

## KETOGENIC DIET AS ANTIEPILEPTIC THERAPY: NEUROTRANSMISSION EFFECTS

AGATA MALTESE<sup>1</sup>, MARGHERITA SALERNO<sup>2</sup>, PALMIRA ROMANO<sup>3</sup>, ANNACLAUDIA RICCIARDI<sup>3</sup>, TERESA DI FILIPPO, GABRIELE TRIPÌ<sup>4,5</sup>

<sup>1</sup>Department of Psychological, Pedagogical and Educational Sciences, University of Palermo, Italy - <sup>2</sup>Sciences for Mother and Child Health Promotion, University of Palermo, Italy- <sup>3</sup>Clinic of Child and Adolescent Neuropsychiatry, Department of Mental Health and Physical and Preventive Medicine; Università degli Studi della Campania “Luigi Vanvitelli”, Italy - <sup>4</sup>Department PROSAMI, University of Palermo, Italy - <sup>5</sup>Childhood Psychiatric Service for Neurodevelopmental Disorders, CH Chinon, France

### ABSTRACT

*The Ketogenic diet (KD) presents many effects on neurotransmitters pathways.*

*KD may act on potassium channels sensitive to ATP (KATP), inhibiting rapamycin pathway in mammals or glutamatergic synaptic transmission or mediated by peptide hormones.*

**Keywords:** *ketogenic diet, epilepsy, cholesterol, free fatty acids.*

DOI: 10.19193/0393-6384\_2017\_5\_114

**Received** April 30, 2017; **Accepted** May 20, 2017

### Neurotransmission alteration

The Ketogenic diet (KD) presents many effects on neurotransmitters pathways.

All of the ketone bodies are converted to acetyl-CoA and enter the Krebs cycle through the pathway of the citrate synthase. This results in the consumption of oxalacetate which is necessary for the transamination of aspartate glutamate by aspartic transaminase (AST). There is thus a buildup of glutamate that becomes more readily available for synthesis of GABA by the glutamic acid decarboxylase (GAD) enzyme. Although the relationship between expression of GAD and GABA levels depends on numerous parameters and is not entirely clear, the increase in GABA, the main inhibitory neurotransmitter, seems to be one of the anti-convulsant mechanisms of ketosis.

There is in fact evidence of high levels of GABA in the liquor of patients responding to the ketogenic diet. However, it is believed that the GABA produced in this way does not act at the level of GABA-A postsynaptic receptors - on which anticonvulsant drugs act instead - but on other types of GABA receptor. Ketone bodies are not the only energy substrate that grows during the diet. Polyunsaturated fatty acids (PUFAs) - which account for more than 90% of total calories - may have an anticonvulsant action directly. Some of them can quickly inhibit the sodium dependent voltage channels and the L-type calcium channels, decreasing the excitability of the neuronal membrane. In addition, some PUFAs act on the mitochondrial level by stimulating the activity of a decoupling protein (UCP). It acts by decreasing the protonic gradient through the internal mitochondrial

membrane necessary for the operation of the complex V (ATP synthase) for the transformation of ADP into ATP. This reduces the formation of ATP and potential energy is dissipated in the form of heat. This also decreases the input of calcium ions into the mitochondria and the production of reactive oxygen species (ROS), resulting in a neuroprotective effect. In fact, the ROSs that are produced during the dramatic bioenergy changes accompanying epileptic seizures are among the major or lower the epileptogenic threshold<sup>(1-45)</sup>.

KD has a dual effect: anticonvulsant - as in animal models it is able to interrupt paroxysmal neuronal discharge; Antiepileptic - due to the property of lowering the epileptogenic threshold. The latter property of modifying the prognosis of epileptic disease is suggested by the fact that many diet-treated patients are also free from crisis even years after its interruption. In addition to PUFAs, ketone bodies are able to protect neurons from oxidative stress induced by hydrogen peroxide and decrease ROS production by mitochondria. The antiradical effect is peculiar, therefore, of the ketogenic diet, and there are no antiepileptic drugs with the same properties. Other action level is represented by potassium channels sensitive to ATP (KATP).

In addition to the pancreas, where they regulate insulin secretion, these channels are also present on the neuronal and glial membranes in some encephalic areas including hippocampus, hypothalamus, nigra substance and vagus nerve nucleus. In particular, the parsiluted nigra substrate (SNPR) appears to play a role in the subcortical modulation of epileptic seizure propagation. According to some experimental studies, ketone bodies are able to block repetitive SNPR neurons by inhibition of KATP channels. KATPs are also present on the internal mitochondrial membrane and their modulation by ketone bodies reduces the formation of KATP channels. ROS. Alternative to KATP would be another type of potassium channel involved in the antiepileptic action of ketone bodies: the K2p that seems to be best to represent the physiological link between neuronal excitability and metabolic activity as its regulatory activity on membrane potential is most influenced by various parameters such as pH, temperature, osmolality, intracranial pressure. K2p is also activated by the PUFAs. The above hypotheses do not represent the only mode of action of the ketogenic diet, as there are certainly other misconceptions or studies. This is well correlated with the complexity of the alterations at the

base of epileptic disease and the onset of crises, from which the need for various clinical approaches. It goes without saying that the therapeutic success of the ketogenic diet is not a single result, but of multiple fundamental mechanisms that are parallel and sometimes synergistic among themselves<sup>(46-70)</sup>.

Moreover, another relevant mechanism of KD on neurotransmitters can be identified in the inhibition of rapamycin pathway in mammals. This pathway has a pathophysiological role in a variety of epilepsy syndromes and animal models of epileptic seizures. The Mammalian target of rapamycin is a serine-threonine protein kinase, characterized as intracellular integrator of metabolic signals. This pathway responds indirectly to a variety of metabolic inputs including the insulin receptor, fasting, ATP/adenosine monophosphate (AMP) ratio, and hypoglycemia. In turn, this pathway regulates protein translation, lipid biosynthesis, autophagy, and mitochondrial biogenesis. Mammalian target of rapamycin pathway proteins localize to synapses and inhibition of the mammalian target of rapamycin with rapamycin impairs late-phase long-term potentiation and long-term depression. However, excessive activity of this pathway is pathological and leads to human disorders including tuberous sclerosis complex, Cowden syndrome, and some forms of cancer<sup>(71-80)</sup>.

Moreover, also the inhibition of glutamatergic synaptic transmission may be identified as long-standing effect of KD. Ketones contribute to the anti-seizure effect of the diet, then the degree of seizure control might correlate with the serum ketone concentration while on KD. Many reports showed better seizure control with higher serum  $\beta$ -hydroxybutyrate levels, but most other clinical reports found no or only a transient correlation between serum  $\beta$ -hydroxybutyrate or acetoacetate concentrations and seizure control. Similarly, some animal studies have found a correlation between serum  $\beta$ -hydroxybutyrate levels and seizure control, and others have not. Together, the clinical studies and animal data indicate that the relationship between ketones and seizure control is unclear.

Finally a new hypothesized mechanism for KD effects on cerebral neurotransmitters pathways involves peptide hormones. In general, several peripheral peptides produced in the gut and associated tissues have been suggested to link changes in body metabolism with central nervous system functions and, thus, may be critical regulators in

various pathophysiological conditions, including control of neuronal excitability in epilepsy. Peptide hormones are short molecules composed of approximately 3-100 amino acid residues, characterized by a structure simpler than that for proteins. Some are also synthesized by neurons and termed neuropeptides. Peptides and neuropeptides act through G-protein coupled receptors diffusely expressed in the nervous system. Neuropeptides can act at a distance by diffusing from the releasing site in the extracellular space to interact with extrasynaptic receptors and produce long-lasting effects. At least one receptor for each peptide hormone has been identified, which means that presumably several hundred receptors can affect a multitude of intracellular transduction pathways, complicating the interpretation of their functions. Many peptides are expressed in neurons that co-express at least one classic transmitter and often more than one neuropeptide<sup>(81-100)</sup>.

## References

- 1) Chieffi S, Messina G, Villano I, Messina A, Esposito M, Monda V, Valenzano A, Moscatelli F, Esposito T, Carotenuto M, Viggiano A, Cibelli G, Monda M. Exercise Influence on Hippocampal Function: Possible Involvement of Orexin-A. *Front Physiol.* 2017 Feb 14; 8: 85. doi: 10.3389/fphys.2017.00085. eCollection 2017.
- 2) Verrotti A, Casciato S, Spalice A, Carotenuto M, Striano P, Parisi P, Zamponi N, Savasta S, Rinaldi VE, D'Alonzo R, Mecarini F, Ritaccio AJ, Di Gennaro G. Coexistence of childhood absence epilepsy and benign epilepsy with centrotemporal spikes: A case series. *Eur J Paediatr Neurol.* 2017 May; 21(3): 570-575. doi: 10.1016/j.ejpn.2017.02.002.
- 3) Villano I, Messina A, Valenzano A, Moscatelli F, Esposito T, Monda V, Esposito M, Precenzano F, Carotenuto M, Viggiano A, Chieffi S, Cibelli G, Monda M, Messina G. Basal Forebrain Cholinergic System and Orexin Neurons: Effects on Attention. *Front Behav Neurosci.* 2017 Jan 31; 11:10. doi: 10.3389/fnbeh.2017.00010.
- 4) Toldo I, Rattin M, Perissinotto E, De Carlo D, Bolzonella B, Nosadini M, Rossi LN, Vecchio A, Simonati A, Carotenuto M, Scalas C, Scirucchio V, Raieli V, Mazzotta G, Tozzi E, Valeriani M, Cianchetti C, Balottin U, Guidetti V, Sartori S, Battistella PA. Survey on treatments for primary headaches in 13 specialized juvenile Headache Centers: The first multicenter Italian study. *Eur J Paediatr Neurol.* 2017 May; 21(3): 507-521. doi: 10.1016/j.ejpn.2016.12.009.
- 5) Messina A, De Fusco C, Monda V, Esposito M, Moscatelli F, Valenzano A, Carotenuto M, Viggiano E, Chieffi S, De Luca V, Cibelli G, Monda M, Messina G. Role of the Orexin System on the Hypothalamus-Pituitary-Thyroid Axis. *Front Neural Circuits.* 2016 Aug 25; 10: 66. doi: 10.3389/fncir.2016.00066.
- 6) Matricardi S, Spalice A, Salpietro V, Di Rosa G, Balistreri MC, Grosso S, Parisi P, Elia M, Striano P, Accorsi P, Cusmai R, Specchio N, Coppola G, Savasta S, Carotenuto M, Tozzi E, Ferrara P, Ruggieri M, Verrotti A. Epilepsy in the setting of full trisomy 18: A multicenter study on 18 affected children with and without structural brain abnormalities. *Am J Med Genet C Semin Med Genet.* 2016 Sep; 172(3): 288-95. doi: 10.1002/ajmg.c.31513.
- 7) Moscatelli F, Valenzano A, Petito A, Triggiani AI, Ciliberti MAP, Luongo L, Carotenuto M, Esposito M, Messina A, Monda V, Monda M, Capranica L, Messina G, Cibelli G. Relationship between blood lactate and cortical excitability between taekwondo athletes and non-athletes after hand-grip exercise. *Somatosens Mot Res.* 2016 Jun; 33(2): 137-44. doi: 10.1080/08990220.2016.1203305.
- 8) Carotenuto M, Esposito M, Cortese S, Laino D, Verrotti A. Children with developmental dyslexia showed greater sleep disturbances than controls including problems initiating and maintaining sleep. *Acta Paediatr.* 2016 Sep; 105(9): 1079-82. doi: 10.1111/apa.13472.
- 9) Franzoni E, Matricardi S, Di Pisa V, Capovilla G, Romeo A, Tozzi E, Pruna D, Salerno GG, Zamponi N, Accorsi P, Giordano L, Coppola G, Cerminara C, Curatolo P, Nicita F, Spalice A, Grosso S, Pavone P, Striano P, Parisi P, Boni A, Gobbi G, Carotenuto M, Esposito M, Cottone C, Verrotti A. Refractory absence seizures: An Italian multicenter retrospective study. *Eur J Paediatr Neurol.* 2015 Nov; 19(6): 660-4. doi: 10.1016/j.ejpn.2015.07.008.
- 10) Morandi A, Bonnefond A, Lobbens S, Carotenuto M, Del Giudice EM, Froguel P, Maffei C. A girl with incomplete Prader-Willi syndrome and negative MS-PCR, found to have mosaic maternal UPD-15 at SNP array. *Am J Med Genet A.* 2015 Nov; 167A(11): 2720-6. doi: 10.1002/ajmg.a.37222.
- 11) Pasquali D, Carotenuto M, Leporati P, Esposito M, Antinolfi L, Esposito D, Accardo G, Carella C, Chiovato L, Rotondi M. Maternal hypothyroidism and subsequent neuropsychological outcome of the progeny: a family portrait. *Endocrine.* 2015 Dec; 50(3): 797-801. doi: 10.1007/s12020-015-0564-3.
- 12) Esposito M, Precenzano F, Sorrentino M, Avolio D, Carotenuto M. A Medical Food Formulation of Griffonia simplicifolia/Magnesium for Childhood Periodic Syndrome Therapy: An Open-Label Study on Motion Sickness. *J Med Food.* 2015 Aug; 18(8): 916-20. doi: 10.1089/jmf.2014.0113.
- 13) Esposito M, Gallai B, Roccella M, Marotta R, Lavano F, Lavano SM, Mazzotta G, Bove D, Sorrentino M, Precenzano F, Carotenuto M. Anxiety and depression levels in prepubertal obese children: a case-control study. *Neuropsychiatr Dis Treat.* 2014 Oct 3; 10: 1897-902. doi: 10.2147/NDT.S69795.
- 14) Verrotti A, Cusmai R, Laino D, Carotenuto M, Esposito M, Falsaperla R, Margari L, Rizzo R, Savasta S, Grosso S, Striano P, Belcastro V, Franzoni E, Curatolo P, Giordano L, Freri E, Matricardi S, Pruna D, Toldo I, Tozzi E, Lobefalo L, Operto F, Altobelli E, Chiarelli F, Spalice A. Long-term outcome of epilepsy in patients

- with Prader-Willi syndrome. *J Neurol*. 2015 Jan; 262(1): 116-23. doi: 10.1007/s00415-014-7542-1.
- 15) Verrotti A, Carotenuto M, Altieri L, Parisi P, Tozzi E, Belcastro V, Esposito M, Guastaferrò N, Ciuti A, Mohn A, Chiarelli F, Agostinelli S. Migraine and obesity: metabolic parameters and response to a weight loss programme. *Pediatr Obes*. 2015 Jun; 10(3): 220-5. doi: 10.1111/ijpo.245.
- 16) Carotenuto M, Parisi P, Esposito M, Cortese S, Elia M. Sleep alterations in children with refractory epileptic encephalopathies: a polysomnographic study. *Epilepsy Behav*. 2014 Jun; 35:50-3. doi: 10.1016/j.yebeh.2014.03.009.
- 17) Perillo L, Esposito M, Caprioglio A, Attanasio S, Santini AC, Carotenuto M. Orthodontic treatment need for adolescents in the Campania region: the malocclusion impact on self-concept. *Patient Prefer Adherence*. 2014 Mar 19; 8: 353-9. doi: 10.2147/PPA.S58971
- 18) Santamaria F, Esposito M, Montella S, Cantone E, Mollica C, De Stefano S, Mirra V, Carotenuto M. Sleep disordered breathing and airway disease in primary ciliary dyskinesia. *Respirology*. 2014 May; 19(4): 570-5. doi: 10.1111/resp.12273.
- 19) Esposito M, Marotta R, Roccella M, Gallai B, Parisi L, Lavano SM, Carotenuto M. Pediatric neurofibromatosis 1 and parental stress: a multicenter study. *Neuropsychiatr Dis Treat*. 2014 Jan 22; 10: 141-6. doi: 10.2147/NDT.S5518.
- 20) Esposito M, Ruberto M, Gimigliano F, Marotta R, Gallai B, Parisi L, Lavano SM, Roccella M, Carotenuto M. Effectiveness and safety of Nintendo Wii Fit Plus™ training in children with migraine without aura: a preliminary study. *Neuropsychiatr Dis Treat*. 2013; 9:1803-10. doi: 10.2147/NDT.S53853.
- 21) Carotenuto M, Esposito M, Di Pasquale F, De Stefano S, Santamaria F. Psychological, cognitive and maternal stress assessment in children with primary ciliary dyskinesia. *World J Pediatr*. 2013 Nov; 9(4):312-7. doi: 10.1007/s12519-013-0441-1
- 22) Di Filippo T, Orlando MF, Concialdi G, La Grutta S, Lo Baido R, Epifanio MS, Esposito M, Carotenuto M, Parisi L, Roccella M. The quality of life in developing age children with celiac disease. *Minerva Pediatr*. 2013 Dec; 65(6): 599-608.
- 23) Esposito M, Parisi L, Gallai B, Marotta R, Di Dona A, Lavano SM, Roccella M, Carotenuto M. Attachment styles in children affected by migraine without aura. *Neuropsychiatr Dis Treat*. 2013; 9: 1513-9. doi: 10.2147/NDT.S52716.
- 24) Esposito M, Gimigliano F, Ruberto M, Marotta R, Gallai B, Parisi L, Lavano SM, Mazzotta G, Roccella M, Carotenuto M. Psychomotor approach in children affected by nonretentive fecal soiling (FNRFs): a new rehabilitative purpose. *Neuropsychiatr Dis Treat*. 2013; 9:1433-41. doi: 10.2147/NDT.S51257;
- 25) Bellini B, Arruda M, Cescut A, Saulle C, Persico A, Carotenuto M, Gatta M, Nacinovich R, Piazza FP, Termine C, Tozzi E, Lucchese F, Guidetti V. Headache and comorbidity in children and adolescents. *J Headache Pain*. 2013 Sep 24; 14: 79. doi:10.1186/1129-2377-14-79.
- 26) Esposito M, Roccella M, Gallai B, Parisi L, Lavano SM, Marotta R, Carotenuto M. Maternal personality profile of children affected by migraine. *Neuropsychiatr Dis Treat*. 2013; 9:1351-8. doi: 10.2147/NDT.S51554.
- 27) Perillo L, Esposito M, Contiello M, Lucchese A, Santini AC, Carotenuto M. Oculusal traits in developmental dyslexia: a preliminary study. *Neuropsychiatr Dis Treat*. 2013; 9: 1231-7. doi: 10.2147/NDT.S49985.
- 28) Esposito M, Marotta R, Gallai B, Parisi L, Patriciello G, Lavano SM, Mazzotta G, Roccella M, Carotenuto M. Temperamental characteristics in childhood migraine without aura: a multicenter study. *Neuropsychiatr Dis Treat*. 2013; 9: 1187-92. doi: 10.2147/NDT.S50458.
- 29) Esposito M, Antinolfi L, Gallai B, Parisi L, Roccella M, Marotta R, Lavano SM, Mazzotta G, Precenzano F, Carotenuto M. Executive dysfunction in children affected by obstructive sleep apnea syndrome: an observational study. *Neuropsychiatr Dis Treat*. 2013; 9: 1087-94. doi: 10.2147/NDT.S47287.
- 30) Esposito M, Gallai B, Parisi L, Castaldo L, Marotta R, Lavano SM, Mazzotta G, Roccella M, Carotenuto M. Self-concept evaluation and migraine without aura in childhood. *Neuropsychiatr Dis Treat*. 2013; 9: 1061-6. doi: 10.2147/NDT.S49364.
- 31) Esposito M, Gallai B, Parisi L, Roccella M, Marotta R, Lavano SM, Mazzotta G, Patriciello G, Precenzano F, Carotenuto M. Visuomotor competencies and primary monosymptomatic nocturnal enuresis in prepubertal aged children. *Neuropsychiatr Dis Treat*. 2013; 9: 921-6. doi: 10.2147/NDT.S46772.
- 32) Esposito M, Parisi P, Miano S, Carotenuto M. Migraine and periodic limb movement disorders in sleep in children: a preliminary case-control study. *J Headache Pain*. 2013 Jul 1; 14:57. doi: 10.1186/1129-2377-14-57;
- 33) Gallelli L, Avenoso T, Falcone D, Palleria C, Peltrone F, Esposito M, De Sarro G, Carotenuto M, Guidetti V. Effects of acetaminophen and ibuprofen in children with migraine receiving preventive treatment with magnesium. *Headache*. 2014 Feb; 54(2): 313-24. doi: 10.1111/head.12162.
- 34) Carotenuto M, Gimigliano F, Fiordelisi G, Ruberto M, Esposito M. Positional abnormalities during sleep in children affected by obstructive sleep apnea syndrome: the putative role of kinetic muscular chains. *Med Hypotheses*. 2013 Aug; 81(2): 306-8. doi: 10.1016/j.mehy.2013.04.023.
- 35) Esposito M, Gallai B, Parisi L, Roccella M, Marotta R, Lavano SM, Mazzotta G, Carotenuto M. Primary nocturnal enuresis as a risk factor for sleep disorders: an observational questionnaire-based multicenter study. *Neuropsychiatr Dis Treat*. 2013; 9: 437-43. doi: 10.2147/NDT.S43673.
- 36) Carotenuto M, Esposito M. Nutraceuticals safety and efficacy in migraine without aura in a population of children affected by neurofibromatosis type I. *Neurol Sci*. 2013 Nov; 34(11): 1905-9. doi: 10.1007/s10072-013-1403-z.
- 37) Esposito M, Carotenuto M. Intellectual disabilities and power spectra analysis during sleep: a new perspective on borderline intellectual functioning. *J Intellect Disabil Res*. 2014 May; 58(5): 421-9. doi: 10.1111/jir.12036.
- 38) Esposito M, Gallai B, Parisi L, Roccella M, Marotta R, Lavano SM, Gritti A, Mazzotta G, Carotenuto M. Maternal stress and childhood migraine: a new perspec-

- tive on management. *Neuropsychiatr Dis Treat*. 2013;9:351-5. doi: 10.2147/NDT.S42818;
- 39) Esposito M, Roccella M, Parisi L, Gallai B, Carotenuto M. Hypersomnia in children affected by migraine without aura: a questionnaire-based case-control study. *Neuropsychiatr Dis Treat*. 2013;9:289-94. doi: 10.2147/NDT.S42182.
- 40) Parisi L, Di Filippo T, La Grutta S, Lo Baido R, Epifanio MS, Esposito M, Carotenuto M, Roccella M. Sturge-weber syndrome: a report of 14 cases. *Ment Illn*. 2013 Jun 3;5(1):e7. doi: 10.4081/mi.2013.e7;
- 41) Carotenuto M, Gallai B, Parisi L, Roccella M, Esposito M. Acupressure therapy for insomnia in adolescents: a polysomnographic study. *Neuropsychiatr Dis Treat*. 2013; 9: 157-62. doi: 10.2147/NDT.S41892.
- 42) Esposito M, Pascotto A, Gallai B, Parisi L, Roccella M, Marotta R, Lavano SM, Gritti A, Mazzotta G, Carotenuto M. Can headache impair intellectual abilities in children? An observational study. *Neuropsychiatr Dis Treat*. 2012; 8: 509-13. doi:10.2147/NDT.S36863.
- 43) Carotenuto M, Esposito M, Parisi L, Gallai B, Marotta R, Pascotto A, Roccella M. Depressive symptoms and childhood sleep apnea syndrome. *Neuropsychiatr Dis Treat*. 2012; 8: 369-73. doi: 10.2147/NDT.S35974.
- 44) Esposito M, Verrotti A, Gimigliano F, Ruberto M, Agostinelli S, Scuccimarra G, Pascotto A, Carotenuto M. Motor coordination impairment and migraine in children: a new comorbidity? *Eur J Pediatr*. 2012 Nov;171(11):1599-604. doi: 10.1007/s00431-012-1759-8.
- 45) Verrotti A, Agostinelli S, D'Egidio C, Di Fonzo A, Carotenuto M, Parisi P, Esposito M, Tozzi E, Belcastro V, Mohn A, Battistella PA. Impact of a weight loss program on migraine in obese adolescents. *Eur J Neurol*. 2013 Feb; 20(2): 394-7. doi: 10.1111/j.1468-1331.2012.03771.x.
- 46) Elia M, Amato C, Bottitta M, Grillo L, Calabrese G, Esposito M, Carotenuto M. An atypical patient with Cowden syndrome and PTEN gene mutation presenting with cortical malformation and focal epilepsy. *Brain Dev*. 2012 Nov; 34(10): 873-6. doi: 10.1016/j.braindev.2012.03.005;
- 47) Esposito M, Ruberto M, Pascotto A, Carotenuto M. Nutraceutical preparations in childhood migraine prophylaxis: effects on headache outcomes including disability and behaviour. *Neurol Sci*. 2012 Dec; 33(6): 1365-8. doi: 10.1007/s10072-012-1019-8.
- 48) Carotenuto M, Esposito M, D'Aniello A, Ripa CD, Precenzano F, Pascotto A, Bravaccio C, Elia M. Polysomnographic findings in Rett syndrome: a case-control study. *Sleep Breath*. 2013 Mar;17(1):93-8. doi: 10.1007/s11325-012-0654-x. Epub 2012 Mar 7. Erratum in: *Sleep Breath*. 2013 May;17(2):877-8.
- 49) Guzzetta A, D'Acunto MG, Carotenuto M, Berardi N, Bancale A, Biagioni E, Boldrini A, Ghirri P, Maffei L, Cioni G. The effects of preterm infant massage on brain electrical activity. *Dev Med Child Neurol*. 2011 Sep; 53 Suppl 4: 46-51. doi: 10.1111/j.1469-8749.2011.04065.x.
- 50) Carotenuto M, Esposito M, Precenzano F, Castaldo L, Roccella M. Cosleeping in childhood migraine. *Minerva Pediatr*. 2011 Apr; 63(2): 105-9.
- 51) Esposito M, Carotenuto M, Roccella M. Primary nocturnal enuresis and learning disability. *Minerva Pediatr*. 2011 Apr; 63(2): 99-104.
- 52) Esposito M, Carotenuto M. Ginkgolide B complex efficacy for brief prophylaxis of migraine in school-aged children: an open-label study. *Neurol Sci*. 2011 Feb; 32(1): 79-81. doi: 10.1007/s10072-010-0411-5.
- 53) Esposito M, Carotenuto M. Borderline intellectual functioning and sleep: the role of cyclic alternating pattern. *Neurosci Lett*. 2010 Nov 19; 485(2): 89-93. doi: 10.1016/j.neulet.2010.08.062,
- 54) Carotenuto M, Esposito M, Pascotto A. Facial patterns and primary nocturnal enuresis in children. *Sleep Breath*. 2011 May; 15(2): 221-7. doi: 10.1007/s11325-010-0388-6.
- 55) Guzzetta A, Pizzardi A, Belmonti V, Boldrini A, Carotenuto M, D'Acunto G, Ferrari F, Fiori S, Gallo C, Ghirri P, Mercuri E, Romeo D, Roversi MF, Cioni G. Hand movements at 3 months predict later hemiplegia in term infants with neonatal cerebral infarction. *Dev Med Child Neurol*. 2010 Aug; 52(8): 767-72. doi: 10.1111/j.1469-8749.2009.03497.x.
- 56) Carotenuto M, Santoro N, Grandone A, Santoro E, Pascotto C, Pascotto A, Perrone L, del Giudice EM. The insulin gene variable number of tandem repeats (INS VNTR) genotype and sleep disordered breathing in childhood obesity. *J Endocrinol Invest*. 2009 Oct;32(9):752-5. doi: 10.3275/6398.
- 57) Elia M, Falco M, Ferri R, Spalletta A, Bottitta M, Calabrese G, Carotenuto M, Musumeci SA, Lo Giudice M, Fichera M. CDKL5 mutations in boys with severe encephalopathy and early-onset intractable epilepsy. *Neurology*. 2008 Sep 23;71(13):997-9. doi: 10.1212/01.wnl.0000326592.37105.88.
- 58) Carotenuto M, Bruni O, Santoro N, Del Giudice EM, Perrone L, Pascotto A. Waist circumference predicts the occurrence of sleep-disordered breathing in obese children and adolescents: a questionnaire-based study. *Sleep Med*. 2006 Jun; 7(4): 357-61.
- 59) Carotenuto M, Guidetti V, Ruju F, Galli F, Tagliente FR, Pascotto A. Headache disorders as risk factors for sleep disturbances in school aged children. *J Headache Pain*. 2005 Sep; 6(4): 268-70.
- 60) Coppola G, Auricchio G, Federico R, Carotenuto M, Pascotto A. Lamotrigine versus valproic acid as first-line monotherapy in newly diagnosed typical absence seizures: an open-label, randomized, parallel-group study. *Epilepsia*. 2004 Sep; 45(9): 1049-53.
- 61) Coppola G, Licciardi F, Sciscio N, Russo F, Carotenuto M, Pascotto A. Lamotrigine as first-line drug in childhood absence epilepsy: a clinical and neurophysiological study. *Brain Dev*. 2004 Jan; 26(1): 26-9.
- 62) Capovilla G, Beccaria F, Montagnini A, Cusmai R, Franzoni E, Moscano F, Coppola G, Carotenuto M, Gobbi G, Seri S, Nabbout R, Vigeveno F. Short-term nonhormonal and nonsteroid treatment in West syndrome. *Epilepsia*. 2003 Aug; 44(8): 1085-867.
- 63) Precenzano F, Ruberto M, Parisi L, Salerno M, Maltese A, Vagliano C, Messina G, Di Folco A, Di Filippo T, Roccella M. Executive functioning in preschool children affected by autism spectrum disorder: a pilot study. *Acta Medica Mediterranea*, 2017, 33: 35-39; DOI: 10.19193/0393-6384\_2017\_1\_005.

- 64) Precenzano F, Lombardi P, Ruberto M, Parisi L, Salerno M, Maltese A, D'alessandro I, Della Valle I, Magliulo RM, Messina G, Roccella M. Internalizing symptoms in children affected by childhood absence epilepsy: a preliminary study. *Acta Medica Mediterranea*, 2016, 32: 1749-1753; DOI: 10.19193/0393-6384\_2016\_6\_158.
- 65) Precenzano F, Ruberto M, Parisi L, Salerno M, Maltese A, D'alessandro I, Grappa MF, Magliulo RM, Messina G, Roccella M. Borderline intellectual functioning and parental stress: an italian case-control study. *Acta Medica Mediterranea*, 2016, 32: 1761-1765; DOI: 10.19193/0393-6384\_2016\_6\_160.
- 66) Ruberto M, Precenzano F, Parisi L, Salerno M, Maltese A, Messina G, Roccella M. Visuomotor integration skills in children affected by obstructive sleep apnea syndrome: a case-control study. *Acta Medica Mediterranea*, 2016, 32: 1659; DOI: 10.19193/0393-6384\_2016\_5\_146.
- 67) Parisi L, Ruberto M, Precenzano F, Di Filippo T, Russotto C, Maltese A, Salerno M, Roccella M. The quality of life in children with cerebral palsy. *Acta Medica Mediterranea*, 2016, 32: 1665; DOI: 10.19193/0393-6384\_2016\_5\_147.
- 68) Epifanio, M.S., Genna, V., De Luca, C., Roccella, M., La Grutta, S. Paternal and maternal transition to parenthood. The risk of postpartum depression and parenting stress. *2015 Pediatric Reports*, 7 (2), pp. 38-44.
- 69) Parisi, L., Di Filippo, T., Roccella, M. The child with Autism Spectrum Disorders (ASDS): Behavioral and neurobiological aspects. *Acta Medica Mediterranea*, 2015, 31 (6), pp. 1187-1194.
- 70) Vecchio D, Salzano E, Vecchio A, Di Filippo T, Roccella, M. A case of femoral-facial syndrome in a patient with autism spectrum disorders. *Minerva Pediatrica*, 2011, 63 (4), pp. 341-344.
- 71) Parisi, L., Di Filippo, T., Roccella, M. Hypomelanosis of Ito: Neurological and psychiatric pictures in developmental age. *Minerva Pediatrica*, 2012, 64 (1), pp. 65-70.
- 72) Di Filippo, T., Parisi, L., Roccella, M. Psychological aspects in children affected by Duchenne de Boulogne muscular dystrophy. *Mental Illness*, 2012, 4 (1), pp. 21-24.
- 73) Epifanio MS, Genna V, Vitello MG, Roccella M, La Grutta S. Parenting stress and impact of illness in parents of children with coeliac disease. *Pediatr Rep*. 2013 Dec 19; 5(4): e19. doi: 10.4081/pr.2013.e19.
- 74) Precenzano F, Ruberto M, Parisi L, Salerno M, Maltese A, D'alessandro I, Della Valle I, Visco G, Magliulo RM, Messina G, Roccella M. ADHD-like symptoms in children affected by obstructive sleep apnea syndrome: case-control study. *Acta Medica Mediterranea*, 2016, 32: 1755-1759; DOI: 10.19193/0393-6384\_2016\_6\_159.
- 75) Parisi L, Salerno M, Maltese A, Tripi G, Romano P, Di Folco A, Di Filippo T, Roccella M. Anxiety levels in mothers of children affected by X-fragile syndrome. *Acta Medica Mediterranea*, 2017, 33: 495; DOI: 10.19193/0393-6384\_2017\_3\_074.
- 76) Parisi L, Salerno M, Maltese A, Tripi G, Romano P, Di Folco A, Di Filippo T, Roccella M. Autonomic regulation in autism spectrum disorders. *Acta Medica Mediterranea*, 2017, 33: 491; DOI: 10.19193/0393-6384\_2017\_3\_073.
- 77) Parisi L, Salerno M, Maltese A, Tripi G, Romano P, Di Folco A, Di Filippo T, Messina G, Roccella M. Emotional intelligence and obstructive sleep apnea syndrome in children: preliminary case-control study. *Acta Medica Mediterranea*, 2017, 33: 485; DOI: 10.19193/0393-6384\_2017\_3\_072.
- 78) Parisi L, Salerno M, Maltese A, Tripi G, Romano P, Di Folco A, Di Filippo T, Roccella M. Paternal shift-working and sleep disorders in children affected by primary nocturnal enuresis. *Acta Medica Mediterranea*, 2017, 33: 481; DOI: 10.19193/0393-6384\_2017\_3\_071.
- 79) Moscatelli F, Valenzano A, Monda V, Ruberto M, Monda G, Triggiani AI, Monda E, Chieffi S, Villano I, Parisi L, Roccella M, Messina A. Transcranial Magnetic Stimulation (TMS) application in sport medicine: A brief review. *Acta Medica Mediterranea*, 2017, 33: 423; Doi: 10.19193/0393-6384\_2017\_3\_062.
- 80) Parisi L, Faraldo Ma, Ruberto M, Salerno M, Maltese A, Di Folco A, Messina G, Di Filippo T, Roccella M. Life events and primary monosymptomatic nocturnal enuresis: a pediatric pilot study. *Acta Medica Mediterranea*, 2017, 33: 23; DOI: 10.19193/0393-6384\_2017\_1\_003;
- 81) Precenzano F, Ruberto M, Parisi L, Salerno M, Maltese A, Verde D, Tripi G, Romano P, Di Folco A, Di Filippo T, Messina G, Roccella M. Sleep habits in children affected by autism spectrum disorders: a preliminary case-control study. *Acta Medica Mediterranea*, 2017, 33: 405; Doi: 10.19193/0393-6384\_2017\_3\_059.
- 82) Parisi L, Fortunato MR, Salerno M, Maltese A, Di Folco A, Di Filippo T, Roccella M. Sensory perception in preschool children affected by autism spectrum disorder: A pilot study. *Acta Medica Mediterranea*, 2017, 33: 49; Doi: 10.19193/0393-6384\_2017\_1\_007.
- 83) Panico A, Messina G, Lupoli GA, Lupoli R, Cacciapuoti M, Moscatelli F, Esposito T, Villano I, Valenzano A, Monda V, Messina A, Precenzano F, Cibelli G, Monda M, Lupoli G. Quality of life in overweight (obese) and normal-weight women with polycystic ovary syndrome. *Patient Prefer Adherence*. 2017 Mar 2;11:423-429. doi: 10.2147/PPA.S119180.
- 84) Precenzano F, Ruberto M, Parisi L, Salerno M, Maltese A, Gallai B, Marotta R, Lavano SM, Lavano F, Roccella M. Visual-spatial training efficacy in children affected by migraine without aura: a multicenter study. *Neuropsychiatr Dis Treat*. 2017 Jan 27; 13: 253-258. doi: 10.2147/NDT.S119648.
- 85) Alesi, M., Battaglia, G., Roccella, M., Testa, D., Palma, A., Pepi, A. Improvement of gross motor and cognitive abilities by an exercise training program: Three case reports (2014) *Neuropsychiatric Disease and Treatment*, 10, pp. 479-485;
- 86) Parisi, L., Di Filippo, T., Roccella, M. Behavioral phenotype and autism spectrum disorders in Cornelia de Lange syndrome. (2015) *Mental Illness*, 7 (2), pp. 32-35.
- 87) Epifanio MF, Genna V, Di Marco S, Furnari ML, Pardo F, Collura, M., Roccella, M., La Grutta, S. Quality of life, affect regulation and resilience in adult patients with cystic fibrosis (2013) *Gazzetta Medica Italiana Archivio per le Scienze Mediche*, 172 (9), pp. 705-711;
- 88) Messina G, Vicidomini C, Viggiano A, Tafuri D, Cozza V, Cibelli G, Devastato A, De Luca B, Monda M.

- Enhanced parasympathetic activity of sportive women is paradoxically associated to enhanced resting energy expenditure. *Auton Neurosci Basic Clin.* 2012; 169(2): 102-106. doi:10.1016/j.autneu.2012.05.003.
- 89) Di Bernardo G, Messina G, Capasso S, Del Gaudio S, Cipollaro M, Peluso G, Casale F, Monda M, Galderisi U. Sera of overweight people promote in vitro adipocyte differentiation of bone marrow stromal cells. *Stem Cell Res Ther.* 2014; 5(1):4. doi:10.1186/scrt393;
- 90) Viggiano A, Chieffi S, Tafuri D, Messina G, Monda M, De Luca B. Laterality of a second player position affects lateral deviation of basketball shooting. *J Sports Sci.* 2013;(October 2013): 37-41. doi:10.1080/02640414.2013.805236.
- 91) Chieffi S, Iavarone A, Iaccarino L, La Marra M, Messina G, De Luca V, Monda M. Age-related differences in distractor interference on line bisection. *Exp Brain Res.* 2014; 232(11): 3659-64. doi:10.1007/s00221-014-4056-0.
- 92) Chieffi S, Iachini T, Iavarone A, Messina G, Viggiano A, Monda M. Flanker interference effects in a line bisection task. *Exp Brain Res.* 2014; 232(4): 1327-1334. doi:10.1007/s00221-014-3851-y.
- 93) Monda M, Messina G, Scognamiglio I, Lombardi A, Martin GA, Sperlongano P, Porcelli M, Caraglia M, Stiuso P. Short-term diet and moderate exercise in young overweight men modulate cardiocyte and hepatocarcinoma survival by oxidative stress. *Oxid Med Cell Longev.* 2014; 2014. doi:10.1155/2014/131024.
- 94) Messina G., Monda V, Moscatelli F, Valenzano AA, Monda G, Esposito T, Blasio SD, Messina A, Tafuri D, Barillari MR, Cibelli G, Chieffi S, Varriale B, Monda M. Role of orexin system in obesity. *Biol Med.* 2015; 7(4). doi:10.4172/0974-8369.1000248.
- 95) Messina G, Palmieri F, Monda V, Messina A, Dalia C, Viggiano A, Tafuri D, Messina A, Moscatelli F, Valenzano A, Cibelli G, Chieffi S, Monda M. Exercise Causes Muscle GLUT4 Translocation in an Insulin-Independent Manner. *Biol Med.* 2015; s3. doi:10.4172/0974-8369.1000s3007.
- 96) Rinaldi B, Guida F, Furiano A, Donniacuo M, Luongo L, Gritti G, Urbanek K, Messina G, Maione S, Rossi F, de Novellis V. Effect of Prolonged Moderate Exercise on the Changes of Nonneuronal Cells in Early Myocardial Infarction. *Neural Plast.* 2015; 2015: 265967. doi:10.1155/2015/265967.
- 97) Messina G, Viggiano A, Tafuri D, Palmieri F, De Blasio S, Messina A, De Luca A, Chieffi S, Monda M. Role of orexin in obese patients in the intensive care unit. *J Anesth Clin Res.* 2014; 5(3). doi:10.4172/2155-6148.1000395.
- 98) La Grutta S, Lo Baido R, Schiera G, Trombini E, Trombini G, Sarno L, Roccella M. Symbolic function explored in children with epilepsy and headache. *Minerva Pediatr.* 2007 Dec ;59(6): 745-54.
- 99) Pisano S, Catone G, Coppola G, Carotenuto M, Iuliano R, Tiano C, Montesanto AR, D'Esposito V, Miraglia EDG, Formisano P, Bravaccio C. Different Immune Signature in Youths Experiencing Antipsychotic-Induced Weight Gain Compared to Untreated Obese Patients. *J Child Adolesc Psychopharmacol.* 2017 Apr 28. doi:10.1089/cap.2016.0203.
- 100) La Grutta S, Guarneri M, Nastri L, Schiera G, Lo Baido R, Sarno L, Roccella M. Expressions of discomfort in adolescents. Clinical reflections resulting from an exploratory study of a group of students. *Minerva Pediatr.* 2006 Dec; 58(6): 513-24.

---

*Corresponding author*  
MARGHERITA SALERNO, MD  
Sciences for Mother and Child Health Promotion  
University of Palermo  
(Italy)