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Combined Oxidative Phosphorylation Deficiency-20-Exome as a Diagnostic Implement

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Abstract

Mitochondrial disorders are phenotypically varied, with serious clinical repercussions. Among them, there is the deficiency of combined oxidative phosphorylation of type 20, which occurs due to a defect in the VARS2 gene. This article presents a case of a 2-year-old female with progressive myoclonic epilepsy and psychomotor regression, with refractoriness to multiple anticonvulsants. The diagnosis was only made after the examination was carried out. Therefore, this article highlights the aspects of this rare disease and the importance of the exome for the diagnosis of rare conditions.

Keywords

Oxidative Phosphorylation, Epilepsy, Exome, Mitochondrial Defect, VARS2

1. Introduction

Mitochondrial disorders are phenotypically heterogeneous, rare, little-known clinical syndromes that can cause severe clinical repercussions. They are caused by mitochondrial and nuclear DNA mutations, which results in defective activity of the mitochondrial respiratory chain and, consequently, impairs ATP production. [1] These disorders can occur at any time in life and can also be associated with neurological dysfunction, often leading to severe disability and premature death. [2]

Here, we describe a type 20 combined oxidative phosphorylation deficiency, a

mitochondrial disorder with a prevalence of 1/1,000,000. [3] This irregularity is caused by a defect in the VARS2 gene, which encodes an important enzyme in mitochondrial protein synthesis, aminoacyl-tRNA synthetase, and it is reported here in a case involving a two-year-old girl. Biallelic changes in VARS2 have been described in just over 17 individuals, with clinical conditions generally involving refractory epilepsy, cardiomyopathy and delay or regression in neuropsychomotor development. [4] [5]

It is a genetic disease without a phenotypic pattern, so tests that assess the genome are of fundamental importance for the diagnosis. Exome Sequencing has changed the diagnostic approach, using a next-generation sequencing platform. Millions of fragments are sequenced and, with this method, it is possible to diagnose rare and ultrarare diseases. [6]

2. Acquisition of a Clinical Case

The case was obtained through the neuropediatrics outpatient clinic, where the patient was monitored. Data were provided by family consent.

3. Case Presentation

MEB, 2 years old, female, white, non-consanguineous parents, mother 17 years old, father 45 years old. The pregnancy, birth and delivery were uneventful. She already had eye contact, a social smile and cervical control when, at 4 months of age, progressive myoclonic epilepsy began and progressed with psychomotor regression characterized by intense hypotonia and loss of previously acquired skills. Despite the use of multiple antiepileptic drugs in doses recommended for their age and weight, including clobazam, clonazepam, lamotrigine, levetiracetam, vigabatrin, carbamazepine, cannabidiol, coenzyme Q10 and oral pyridoxine, she persisted with refractory epilepsy. Furthermore, her convulsive condition worsened after using valproic acid. However, there was a significant improvement in epileptic seizures after using a ketogenic diet. Her neuropsychomotor development remains without progress to this day, despite the efforts of multidisciplinary therapies. In her family history, there are reports of a maternal cousin with epilepsy.

3.1. Physical Exam

Head circumference was at the lower limit of normality and there was no visual contact. Blinks to the sound of clapping; absent social smile; significant axial and appendicular hypotonia; does not support the cephalic pole. Does not show interest or pick up objects. Exalted myotatic reflexes in all four limbs.

3.2. Diagnostic Investigation

At 6 months, a Magnetic Resonance Imaging (MRI) was performed, which revealed mild cerebellar atrophy (**Figure 1**) and a slight delay in myelination, most evident in the semiovale centers and the pons. The electroencephalogram (EEG)

was abnormal, with marked disorganization of baseline activity and spike and polyspike epileptiform paroxysms in bilateral frontal regions, compatible with diffuse encephalopathy and focal epilepsy with very active epileptogenesis. Auditory and visual assessments were unremarkable.

Initially, a genetic panel was carried out to screen for treatable diseases, where no changes were identified in the genes analyzed, which in themselves could be responsible for the clinical picture. Therefore, the probability of developing diseases related to these genes is very low. Two heterozygous variants were identified in the G6PD (Glucose-6-phosphate dehydrogenase) gene: ChrX: 153,764,217 C>T and ChrX: 153,763,492 T>C. However, women heterozygous for G6PD deficiency variants are mostly asymptomatic and there is no need for hemolysis prevention measures.

The lipofuscinosis test with a blood sample impregnated on filter paper resulted in Palmitoyl thioesterase (CLN1) with normal activity and Tripeptidyl peptidase (CLN2) with reduced activity. However, although tripeptidyl peptidase activity is below the lower reference limit, it is not that normally found in patients with neuronal ceroid lipofuscinosis type 2 (CLN2). Another genetic test was also carried out that looked for changes in 149 genes, which included an epilepsy panel and a search for other genes involved in glycine encephalopathy. The result was unclear, as it found several gene variants of uncertain significance.

In view of non-specific changes in previous exams, the clinical exome was requested (Table 1), which showed the presence of a homozygous pathogenic variant in exon 11 of the VARS2 gene (chr6: g.30918851C>T; depth: 445×), which results in the substitution of the amino acid Threonine by Isoleucine at codon 367 (p.Thr367IIe; ENST0000541562.5). This finding is compatible with combined-20 oxidative phosphorylation deficiency, which is autosomal recessive.

Given this, it is clear that the early use of the exome could reduce costs, since previous tests are carried out in large centers and are expensive for the patient or the health system.

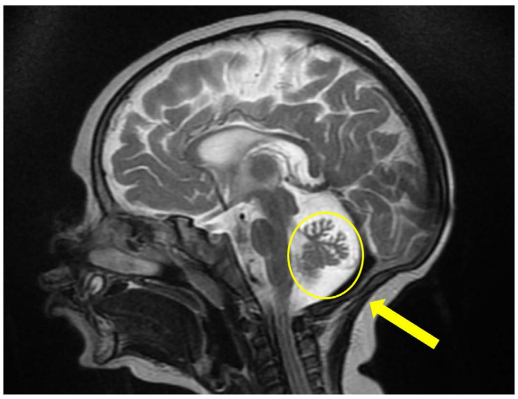

Figure 1. Magnetic Resonance Imaging (MRI) was performed, which revealed mild cerebellar atrophy and a slight delay in myelination, most evident in the semiovale centers and the pons.

Table 1. Exome result associated with reported phenotype.

Gene	Location	Variants	Zygosity	OMIM disease	Heritage	Variant classification
VARS2 (+) (ENST00000541562.5)	Exon 11	C.1100C>T **(p.Thr367Ile)**	Homozygosity	Combined Oxidative Phosphorylation Deficiency-20	Autosomal recessive	Pathogenic

OMIM: Online Mendelian Inheritance in Man.

4. Discussion and Literature Review

4.1. Epidemiology, Etiology and Pathophysiology

Mitochondrial respiratory chain defects are the main cause of childhood neurometabolic illness with a prevalence of 1:5000 live births. One-third of these patients have defects in several complexes of the respiratory chain, which indicate defects in the synthesis of several proteins inside the mitochondria. [7] Deficiency of combined oxidative phosphorylation-20 is a disorder with low prevalence, less than 1/1,000,000 [3], with onset in childhood and related to autosomal recessive inheritance. There is a similar prevalence between males and females. [1]

The production of energy by mitochondria occurs through oxidative phosphorylation (OXPHOS). The proteins involved are under the genetic control of mitochondrial DNA and nuclear DNA. [4] The VARS2 gene contains 30 exons and encodes mitochondrial valyl tRNA synthetase. In the homozygous pathogenic mutation of the VARS2 gene, there is a defect in the coding of the mitochondrial valyl tRNA synthetase, in order to prevent the process from occurring normally, promoting difficulty in the production of ATP and causing encephalopathy or cardiomyopathy of a mitochondrial nature. [2]

4.2. Clinical Condition

Patients with VARS2 mutations typically begin experiencing symptoms before the first year of life. Severe encephalopathy associated with hypotonia is common. Additionally, microcephaly, facial dysmorphism, eyelid ptosis, progressive external ophthalmoplegia, and nystagmus may occur. [1] [5]

In the central nervous system, delayed psychomotor development, ataxia, periventricular white matter abnormalities, dystonic movements, and seizures have been reported. The latter generally progresses to status epilepticus and refractory epilepsy over 2 to 4 years. [1] [5]

In addition, they may also present cardiac involvement, with hypertrophic cardiomyopathy (most common), as well as pericardial effusion. Regarding neuroimaging, there is a progressive loss of brain volume, with cerebellar atrophy being common. On the other hand, plasma alanine and lactate levels can be increased in laboratory tests. [1] [5]

4.3. Diagnosis

Currently, evaluation by laboratory or imaging tests, associated with clinical

manifestations, is not enough to define a diagnosis of mitochondrial defect. For this reason, although there is not a specific treatment available, defining the etiology is important for reliable genetic counseling, prenatal diagnosis and to prepare for possible genotype-specific complications. [7] In this context, the use of genetic tests has been increasing, including a panel for epilepsy and screening for treatable genetic diseases. However, when it comes to a mitochondrial defect, these tests are not too helpful.

With the advancement of genetics, exome sequencing emerged, a test that transformed the approach to rare and ultra-rare diseases by enabling their diagnosis. This occurs because this tool simultaneously sequences millions of short fragments of the coding region. [7] This is a non-invasive, detailed and not expensive test, and essential. [1] This test searches for variations compatible with the patient's clinical condition. [7]

The diagnosis established after performing the exome alters medical management in up to a third of diagnosed cases. This includes not only treatment, but also surveillance for additional manifestations and investigation of new medications. Furthermore, confirmation of the diagnosis reduces the anguish of some families who constantly search for the cause of their family member's clinical repercussions. [6] In our patient, the use of Exoma alone made it possible to reach a solid diagnosis. This test showed a homozygous mutation in the *VARS*2 gene, at location 6p21.33, suggesting COXPD20 disease (phenotype MIM number 615917).

4.4. Treatment

Combined Oxidative Phosphorylation Deficiency-20 can lead to various consequences, and the treatment is to address the respective existing disorders. Epilepsy, which is commonly present, poses a significant challenge as the seizures can be difficult to manage, necessitating multiple treatment protocols. Typically, when abnormalities in the EEG indicate epileptic syndromes, the administration of antiepileptic drugs is initiated, along with the use of rescue medications in emergency situations. [8] [9]

Additionally, dietary modifications such as the ketogenic diet can be beneficial. Although the exact mechanism is not fully understood, several studies have demonstrated that ketone bodies reduce the release of excitatory neurotransmitters, thereby improving seizure control. [8] [9]

5. Conclusions

The use of exome as a tool in the diagnosis of rare and ultra-rare diseases has proven important. It contributes to elucidating the etiology of part of the mitochondrial changes, not identified by any other tests. While specific therapies for mitochondrial diseases are lacking, delays in diagnosis hinder the prompt initiation of alternative treatments.

Hence, we proposed that when encountering patients with a similar profile,

who do not fit into conventional epileptic syndromes, exome sequencing should be considered as an initial diagnostic tool. Future studies should evaluate the clinical outcomes associated with early exome sequencing in patients with atypical epileptic presentations.

Conflicts of Interest

The authors report no conflict of interest.

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