Compound heterozygous mutation of the IARS2 gene: a rare cause of Leigh Syndrome

Mutação heterozigótica composta do gene IARS2: uma causa rara da Síndrome de Leigh

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ABSTRACT
Described in 2005 by Bonnefond, L. et al, IARS2 (OMIM 612801) is a mitochondrial isoleucyl-tRNA synthetase encoded in the nucleus. Phenotypically, the mutation in the IARS2 is expressed in a broad clinical spectrum, which includes Leigh Syndrome (LS) as well as extra-neurological effects. We described a 7-year-old boy who presented global developmental delay, hypotonia and epilepsy, evolving with epileptic encephalopathy. An MRI showed diffuse brain atrophy and areas of capsular changes bilaterally, while the exome showed compound heterozygous mutation in the IARS2 gene, a probable pathogenic variant inherited from the mother - p.[(Arg201His)], and a pathogenic variant inherited from the father - p.[(Trp520*)]. In the literature, we found 11 cases of patients who presented phenotypically as LS with mutation of the IARS2 gene. This report shows a patient with pathogenic variants never described in IARS2 compound heterozygosity, reinforcing the hypothesis of association of the IARS2 gene with this syndrome.

Keywords: Leigh Syndrome, IARS2 gene, neurodevelopmental delay, epilepsy.

RESUMO
Descrita em 2005 por Bonnefond, L. et al, a IARS2 (OMIM 612801) é uma isoleucil-tRNA sintetase mitocondrial codificada no núcleo. Fenotipicamente, a mutação na IARS2 é expressa em um amplo espectro clínico, que inclui a Síndrome de Leigh (LS), bem como efeitos extraneurológicos. Descrevemos um menino de 7 anos que apresentou atraso global no desenvolvimento, hipotonia e epilepsia, evoluindo com encefalopatia epiléptica. Uma ressonância magnética mostrou atrofia cerebral difusa e áreas de alterações capsulares bilateralmente, enquanto o exoma mostrou mutação heterozigótica composta no gene IARS2, uma provável variante patogênica herdada da mãe - p.[(Arg201His)] e uma variante patogênica herdada do pai - p.[(Trp520*)]. Na literatura, encontramos 11 casos de pacientes que se apresentaram fenotipicamente como LS com mutação do gene IARS2. Este relato mostra um paciente com variantes patogênicas nunca descritas na heterozigosidade composta do IARS2, reforçando a hipótese de associação do gene IARS2 com essa síndrome.

Palavras-chave: Síndrome de Leigh, gene IARS2, atraso no desenvolvimento neurológico, epilepsia.
1 INTRODUCTION

Primary mitochondrial diseases are a heterogeneous group of disorders caused by impaired energy production, with multiple different genotypes and diverse clinical presentations affecting individuals of all age groups (LAKE). Leigh syndrome (LS), subacute necrotizing encephalopathy, is the most common primary mitochondrial phenotype in children and has high morbidity and mortality. (ALVES).

In the current paper, we report a rare case of a male infant with novel compound heterozygous in Isoleucyl-tRNA Synthetase 2 (IARS2) gene detected by Whole Exome Sequencing (WES), which encodes mitochondrial isoleucine-tRNA synthetase. Pathogenic variants in the IARS2 gene are associated with mitochondrial disease. The current patient presented with developmental delay, diffuse encephalopathy, seizures, dystonia, quadriplegic hypotonia and abnormal brain Magnetic resonance imaging (MRI). Our findings expand the understanding spectrum of IARS2-related disorders.

2 CASE REPORT

A seven years old boy, first child of a 30 years old mother and a 29 years old father, both healthy, non-consanguineous. Prenatal care without infectious complications, exposure to drugs or specific pregnancy diseases. He was born by cesarean section at 38 weeks and 4 days due to fetal distress. Apgar in the first and fifth minutes, respectively, 8 and 8, meconium amniotic fluid but no need for resuscitation maneuvers. At birth, he weighed 4060 g (97th percentile), stature 53 cm (98th percentile) and head circumference 36.5 cm (98.6th percentile). Normal neonatal screenings.

At 4 months, he had no cervical support, no protected airway and had lower limbs in abducted position. He was hospitalized for bronchiolitis at 4 and 7 months. During the last hospitalization, prolonged drowsiness and difficult awakening was observed in the child. At 10 months a brain MRI was performed, with findings of global and symmetrical cerebral atrophy, hypoplastic corpus callosum. In the meantime, he was referred for outpatient follow-up with occupational and physical therapists, improving cervical and trunk support.

At 12 months he still maintained global developmental delay, presented first seizure described as a tonic posture with abdominal contraction and hypertonicity in the lower limb. He started carbamazepine, and had a lack of response. At 4 years old, seizure episodes occur manifested with abdominal cramps, release and duration of approximately two minutes, manifesting frequently and cyanosis twice a month. He had a broad seizure
semiology spectrum and also started showing regression of cervical and trunk tonus, reduction of social interaction, and worsening drowsiness.

In 2017, at age 5, he had a head trauma, evolving to reentrant seizures due acute subdural hematoma. In this context, he was accepted in the Pediatric Intensive Care Unit (PICU) for hematoma drainage and management of status epilepticus, with partial improvement of the seizures. During the hospital standing vigabatrin and lacosamide were associated with partial improvement.

In the outpatient follow-up a large number of exams were performed in an attempt to elucidate the patient's diagnosis. No abnormalities in spine, long bones and pelvis radiographs. Video-electroencephalogram compatible with epileptic encephalopathy (IMAGE 1).

Exams such as transferrin isoelectric focusing, MLPA, FGF/GDF, ceruloplasmin, plasma biotinidase, acylcarnitine profile, very long-chain fatty acids, panel of treatable inborn errors of metabolism, IGF1, IGFBP3 and other organics showed no changes. An MRI was performed and showed diffuse brain atrophy and areas of capsular alterations (striated nuclei) bilaterally, suggesting mitochondrial disease. (IMAGE 2).

Image 1: EEG suggesting epileptic encephalopathy

Source: Authors
Although the WES showed compound heterozygosity mutations in the \textit{IARS2} gene, a likely pathogenic variant inherited from the mother - p.[(Arg201His)], and a pathogenic variant inherited from the father - p.[(Trp520*)].

Currently, the child is on an outpatient basis in the neurogenetics service at a tertiary pediatric hospital in Fortaleza - Ceará. At the physical exam the patient has central hypotonia, quadriplegia, limb dystonia, in addition to global hyperreflexia and cutaneous-plantar reflex in extension.

He has regular physiotherapy and occupational therapy sessions, in addition to being followed up with an ophthalmologist for myopia, geneticist for family genetic counseling, and also pediatrician and neurologist. He maintains drowsiness, is fed by gastrostomy, uses supplemental oxygen during sleep, and partial control of seizures.

3 DISCUSSION

Described in 2005 for Bonnefond, L. et al, \textit{IARS2} (OMIM 612801) is a nuclear-encoded mitochondrial isoleucyl-tRNA synthetase, which is a class I mitochondrial aminoacylRNA synthetase (ARS), that is imported from the cytosol into the mitochondria where it catalyzes the attachment of an isoleucine residue to a cognate mt-tRNA\textsubscript{I}. (Vona B, 2018, Takezawa, Y 2018) Pathogenic mutations in IARS2 gene (OMIM: 612801) on chromosome 1q41 have been reported to cause two distinct clinical phenotypes including cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, and skeletal dysplasia (CAGSSS) and Leigh syndrome with autosomal recessive inheritance. (Schwartzentrube 2015; Upadia 2022).
Mutations in IARS2 (OMIM *612801), which encodes mitochondrial isoleucyl-tRNA synthetase, were first reported in a French-Canadian family with the syndrome abbreviated as CAGSSS in 2014 (Schwartzentruber, 2018). Since then fewer than 30 patients have been reported in the literature presenting pathogenic mutations on IARS2 (upadia j, 2022). This condition has a broad spectrum evolving in neurological dysfunction as well as extra-neurological effects. Mortality is high among patients with neurological phenotype which is primarily attributed to progressive neurologic disease (UPADIA J, 2022)

LS (OMIM #25600) is a clinically and genetically heterogeneous disorder resulting from defective mitochondrial energy generation (LAKE, 2015). This condition was first described by Leigh (1951) in a patient with foci of necrosis and capillary proliferation in the brainstem and it is relatively common, with an incidence of 1 in 40,000 births, although certain populations have higher incidences (Ruhoy IS, 2014.).

More than 95 genes with variable pathogenic variants across the nuclear (nDNA) and mitochondrial (mtDNA) are known to cause LS (Alves, C. A. P. F.,2020). Schwartzentruber J. reported for the first time associations between Leigh and IARS2 gene, in a 18 months, male, Scandinavian-Caucasian who presented as developmental delay. Takezawa et al. reported 2 Japanese sisters with compound missense heterozygotes on the IARS2 gene and an unusual presentation of CAGSSS manifested as intractable infantile-onset seizures (West syndrome) and LS. The compound heterozygous missense mutations in IARS2, p.[(Phe227Ser)];[(Arg817His)] were found by WES and confirmed by Sanger sequencing, segregated the disorder in the family.

The patient in our report also presented two compound heterozygous variants in the IARS2 gene - The chr1:220,102,180 G>A variant (or alternatively c.602G>A - ENST00000366922), which promotes replacement of the arginine amino acid at codon 201 by histidine (p.Arg201His).

Arginine at position 201 is highly conserved in the various biological species and computational programs for prediction "in silico" of pathogenicity suggest that its replacement by histidine is potentially deleterious. This variant is present in heterozygosity and has never been previously described in the medical literature. Additionally, their presence was confirmed by Sanger sequencing in patient and researched on his parents, having been inherited from his mother, being in trans with variant p.Trp520*, thus being considered probably pathogenic.
The variant chr1:220.114.394 G>A (or alternatively c.1560G>A - ENST00000366922), which promoting the replacement of the tryptophan amino acid at position 520 by a protein translation stop codon (p.Trp520*). This variant has never been previously described in medical literature.

The combination of the molecular mechanism, with early interruption of protein translation, characteristics of the region where it is found and correlation of this gene with clinical symptoms indicate that this variant is pathogenic (Schwartzentruber, 2014). Additionally, its presence was confirmed by Sanger sequencing in patients and researched in his parents, having been inherited from his father, being in trans with variant p.Arg201His, thus being considered probably pathogenic.

Segregation study allowed to determine that the variants identified in this analysis are in trans therefore, it is a compound heterozygosity.

Till this date there's 12 patients, including the one reported in this paper, who presents phenotypically as LS and had IARS2 gene mutation. These patients have presented with a broad range of clinical phenotypes. Not all of these patients fulfill the criteria for a specific syndrome and some also display features of other syndromes. (Vona, B, 2018) Among 11 reported patients (TABLE 1), in all of them the symptoms starts under 24 months also presented as developmental delay; into the neurological phenotype 4 have West syndrome (36,3%), 2 had microcephaly (18,1%), 6 had hypotony (54,5%).
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**WES**

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+: present; - : absent; nd: non described; WPW: wolf-parkinson-white; WES = whole exome sequence
Also, in a lower frequency conditions such as have sideroblastic anemia, cardiomyopathy, Wolff-Parkinson-White syndrome, short stature, hypoparathyroidism, pancreatic dysfunction, renal tubulopathy and neuropathy were reported in association to IARS2 gene mutations in LS patients.

In this paper, epileptic encephalopathy without hypsarrhythmia, suggesting no West syndrome, was reported for the first time as a phenotype characteristic in patients with IARS2 related syndrome, thus helping to improve the knowledge about this condition.

The pathogenic mechanism of IARS2 and its association with the clinical spectrum of IARS2 and LS are not yet fully clarified. But the IARS2 gene has been asserting itself as the cause of LS. More studies are needed to identify the clinical spectrum of IARS2-related disorders.

4 CONCLUSION

This is a case reporting LS in a patient with a never described pathogenic variants in compound heterozygosis IARS2 without CAGSSS features, reinforcing the hypothesis that the IARS2 gene is related to this severe and lethal syndrome in which remains a challenging condition with no fully known genetic basis and associated with a variable phenotypes.
REFERENCES


