De novo mutation in the DEAF1 gene and its relation to autism: a case study

Mutação de novo no gene DEAF1 e sua relação com o autismo: estudo de caso

Mutación de nuevo en el gen DEAF1 y su relación con el autismo: estudio de caso

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RESUMO

Objetivo: Analisar as implicações, impactos e o desenvolvimento de um indivíduo diagnosticado com TEA e portador da mutação de novo no gene DEAF1, a partir das várias perspectivas de intervenções realizadas. **Método:** Trata-se de um estudo descritivo com histórico dos tratamentos, resultados laboratoriais e genéticos mais recentes do paciente. **Resultados:** Sintomas notados aos 2 anos e diagnóstico específico aos 5. Aos 8 anos teve a primeira crise convulsiva tônico-clônica e o Eletroencefalograma alterado. Após obteve o diagnóstico molecular confirmado. Possuía epilepsia refratária de difícil controle, que houve piora com uma tentativa do uso de derivados canabinoides em conjunto com estimulação elétrica transcraniana. No momento, com os tratamentos, atendimentos multidisciplinares, dieta de exclusão de alérgenos e medicações de controle individual, diminuíram a intensidade das crises epiléticas e houve melhor controle do seu estado geral. **Conclusão:** Este estudo descreve como a mutação de novo no gene DEAF1 está relacionada com o TEA e com o comprometimento do desenvolvimento neurocognitivo. As terapias e métodos devem respeitar cada paciente na sua individualidade.
Descritores: Cromossomos Humanos Par 11; Mutação Pontual; Transtorno do Espectro Autista.

ABSTRACT

Objective: To analyze the implications, impacts and development of an individual diagnosed with ASD and carrying a de novo mutation in the DEAF1 gene, from the various perspectives of interventions performed. **Method:** This is a descriptive study, with the patient's history of treatments, and most recent laboratory and genetic results.**Results:** Symptoms were noticed at 2 years old and specific diagnosis at 5. At 8 years old he had his first tonic-clonic seizure and the electroencephalogram was altered. After, it was obtained the confirmed molecular diagnosis. He had refractory epilepsy that was difficult to control and aggravated with an attempt to use cannabinoid derivatives in conjunction with transcranial electrical stimulation. At the moment, treatments, multidisciplinary care, allergen exclusion diet and individual control medications, reduced the intensity of epileptic seizures and there was better control of his general condition. **Conclusion:** This study describes how the de novo mutation in the DEAF1 gene is related to ASD and neurocognitive development impairment. Therapies and methods must respect each patient in their individuality.
Descriptors: Chromosomes Human Pair 11; Point Mutation; Autism Spectrum Disorder.

RESUMEN

Objetivo: Analizar las implicaciones, impactos y desarrollo de un individuo diagnosticado de TEA y portador de una mutación de novo en el gen DEAF1, desde las distintas perspectivas de las intervenciones realizadas. **Método:** Este es un estudio descriptivo, con el historico de tratamientos del paciente y los resultados genéticos y de laboratorio más recientes. **Resultados:** Los síntomas se notaron a los 2 años y el diagnóstico específico a los 5. A los 8 años tuvo su primera crisis tónico-clónica y se alteró el electroencefalograma. Posteriormente se obtuvo el diagnóstico molecular confirmado. Tenía epilepsia refractaria que era difícil de controlar y se agravaba con un intento de utilizar derivados cannabinoides junto con estimulación eléctrica transcraneal. En el momento, los tratamientos, la atención multidisciplinar, la dieta de exclusión de alérgenos y los medicamentos de control individual, redujeron la intensidad de las crisis epilépticas y hubo un mejor control de su estado general. **Conclusión**: Este estudio describe cómo la mutación de novo en el gen DEAF1 se relaciona con el TEA y el deterioro del desarrollo neurocognitivo. Las terapias y los métodos deben respetar a cada paciente en su individualidad.
Descriptores: Cromosomas par humano 11; Mutación pontual; Trastorno del Espectro Autista.

ORIGINAL

Introduction

Autism is a spectrum of phenotypic disorders of multifactorial origin, involving genetic and environmental components. Being qualified with phenotypes other than neurodevelopment is considered autistic spectrum disorder (ASD). [1]

This disease often has other associated conditions, including depression, epilepsy, anxiety, attention deficit hyperactivity disorder(ADHD). Some children with ASD stop talking and lose certain social skills already acquired around 12 to 24 months. [2]

Some risk conditions include infections and the use of certain medications during pregnancy, low birth weight, having a brother with ASD, older parents, having certain genetic requirements such as Down syndrome, fragile X syndrome, Rett syndrome, among others. It is estimated that ASD is hereditary in about 50 to 90% of cases, which demonstrates the importance of genetic factors in the pathogenesis of the disease. Most cases of ASD are idiopathic and apparently due to complex patterns of genetic inheritance. [1-3]

However, other cases of ASD present rare mutations with great deleterious effect on neuronal development. Only a single high-risk mutation is associated with high genetic penetrance. In these cases, when the mutation was not inherited from any of the parents, but developed during the formation of gametes or zygotics, being exclusive to the child, it is called the mutation "de novo".[4-5]

The DEAF1 gene encodes a transcriptional binding factor, is highly expressed in the central nervous system and is a serotonin receptor regulator 1A receptor (5HT1A). The longer transcribed gene results in polypeptides of 565 amino acids, which is fundamental for transcriptional regulation of serotoninergic synapses. Mutations described in the DEAF1 gene have already been associated with dyslexia, seizures, recurrent infections, cancer, epilepsy, type 1 diabetes mellitus, ASD, speech impairment and intellectual development.[5-7]

To date, there is no biological marker for ASD, as it is a multifactorial disorder, and, likewise, a therapy that completely reverses its symptoms. Most treatments for the central symptoms of ASD are based on behavioral and cognitive interventions. [8]

Therefore, new mutations in the DEAF1 gene are poorly described in the scientific literature, with the vast majority of studies published in other countries and only recently have their impacts on human health been shown. In this sense, the objective of this study was to report the implications and impacts of the new mutation in the DEAF1 gene, as well as the treatments and clinical history of an 11-year-old male patient in autism spectrum disorder.

Method

The study was conducted from March to November 2019. To obtain data, patient information was collected through semi-structured interviews with the child's mother. The data obtained were analyzed from the prenatal family history up to the moment of the interview, based on the results of laboratory tests, genetics, images and treatments used. Retrospective data were observed as a

method of analysis of pathophysiological characteristics and impairments of case evolution.

It is emphasized that all examinations, conducts and prescriptions analyzed were requested by physicians responsible for the treatment of the patient and the procedures and therapies were followed by a multidisciplinary team. The information contained in this article is intended for individual interpretation of the case described for academic purposes and is not intended to be interpreted as generalized medical advice. Only the physicians responsible for each case can diagnose diseases and prescribe treatments and medications.

The study had all ethical procedures required by CNS Resolution 466/2012 complied with and was approved by the Ethics Committee on Research in Human Beings of the Paulista University (UNIP), Campus Indianópolis - SP, number 3.425.613 - CAAE 15143519.5.0000.5512. The term free and informed consent (TCLE) was signed by the person responsible for free will before the interview.

Results

The child under study is male, 11 years old, lives with parents and a neurotypical brother of 13 years. The primary diagnosis of autism was at 2 years and 5 months of age and the specific diagnosis at 5 years of age.

The parents are healthy and non-consanguineous, presented two spontaneous abortions after the birth of the firstborn and the patient's pregnancy. They do not have relevant cases of neurocognitive diseases in family history.

Development and first symptoms of ASD

During pregnancy the mother had gestational diabetes, the delivery was cesarean section and the Kristeller maneuver was performed. The Apgar 9/10 test had severe Jaundice ABO and found the difference in blood typing after birth (patient is B+ and mother O+). The baby did not require an incubator or oxygen and did not present infectious disease. Birth weight: 3600g, Length at birth: 50cm, Head circumference: 36cm.

She breastfed exclusively until she was 5 months old and did not receive supplements or formulas before 6 months of age. Food was introduced at 5 months, and breastfed until 2 years of age. He raised his head at 3 months, kittened about 8 months, walking with 1 year and fully balanced with 1 year and 4 months.

She presented orality before 18 months of age and since the age of two years she undertook uninterrupted speech therapy. His oral expressiveness is really an unelucidated part of the diagnosis, he had speech and gradually lost this aptitude. The fever improves his oral expression, especially high fever, as he returned to speak for a whole week after an episode of fever. The higher, the greater the improvement of the overall picture. Even after epilepsy.

Ever since I was a baby, I've been crying excessively at night. The nocturnal awakening only stopped with the anticonvulsants, this condition is called "night terror", is an abnormal activity of sleep and is part of a category of nocturnal manifestations known as parasomnia. He ceased with the episode when he started the Digestive System Syndrome and Psychology Diet (GAPS),

but still woke up at night, euphoric and interacting for hours. This pattern continued until the beginning of epileptic conditions, from then on the diet had no more beneficial effect.

Eye contact alternated from epileptic seizures, even developed a mild strabismus. It presents self-inceaning behaviors and only stopped hitting the head excessively after 6 months with the inclusion of the gluten-free diet, without casein and with anticonvulsants. It has gait alterations, hyperactive behavior and stereotypes. He gained control of the urethral sphincter about 7 years after quelation treatment in the United States and still does not have control of the anal canal sphincter. However, with the period of 100 daily seizures, urethral control was lost.

It has greater tolerance to pain, at times where there is a worsening of the general condition this tolerance is more pronounced. Fever improves your oral expression, especially high fever. But rarely (before anticonvulsants) became ill or had a fever. The mother clearly describes an improvement in oral communication skills in fever and inflammation events such as infections. And reports that the child returned to speak for a whole week after an episode of fever. The higher, the greater the improvement of the overall picture. Even after epilepsy. Currently seizures and absence seizures are daily and at intervals of 20 minutes.

The symptoms of autism began to be noticed at 2 years and 4 months by the kindergarten teacher. The mother reports progressive regression in speech since he entered school, 1 years and 11 months old. At 2 years and 5 months he was diagnosed with Invasive Developmental Disorder (EDT), where he began to present stereotyped movements and at 3 years of age he ceased to speak after a period of regressions of communication skills.

At 5 years of age, absence crises and spasms were observed, with intervals of up to 20 days between one crisis and another, but without changes in the Electroencephalogram (EEG). Specific diagnosis of autism (ICD 10 - F84.1) was given at 5 years by a Neuropediatrician. At 8 years and 9 months, he had the first tonic-clonic convulsive crisis, altered EEG and slowing the base rhythm. A notable aspect of his epilepsy is that events began after transcranial electrical stimulation and seizure control worsened with the use of cannabinoid derivatives.

Molecular diagnosis

Due to refractory epilepsy that was difficult to control, which at the time was already having many daily seizures, they were referred to a geneticist and in January 2018 did the Complete Sequencing of exoma (SCE). The diagnosis of the mutation was made by means of the SCE, carried out in a private laboratory, with an exon capture method with Agilent SureSelect Clinical Research Exome V2®, followed by new generation sequencing with Illumina HiSeq®. Alignment and identification of variants using bioinformatics protocols, using as reference the GRCh37 version of the human genome. It was identified, in heterozygosis, in the DEAF1 gene (Deformed epidermal autoregulatory factor 1, homolog, OMIM 602635) variant Chr11:681.080 C>G (or alternatively c.880 G>A - ENST0000382409), promoting the replacement of the mistellin amino acid at position 294 by leucine (p. Val294Leu), missense mutation. This variant has not

been previously described in the medical literature and is absent among about 140,000 individuals in the world population.

The combination of the molecular mechanism, characteristics of the region where it is located and the correlation of this gene with clinical symptoms, suggest that this variant is probably pathogenic. Additionally, the variant p.Valina 294Leukin was confirmed by sequencing by the Sanger method in the patient, but is not present in its parents. This variant was then classified as a mutational event "again", thus reinforcing its deleterious character.

Socio-environmental factors

He started school at 1 year and 11 months and attended approximately up to 3 years and 5 months of age, returned at 7 years to the class of global development disorders (TGD). At home they are working on parallel literacy, basic science content, geography and psychomotricity. They conducted online training at the Autism Treatment Center of America and follow the therapeutic form Son-Rise®, a home therapy for children with autism spectrum. Hippotherapy, skateboarding and swimming were interrupted due to epileptic seizures and discontinued with Occupational Therapy over the years. Currently, after a crisis control, he has assistance by psychologist, speech therapist, psychopedagogue, intermediated therapy with animals, psychomotricity and art therapy. In total, including the two hours a day you spend at school, there are about 40 hours of weekly stimulation.

It has dietary restrictions to gluten, casein, soy, sugar, maltodextrin, chemical yeast, purple cabbage, coffee, pork, dyes, cocoa, almond, coconut, beans, fish, ginger and white rice. They also avoid mint, mint and large doses of orange, because of epilepsy. The parents observed that with the exclusion of allergens there was a better response of the general picture. She had gastroesophageal reflux from the first month of life and up to 8 months was constant.

Ineffective treatments / partially effective

All treatments are within therapeutic protocols for ASD and epilepsy and have been recommended by medical experts, as well as clinical observations.

• Injectable macrophage activation therapy (GcMaf) to restore the immune system, but there was an increase in absence seizures.
• Chlorine dioxide to promote bacteria detoxification. At the beginning of treatment there was an improvement in cognition and decreased hyperactivity, but increased absence crises.
• Nystatin for Candida albicans, made him more hyperactive.
• SCIA Protocol – Ibuprofen, to promote decreased brain inflammation and viral replication, there were no adverse reactions or improvements.
• Intravenous rectal ozone therapy, get improvement in the immune system, there was hyperactivity and rapid intoxication.
• Digestive enzymes and lactobacilli to improve the intestinal microbiota. There were no significant changes and the coprological examination continued to accuse poorly digested foods.

• Carnosine, for improvement of oralization and central nervous system, no benefit was observed.
• Carnitine, repair the metabolism of cellular energy, also without changes.
• Omega 3 for anti-inflammatory action, the patient became more hyperactive and with rapid intoxication.
• Methyl-B12 injectable, improve cognition and prevent oxidative stress. It got more communicative, but the improvement was irrelevant.
• REAC - therapy with electromagnetic waves, to optimize the response of the nervous system through the use of asymmetric electrical radio currents making possible the optimization of Neuro-Psycho-Relational Physics. There was a slight improvement in cognition, but spasms worsened.
• Ding Xian Wan - Chinese phytotherapy, used to contain seizures and epilepsy. For a month he was calm, then self-aggressive for 15 days.
• Houston complex homeopathy, improve the immune system. He became less hyperactive, but during the homeopathic quelling of the polio vaccine he had fever and became prostrate.
• Neocate® infant food formula. With 3 doses he became spasmodic and hyperactive, he seemed to convulse.
• Implantation of hematopoietic stem cells with platelet-rich Plasma Implant, integrated with Transcranial Magnetic Stimulation, in order to minimize the behavioral symptoms of ASD. He returned from the spasmodic implant and after one month had the first clonic tonic seizure and started epilepsy difficult to control.
• Cannabidiol without THC - Associated with Depakene®, minimize behavioral symptoms and epilepsy. He became more hyperactive and with about 1 month of use he went into a state of ill and went to the ICU.
• Valpakine®, for the treatment of epilepsy and seizures. It's decreased the tonic clonic seizures, it's already dependent and convulsion if they withdraw. She had severe anemia and decreased the dose.
• Acetazolamine, adjuvant treatment of edema due to epilepsy. Increased the frequency of seizures.
• Urbanil, for anxiolytic use. It accelerated for a few hours after administration of the drug. They discontinued, as it altered the mood and created dependence.
• Etossuximine, treatment for absence and epilepsy seizures. He had more spasms and tonic clonic seizures.
• Phenobarbital, anticonvulsant. Self-aggression, headaches and uncontrollable hyperactivity.
• Lamotrigine, an adjunct to the treatment of partial and generalized seizures, including tonic-clonic seizures. Hyperactivity after administration of the drug and discontinued because it did not have effects on seizures.
• Trileptal®, treatment of epilepsy and seizures. Tremor in the hands, less fine motor coordination and drowsiness after administration of the drug.
• Keppra, antiepileptic therapy. He held the seizures, but had headaches, self-aggression and hyperactivity.
• Vimpat, an adjunct medicine used to treat uncontrolled epilepsy. It showed priaprism.
• Hydrogenius homeopathy, helps minimize behavioral symptoms and epilepsy. From 100 seizures went to 30 a day, but after a flu stopped having any effect.

• Hyosciamus homeopathy, calming effect. Improved behavior and reactions to anticonvulsants, but after a period there was no further therapeutic effect.
• 5HTP – Hydroxytryptophan, promote increased serotonin production. No adverse reactions.

Effective treatments

Better control of epileptic seizures, seizures, sleep, motor coordination, hyperactivity, absence crises, digestion and gastric functions was observed.

• Melatonin, improve sleep quality. He fell asleep more easily.
• Magnesium citrate, repair neuronal function and muscle stiffness. Improved muscle stiffness, spasms and use sporadically.
• Quelation (DMSO and EDTA), intravenous therapy to eliminate heavy metals. Improved hyperactivity, spasms and acquired control of the sphincters.
• Implantation of autologous adipose stem cells to minimize behavioral symptoms of ASD. There was an improvement in fine motor coordination, urea rate and cognition. In addition to rapid rapid recovery liposuction.
• Rivotril® and Diazepam use in emergencies in case of illness or risk of respiratory arrest. It makes you more relaxed and takes you out of epileticus status.
• Zonegran®, a side-adjunct medicine used to treat epilepsy. It decreased the diurnal seizures to almost zero, but initiated the nocturnal clonic tonic seizures. More jerky during the day and touch-sensitive.
• Traditional Chinese medicine with use of herbs to reduce side effects of Zonegran®. Decreased the amount and intensity of nocturnal seizures.

Laboratory tests

The results of laboratory tests of the patient relevant to ASD were performed in October 2019. The reference values are according to gender and age of the patient under study (Table 1). Another characteristic present, which is not necessarily autism and has been accompanying it for about 3 years, is pulmonary hyperventilation, which was confirmed on venous blood gas analysis and urine acid testing.

Table 1 - Relevant examinations in relation to people with ASD.

Test	Result	Alteration	Reference Value
Vitamin D3	15,36 ng/mL	Low	30 to 60 ng/mL
Vitamin K	0,3 µg/L	Low	0,5- 5 µg/L
Vitamin B6	43,5 mcg/L	Stable	5,0 to 30,0 mcg/L
Selenium	64,2 µg/L	Stable	55,0 to 135,0 µg/L
Eric Zinc	74,00 mcg/dL	Low	75,0 to 129,0 mcg/dL
Ammonia	96,1 mcg/dL	High	19,0 to 60,0 mcg/dl
Urea	58 mg/dl	High	19 to 49 mg/dl
Creatine	37,2mcmol/L	Stable	25 to 69 mcmol/L
Serotonin	80,50 ng/mL	Stable	50,00 to 250,00 ng/mL
Histamine	0,13 µg/dL	High	Below 0,11 µg/dl
Specific Enolase	16,76 mcg/L	High	Until 18,3 mcg/L

Ceruloplasmin	24,0 mg/dl	Stable	20 to 60 mg/dl
Antistreptolysin "O"	< 25 IU/mL	Stable	Until 200 IU/mL
Alpha-1 Acid glycoprotein	64,5 mg/dL	Stable	58 to 155 mg/dL
Ferritin	47,8 ng/dL	Stable	22,0 to 322,0 ng/dL
Eric Iron	90 µg/dL	Stable	65 to 175 µg/dL
Uric Acid	4,8 mg/dL	Stable	2,0 to 5,0 mg/dL
Glucose 6 Phosphate	13,3 U/g Hb	Stable	> = 6,7 U/g Hb
Homocysteine	7,8 µmol/L	Stable	5,0 to 12,0 µmol/L
Creatinine	0,44 mg/dL	Stable	0,42 to 0,71 mg/dL
Covers	87,0 mcg/dL	Stable	80,0 to 160,0 mcg/dL
Glucose Fasting	68 mg/dL	Low	70 to 99 mg/dL
Calcium	9,0 mg/dL	High	4,0 to 7,0 mg/dL
Phosphorus	5,9 mg/dL	Stable	4,0 to 7,0 mg/dL
Magnesium	2,3 mg/dL	Stable	1,3 to 2,7 mg/dL
Potassium	3,9 mEq/L	Stable	3,5 to 5,5 mEq/L
Vitamin B12	514 pg/mL	Stable	180 to 900 pg/dL
Vitamin B1	69,1 mcg/L	Stable	28,0 to 85,0 mcg/L
Vitamin A	53,0 mcg/dL	High	26,0 to 49,0 mcg/dL
Total Lipids	446 mg/dL	Stable	317 to 819 mg/dL
Cortisol	16,28 µg/L	Stable	5,27 to 22,45 µg/L
Biotin	184 ng/L	Low	Over 200 ng/L
Oxcarbazepine	25,5 mcg/mL	Stable	Therapeutic level: 13 to 30 mcg/mL
T3 Triiodothyronine Hormone	127 ng/dL	Stable	105 to 207 ng/dL
T4 Hormone Thyroxine	5,00 mcg/dL	Low	5,5 to 12,1 mcg/dL
Thyroid TSH	2,77mcUI/mL	Stable	0,51 to 4,94 mcUI/mL
Rheumatoide Factor	< 9,3 IU/mL	Stable	Below 14 IU/mL
ANA - autoantibodies	NEGATIVE	Stable	NEGATIVE
Tumor Necrosis Factor (TNF)	27,20 pg/mL	High	Below 8,1 pg/mL
Interleukin 6	7,30 pg/mL	High	Below 3,4 pg/mL
Fecal calprotectin	< 5.00 mcg/g	Stable	Below 50 mcg/g

Source: Sabin Laboratory reference values, Brasília, DF, 2019.

Discussion

The DEAF1 variants of new missense described in the literature result in a nonspecific phenotype, more frequent in males, born to healthy and non-consanguineous parents. As observed in the patient in question, the other patients also present developmental delay, epilepsy, seizures, ASD, high threshold pain, gait abnormalities, speech, gastrointestinal abnormalities, hyperactivity and sleep disorders. [6] In the literature there is also a case report of microcephaly. [7]

The use of reliable evaluation scales developed from research and systematizations are useful, as they give objectivity to observation without risking forgetting details. It is interesting, in cases of ASD and mutation in the

DEAF1 gene, to verify the family history for other cases of developmental or neuropsychiatric disorders, as evidence is consolidated in the scientific literature that there are associations between these conditions.[6-7] In this sense, the present study was useful to explain the patient's history. Early intervention in treatment consists of a set of therapeutic modalities aimed at increasing the potential of physiological, social and communication development of the child, protecting intellectual functioning by reducing harm and improving quality of life. Parents should observe the individualized need of each child with ASD and that is in accordance with its functionality, because the treatment involves multidisciplinarity.[3,5,9]

The onset of seizures was observed in the patient using cannabinoid derivatives, Transcranial Magnetic Stimulation, with hematopoietic stem cell implantation and platelet-rich plasma. Usually, these therapies are used to reduce seizures. In addition to being recommended for sleep disorders, ADHD, anxiety and other psychiatric problems.10 There is a gap on recommended treatments and studies are needed before stating any conclusion on the therapeutic potential to prevent or mitigate crises and disorders associated with ASD.[11-12]

The use of modern tools such as genetic analysis, electroencephalographic study, magnetoencephalography, proton emission tomography (PET), neuronal interaction network studies and neurotransmitter analyses are fundamental to establish a better association between ASD and epilepsy. They also enable accurate diagnosis and better planning of therapeutic management.[13]

Laboratory markers are important to check the general status or detect diseases by preventive character, in addition to verifying whether the treatments used, as well as nutritional therapy, are presenting beneficial effect on the patient. Caregivers should monitor the consumption of certain supplements relevant to neuronal development, such as Selenium, Serotonin, Zinc, among others. In addition to checking vitamin D3 levels, hormonal and intoxication by the use of medications.[12] As observed, the patient in this study presented changes in some of the tests and stability in others, showing the clinical diversity in which people with ASD may present.[6]

Children born to mothers with type 1, type 2 or gestational diabetes are more likely to receive a diagnosis of ASD compared to children born to mothers without diabetes during pregnancy. Maternal diabetes, if not well treated, means hyperglycemia in the uterus, which increases uterine inflammation, oxidative stress and hypoxia. These conditions can alter gene expression, disrupt the development of the fetal brain, increasing the risk of neural behavior disorders such as autism.[10] Other risk factors during pregnancy are associated with obesity, hypertension, antidepressant use, low vitamin D levels, advanced maternal and paternal age, smoking and exposure to pollution[14], but these were not observed in the present study.

Newborns who suffer jaundice, such as the patient in this study, have a higher risk of suffering autism. The high rate of bilirubin is neurotoxic and can cause long-term developmental problems. Babies genetically predisposed to autism are likely to be more vulnerable to more severe cases of jaundice.[15]

As also observed in the present study, in cases of ASD, changes in eating habits and associations of gastrointestinal symptoms may occur, such as

constipation, diarrhea, gas distension and abdominal pain. However, working diet therapy individually can improve these symptoms.[16]

Conclusion

This study describes how the de novo mutation in the DEAF1 gene is related to autism and impaired neurocognitive development. Different standard or alternative therapies were used in the patient, which resulted in improved behavior and frequency of epileptic seizures. The practice of personalized dietary interventions seems to favor children with ASD and have action on the central nervous system, such as the exclusion of allergenic foods. The need for specific interventions is emphasized, respecting the individuality of each person and highlighting the importance of the multidisciplinary team, having an impact on the patient's quality of life.

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References

1. Folstein SE, Rosen-Sheidley B. Genetics of austim: complex aetiology for a heterogeneous disorder. Nat Rev Genet. 2001; 2(12):943-55.
2. Gomes PT, Lima LH, Bueno MK, Araújo LA, Souza NM. Autismo no Brasil, desafios familiares e estratégias de superação: revisão sistemática. J Ped. 2015; 91(2):111-21.
3. Griesi-Oliveira K, Sertié AL. Transtornos do espectro autista: um guia atualizado para aconselhamento genético. Einstein (São Paulo). 2017; 15(2):233-8.
4. Lupski JR. New mutations and intellectual function. Nat Genet. 2010; 42(12):1036-8.
5. Sanders SJ, Murtha MT, Gupta AR, Murdoch JD, Raubeson MJ, Willsey AJ, et al. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. Nature. 2012;485(7397):237-41.
6. Vulto-van Silfhout AT, Rajamanickam S, Jensik PJ, Vergult S, De Rocker N, Newhall KJ, et al. Mutations affecting the SAND domain of DEAF1 cause intellectual disability with severe speech impairment and behavioral problems. Am J Hum Genet. 2014 ;94(5):649-61.
7. Sá MJ, Jensik PJ, McGee SR, Parker MJ, Lahiri N, McNeil EP, et al. De novo and biallelic DEAF1 variants cause a phenotypic spectrum. Genet Med. 2019; 21(9):2059-69.
8. Tchaconas A, Adesman A. Autism spectrum disorders: a pediatric overview and update. Curr Opin Pediatr. 2013; 25(1):130-43.
9. Antoniuk SA, Omairi C, Valiati MRMS, Wehmuth M. Transtorno do Espectro Autista: Aspectos Gerais e Critérios Diagnósticos. In: Autismo: perspectivas no dia a dia. Ed. Ìthala. p. 25-33, 2013.
10. Muñoz Yunta JA, Montserrat PB, Salvadó Salvadó B, Valls Santasusana A. Autismo y epilepsia. Acta Neurol Colomb. 2006; 22(2):112-7.

11. Poleg S, Golubchik P, Offen D, Weizman A. Cannabidiol as a suggested candidate for treatment of autism spectrum disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2019; 89:90-6.
12. Fernandes T, Dias AL, Santos NA. Estimulação transcraniana por corrente contínua no autismo: uma revisão sistemática. Psicol: Teor Prática. 2017; 19(1):176-91.
13. da Rocha CC, Gondim CB, Gomes TA, dos Santos LC, de Almeida Cavalcante I. Autismo associado à epilepsia: relato de caso. Rev Eletrônica Acervo Saúde. 2019; 3(20):e337.
14. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-related air pollution, particulate matter, and autism. JAMA psychiatry. 2013; 70(1):71-7.
15. Maimburg RD, Bech BH, Vaeth M, Møller-Madsen B, Olsen J. Neonatal jaundice, autism, and other disorders of psychological development. Pediatrics. 2010; 126(5):872-8.
16. de Oliveira Andrade J, Lacerda MA, de Oliveira Andrade V, Morais LK, Freires JD, Leite NL, et al. Terapia Nutricional para Crianças Portadoras do Transtorno do Espectro Autista–uma Revisão Literária. Int J Nutrology. 2018;11(S 01):Trab755.

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