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CASE REPORT

Neurological manifestations of Ogden Syndrome: Case report

Rui Carlos Silva Júnior[1], Maria Rigotto de Almeida[2], Lorena Vilela Rezende[1], Mariah Pereira de Andrade Vallim[1], Davi Leitner Carboni[3], Giulia Vilela Silva[1], Mara Lúcia Schmitz Ferreira Santos[1], Josiane de Souza[4], Michelle Silva Zeny[1], Daniel Almeida do Valle[1]

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Abstract

Introduction: The syndrome related to a mutation in the N-alpha-acetyltransferase 10 (NAA10) gene, an X-linked recessive disorder, Ogden Syndrome, presents in boys with severe developmental delay, central hypotonia, dysmorphic features, cardiac malformations, and early death in the first months of life. **Case Report:** Male infant with hypotonia and craniofacial dysmorphisms: prominent forehead, triangular facies, bilateral microphthalmia, superior oblique palpebral fissure and epicanthus, increased nasolabial filter, tapered upper lip, sparse blond hair, long and light eyelashes. Delay in neuropsychomotor development, brief episodes of oromasticatory movements, sialorrhea, horizontal nystagmus, excessive sleepiness, and hypo-responsiveness, with oxygen saturation drop and bradycardia. Electroencephalogram: bursts of diffuse slow waves. Echocardiogram and electrocardiogram without alterations. Cranial resonance: cortical thickening in the right frontal lobe, small encephalomalacic area; signs of previous ischemic insult in the territory of the right posterior cerebral artery; areas of signal alteration in the central and deep white matter adjacent to the lateral ventricles with mild compensatory dilation of the same; and diffuse thinning of the corpus callosum of undetermined nature, treatment initiated. Genome identified a likely pathogenic variant in the NAA10 gene. Under treatment with phenobarbital and oxcarbazepine, and multiprofessional follow-up. **Discussion/Conclusion:** Many patients present neuroimaging alterations, mainly: corpus callosum hypoplasia and microcephaly. Epilepsy around 69%, generalized, described eyelid myoclonias or spasms, or as identified in this patient: oromasticatory automatism. There is a need to include Ogden Syndrome in differential diagnoses and investigate the NAA10 gene in epilepsy and intellectual disability panels, even without multisystemic manifestations.

[1] Hospital Pequeno Príncipe, Departamento de Neurologia Infantil, Curitiba, PR, Brazil.
[2] Universidade Positivo, Acadêmico, Curitiba, PR, Brazil.
[3] Pontifícia Universidade Católica do Paraná, Acadêmico, Curitiba, PR, Brazil.
[4] Hospital Pequeno Príncipe, Departamento de Genética Médica, Curitiba, PR, Brazil.

Correspondence to:
Rui Carlos Silva Júnior.
Hospital Pequeno Príncipe, Departamento de Neurologia Infantil - Curitiba, PR, Brazil. Rua Brigadeiro Franco, 2700 B, Água Verde, Curitiba, PR, Brazil.
CEP: 80250-060. E-mail: dr.ruijr@gmail.com

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INTRODUCTION

The N-alpha-acetyltransferase 10 (NAA10) gene is responsible for the production of the N-acetyltransferase 10 protein (NAA10), with a crucial role in protein acetylation during protein synthesis. Protein synthesis is altered when this gene undergoes a mutation, which can negatively affect several cellular processes. It includes gene expression regulation and the assembly of protein complexes. It also affects the function of proteins involved in the development of the nervous system and cardiac function[1].

The syndrome related to this alteration, an autosomal recessive genetic condition linked to the milder NAA10-related intellectual disability (ID) caused by different variants in men and women. Since the initial discovery of OS in 2011, several groups have reported additional variants in NAA10 in men and women[1,2].

Affected boys present severe delay in neuropsychomotor development, central hypotonia, craniofacial dysmorphia, cardiac malformations and early death in the first months of life, mainly due to cardiac arrhythmias.[3]

This is a case report of a rare genetic syndrome with severe neurological manifestations with a high risk of death, in addition to a bibliographic review, a search was carried out in the scientific literature in journals such as: pubmed, scielo and lilacs, considering publications of the last 20 years.

CASE DESCRIPTION

Patient, 2 years and 4 months old, male, followed at the Child Neurology outpatient clinic of a tertiary hospital in Curitiba – PR.

Son of healthy and non-consanguineous parents, pregnant at 40 years of age, without comorbidities. She had no complications during pregnancy. Maternal half-brother with epileptic encephalopathy that began at age 7, with thrombosis, increased methylmalonic acid and death without a defined cause at age 12. Paternal cousins with a history of epilepsy and global neuropsychomotor development delay.

Hypotonia and respiratory stridor were identified at 3 months. Upon examination, he presented a prominent forehead, triangular facies, bilateral microphthalmia, upper oblique palpebral fissure and epicanthus, enlarged nasolabial philtrum, thin upper lip, sparse blond hair, and long, light eyelashes. Axial hypotonia, partial cervical support, global grade 3 strength with hyporeflexia and mild hypotrophy. He presented short-term episodes of oromastigatory movements, sialorrhea, horizontal nystagmus, followed by excessive drowsiness and hyporesponsiveness with a drop in oxygen saturation and bradycardia. He had episodes of decreased level of consciousness requiring orotracheal intubation for 2 days. Cardiovascular clinical examination was unremarkable.

Electroencephalogram (EEG) with occasional bursts of diffuse slow waves. Magnetic resonance imaging of the skull: cortical thickening in the right frontal lobe of undetermined nature; small area of encephalomalacia; signs of previous ischemic disorder in the irrigation territory of the right posterior cerebral artery; areas of signal alteration involving the central and deep white matter adjacent to the lateral ventricles with slight compensatory ectasia thereof; and diffuse thinning of the corpus callosum of undetermined nature. Due to phenomenology suggestive of an epileptic seizure, antiepileptic drug (AED) was started. Initial investigation, including metabolic screening, karyotyping, and microarray, were all normal. Echocardiogram with DOPPLER within normal limits and electrocardiogram without changes.

The child had overall neuropsychomotor development delay (ONPDD), little eye contact, social laughter and head support at 4 months, sitting with support with difficulty at 7 months, rolling over at 8 months and emitting guttural sounds at 2 years. Currently, he laughs, does not stand up even with support, turns to the call, picks up objects since the age of 1 year and 10 months, says he takes objects to his mouth.

24-hour videoelectroencephalogram performed during wakefulness, NREM sleep and REM sleep: symmetric base activity and slightly disorganized for the age, very frequent epileptiform discharges of irregular morphology and high amplitude, with independent focal projection from outside in both temporo-parieto-regions. occipital, with frequent bilateral and synchronous involvement, in all states of consciousness and activated in non-REM sleep.

Genome sequencing identified the presence of a likely pathogenic variant in the NAA10 c.346 C>T p gene. (Arg116Trp)

Currently, the patient continues to use phenobarbital and oxcarbazepine, multidisciplinary monitoring with motor and respiratory physiotherapy, psychotherapy, speech therapy and occupational therapy. Given reports of behavioral worsening and sleep disorder, levomepromazine was started.

DISCUSSION

The NAA10 gene, located on chromosome Xq28 and composed of 8 exons, is responsible for encoding the NAA10 subunit of the Nat10 enzyme, responsible for fundamental processes for cellular functioning in humans[1-3]. The mutation of this gene reduces the activity of the NAA10 unit, preventing the correct acetylation of several eukaryotic proteins from occurring, leading to pathological syndromic conditions[3].

In a study published by Rope et al. in 2011[5], a common mutation in the NAA10 gene was identified in 8 patients, a condition later called Ogden Syndrome[4]. This study was the precursor to dozens of reports of diseases with similar mutations, opening space for a broad discussion about the mechanisms involved in this condition rare. Currently, there are several variants of diseases related to mutations in the NAA10 gene reported in the scientific literature, including: p.Ser37Pro, p.Tyr43Ser, p.Arg83Cys, p.Val107Phe, p.Arg116Trp, p.Phe128Ile and p.Phe128Leu.[5] The patient discussed in this paper presents the p.Arg116Trp mutation, identified in only 2 individuals until 2018, according to the literature consulted[1].

This variant consists of a substitution of an Arginine for a Tryptophan in codon 116 of the translated protein (c.346C>T).[3]

Rauch et al., in 2012, first showed that another de novo variant of NAA10, Arg116Trp, could be the cause of a non-lethal phenotype in a male patient with non-specific severe ID et al.[5,14]. In 2015, Casey et al.[6] reported that the correlation between catalytic capacity and phenotype found in each NAA10 variant proved to be much more complex than in vitro studies indicated, more studies are needed to prove or rule out this hypothesis[6,7]. Partial loss of protein function was also associated with syndromic microphthalmia in boys[7-9], as presented in the current case, in addition to other malformations in several organs and systems.

There are conflicts in the nomenclature of the syndrome in the literature, since it was described by Wu & Lyon, in 2018[1], that the name Ogden Syndrome should be reserved for exclusive cases of newborn male patients with fatal presentation. This means that other variants, other than Ser73Pro, should be characterized as diseases related to mutations in the NAA1010 gene. Functional studies of nonsense variants of NAA10, demonstrating a variable effect on the ability of NAA10 to acetylate substrates, are supporting the hypothesis that the level of acetylation dysfunction and affected substrates is an important underlying pathogenic mechanism with a possible correlation with the clinical phenotype[13,14].

Most patients have at least one brain abnormality with hypoplasia of the corpus callosum and microcephaly being by far the most common, followed by periventricular leukomalacia. In some cases, there may be brain atrophy[2,11,12]. Sidhu and collaborators (2017)[12] described a female patient who developed leukodystrophy and progression of clinical condition, with hypersomnolence and extrapyramidal symptoms.

Epilepsy is described in around 69% of patients[9] and may be the predominant symptom in some patients[12]. Epilepsy is usually generalized, with attacks of eyelid myoclonus[12] or spasms[10] being described, or as identified in this patient, with crises of masticatory automatism.

Behavioral changes are described in all patients, especially ONPDD and specific expressive language disorder[2,10]. The severity of the impact on neurodevelopment is variable[3]. The phenotype of a heterozygous female can range from asymptomatic to having some of the same clinical features as affected boys, such as a variable degree of ID and cardiovascular changes. The varied phenotypes in girls depend not only on specific NAA10 variants, but also on X chromosome deviation[1].

CONCLUSION

Ogden Syndrome, a rare genetic condition with a broad phenotypic spectrum for the alleles involved, affects multiple organs and systems, but it is possible to highlight that neurological symptoms are predominant. The present report points to the need to include Ogden Syndrome within the differential diagnoses of global delay in neuropsychomotor development, especially in the presence of dysmorphia; in addition, there is a need to include investigation of the NAA10 gene in epilepsy and intellectual disability patients to expand the diagnostic possibility of the syndrome.

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