Diagnosing Mitochondrial Disorder without Sophisticated Means

Josef Finsterer[1] and Marlies Frank[2]

[1] *Department of Neurology, Krankenanstalt Rudolfstiftung, Vienna, Austria*

[2] *Department of Medicine, Krankenanstalt Rudolfstiftung, Vienna, Austria*

Received: 22 Oct. 2013; Accepted: 29 May 2014

Abstract- Mitochondrial disorders (MIDs) require biochemical or genetic investigations for being diagnosed. In some cases, however, the diagnosis can be suspected upon the syndromic phenotype or upon clinical presentation and family history, as in the following case. The patient was a 74-year-old male admitted for worsening of pre-existing left-sided ptosis and ophthalmoparesis after a birthday party. The history was positive for arterial hypertension, hypertrophic cardiomyopathy with systolic dysfunction, diabetes-type 2, mild renal insufficiency, thyroiditis, and polyneuropathy. Instrumental investigations additionally revealed hepatopathy, hyperlipidemia, hyperuricemia, bifascicular block, white matter lesions, and subacute stroke. Systolic dysfunction resolved upon adequate cardiac treatment. On hospital day 11 the patient suddenly developed asystole. He was successfully resuscitated but died a few hours later from acute myocardial infarction. Surprisingly, a more extensive family history was positive for myopathy (patient, brother, daughter), neuropathy (patient), hypoacusis (patient), Parkinson syndrome (mother), spasticity (son), diabetes (patient, son), renal failure (patient), and generalized atherosclerosis (patient). The individual and family history was strongly suggestive of an MID. In conclusion, individual and family history may strongly suggest MID. Phenotypic variability may be high between family members affected by an MID. MID may be associated with an increasing atherosclerotic risk lastly resulting in coronary heart disease and death.

Acta Med Iran 2015;53(10):659-662.

Keywords: Mitochondrial disorder; Myopathy; Neuropathy; Cardiac involvement; Cognitive decline; Diabetes; Hypoacusis

Introduction

According to established criteria (Walker, Bernier, Wolf), mitochondrial disorders (MIDs) are diagnosed according to the clinical presentation (phenotype), instrumental investigations other than a muscle biopsy, morphological, ultrastructural, biochemical muscle biopsy findings, and genetic tests (1,2). Depending on the evidence level, definite, probable and possible MIDs are differentiated. To establish the diagnosis of a definite MID, biochemical or genetic investigations are required (1,2).

In some cases, however, the diagnosis can be made upon the syndromic phenotype or upon the clinical presentation and the family history. Here we report a patient in whom the family history taken after deceased supported by instrumental investigations strongly suggested an MID.

Case Report

The patient was a 74-year-old, Caucasian male, height 180cm, weight 80kg, who was admitted for nausea and dull frontal headache bilaterally, starting two days before admission after having drunken alcohol at his daughter's birthday party one day earlier, worsening of a mild, left-sided ptosis recognised already since five years, and immobility of the left bulb starting one day before admission. His previous history was noteworthy for arterial hypertension since years, hypertrophic cardiomyopathy with episodes of heart failure since age 54 years, diabetes since age 56 years requiring insulin since age 66 years, mild renal insufficiency, polyneuropathy with unknown onset, Hashimoto-thyroiditis since a few months, and cognitive decline. Taking the family history with the patient only revealed that his mother had had cardiac problems and that she had developed Parkinson syndrome.

Corresponding Author: J. Finsterer
Department of Neurology, Krankenanstalt Rudolfstiftung, Vienna, Austria
Tel: +43 1 71165, Fax: +43 1 4781711, E-mail address: fifigs1@yahoo.de

Clinical neurologic investigation on admission revealed complete left-sided ptosis, ophthalmoparesis of the left bulb, bilateral hypoacusis, reduced biceps tendon reflexes, a reduced right triceps tendon reflex, an exaggerated left triceps tendon reflex, absent reflexes on the lower limbs, slight wasting of the small foot muscles, bilateral stocking-type hypoesthesia, and a broad-based gait. Blood pressure was 129/73mmHg. ECG showed sinus arrhythmia, left anterior hemiblock, AV-block 1, some monotonic ventricular ectopic beats, R/S-transition in V5, and some non-specific repolarization abnormalities. Blood chemical investigations on admission were indicative of diabetes, mild renal insufficiency, hepatopathy, mild hyperlipidemia, hyperuricemia, elevated lipase, and mildly elevated troponin-T values (Table 1).

Table 1. Blood chemical results of the index patient

Parameter	RL	hd1	hd2	hd6	hd7	hd9	hd11	hd11
CK	**38-174U/l**	170	nd	1009	1364	455	196	289
CK-MB	**0-24U/l**	nd	nd	40	33	26	nd	63
Trop-T	**0.000-0.014ng/ml**	0.072	nd	nd	nd	nd	nd	nd
GOT	**0-50U/l**	nd	nd	71	101	nd	73	1014
GPT	**0-50U/l**	nd	24	37	45	nd	46	533
GGT	**0-60U/l**	nd	48	222	206	nd	259	221
Amylase	**28-100U/l**	58	54	42	40	nd	29	nd
Lipase	**13-60U/l**	nd	152	nd	nd	nd	nd	nd
Glucose^	**82-115mg/dl**	211	170	109	63	nd	149	320
HbA1c	**0-6%**	nd	7.4	nd	nd	nd	nd	nd
Creatinine	**0.7-1.2mg/dl**	2.06	2.02	2.33	2.38	1.17	1.43	2.39
GFR	**>90mL/min/1.73m^{2BS}**	32	32	28	27	61	48	27
Uric acid	**3.5-7mg/dl**	nd	7.6	nd	nd	nd	nd	nd
Ery	**4.2-5.5T/**	4.56	4.2	4.58	4.09	3.9	4.42	3.26
Hb	**14-17g/dl**	13.3	12.1	13.4	11.6	11.1	12.8	9.4
Hk	**40-50%**	38.7	36.1	38.4	34.6	32.4	36.4	28
CRP	**0-5mg/l**	195.4	86.8	102.2	244	152.7	146.9	94.4
BSR	**<20/40**	nd	40/64	nd	nd	55/80	nd	nd
proBNP	**0-486ng/l**	nd	406	nd	nd	nd	nd	nd

RL: reference limits, hd: hospital day, CK: creatine-kinase, Trop-T: troponin-T, GOT: glutamate-oxalate transaminase, GPT: glutamate-pyruvate transaminase, GGT: gamma-glutamyl transpeptidase, GFR: glomerular filtration rate, Ery: erythrocytes, Hb: hemoglobin, Hk: hematocrit, CRP: C-reactive protein, BNP: brain-natriuretic peptide, BSR: blood sedimentation rate, RL: reference limits, nd: not done

MRI of the cerebrum revealed extensive leucoaraiosis, an enhancing lesion in the right central region, which was hyperintense on diffusion-weighted images and hyperintense on TIRM sequences, and was interpreted as subacute stroke, and a small old stroke posterior to the subacute lesion. Carotid ultrasound revealed mild stenoses of the internal carotid artery on the right (50%) and left side (50-70%). Cerebro-spinal fluid investigations showed slightly elevated protein and a lactate of 2.4 mmol/l (n, 1.1-2.4 mmol/l). Transthoracic echocardiography on hospital day (hd) 3 revealed slight myocardial thickening (12 mm), marked systolic dysfunction, slightly enlarged left atrium, and mild tricuspid and mitral insufficiency. Nerve conduction studies showed primary, axonal, sensorimotor polyneuropathy. Gastroscopy revealed a hiatal hernia, reflux-esophagitis, gastritis, and duodenal ulcer. Echocardiography on hd10 revealed improvement of systolic function but was otherwise unchanged compared to the initial investigation. Abdominal ultrasound revealed steatosis hepatitis and multiple cortical renal cysts on the left side.

During hospitalization, the patient experienced an infection of unknown origin, which resolved upon antibiotic treatment with sultamicillin between hd 6-11, and azithromycin (hd 11), and cefotaxime (hd 11). Left-sided ptosis and ophthalmoparesis did not improve before hd 11 when he actively opened the right eye again. MR-angiography excluded an intracerebral aneurysm. Myasthenia was excluded upon normal levels of acetylcholine receptor antibodies and normal low-frequency repetitive stimulation. Antibodies against *Borrelia burgdorferi*, hepatitis, and other viruses were negative. Parathormone levels were normal, but there was mild vitamin-D and folic acid deficiency. His last therapy included clopidogrel, nebivolol, lisinopril, magnesium, atorvastatin, gliclazide, trazodone, esomeprazole, vitamins, and enoxaparin. Unexpectedly, the patient was found asystole and comatose on late hd11 but could be successfully resuscitated for a few

hours to die from ventricular fibrillation on the same day on the intensive care unit. Autopsy revealed that he had experienced an acute myocardial infarction, obviously leading to severe ventricular arrhythmias and asystole.

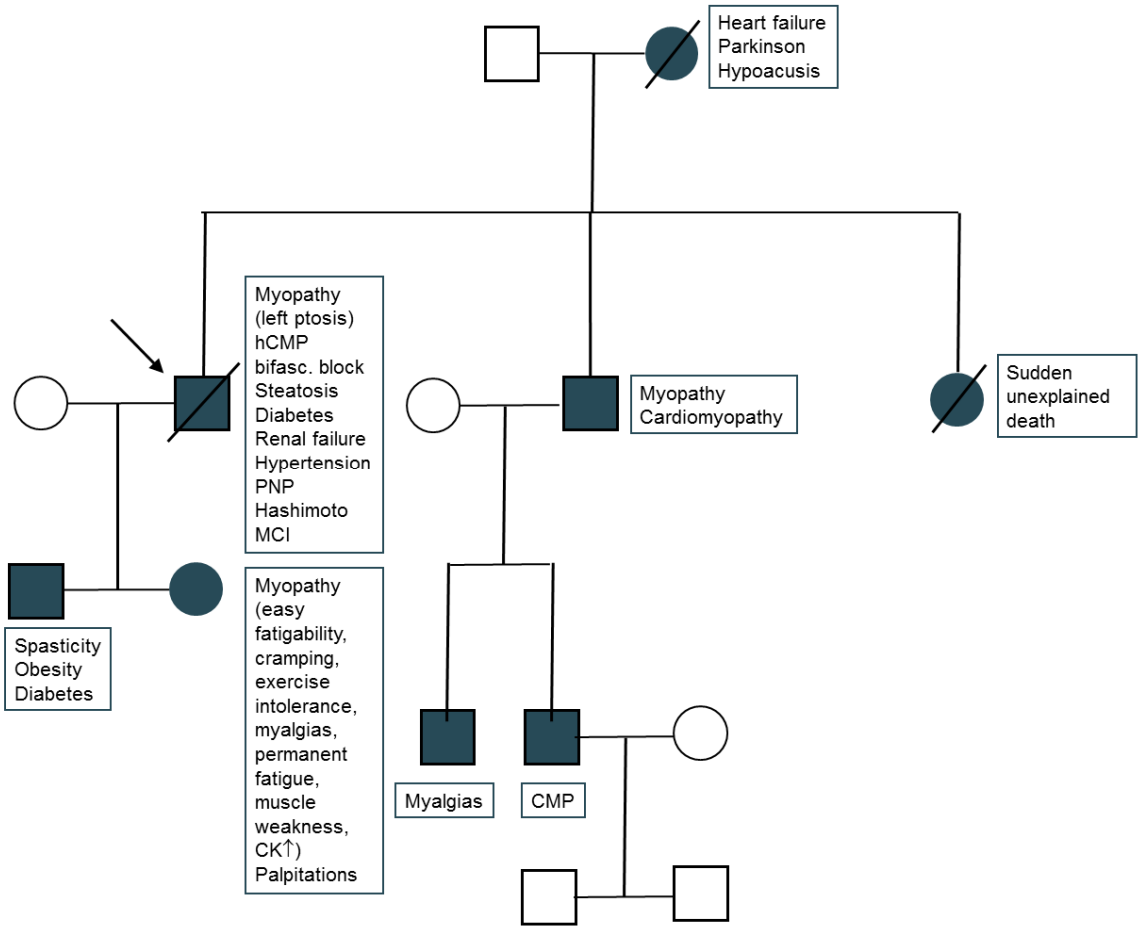

Figure 1. Family tree showing variability of clinical manifestations of the presented MID
The mode of inheritance was autosomal dominant. An arrow indicates the index case.

When taking the family history with the patient's daughter days after decease, it soon became evident that the whole family was suffering from a hereditary metabolic disease. The patient's mother had a "weak" heart with episodes of heart failure since age 60y, Parkinson's disease, and hypoacusis. His sister had died from sudden death at an early age. His brother was wheel-chair bound due to myopathy and quadruspasticity since age 20y and also had cardiac problems. One of his nephews experienced cardiac problems and weakness of the left arm. The patient's son suffered from quadruspasticity since birth, diabetes, and obesity. Most interestingly, however, were the complaints of his daughter. She reported myalgias, muscle cramps, easy fatigability, exercise intolerance, permanent fatigue, weak muscles, exhaustion after routine tasks, prolonged recovery after general anesthesia, and frequent palpitations and was meteorosensitive. Though she recurrently had elevated CK-levels, a muscle biopsy was normal. The daughter reported that her father had to give up his training to become a sports teacher because he always needed a rest after exercises.

Discussion

The presented patient is interesting because he and some of the family members most likely suffered from an MID due to respiratory chain dysfunction. The case also shows how important it is to take a thorough individual history and, in particular, an extensive family

history. Obviously, the family suffers from a multisystem disease (mitochondrial multiorgan disorder syndrome (MIMODS)) with high phenotypic variability but also some similarities between affected members. The diagnosis of an MID is based on the clinical presentation of the index case and on the variably affected other family members, which exhibited diverse clinical presentations (3). Suggestive of a MID in the presented family are the myopathy (index patient, daughter, brother), neuropathy (index patient), hypoacusis (index patient), spasticity (brother, son), diabetes (index patient, son), renal insufficiency (index patient), generalized atherosclerosis (index patient), and easy fatigability (index patient, daughter) (Figure 1) (3,4).

One of the organs most frequently affected in the presented family was the heart (index patient, mother, sister, nephew). Cardiomyopathy is indeed a frequent manifestation of MIDs and may manifest as hypertrophic, dilative, restrictive, or unclassified cardiomyopathy (5). Cardiac involvement may also manifest in the form of supraventricular or ventricular arrhythmias or even sudden cardiac death (6). Though the cause of sudden death in the index patient's sister remains elusive, it cannot be excluded that it was due to a malignant ventricular arrhythmia without spontaneous recovery. The cause of cardiac disease in the index patient's mother remains unclear, but most likely she suffered from a type of cardiomyopathy. Though the index patient had developed several classical cardiovascular risk factors, which could be made responsible for the development of coronary heart disease, it cannot be excluded that they were also due to the underlying genetic defect.

Most of the affected patients in this family also developed myopathy or neuropathy. Myopathy may be the cause of the long-standing ptosis, easy fatigability muscle cramping, and the ophthalmoparesis in the index patient (7). Since diabetes seems to have been well controlled on admission, it is quite unlikely that it was responsible for severe axonal polyneuropathy. Other causes of axonal polyneuropathy were excluded upon the history and blood chemical investigtations. More likely, polyneuropathy was also a manifestation of the MID, which has been repeatedly reported (8,9). Ptosis and ophthalmoparesis were most likely due to affection of the muscle, possibly enhanced by transient alcohol consumption. Neuropathy due to diabetes was rather excluded since diabetes was well-controlled, even without insulin.

Limitations of this presentation are that no biochemical investigations for respiratory chain dysfunction were carried out and that no genetic investigations for mtDNA or nDNA mutations were initiated to confirm the MID. Additionally, no lactate stress test and no systematic family screening had been carried out.

In conclusion, this case shows that MIDs can be diagnosed also upon a thorough individual and family history. High phenotypic variability between variably affected families members may be a typical feature of an MID. MID may be associated with an increasing atherosclerotic risk lastly resulting in coronary heart disease and death.

References

1. Walker UA, Collins S, Byrne E. Respiratory chain encephalomyopathies: a diagnostic classification. Eur Neurol 1996;36(5):260-7.
2. Bernier FP, Boneh A, Dennett X, et al. Diagnostic criteria for respiratory chain disorders in adults and children. Neurology 2002;59(9):1406-11.
3. DiMauro S, Schon EA, Carelli V, et al. The clinical maze of mitochondrial neurology. Nat Rev Neurol 2013;9(8):429-44.
4. Finsterer J, Jarius C, Eichberger H. Phenotype variability in 130 adult patients with respiratory chain disorders. J Inherit Metab Dis 2001;24(5):560-76.
5. Ahuja P, Wanagat J, Wang Z, et al. Divergent mitochondrial biogenesis responses in human cardiomyopathy. Circulation 2013;127(19):1957-67.
6. Vallance HD, Jeven G, Wallace DC, et al. A case of sporadic infantile histiocytoid cardiomyopathy caused by the A8344G (MERRF) mitochondrial DNA mutation. Pediatr Cardiol 2004;25(5):538-40.
7. Gorman GS, Taylor RW. Mitochondrial DNA abnormalities in ophthalmological disease. Saudi J Ophthalmol 2011;25(4):395-404.
8. Finsterer J. Inherited mitochondrial neuropathies. J Neurol Sci 2011;304(1-2):9-16.
9. Vital A, Vital C. Mitochondria and peripheral neuropathies. J Neuropathol Exp Neurol 2012;71(12):1036-46.