronic cluster headache: a large sample prospective analysis

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Background: Greater occipital nerve blockade (GONB) has been shown to be effective in episodic cluster headache (CH). However, its

use in chronic cluster headache (CCH) is less certain. The study aims to prospectively assess the efficacy and consistency of response to GONB in a large series of CCH patients.

Methods: CCH patients referred to The National Hospital for Neurology and Neurosurgery between 2007 and 2010, who had a unilateral GONB, were prospectively studied. Headache characteristics were collected using headache diaries pre and post procedure. In a subgroup of responders the outcomes of serial GONB performed at three monthly intervals were also analysed.

Results: Eighty-three CCH patients were studied. After the first GONB, a positive response was observed in 59 (71 %) patients; 42 (51 %) were rendered pain free, 16 (27 %) had a partial benefit and 1 patient obtained less than 50 % improvement. The duration of a positive response lasted a median of 18 days (range: 1–504 days). Overall, among those who obtained at least 50 % improvement from the first GONB, 47 patients (81 %) continued to report the same level of improvement at day 7, 34 patients (59 %) at day 15, 16 patients (28 %) at day 30 and three patients (5 %) at day 90. There was a transient worsening of condition in 6 % of patients. No serious adverse events were reported after the injections. Mild and self-limited tenderness at the injection site, neck stiffness and dizziness were reported by 34 % of the sample population. The overall rate and average duration of response remained similar after the second (n = 43, 35 responders: 81 %; median duration: 18 days), third (n = 28, 20 responders: 71 %; median duration: 25 days), and fourth (n = 14, 10 responders: 71 %; median duration: 23 days) injections.

Conclusion: GONB seems to be an efficacious treatment with reproducible effects in CCH patients. Performed three monthly, GONB may have a useful role in the management of CCH allowing periods of relief from this disabling disorder.

Botulinum A toxin for treatment of chronic migraine

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Introduction: Chronic migraine is a common and debilitating headache syndrome. Botulinum neurotoxin (BoNT), a potent toxin produced by the anaerobic bacterium *Clostridium botulinum*, used for treatment of disorders associated with increased muscle tone and hyperhidrosis, has been recently employed for patients suffering from chronic migraine.

Aim: As the significant population of chronic migraine patients, refractory to common therapeutic prophylaxis, BoNT has been used in our clinical experience for treating patients referring to our headache centre and suffering from chronic migraine with medication overuse.

Method: Ten patients have been submitted to a withdrawal from medications in a day hospital setting and after that, they have been treated by BoNT A injection in multiple sites according to the protocol of the PREEMPT study at the dosage of 150 U for 31 sites. Every session of local injection (150 U per 31 sites) was repeated every 3 months for a period of 1 year. A second group of eight patients, after withdrawal, was treated by BoNT A injection, multiple sites, at the dosage of 100 U; every session of local injection has been repeated every 3 months for a period of 1 year. Number of medication intake and days of headache per month were recorded by an headache daily diary.

Results: Data concerning the first group of patients evidenced that days of headache/month decreased during the period of treatment at

150 U (pre 21.4 + 7.9 post 13.8 + 10.9 p < 0.01). Also medication intake decreased (pre 19.6 + 8 post 11.7 + 9.5 p < 0.01).

In the second group of patients, treated with 100 U, results were not significant: only 3 patients completed the treatment with 4 sessions; 5 patients dropped for different reasons (side effects, no benefit, low compliance).

Discussion: Although these results are preliminary they led to intense efforts to evaluate analgesic properties of BoNT A and to assess their clinical applicability. The pharmacological profile of BoNT A makes it a good candidate for migraine prevention at the adequate dosage of 150 U as proposed in the PREEMPT study. Its long duration of action (3 months) makes it particularly attractive for patients who are not compliant with the daily use of preventive medications, or if they cannot tolerate it or when they are refractory to preventive medications. On the other side we cannot confirm the efficacy of lower dosage (100 U) for patients with chronic migraine after withdrawal.

SUNCT/SUNA with neurovascular conflict: new cases and critical literature review

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Background: Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and Short-Lasting Unilateral Neuralgiform Headache with Cranial Autonomic Symptoms (SUNA) are primary headache syndromes. A growing body of literature has focused on brain MRI evidence of neurovascular conflict (NVC) in those syndromes.

Objective: To assess whether SUNCT is a subset of SUNA or the two are separate syndromes and clarify the role of neurovascular conflict.

Method: We describe three new SUNCT cases with MRI finding of NVC and we critically reviewed all primary published SUNCT/SUNA cases.

Results: Our first SUNCT patient with NVC achieved complete remission with carbamazepine and the second one after microvascular decompression of the trigeminal nerve (MVD). The third case tried no medical treatment before unsuccessful gamma knife, MVD, and a second gamma knife. Following the MVD he started experiencing continuous burning pain involving all three branches of the right trigeminal nerve, and exacerbation of SUNCT attacks. MRI showed higher thickness and contrast enhancement of the right trigeminal nerve, which may be compatible to Gamma-Knife side effect. He achieved partial response only with oxcarbazepine and lamotrigine. Our three patients with NVC added to the 34 cases previously described (16.9 %) among the 222 SUNCT/SUNA cases published (189 SUNCT, 31 SUNA, 2 with both SUNCT and SUNA attacks). SUNCT and SUNA patients share the same clinical features and therapeutic options. There is no available abortive treatment of attacks. Lamotrigine was effective in 52/81 (64 %) patients; topiramate and gabapentin in about one-third of cases. Of the 34 cases with neurovascular conflict seven responded to drug treatments, 16 patients underwent MVD, with effectiveness in 12 (75 %) cases.

Conclusions: We suggest that SUNCT and SUNA should be considered clinical phenotypes of the same syndrome. Brain MRI should always be performed with dedicated view to exclude neurovascular conflict. Patients with a vascular loop imprinting the trigeminal nerve

may benefit from pharmacological therapies. MVD may represent a treatment option in refractory cases. The high percentage of remittance after MVD supported the pathogenetic role of NVC.

A case of Idiopathic Intracranial Hypertension without Papilledema and Meniere Disease in comorbidity responsive to repeated lumbar punctures: a possible link between two enigmatic conditions

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Recent evidence suggests that sinus venous stenosis-associated idiopathic intracranial hypertension without papilledema (sIIHWOP) is a very frequent condition running almost asymptotically in most affected individuals (De Simone, Cephalalgia 2010) but it could represent a risk factor for progression of primary headache (De Simone, Curr Pain Headache Rep. 2012). Although Meniere Disease (MD) pathogenesis is still unknown, an impaired balance between cerebrospinal fluid (CSF) and the inner ear fluids pressures, leading to endolymphatic hydrops, might be of pathogenetic relevance (Salt, Otolaryngol Clin North Am. 2010). We report a case of a 42-year-old woman diagnosed with migraine without aura since childhood, evolved to a refractory chronic migraine (20–25 attacks/month) in the last 2 years, associated to almost daily brief stabs of pain in the temporal and parietal area indistinguishable from a primary stabbing headache. Due to the occurrence of ear fullness, hypoacusia, vertigo, and tinnitus she had also been diagnosed with MD about 10 years before. MR-venography (MRV) showed bilateral flow gaps at transverse sinuses level. Funduscopy revealed no papilledema. A lumbar puncture (LP) showed an opening pressure (OP) of 265 mmH₂O, lowered to 100 mmH₂O after 30 ml of CSF withdrawal, and was diagnosed with sIIHWOP. Soon after LP the patient reported an improvement of migraine attacks frequency (6–7 per month) and the remission of the stabbing pain. Moreover, she reported the disappearance of ear fullness and vertigos and an improvement of tinnitus and hypoacusia, the latter confirmed at the audiometric examination. A new MRV performed after the LP showed the resolution of the right transverse sinus flow gap. Seven months later, the patient referred to our centre because of the sudden worsening of migraine attacks frequency and the re-appearance of choleo-vestibular symptoms. A second LP showed an OP of 250 mmH₂O that was lowered to 100 mmH₂O after 30 ml of CSF subtraction. Soon after the second LP, she reported the remission of the chronic headache (6–8 migraine attacks/month), coincident with the disappearance of ear fullness and vertigo and a new improvement of hypoacusia. The patient is currently asymptomatic 3 months after the repeated LP. Our observation confirms that sIIHWOP is causatively involved in migraine progression. Moreover, the improvement of the co-morbid MD after ICP normalization, observed also after the second PL, suggests that Meniere-like symptoms could be related to IHH. The putative pathogenetic link could lie in the imbalance, in predisposed subjects, of CSF/inner ear fluids dynamics in course of IHH.

Persistent unilateral mydriasis and migraine with aura: a case report

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Mydriasis can be alarming sign that often raises about serious intracranial condition. In the majority of patients have a benign process such Adie tonic pupil. Often in migraine a disorder of chronic sympathetic dysfunction is present. Transient mydriasis as variant of ophthalmoplegic migraine or in migraine without aura has been documented; and a pathogenetic link between pupil dysfunction and migraine has been suggested. None case has been described about permanent mydriasis in migraine with aura.

Case report: A 29-year old man came to our observation after an ophthalmological examination performed for recurrent blurred vision episodes and finding of marked anisocoria. Ocular examination suggests that right eye mydriasis could be attributed to parasympathetic dysfunction. The great hyporesponsiveness to light and accommodation, the slow convergence (near response), and the increased symptomatic pupil dilatation after application of phenylephrina prove this dysfunction. He had personal history of migraine with aura (MA) recurring since the age of thirteen. When patient is referred to our observation the mydriasis was present during the MA free period, and during the 4 months of the follow-up the patient maintains the pupillary impairment ipsilateral to the side of aura. Neurological examination was normal except right-side mydriasis; brain CT, EEG, PEV were normal. Brain MRI/angio-MRI did not show relevant aspects. The headache attacks were responsive to almotriptan and acetylsalicylic acid 100 mg.

Discussion: We do not know if the pupillary alteration was present in the early stage of migraine, and during the attack or in the free period. In our case, pupillometric findings are consistent with an Adie's pupil, but the persistent mydriasis could be suitable with ciliary ganglion impairment. We debate about the differential diagnosis between Adie's pupil and the autonomic dysfunction of Migraine, and if the mydriasis can be a complication produced by frequent MA attacks, or a distinctive sign of a kind of migraine patient.

Incidence of remission in MOH: a population based study

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Background: Chronic daily headache (CDH) includes a group of headache disorders occurring at least 15 days per month. CDH occurs in 3–5 % of the population, instead the epidemiology of MOH is uncertain. No epidemiological data are available about the incidence of spontaneous remission in MOH.

Objectives: the aim of this study was to reassess after 3 years all the patients who have received a diagnosis of MOH in Spartacus study in order to investigate the incidence of spontaneous remissions in MOH and to evaluate risk factors associated to MOH.

Methods: Spartacus was an observational, cross-sectional study based on an ad hoc validated questionnaire (sensitivity 97 %, specificity 86 %) sent to 25163 adult subjects registered in the lists of 20 GPs (general practitioners) in Casalecchio di Reno district. Patients diagnosed as CDH through a screening questionnaire were interviewed by their GPs who indicated if subjects were known as patients suffering from CDH with medication overuse (MO), CDH without MO, episodic headache (EH) or non-headache sufferers. 3 years later, all the patients with a diagnosis of MOH (ICHD-2R 2006) were interviewed by a neurologist expert in headache to evaluate the current diagnosis.

Results: 16,577 subjects returned the completed questionnaire (65.88 %), 3.84 % of which were affected from CDH, of those 1.44 % with MO and 2.40 % without MO. CDH patients' complete questionnaires were 435/636: 127 with MO and 308 without MO. 29 of 127 patients with MO refused the follow-up interview by the neurologist. Among the remaining 98 with MO (75 female and 23 male, mean age 49.21 ± 13), 54.1 % referred remission from MOH; among them 51 % have had a spontaneous remission, 34 % have had a remission with prophylactic drugs, and 15 % with other conditions (withdraw by hormonal therapy and with behavioural therapy).

Conclusion: CDH incidence in this epidemiological study confirms the data occurring in literature, showing an incidence of MOH equal to 1.44 %. Furthermore we found a spontaneous remission in more than half of MOH patients after a 3-years follow-up period.

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Long term occipital neurostimulation in drug refractory chronic cluster headache: the Italian experience

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Introduction: Drug refractory chronic cluster headache (dr-CCH) is an extremely severe and debilitating condition. A variety of surgical procedures ranging from invasive to semi-invasive techniques methods have been introduced in the last decades as treatment. Current evidence suggests occipital nerve stimulation (ONS) as an effective option for the treatment of dr-CCH patients. The objective of this study is to report on ONS efficacy in a large group of dr-CCH patients after long-term follow-up.

Patients and methods: Thirty (27 males) dr-CCH patients underwent ONS at our department between 2004 and 2012. CCH was diagnosed according to the International Headache Society criteria (IHS); additional criteria to be eligible for neurostimulation were: complete drug-resistance, daily attacks, at least 1 year of the condition, absence of psychiatric disorders. Three patients had CCH at onset, and in the others the chronic form evolved from episodic CH. Mean age was 43.3 years; mean illness duration was 15 years (range 9–32), mean duration of the chronic phase was 7.6 years. Bilateral suboccipital stimulators were implanted in all patients.

Results: The mean follow-up is 46 months (ranges 5–86 months). Eighteen (60 %) out of the 30 patients showed a headache frequency

reduction >50 % and were defined as responders; in this group mean headache frequency dropped from 145 attacks per month (5/day) to 13 attacks per month. Twelve patients did not improve; 5 of these were implanted between 2004 and 2005 and received occipital stimulation for a short period (<5 months) because at that time it was thought ONS should exert its effect in a short period like reported in migraine. Adverse events were electrode displacement (n = 2), battery replacement (n = 4), infections (n = 3).

Conclusions: Our data confirm the efficacy of ONS as a treatment of dr-CCH after long-term follow-up.

Basilar-Type migraine presenting in patient with previous cerebral venous thrombosis: a case report

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Background: basilar-type is a rare form of migraine (BM) characterized by aura symptoms originating from the brainstem or from both hemispheres simultaneously. BM attacks are mostly seen in young adults who often also suffer from migraine with typical aura. Attacks of basilar-type symptoms require diagnostic caution, the main differential diagnosis is cerebrovascular disease.

Methods: we report the case of a 19 year-old man with a past history of a cerebral venous thrombosis (CVT) of superior sagittal sinus and transverse sinus. When diagnostic evaluation was performed mild hyper-homocysteinemia with *heterozygous MTHFR C677T mutations* was found. Follow-up MRI-angiography demonstrated irregular opacification of the left transverse sinus. He was referred to our Emergency Department for sudden onset of severe diffuse headache, transient upper extremities paraesthesias and transient speech disturbance. In consideration of the anticoagulant therapy suspension, occurred 6 month before, a CVT recurrence was suspected. Cerebral MRI and digital cerebral angiography were performed with no evidence of parenchymal lesions or new cerebral venous thrombosis. Right after digital angiography procedure the patient reported a new episode characterized by headache, nausea and emesis. Transient visual impairment, followed by four limbs paraesthesias, anarthria and impaired consciousness was also referred. A cerebral MRI with DWI sequences, performed during neurological signs, showed no acute brain injuries. Considering that the referred symptoms were transient, stereotyped and always followed by headache and that both neurological/neuroradiological examinations were negative, we postulated a basilar-type migraine. At discharge a topiramate prophylaxis was started.

Conclusions: this case report underlines the potential differential diagnostic problems raised by basilar-type symptoms. In our case the previous diagnosis of CVT could have been a misleading factor in the diagnostic evaluation. Moreover no migraine attacks were reported in the past. Despite being a rare form of migraine with aura, it is important in clinical practice to detect the clinical features that may help distinguishing BM from its differential diagnoses.

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Migraine and emotions: a group psycho-educational experience at the San Paolo Hospital of Milano

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Introduction: Literature shows that psycho-educational interventions for chronic diseases are useful to increase patients' emotional ability to cope with their disease (e.g., Sarkadi et al. 2004). Headache is a severe and disabling chronic disease. We will describe a psycho-educational intervention planned and conducted at the Psychology Unit of San Paolo Hospital-University of Milano in collaboration with the Headache Center of the same hospital.

Patients' recruiting: Inclusion criteria for adults were: age >18 - years; absence of overt psychiatric illness; diagnosis of primary headache according to the IHS criteria or tension headache or migraine with or without aura; willingness to have a psychological support; suitability to the techniques of Autogenic Training. Teens inclusion criteria were the same as for adults, except the age (15–18 years).

Psycho-educational intervention: 9 meetings including: 1 first individual interview aimed at describing the intervention and 8 group-meetings, one every 2 weeks, lasting 90 min each. The 8 group-meetings had the following goals: to share emotions through active methodologies of psychodrama; to explore/increase the knowledge about headache; to learn techniques of Autogenic Training.

Outcome indicators: Before and after the treatment, patients filled in the following questionnaires: COPE; STAI Y2; STAXI Y2. At the end of the treatment, patients also filled in a satisfaction questionnaire. We also analysed the patients' diary of frequency and intensity of headache attacks, comparing the data gathered the month before the inception of treatment with those gathered the month after the intervention.

Preliminary results: We completed 4 groups for adults, each involving 8 people, and now we are conducting the first group for teenagers. The analysis of the treatment effectiveness is still ongoing. The analysis of the satisfaction questionnaires highlighted that all the participants rated the intervention as useful or very useful (score of 4 or 5 on a 5-point Likert scale).

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Default-mode network connectivity in patients with chronic cluster headache

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Cluster headache (CH) is an autonomic trigeminal cephalalgia (TAC) (International Headache Society 2004). In the last years several steps were done in the comprehension of the physiopathology of CH. Using

neuroimaging, investigators have reported the activation of postero-inferior hypothalamus during CH attacks (May et al. 1998, May et al. 2000, Sprenger et al. 2004, May et al. 2006), as well as an increased volume of this brain area (May et al. 1999). These neuroimaging data, the typical chronobiological course of the disease and the derangement of the hypothalamic-pituitary axis showed in CH patients have prompted the suggestion that hypothalamus is involved in CH pathophysiology and could be the generator of CH attacks. It has been recently proposed (Leone et al. 2009) that CH attacks could be the results of a disinhibition of the hypothalamo-trigeminal pathway due a permissive state produced by abnormal functional connectivity among different brain areas involved in pain control.

One of the most suitable approach to explore functional brain connectivity is resting-state fMRI (RS-fMRI). In combination with independent component analysis (ICA), RS-fMRI allows characterization of the spatio-temporal distribution of spontaneous coherent fluctuations of BOLD signals between temporally correlated brain regions.

In order to test the hypothesis of a presence of a pathological functional connectivity among different brain areas in CH, 6 patients with chronic CH (outside painful attacks) and 6 healthy subjects were submitted to resting-state fMRI (RS-fMRI) acquisitions with a 3 T scanner (Philips).

The functional integrity of the default-mode network (DMN) was assessed using ICA. DMN (Greicius et al. 2003) is a network of brain regions consistently more activated during a resting condition than during active goal-directed analysis of environmental stimuli. DMN abnormalities have been reported in several neurodegenerative disorders and chronic pain.

Our preliminary findings reveals a disruption of the DMN in chronic CH, suggesting a diffuse dysfunctions of functional brain connectivity in this condition.

Diagnosis and therapeutic management of primary headache in an emergency setting

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Introduction and aim: Much headaches are under or mis-diagnoses and data regarding the proportion of patients attending an emergency department (ED) because of headache are still few. We conducted a retrospective, observational study in an ED with the following aims: (a) estimate the proportion of headache attending to an ED, (b) to estimate and describe the therapeutic management of primary headache and (c) to assessment the exam most frequently requested.

Materials and methods: We collected data regarding patients diagnosed with headache consecutively attending the ED, of the University of Palermo, between September 2011 and March 2012. The study was approved by the ethics committee.

Results: Between the semester evaluated, 25,110 subjects were admitted to ED, headache sufferers were equal to 1.6 %. Of these 263 (63.1 %) were woman and 154 (36.9 %). Mean age was 44.2 (DS ± 18.4) years (p = 0.068). According to ED registry, headache admission was as follow assigned: 76.5 % with a diagnosis of headache, 22.8 % with a secondary headache, 0.7 % with Trigeminal Autonomic Cephalgias (TACs). Among those with a primary headache about 36 % of patient did not received a pharmacological treatment. Monotherapy was prescribed less frequently than

combination therapy (19.1 vs 44.5 %). In monotherapy the most frequent medication were NSAIDs (28.3 %), benzodiazepines (26.7 %) and dopamine antagonists (11.7 %). Among those with a primary headache a CT scan was performed in the 124 subjects and 111 (34.8 %) had a neurologist consultation.

Discussion: Our data are in line with the one previously reported in literature. The most frequently medication in the Italian ED were

NSAIDs, benzodiazepines, dopamine antagonists and steroids. Nevertheless our data unlikely can be compared to other study give a snapshot. We believe that much more can be done to improve treatment of primary headache in ED.