

Mitochondrial Disorders in Two Children of a Family: A Case Report

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Abstract

Mitochondrial disorders belong to the group of metabolic diseases, that may cause various symptom. It may present at any ages and have harmful effects on different tissues. We present two children of a family, a 5-year-old boy and an 8-year-old girl, that came with complaint of gait imbalance and repeated fallings. Both of them had normal history of birth and developmental status, but when the girl was 6 years old, gait imbalance and ataxia started, that slowly progress. And the same sign started in a boy when he was 4-year-old. In electrodiagnostic study, we found peripheral polyneuropathy (demyelinating type) with a proximal myopathy. All findings include history and physical exam, laboratory data and electrodiagnostic study were in favour of mitochondrial disorders that confirmed by muscle biopsy. Mitochondrial disorders should be considered any time if a disorder present with more than one organ involvement. The prognosis of patients varies impressively from one patient to the other. With timely diagnosis and treatment of symptoms, better outcome will be expected.

Keywords: Mitochondrial, Disorders, Family, Children, Case report

1. Introduction

Mitochondrial disorders are a group of metabolic diseases, which may cause various symptoms, may present at any ages, have harmful effects on any tissues (Menezes & Ouvrier, 2012). Mitochondria is a vital organelle and due to its dysfunction may cause various features in cells, tissues, organs and systems. The final result of mitochondrial diseases is failure in cells to produce energy in the form of adenosine triphosphate (ATP) and leading to multi system dysfunction (Chinnery, Elliott, Hudson, Samuels, & Relton, 2012). The organs that is most related to production of energy by mitochondria will be the most symptomatic in mitochondrial diseases, including the central nervous system, heart, skeletal muscle, endocrine organs and kidney. Organs with completed active mitosis at birth, including the brain, muscles nerve, retina, pancreas, liver, and kidney, may be vulnerable for several reasons.

The prevalence is estimated around 1 in 5000 in patients tested for deletions and for common mutations of mtDNA

which account for 5-40% of cases, depending on the study (Bannwarth et al., 2013; Thorburn, 2004).

These diseases can present in childhood to adulthood and progress subsequently with significant suffering that result in heavy burdens on affected families (McFarland, Taylor, & Turnbull, 2010).

Signs, symptoms and organ involvement are greatly heterogeneous from one individual to the other, which is the reason for a high degree of inter- and intra-familial variability. This is the cause why each affected subject will have a different prognosis. Early recognition and treatment of symptoms are crucial for improving the prognosis.

2. Case presentation

Two siblings, 5 years old boy and an 8 years old girl, came with complaint of gait imbalance and repeated fallings tour clinic. Both of them were born on time, 39-40 weeks of pregnancy, and had normal development. When the girl was 6 years old, gait imbalance and ataxia started, that was slowly progressive. The same sign started in boy

when he was 4 years old. The girl was completely ataxic and her speech not easily understandable. In physical examination the strength of proximal and distal muscles of the lower limbs was 4/5. Deep tendon reflexes in upper and lower limbs were 3+ except for both Achilles, that were absent and plantar reflexes were down. She had dysmetria in finger to nose test was abnormal. Truncal ataxia and

impaired tandem gait were noted as well. Cranial nerves examination revealed no significant impairment. EEG findings were normal. There were abnormal signals in white matter of both cerebellar cistern and next to trigone of lateral ventricle on either side mostly hypo myelination in brain MRI (Fig. 1).

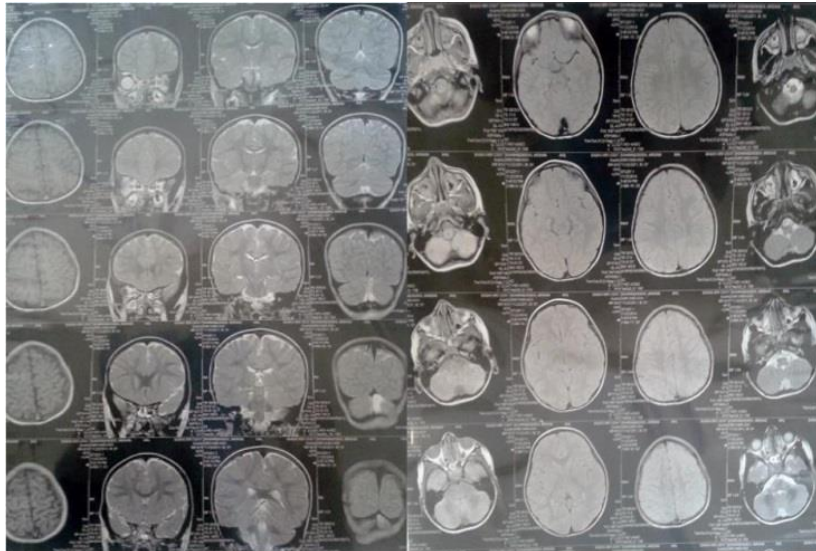


Fig. 1. Abnormal signal in the white matter of both cerebellar cistern and next to trigone of lateral ventricle

The boy walked in a clumsy manner. He was uncooperative in manual muscle test but upper and lower limbs deep tendon reflexes were absent and plantar reflexes were down. Serum lactate was high (23mg/dl) and ammoniac level was lower than normal ranges (17mmol/lit) as well.

Results of EDX study for both them were similar (Tables 1-4). Upper and lower limbs SNAPs were absent and distal latencies of their CMAPs were prolonged. Nerve

conduction velocities were decreased as well in both upper and lower limbs. In needle electromyography a myopathic process (easy recruitment) without active spontaneous activity existed in proximal muscles of upper and lower limbs. Therefore, they had sensory motor peripheral neuropathy, mainly demyelinating type concomitant with proximal myopathy. According to history and physical examination, lab data and electrodiagnostic findings, mitochondrial myopathy strongly expressed.

Table 1
Nerve conduction study of the boy

Nerve	Side	Sensory			Motor			H-Reflex	F Wave
		Latency	Amplitude	NCV	Latency	Amplitude	NCV		
Median	RT	NR	NR	NR	5.2	4.6	25	NR	27
Median	LT	NR	NR	NR	5	5	22	NR	28
Ulnar	LT	NR	NR	NR	2.9	6.5	28		28
Ulnar	RT	NR	NR	NR	3	6.2	27		28
Radial	RT	NR	NR	NR	3.1	2	21		
Radial	LT	NR	NR	NR	3.2	2.1	22		
Deep Peroneal	RT				4.6	3.0	26	NR	50
Deep Peroneal	LT				4.5	3	28	NR	51
Tibial	LT				6.5	8	27		51
Tibial	RT				6.7	7.9	28		52
Sural	RT	NR	NR	NR					
Sural	LT	NR	NR	NR					
Superficial Peroneal	RT	NR	NR	NR					
Superficial Peroneal	LT	NR	NR	NR					

*NR: Non Responsive. RT: Right, LT: Left

Table 2

Needle electromyography of the boy

Side	Muscle	Nerve	IA	Fib	PSW	Amp	Poly	Volition
Right	Quadriceps	Femoral	N	0	0	N	N	Full
Right	Tibialis Ant	DPN	N	0	0	N	N	Full
Right	Peroneus Longus	SPN	N	0	0	N	N	Full
Right	Gastrocnemius	Tibial	N	0	0	N	N	Full
Right	Gluteus Maximus	Inferior gluteal	N	0	0	N	N	Easy recruitment
Right	Flexor Carpi Radialis	Median	N	0	0	N	N	Full
Right	Deltoid	axillary	N	0	0	N	N	Easy recruitment

*I.A. Insertional Activity Fib: Fibrillation PSW: Positive Sharp Wave

Poly: Polyphasic Motor Units

N:Normal

Table 3

Nerve conduction study of the girl

Nerve	Side	Sensory			Motor			H-Reflex	F Wave
		Latency	Amplitude	NCV	Latency	Amplitude	NCV		
Median	RT	NR	NR	NR	4.5	3.6	22	NR	29
Median	LT	NR	NR	NR	4.7	3.5	21	NR	28
Ulnar	LT	NR	NR	NR	3.9	5.5	26		29
Ulnar	RT	NR	NR	NR	3.6	5.2	24		28
Radial	RT	NR	NR	NR	3.3	3.2	24		
Radial	LT	NR	NR	NR	3.1	3.1	23		
Deep Peroneal	RT				4.9	2.9	25	NR	54
Deep Peroneal	LT				5.5	2	26	NR	54
Tibial	LT				6.8	5	24		53
Tibial	RT				6.9	4.9	25		52
Sural	RT	NR	NR	NR					
Sural	LT	NR	NR	NR					
Superficial Peroneal	RT	NR	NR	NR					
Superficial Peroneal	LT	NR	NR	NR					

*NR: Non Responsive. RT: Right, LT: Left

Table 4

Needle electromyography of the boy

Side	Muscle	Nerve	IA	Fib	PSW	Amp	Poly	Volition
Right	Quadriceps	Femoral	N	0	0	N	N	Easy recruitment
Right	Tibialis Ant	DPN	N	0	0	N	N	Full
Right	Peroneus Longus	SPN	N	0	0	N	N	Full
Right	Gastrocnemius	Tibial	N	0	0	N	N	Full
Right	Gluteus Maximus	Inferior gluteal	N	0	0	Decreased	Increased	Easy recruitment
Right	Flexor Carpi Radialis	Median	N	0	0	N	N	Full
Right	Deltoid	axillary	N	0	0	Decreased	Increased	Easy recruitment

*I.A. Insertional Activity Fib: Fibrillation PSW: Positive Sharp Wave

Poly: Polyphasic Motor Units

N:Norma

3. Discussion

Mitochondrial disorders are rare conditions and it should be suspected anytime a person presents with more than one tissue and/or organ involvement especially when both central and peripheral nervous system are affected simultaneously (neurometabolic disorders). As other genetic disorders, mitochondrial disorders usually occurs in siblings. Serum lactate increased level reinforces the diagnosis and prompts further diagnostic procedures.

Our patients had signs of central and peripheral nervous system (ataxia and absent sensory response in nerve conduction study) and muscular tissue (myopathy) involvement simultaneously. Amino acid analysis was

normal. Lactate level was higher and ammoniac was lower than normal range.

Symptoms of mitochondrial disease may be progressive or recurrent and sometimes with partial recovery after a decline. Frequently, symptoms are precipitated by a metabolic stressor, such as infection, fasting, surgery, or medication. Mitochondrial disease should be considered when there is an unexplained association of neuromuscular and non-neuromuscular symptoms, when the course is rapidly progressive, and when symptoms involve unrelated organs. There are well-established red flag symptoms of mitochondrial disease, many of which affect the nervous system (Haas et al., 2007; Parikh, 2010).

Gait disorder in mentioned cases had been worsening as the time passed.

In brain MRI of our patients, abnormal signals in white matter of both cerebellar cistern and next to trigone of lateral ventricle on either side mostly hypomyelination.

In childhood the manifestations spectrum can range from severe neonatal hypotonia, seizures and failure to thrive. In older children sensorineural deafness and learning disabilities can be mentioned. Among children with progressive neurologic, cardiac, and hepatic dysfunction, mitochondrial disease should be in the differential diagnosis (for any multisystemic disease presentation).

Patients can have minimal objective findings early in the disease course, possibly because in early stages of myopathy, weakness and fatigability are difficult to quantify with usage of manual muscle testing. As the illness progresses, muscle strength and bulk reduce and muscles develops atrophy, at the end stages of the disease might be replaced by fatty infiltration. Myopathy weakness is often more apparent in more proximal muscles. Once a patient begins to use their arms to help themselves rise up off the floor or out of a chair, the weakness is easier to quantify. Other helpful features include atrophy of the intrinsic muscles of the hands or feet, facial muscles or other muscle groups symmetric atrophy.

Peripheral neuropathy is also a well-recognized manifestation, although its characteristics and prevalence vary considerably among different syndromes and genetic causes. It can be a major or common feature of several nuclear DNA defects (Holt, Harding, Petty, & Morgan-Hughes, 1990).

In one series 85 % of patients had mild or moderate muscle weakness, 60 % vibration sensation reduction, 13 % axonal polyneuropathy, and 26 % myopathic electromyographic findings. In half of patients with myopathic findings on muscle biopsy muscle atrophy occurred (Voermans et al., 2009).

In Alejandro Horga et al study, among several individuals' clinical features, peripheral neuropathy was the most important in prediction of the genetic defect in patients with progressive external ophthalmoplegia caused by mitochondrial disease followed by family history and hearing loss (Horga et al., 2014).

In our cases, upper and lower limbs SNAPs were absent and distal latencies of their CMAPs were prolonged. Nerve conduction velocities were decreased as well in both upper and lower limbs was noticed. Hence, peripheral neuropathy was well documented in our patients undoubtedly.

The prognosis for patients varies greatly from one patient to the other because disease progression depends on the disease type and the degree of various organs involvement.

The mitochondria is a potential site of action for general anesthetic agents, and children with mitochondrial disease can respond abnormally to anesthetic drugs (Shipton and Prosser, 2004).

It is important to emphasize that any acute or chronic mitochondrial disorders symptoms or complications should be approached and treated in the same way they would be treated when they caused by non-mitochondrial etiologies (i.e. insulin for diabetes) (McFarland et al., 2010).

Abnormalities of balance, tone, posture and power often complicate the disease in patients of all ages. Rehabilitative solutions include, for example, the use of special seats to support hypotonic infants/children to help them keeping an upright posture, developing axial tone and having more comprehensive visual engagement with the environment. Management of spasticity and dystonia with performing daily range of motion, splinting, botulinum toxin, and pharmacotherapy can help affected individuals at many disease stages and lower the fall risk as well. It is very useful to assess function of patients at home because this reveals their main areas of difficulties and help to plan personalized healthcare support such as mobility and hygiene aids. Management of respiratory problems, including prevention of aspiration pneumonia, is another important issue that should be considered (Shipton & Prosser, 2004)

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