KETOGENIC DIET AS ANTIEPILEPTIC THERAPY: ADMINISTRATION AND FORMULAS

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ABSTRACT

In 1921 Wilder defined classical cholesterol diet providing the patient with a daily calorie intake of less than 20% compared to age-related requirements. The main macronutrient is represented by saturated and long chain unsaturated fatty acids, in the ratio of 4: 1 to carbohydrates and proteins (4 grams of lipids per gram of carbohydrates and proteins). One of the first therapeutic protocols proposed is that of John Hopkins that the onset of the diet should take place in a hospital environment to assess the patient's response in a controlled situation.

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

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Methods of administration and formulas of the ketogenic diet

In 1921 Wilder defined classical cholesterol diet providing the patient with a daily calorie intake of less than 20% compared to age-related requirements. The main macronutrient is represented by saturated and long chain unsaturated fatty acids, in the ratio of 4: 1 to carbohydrates and proteins (4 grams of lipids per gram of carbohydrates and proteins). One of the first therapeutic protocols proposed is that of John Hopkins that the onset of the diet should take place in a hospital environment to assess the patient's response in a controlled situation. This will also help monitor possible side effects and show families the correct therapy management[(1-20)].

A careful clinical history should be made to consider, among other things, the patient's eating habits and the possible presence of pathologies that contraindicate the diet, such as fatty acid oxidation deficiency, porphyria, Pyruvate decarboxylase deficiency (E1) and carnitine deficiency. Treatment begins with the gradual decrease of carbohydrates until the fasting lasts for 24 hours (fluid administration is not interrupted). Ketonuria should be checked 2-3 times a day, blood glucose every 6 hours; Glucose levels of 25 - 40 mg / dL should not be treated if asymptomatic (lethargy, emesis). On the first day (post-fast), the patient should be given 1/3 of the preset calories; On second day 2/3; On the third day the total calories. The main meals are three per day, ranging from two meals. The nutrition regime should be increased by the addition of

supplements, being the poor diet of certain substances such as calcium, selenium, zinc and copper. Patients with familial history of nephrolithiasis or with increases in calcium should be added Citrate Salts to avoid the onset of renal calculus. To facilitate the maintenance of appropriate proportions of all the macro and micronutrients, there are now available, in the form of soluble powder, balanced vanilla flavored formulas, or other flavors, to favor palatability. During the introduction and continuation of the diet, it is necessary to monitor the Glycemia and ketonuria. The latter should remain between 2 and 12 mmol/l. This is easily possible, even at the patient's domicile, through reactive strips (ketostix and destrostix)[21-40].

Due to the modern photo refractometers, it is also possible to evaluate domicilially, using a single device, ketonemia and blood glucose. In addition to being needed to monitor the patient's vital parameters, it is essential to educate parents about how to administer the diet and prepare the menus. In fact, they have to be told that it is necessary to avoid the introduction of "foreign" sugars, for example in medicinal products. Guidelines are also given for the management of any difficulties related to dietary practice and the recognition of symptoms indicating the occurrence of side effects. Even after resignation, parents need to keep in close contact, even telephone, with the child and adolescent neuropsychiatrist and nutritionist, so that all the needs of the small patient are met and the clinical effectiveness monitored. Check-ups are scheduled for the first month of treatment and, in the following months, at pre-established intervals or where appropriate. Once the efficacy of diet therapy has been evaluated - usually within 3 to 6 months - pharmacological therapy begins to be suspended, which may also occur prior to the indicated period if the patient exhibits significant adverse reactions to antiepileptic drugs. However, the possibility of early withdrawal of antiepileptic drugs (within one month) has been evaluated. This option does not have a significant effect on 3-month crisis control and, although it involves the need to prolong the life of the diet for a few months, improves the participation and attentive performance of the patient more quickly. The constant task of family members is to monitor the frequency of crises, ketonuria and ketonemia. Dietary changes can only be introduced if there is a sharp increase in the number of crises in the absence of precipitating factors (accidental ingestion of glucose, fructose, malt destrine, etc.) or if the patient loses too much weight. If weight gain occurs, but there is an excellent crisis control, therapy should not be altered. Crisis control can be optimized, and growth delay is avoided by varying the ketogenicity ratio (4: 1, 3: 1), caloric intake and the amount of fluids. Amongst the unavoidable reasons of diet breakdown, it should be emphasized: evidence of toxicity, clinical inefficiency, crisis disappearance for at least 2 years, patient inability to maintain the diet, explicit request for parental discontinuation of treatment[51-60]. When the interruption is due to the disappearance of the crisis, this must be gradual; Carbohydrates should not be reintroduced suddenly, reducing the lipid / carbohydrate + protein ratio (4: 1 → 3: 1 → 2: 1, etc.) by appropriate dietary strategies by the nutritionist. Some changes have been made to this protocol to improve its effectiveness and tolerability. The early day of fast pre-treatment proved to be indispensable for achieving ketonemia and crisis control. Moreover, its elimination has shown the advantage of not exposing the patient to the risk of acidosis, hypoglycemia, and heavy weight loss. Hypoglycemia can also be treated when less than 45 mg / dL without affecting the achievement of ketonemia (Kim et al., 2004). The quality of the fats used in the ketogenic diet has also been studied. Huttenlocher in 1971 showed that the introduction of medium chain fatty acids (MCTs), instead of the long chain fatty acids (LCTs) used earlier, made the diet more ketogenic[41-60].

This allowed a lesser restriction on the amount of protein and carbohydrates so as to improve their taste. However, these substances caused abdominal swelling and diarrhea, where LCTs caused constipation. To overcome these drawbacks, Schwartz in 1989 suggested the inclusion of both fatty acid types (MCT and LCT) in the diet. This type of formulation is still used today and includes long and medium chain fatty acids: saturated, monounsaturated and polyunsaturated. Pre-dosed soluble powder formulations containing the above mentioned fatty acids, complete with vitamins, minerals, essential amino acids and all the nutrients required for the proper dietary balance have been developed. This option is very useful both to be accompanied by foods prescribed in the ketogenic diet as well as as a single meal in gastrostomy patients and infants. Over time, many variations have been proposed on the classical scheme of the ketogenic diet to extend its effectiveness to typologies of epilepsy etiologically different and more and more patient tolerance

and acceptability. Among these are the modified Atkins diet, the Low Glycemic Diet, and others that are still being experimented (diet with branched amino acids 2.5: 1).1.4 Mechanisms of action. From empirical therapy to scientific evidence. Since its introduction, there have been many questions about the dynamics of action of the ketogenic diet. It is known that dietary factors may affect brain functions, and the concept of treating a chronic disorder such as epilepsy with a nutritional approach has an intrinsic reason to be. But specifically what is the mechanism by which the diet exposes its anticonvulsant action? The purpose of the ketogenic diet is to mimic the fasting condition, and it is during fasting that physiologically produced by endogenous anticonvulsant agents: the ketone bodies. There are historical references to the anticonvulsant action of acetone; but the more precise characterization of anticonvulsant effect of this substance may be identified in dose-dependence effect in the suppression of epileptic episodes in animal models[61-80].

Dietetic therapy was susceptible to animals in which the concentration of acetone at the cerebral level was greater than 1 mM. Hereinafter, the fasting state leads to the production of ketone bodies. When present in appropriate amounts, the Glucose is the preferred energy source for most tissues in our body, and the only one that the brain can use. The major source of glucose comes from the introduction of carbohydrates with the diet. When blood glucose levels fall, they are immediately reported in the standard glucagon stimulating glycogenolysis. Once the liver and muscle deposits of glycogen are exhausted, new glucose is produced by neoglucogenesis starting from alanine and glutamine (neoglucogenic amino acids).

The only source of deposition of amino acids is muscle tissue, so protein catabolism will result in muscle mass loss, but it only occurs in the early hours of fasting. So, in the first few weeks of a ketogenic diet, it is possible to add neoglucogenic amino acids in order to prevent the catabolism of muscle tissue. Subsequently, an adaptation to hypoglycemia will occur which will result in a decrease in glucose utilization by the body, without the consent of the protein pool. As the hypoglycemia continues, the catabolic process of fatty acids, beta-oxidation, begins. In fact, on the third day of ketosis, proteins cease to be catabolized and the only energy sources are free fatty acids and ketone bodies. This is due to the prolongation of hypoglycemia which further increases the release of hormones against insulars, which in turn responsible for the activation of hormone-sensitive lipase. It hydrolyses triglycerides by mobilizing them from the white fatty tissue and makes them available as an energy substrate. The free fatty acids thus obtained are catabolized to acetyl-CoA, a dicarboxylic acid molecule entering the Krebs cycle resulting in further energy production. Under glucose deficiency, less pyruvate is produced by glycolysis and, consequently, for the Krebs cycle, less acetyl-CoA acceptor oxalacetate is available: the rate of formation of acetyl-CoA becomes therefore higher compared to its use. This results in accumulation and condensation with itself, giving rise to ketone bodies: acetic acid, beta-hydroxybutyrate and acetone. This is the process of chetogenesis that occurs in liver mitochondria. When available, free fatty acids can be used as a source of energy from many tissues including the heart and skeletal muscle. Instead, tissues such as the brain, red blood cells, kidney bone marrow, bone marrow and type II muscle fibers, while not being equipped with the metabolic device that they use, need glucose. It is true, however, that the brain and other organs, in the absence of glucose, are able to use ketone bodies as alternate fuels when they are present in sufficient concentration. Continue ketosis in the third week causing a decrease in consumption of ketone bodies from extracerebral tissue by down-regulation of hormones responsible for their use, That there is greater availability for the brain. After the third week, most tissues extract their energy exclusively from the catabolism of free fatty acids, making it possible to maintain adequate levels of ketone bodies for the brain. It is thus clear that the only condition in which the blood level Of ketone bodies is increased, beyond type I diabetes, the increased use of fatty acids by the body, and this can be achieved, as well as with prolonged fasting, by dietary restrictions on carbohydrates. 'Carbohydrate inhibition blocks the fatty acid catabolism, minimizing the introduction of carbohydrates, maximizing lipid catabolism. The correlation between levels of glucose and free fatty acids is called Randle free fatty acid glucose cycle. At the encephalic level, what determines the preferential use of ketone bodies is their blood concentration, which is why it must be kept constantly higher than 2 mmol / l Acetoacetate and 3-beta-hydroxybutyrate represent 75% of energy consumed by the brain under ketosis. These, converted into acetyl-CoA, are catabolized into the Krebs cycle.

A variable amount of pyruvate is normally converted to acetyl-CoA via pyruvate dehydrogenase, but ketone bodies represent the major source of acetyl-CoA (81-100).

Summarizing, there are several hypotheses regarding the molecular mechanism responsible for the therapeutic action of KD:

• Degeneration of the enc ephalic pH (acidosis favors neuroinhibition by direct action on proton-sensitive ion channels)

• Variations in water and electrolytic balance;

• Direct inhibitory effect of polyunsaturated free fatty acids

• Changes in neurotransmission

• Changes in energetic metabolism due to the formation of ketone bodies.

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, Sciruicchio 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, Maffeis 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, Guastaferro 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.S55518.

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. Occlusal 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 perspective 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 with-

out 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, Rippa 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, Vigevano 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.

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