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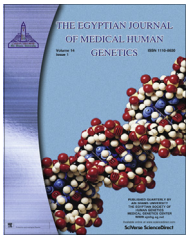

CASE REPORT

Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes in a Japanese child: Clinical, radiological and molecular genetic analysis

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Abstract Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes is a mitochondrial multisystem disorder. This disease has mainly been associated to the mitochondrial DNA mutation A3243G located in the tRNA Leucine gene. In this article, we report the clinical, radiological and molecular results of a 10 years old Child with the classical Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes phenotype. A 10 years old male Japanese child presented with recurrent episodes of headache, nausea and vomiting of 5 years duration and hyperlactic acidemia. These episodes were associated with motor weakness on the right side, with difficulties in language and memory and visual disturbance. Neurological examination revealed generalized muscle weakness with mild right sided hemiparesis. The Magnetic Resonance Imaging revealed infarct like lesions in the left occipital regions and the left medial temporal. The mitochondrial DNA mutations A3243G, T3271C and G13513A were tested using Polymerase Chain Reaction- Restriction Fragment Length Polymorphism analysis and direct sequencing. The heteroplasmic A3243G mutation was detected in the blood of the patient and his mother. L-Arginine is reported to be beneficial for the patients and a preventive treatment was given in the form of arginine 500 mg twice per day.

1. Introduction

Mitochondria are key to many cellular processes. Oxidative phosphorylation (OXPHOS) is one of the most important mechanisms resulting in the production of cellular energy in the form of adenosine triphosphate (ATP) [1,2].

Disorders of mitochondrial origin are a heterogeneous group of diseases commonly manifesting in high-energy demanding tissues such as muscles, brain, heart and nerves, hence the name "mitochondrial encephalomyopathies" [3].

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The clinical presentations of mitochondrial diseases (MCDs) are highly variable and the symptoms are often vague and non-specific [4,5]. The clinical recognition of MCDs is often challenging [6]. These diseases should be considered in patients with apparently unexplained combinations of symptoms and signs, especially if neurological features are present [1].

The mitochondrial genome encodes 13 essential polypeptides of the OXPHOS system and the necessary RNAs machinery. The remaining structural proteins and those involved in import, assembly and mitochondrial DNA (mtDNA) replication are encoded by the nuclear DNA (nDNA) and are targeted to the mitochondria [7].

More than 100 point mutations of mtDNA that are known to cause mitochondrial dysfunction were identified [8]. Mutations in mtDNA are more common than in nDNA. mtDNA mutates 10–17 times faster than nDNA due to the absence of chromatin and histones. Also the continuous generation of reactive oxygen species (ROS) and the lack of an efficient repairing mechanism further increase the mutation rate [9]. Recent developments in the molecular diagnostics allowed for the exploration of many of pathogenic mutations, thus providing more clues about the molecular basis of these disorders.

Mitochondrial genetics is characterized by maternal inheritance, mitotic segregation, threshold effect and heteroplasmy [10]. Since mitochondria are inherited only from the mother, mtDNA defects result in pedigrees exhibiting a pattern of maternal inheritance [7]. Because there are hundreds or even thousands of mitochondria in each cell, mutation in mtDNA may result in two populations of mtDNA (wild and mutant), a condition known as heteroplasmy [7]. The phenotypic expression of a mtDNA mutation is regulated by the threshold effect, the mutant phenotype is expressed in heteroplasmic cells only when the relative proportion of mutant mtDNAs reaches a certain value [11]. A respiratory chain (RC) defect may become manifest in some tissues, but not in others, if the number of mutant mtDNA exceeds a certain critical threshold [12]. The threshold level for the expression of mtDNA mutations is usually high (85–95%), but varies with different mutations. The threshold varies among tissues, depending on the oxidative energy requirements [7].

Because both mtDNA replication and mitochondrial division are random processes unrelated to cell division, a dividing cell donates variable numbers of mitochondria and mtDNAs to its progeny [11]. This process, known as mitotic segregation, can be important clinically if a patient harbors heteroplasmic populations in tissues, resulting in changing mutation loads in consecutive generations and increasing the phenotypic variation of MCDs [7].

Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome is one of the most frequently occurring MCDs [3]. Patients with MELAS syndrome are usually normal at birth and develop normally during the first years of life [1]. The patients often have episodes of vomiting with severe headache [3] leading to somnolence and coma [1]. Some of these episodes may lead to severe generalized seizures with stroke-like episodes of hemiparesis [3]. Ataxia [13], dementia [14], muscle weakness, sensorineural deafness, exercise intolerance [1] and diabetes mellitus are frequently seen [15]. Cardiomyopathy may also develop in the late stages of the disease [1].

Although nearly 80% of the coding part of the mtDNA is allocated to protein-coding genes and around 10% to tRNA genes, most of the pathogenic point mutations so far described affect tRNA genes [16]. Pathogenic mutations have been identified in most of the 22 tRNA genes, however, some tRNA genes are more frequently affected than others. Among these are the tRNA Leucine (Leu), tRNA –Lysine (Lys) and tRNA-Isoleucine (Ile) .The most common tRNA mutation is tRNA Leu A3243G, which is typically associated with MELAS syndrome [17]. Other tRNA Leu mutations (G3244A, T3258C, C3256T, T3271C, T3291C), mutations in tRNA Val [18] and tRNA His [19] were also found to be associated with the MELAS syndrome [8].

Molecular causes of MELAS other than tRNA mutations have been described [20]. Mutations in the nicotinamide adenine dinucleotide dehydrogenase (NADH) 5 gene of mitochondrial DNA are important. The G13513A mutation emerged as a hotspot. It is therefore important to consider this mutation in patients with Leigh Syndrome (LS), or overlapping features of the MELAS and leigh syndromes [20].

In this article, we report the clinical, radiological and molecular results of a 10 year old child with the classical MELAS phenotype.

2. Case report

A 10 year old male child, born to a Japanese father and Chinese mother, presented to the Inherited Metabolic Disease Unit at the Cairo University Children's hospital with recurrent episodes of headache, nausea and vomiting of 5 years duration. These episodes were associated with motor weakness on the right side with difficulties in language and memory and visual disturbance, mostly right sided homonymous hemianopia. Neurological examination revealed generalized muscle weakness, with mild right sided hemiparesis. These clinical manifestations were reliable to the Magnetic Resonance Imaging (MRI) showing infarction of left posterior parietal, left occipital and left medial temporal regions, without visible vascular abnormality at the Magnetic Resonance Angiography (MRA) (Fig. 1A, B). Laboratory Investigations revealed hyperlactic acidemia and a discrete increase in hepatic transaminases. The patient was clinically suspected to have MELAS syndrome .The mother reported that her brother suffered from the same clinical picture and died by the age of 19 years but the cause of death is not clear (Fig. 2).

3. Methods

3.1. Ethical issue

Written informed consent was obtained from the parents for all the procedures performed.

3.2. DNA extraction from the whole blood samples

Total genomic nDNA and mtDNA were extracted from peripheral blood leukocytes of the patient and his mother and healthy control age and sex matched child. The control was attending the hospital for other different reasons. He reported no symptomatic metabolic, genetic, or ocular disorders regarding family history, past medical problems, and