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Case Report

Mitochondrial Encephalomyopathy due to Cytochrome C Oxidase Deficiency: A Case Report

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Abstract

Introduction: Cytochrome C oxidase deficiency is a clinically and genetically rare heterogeneous disorder, it is caused by a defect in complex IV of the mitochondrial respiratory chain.

Clinical Case: A patient who was detected cytochrome C oxidase deficiency is addressed, by biochemical study of the enzymatic activity of mitochondrial complexes in skeletal muscle biopsy, with clinical manifestation of the encephalomyopathic form.

Conclusion: The great variability in the presentation of mitochondrial pathology reflects the structural, functional, and genetic complexity of the respiratory chain. Therefore, it is necessary to better understand their possible clinical presentations, for an early and accurate diagnosis of these diseases.

Keywords: *Cytochrome C Oxidase Deficiency; Encephalomyopathy; Mitochondrial Respiratory Chain*

Introduction

Mitochondrial or oxidative phosphorylation system (OXPHOS) diseases are a group of disorders caused by poor ATP production [1]. The respiratory chain is located in the mitochondrial inner membrane, is composed of 5 enzyme complexes and two molecules that act as binding points or shuttle (coenzyme Q or ubiquinone and cytochrome C) [2]. Due to the dual nuclear and mitochondrial genetic origin of

the OXPHOS system, mitochondrial genetic diseases can be caused by mutations in mitochondrial DNA genes with maternal inheritance and by mutations in nuclear genes that encode mitochondrial proteins; mutations that affect post-translational processing, the number of proteins by the mitochondria and the assembly of complexes. Most of the genes that make up the OXPHOS system are of nuclear origin, and it can be expected that most of the diseases caused by the deficiency of this system are due to mutations in nuclear DNA [1].

Cytochrome C oxidase (COX) deficiency is a rare metabolic disorder caused by a defect in Complex IV of the mitochondrial respiratory chain. More than 30 genes have been linked to this pathology. As with other components of the mitochondrial respiratory chain, marked clinical and genetic heterogeneity is observed in patients with this deficiency. It can be manifested with varying degrees of severity and affect the entire organism or specific tissues. The onset of the disease ranges from birth to late adulthood. The most frequent clinical phenotypes associated with IV complex deficiencies are encephalomyopathy or myopathy [3-5]. In the encephalomyopathic form, children are usually asymptomatic in the first 6 to 12 months of life, subsequently presenting psychomotor regression, ataxia, optic atrophy, ophthalmoplegia, nystagmus, dystonia, pyramidal signs, respiratory disorders and occasionally seizures [2].

Clinical Case

10-year-old male patient, who presents the following history: product of gestation III, healthy non-consanguineous parents, mother of 22 years at the time of gestation (history of a spontaneous abortion), healthy 14-year-old brother. Two second cousins on paternal branch with genetic syndrome under study. Pregnancy evolved normally, obtained at 40 weeks of gestation, by eutocic delivery without perinatal complications, weight 3400g. According to the interrogation: psychomotor development with cephalic support at 4 months, sedation at 6 months, crawling at 9 months, assisted standing at 12 months.

At 9 months he began his condition with seizures, he was diagnosed with severe myoclonic epilepsy; after a year the parents notice lack of coordination and developmental regression, in addition to sleep disorders and irritability, currently has lost all developmental milestones.

The physical examination shows: weight 19.2 kg (25th percentile), height 106 cm (3rd percentile), cephalic perimeter 45 cm (< 3rd percentile), apparent age less than chronological, does not fix gaze, nor follow objects, flexor pattern of the 4 limbs. Microcephalin, narrow frontal, symmetrical eyes, horizontal nystagmus, flat nasal bridge, nose with bulbous tip, thick lips, thorax slightly keeled, cardiopulmonary without alterations, abdomen with gastrostomy probe, bilateral cryptorchidism, limbs with increased muscle tone, bilateral equine foot adduct.

Several studies have been carried out by the interdisciplinary pediatric team. Pediatric neurology requested an electroencephalogram, which was reported abnormal due to the presence of right parieto-temporal irritative activity. Likewise, magnetic resonance imaging of the skull was requested in which data of subcortical cortical cerebral atrophy, prominent magna cistern, arachnoid cyst was observed. Magnetic resonance angiography showed decrease in the caliber of the anterior, middle, and posterior cerebral arteries. Visual evoked potentials severely altered bilaterally. Lactic acid 33.1 mg/dl. Genetic analysis of mitochondrial DNA was performed with a negative result to the A3243G mutation associated with the pathology of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS).

In the muscle biopsy, peripheral mitochondrial aggregates were observed in some fibers and a small number of fibers with a very weak COX reaction. Minimal and enzymatic structural changes compatible with probable mitochondrial myopathy.

Enzymatic activity of mitochondrial complexes determined in skeletal muscle biopsy (11-06-14): The relationship: II+III/I+III indicative of electron transfer from complexes I and II to complex III through coenzyme Q10 is decreased by 64% (Table 1).

Enzyme	Activities Nmoles/min/mg citrate synthase	Range of normal activities Nmoles/min/mg/protein citrate synthase
Complex I, NADH-DH (sensitive to rotenone)	2.76 (2.23)	1.00- 6.50 (sensitive to rotenone (0.695 - 1.00)
Complex II (Succinate dehydrogenase)	0.070	0.035 - 0.250
Complexes I + III (NADH-Cytochrome C reductase) (Sensitive to rotenone)	0.198 (0.099)	0.170 - 0.600 (0.025 - 0.150)
Complex IV (Oxidized Cytochrome C)	0.026 27% decreased	0.150 - 0.450
Citrate Synthase	42	80 - 200

Table 1

The biochemical study of mitochondrial complexes showed a decrease in the number of mitochondria manifested by a low activity of citrate synthase, an enzyme that marks mitochondrial mass. It is important to note that the activities of the complexes are expressed as a function of this enzyme located in the mitochondrial matrix, which makes cytochrome c oxidase deficiency more significant.

Other information to consider is that the ratio: II+III/I+III indicative of electron transfer from complexes I and II to complex III via coenzyme Q10 is decreased by 64%:

This inhibition suggests a decreased concentration of coenzyme Q10, an essential constituent of the mitochondrial respiratory chain, where it acts as an electron transporter between NADH and succinate dehydrogenase and the cytochrome system.

Treatment with coenzyme Q 10 was given for 6 months, with no clinical improvement.

Discussion

Manifestations of mitochondrial diseases are very varied and can affect all organs and tissues since ATP synthesis occurs in all of them. These can present a series of very specific clinical, morphological and biochemical aspects that give rise to well-characterized syndromes, but, in most cases (mainly in pediatric age) the symptoms are very little informative. Only the presence of neurological abnormalities, sometimes accompanied by increased lactic acid and other secondary clinical symptoms affecting various organs, which gives some guidance in the diagnosis of mitochondrial disease [1]. Such is the case of our patient who presented non-specific symptoms, the guideline for the suspicion of a mitochondrial disease was developmental regression, neurological problems and elevation of lactic acid, the first diagnostic suspicion was mitochondrial encephalomyopathy, lactic acidosis and episodes similar to stroke, so the A3243G mutation associated with this pathology was sought directly in the mitochondrial DNA, however, it was reported negative, so the approach for mitochondrial diseases was continued.

According to the consensus of the Society of Mitochondrial Medicine, muscle biopsies should be performed in routine analysis for mitochondrial disease when the diagnosis cannot be confirmed with DNA tests [6], for this reason muscle biopsy was performed on the patient in which peripheral mitochondrial aggregates were reported in some fibers and a small number of fibers with a very weak COX reaction. Data compatible with mitochondrial myopathy.

In vitro functional tests in tissue (typically muscle) have been the mainstay of the diagnosis of mitochondrial disorders, especially before recent advances in genomics. Functional analyses remain important measures of mitochondrial function. All mitochondrial disease guidelines and diagnostic criteria developed prior to recent advances in genetic techniques and understanding of these, include the results of such biochemical studies to help establish a diagnosis of mitochondrial disease [6], considering the above are performed in skeletal muscle biopsy biochemical tests, this corroborates a deficiency of cytochrome c oxidase.

As additional data of the tests carried out in the patient, a decreased concentration of CoQ10 was reported and considered as a secondary deficiency, so treatment with the supplementation of this enzyme was established, however, at 6 months no clinical improvement was observed. Coenzyme Q10 (CoQ10) has several vital functions in all cells, both mitochondrial and extra-mitochondrial. In addition to its key role in mitochondrial oxidative phosphorylation, CoQ10 serves as a lipid-soluble antioxidant, playing an important role in the metabolism of fatty acids, pyrimidine and lysosomal. CoQ10 deficiency is related to the pathogenesis of a variety of disorders. CoQ10 deficiency is classified into primary or secondary deficiencies. Primary deficiencies are the result of genetic defects in the multi-step biochemical pathway of CoQ10 synthesis, while secondary deficiencies can occur as a result of other diseases [7].

Conclusion

The great variability in the presentation of mitochondrial pathology reflects the structural, functional, and genetic complexity of the respiratory chain. Therefore, it is necessary to better understand their possible clinical presentations, for an early and accurate diagnosis of these diseases. Despite advances in genetic testing, they are not always affordable to all patients, so the biochemical study of the mitochondrial chain remains a great support in the diagnosis of mitochondrial diseases.

Conflict of Interest

The authors declare that they have no conflicts of interest in relation to this article.

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