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Case report

Mitochondrial encephalomyopathy: Towards diagnosis. A case report

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ABSTRACT

Mitochondrial diseases may cause a wide range of central and peripheral nervous system disorders, as well as muscle disorders. The diagnostic workup routinely includes electrophysiological, morphological, neuroimaging and genetic studies. In some cases, the diagnosis may be ascertained only when mitochondrial DNA (mtDNA) examination in the muscle is performed. We report on a case of a 24-year-old woman, with a 7-year history of slowly progressive cerebellar syndrome and bilateral ptosis. Mitochondrial encephalomyopathy was suspected, based on the clinical picture and results of examinations, but the typical red ragged fibers were not found in the muscle biopsy. The results of molecular analysis of mtDNA showed a mtDNA deletion in the muscle and, on a level detectable only with polymerase chain reaction method, in blood leukocytes. This case emphasizes the important role of mtDNA studies in muscle in nonspecific multisystem mitochondrial disorders, even without clinical muscle involvement.

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1. Introduction

Mitochondria are organelles involved in cellular energy production, which contain their own DNA (mtDNA) encoding a small number of essential polypeptides of the oxidative phosphorylation system (OXPHOS). The coding sequences for 2 rRNAs, 22 tRNAs and 13 polypeptides are contiguous and without introns [1]. However, most of the 88 protein subunits of the mitochondrial respiratory chain (RC) complexes as well as the mtDNA replication and most of the expression systems are encoded by the nuclear genome. Thus, the proper operation of the respiratory chain depends on interactions between numerous genes. Mutations in nuclear DNA are transmitted according to Mendelian rules. They occur in genes encoding RC subunits and in genes encoding assembly and auxiliary factors of the RC as well as proteins that affect maintenance and expression of mtDNA or that have functions indirectly linked to OXPHOS [2]. Until now more than 200 mtDNA point mutations, numerous mtDNA deletions as well

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as hundreds of mutations in nuclear genes have been described [3]. However, it is still impossible to establish the genetic defect in 80–95% of patients suspected of having a mitochondrial disorder [4].

Mitochondrial disorders are a heterogeneous group of multi-system disorders resulting from impaired OXPHOS [5]. They may affect multiple organs, but the clinical manifestations vary in respect to age of onset, course and disease severity. Symptoms are diverse and often non-specific [6,7], making it difficult to establish a precise genotype–phenotype correlation and obtain a definite diagnosis [8,9]. The true prevalence of mitochondrial disorders is difficult to assess. It is estimated that up to 9.2 in 100,000 adults aged less than 65 years may be affected [9]. At the genetic level, mitochondrial disorders may result from mutations either in nuclear genes or in mitochondrial DNA (mtDNA). Therefore, the recognition of mitochondrial disorders remains challenging and diagnostic procedures require a wide range of investigations.

In the diagnostic work-up of mitochondrial disorders the most important first step is the precise recognition of the patient's symptoms and signs. Then, the various laboratory tests, electrophysiological studies (electromyography, nerve conduction studies and electroencephalography) and neuroimaging studies including magnetic resonance spectroscopy may be applied. Usually, during further investigation, skeletal muscle or skin biopsies are performed [10–12]. This makes it possible to obtain tissues for morphological, biochemical and supplementary genetic studies.

2. Case report

We present a case report of a 24-year-old woman, a student of psychology, with a 7-year history of ataxia with slurring and scanned speech, and with unremarkable family history. She was referred to the Department of Neurology, Medical University of Warsaw for the first time when she was 17 years old. The first symptoms – arm tremor and difficulties in pronouncing words – occurred when she was 14 years old and slowly progressed. The patient's mother reported compulsory laughter and crying occurring also for 3 years. When she was 16, she started complaining of progressive difficulties with stability and nausea with vomiting.

The neurological examination showed bilateral ptosis, more pronounced in the left eyelid, pseudobulbar syndrome and cerebellar syndrome (scanned speech, tremor of the head, intention tremor of hands, with slight positional tremor, ataxia of upper and lower extremities, walking with slightly widened base). There was no significant cognitive impairment.

During the first hospitalization, the diagnostic methods including laboratory tests in blood and cerebrospinal fluid, neuroimaging and electrophysiological examinations were used. Slight hypocalcemia (2.16 mmol/L; normal range 2.2–2.75 mmol/L) and a decreased level of magnesium (0.67 mmol/L; normal range 0.7–1) were found in routine laboratory tests. The parathormone level was decreased (11.97 pg/mL; normal range 15–95 pg/mL), so hypoparathyroidism was diagnosed. The level of lactic acid in blood was normal. However, an elevated level of protein (155 mg/dL) with a normal level of glucose and normal cytosis in cerebrospinal fluid (CSF) was found. Densitometry of the lumbar spine revealed the first symptoms of decalcification and prophylaxis of osteoporosis was initiated. Cardiomyopathy and cardiac arrhythmias were excluded by echocardiography and 24-h ECG tests. Audiological tests demonstrated significant sensorineural hearing loss in the right ear. Ophthalmologic examination excluded retinitis pigmentosa. Electrophysiological studies revealed normal conduction parameters in peripheral nerves and normal motor unit potentials in muscles. EEG showed generalized discharges of delta waves 3 Hz and theta waves 4–7 Hz with sporadic sharp waves. Magnetic resonance imaging (MRI) of the brain disclosed diffuse involvement of the white matter (Fig. 1A and B). Magnetic resonance spectroscopy (MRS) revealed a high concentration of lactates in white matter of both hemispheres, in basal ganglia and in cerebellar hemispheres. The levels of N-acetylaspartate and choline were low.

Viral infections (Epstein-Barr virus, cytomegalovirus, herpes simplex virus), mycosis and neuroboreliosis were excluded using appropriate tests as well as some forms of leucoencephalopathy as metachromatic leukodystrophy, adrenoleukodystrophy and Krabbe disease.

The history of slowly progressed ataxia with scanned speech and arms tremor, bilateral ptosis, pseudobulbar syndrome with increased level of protein in cerebrospinal fluid, diffuse involvement of the white matter showed in MRI

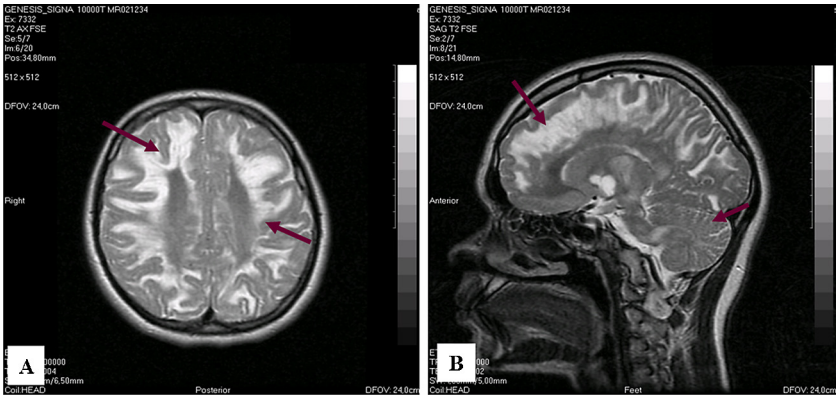

Fig. 1 – (A) MRI. Diffuse hyperintense changes in white matter of both hemispheres (arrows). (B) MRI. Diffuse hyperintense changes in white matter of hemispheres, in cerebellar hemispheres (arrows) and in basal ganglia.

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