

Mimicry between mitochondrial disorder and multiple sclerosis

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Abstract Under certain conditions or at certain stages of the disease course, multiple sclerosis (MS) and mitochondrial disorder (MID) may be differential diagnoses and thus may be confused with each other. In a 30 years old female MS was diagnosed at age 16 year upon recurrent sensory disturbances of the right lower leg, an “inflammatory” cerebrospinal fluid, and a cerebral MRI with multiple non-enhancing white matter lesions. Steroids were repeatedly given but because of rapid deterioration treatment was switched to interferon and mitoxantrone, without improvement. Fourteen years after onset the patient additionally presented with a history of rhabdomyolysis, hypothyroidism, ophthalmoparesis, anarthria, tetraspasticity, tetraparesis, and joint contractures. After MID had been diagnosed in her mother she was re-evaluated and elevated resting lactate, axonal polyneuropathy, and empty sella were additionally found. Muscle biopsy revealed myophagy, fat deposition,

and type-II predominance, and biochemical investigations showed a deficiency of complex I and IV of the respiratory chain. MID was diagnosed also in the index patient. It is concluded that even if CSF investigations or imaging studies suggest MS, differentials such as MIDs need to be excluded before prescribing medication possibly toxic to a MID. An “inflammatory CSF” may also occur in MIDs.

Keywords Multiple sclerosis · Metabolic defect · Respiratory chain · Mitochondrial dysfunction · Metabolic myopathy · Leucoencephalopathy

Introduction

Though of completely different etiology and following different pathomechanisms, multiple sclerosis (MS) and mitochondrial disorder (MID) may be differential diagnoses under certain conditions or at certain stages of the disease and thus may be confused with each other (Harding et al. 1992; Isohanni et al. 2010), as in the following case.

Case report

The patient is a 30 years old female, height 172 cm, weight 85 kg, who developed hypoesthesias and paresthesias on the right lower limb at age 16 year. Diagnostic work-up revealed slightly elevated kappa-light chains in the serum and non-enhancing periventricular, deep, and subcortical white matter lesions on MRI. MRI of the cervical spine was normal. Cerebrospinal fluid (CSF) investigations revealed 21/3 cells, slightly elevated IgG (85 mg/l, n 0–70 mg/l), slightly elevated kappa-light chains, and positive oligoclonal bands. Latencies of visually-evoked potentials were prolonged. MS was diagnosed and since she

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experienced several “relapses”, which responded to prednisolone, she was put on interferon (IFN) beta-1a 22 µg at age 21 year, which was increased to 44 µg a few months later. A few weeks later IFN was discontinued by the patient herself because of ineffectivity. After another “relapse” she was again put on prednisolone 25 mg/day for 2 weeks but she took the drug almost continuously during the next 2 years. Despite this regimen sensory disturbances spreaded also to the distal upper limbs. At age 22 year clinical neurologic examination revealed spontaneous and gaze-dependent nystagmus, a reduced gag reflex, diffuse weakness of the right lower limb (M3-M4), hypotonia and reduced tendon reflexes on the lower limbs, and a positive Babinski sign bilaterally. Since then her condition continuously deteriorated. At age 26 year she was no longer able to ambulate and presented with dysarthria, divergent bulbi, ophthalmoparesis, quadraparesis, tetra-spasticity, and flexion contractures of the right lower limb. The EDSS score was 9. Because of the continuous deterioration, mitoxantrone was administered three times during the next 4 months with a cumulative dosage of 30 mg/m², but was discontinued because of recurrent infections. During an episode of fever at age 26 year she developed rhabdomyolysis with complete remission.

At age 27 year the patient was re-evaluated after she had developed immune-thyroiditis and after her mother, who presented with metabolic myopathy, tetralogy of Fallot, noncompaction, atrial fibrillation, heart failure, hypothyroidism, hepatopathy, anemia, hyponatremia, and short stature, was diagnosed with a MID. Clinical neurologic examination revealed dysarthria, torticollis, weakness (M4) on the upper limbs, reduced tendon reflexes, bilateral ataxia, weakness on the lower limbs (M2-3), contractures of the hips, the right knee and the left ankle, reduced tendon reflexes, a positive Babinski sign bilaterally, and multiple lipomas. Cerebral MRI was similar to that at age 16 year but additionally showed symmetric hyperintensity of the pyramidal tracts (Fig. 1). Spinal MRI showed discrete atrophy of the cervical spinal cord. Echocardiography revealed diastolic dysfunction exclusively. At age 28 years she had undergone lengthening of the left Achilles tendon because of tip-toe walking.

At age 29 year she was no longer able to speak, weakness of the upper limbs had increased to M3-M4 and she was plegic on the lower limbs. There was muscle hypotonia and a foot deformity bilaterally. Resting serum lactate was 3.3 mmol/l (n, <2.0 mmol/l). Nerve conduction studies revealed severe axonal neuropathy. In addition to the supratentorial white matter lesions cerebral MRI showed hyperintensities in the midbrain and the pons and an empty sella (Fig. 1). Muscle biopsy revealed myophagia, fat deposition, and type-II predominance. Biochemical investigations of the muscle homogenate revealed respiratory chain complex I and complex IV deficiency. Based on the history and

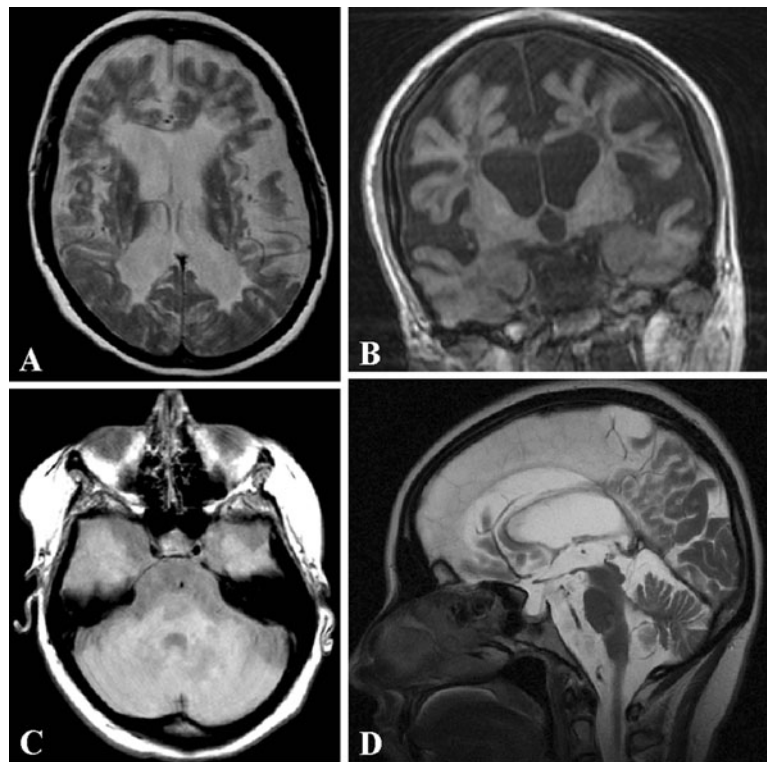
previous and present investigations a MID was diagnosed. Screening for mtDNA or nDNA mutations in the POLG1, twinkle, or ANT1 genes was proposed.

Discussion

This case is interesting for several aspects. First, the MID remained undetected for 14 year although the individual history, family history, occasional hyper-CK-emia, rhabdomyolysis, elevated resting lactate, leucencephalopathy, reduced tendon reflexes, marked cerebral and discrete spinal cord atrophy, and the unusual course, suggested a neurodegenerative disease. Second, the patient received a medication, which could have been toxic to the MID. To which degree, however, steroids, IFN, or mitoxantrone contributed to the progression or deterioration of the MID, remains speculative. Third, periventricular and deep white matter lesions together with marked diffuse supra- and infratentorial atrophy indicate rather a neurodegenerative disorder than MS. White matter lesions have a broad spectrum of differential diagnoses, including MID. White matter lesions in MIDs mimicking leucencephalopathy or even leucodystrophy have been particularly reported in Leber’s hereditary optic neuropathy (LHON) (Olsen et al. 1995), mitochondrial neuro-gastro-intestinal encephalopathy (MNGIE), leucencephalopathy with brainstem and spinal cord involvement and lactic acidosis (LBSL) syndrome, and Leigh-syndrome (LS). Cerebral atrophy has been particularly reported in LS, Kearns-Sayre-syndrome (KSS), myoclonic epilepsy with ragged-red fibers (MERRF)-syndrome, progressive external ophthalmoplegia (PEO), and pontocerebellar hypoplasia (PCH), but also in non-syndromic MIDs (Finsterer 2006; Bargalló et al. 2000; Barragan-Campos et al. 2005; Geldof et al. 2007; Scaglia et al. 2005; Kim et al. 2008). In the present case reduced activity of respiratory chain complexes I and IV was attributed to either an nDNA mutation in the POLG1, twinkle, or ANT1 gene or a mitochondrial tRNA gene mutation.

Though it cannot be definitively excluded that the patient suffered simultaneously from MS and MID, there are several arguments, which favor a MID as the only underlying disease. First, all clinical and laboratory abnormalities, including hypothyroidism, lipomas, torticollis, reduced tendonreflexes, and the “inflammatory CSF”, can be explained by a MID. An “inflammatory” CSF does not exclude a MID since mutated proteins in the central nervous system (CNS) may induce an immunologic reaction by the local immune system, and since pleocytosis (Robeck et al. 1996; Maruyama et al. 1998), elevated protein (Chinnery and Turnbull 1999; Marie et al. 1999), positive oligoclonal bands (Marrie et al. 2001; Pato-Pato et al. 2006; Yiş et al. 2009), and IgG production (Finsterer 2006) have been

Fig. 1 Cerebral MRI at age 29 years showing multiple non-enhancing white matter lesions periventricularly, in the deep white matter and subcortically on axial T2 images (a). Additionally, there was marked atrophy of the cerebrum on coronary T1 images (b) and the cerebellum on sagittal T2 images (d). White matter lesions were also found in the cerebellum bilaterally on an axial TIRM sequence (c)



previously reported in patients with a MID (Table 1). Elevated CSF protein is even a dominant feature of KSS (Marie et al. 1999). Recently, it has been also found that neopterin, interleukin-6, interleukin-8, IFN-gamma and antibodies against the folate receptor are increased in the CSF of patients with Alpers-Huttenlocher syndrome (Hasselmann et al. 2010). In patients with LHON also the CSF trans-thyretin dimer adduct level was increased and the Apo A-IN level increased (D’Aguanno et al. 2008). An “inflammatory CSF” is thus not unique to MS but may be also found in MIDs. Why an “inflammatory” CSF occurs only in single MID patients can be explained by the variable affection of

Table 1 Mitochondrial syndromes, in which elevated CSF protein, pleocytosis, autochthonous IgG production, or positive oligoclonal bands have been reported

MID	Protein ↑	Pleocytosis	IgG ↑	Oligoclonal bands
MELAS	+ [a,b]	+ [e,f]	nr	nr
LHON	nr	nr	nr	+ [g,h]
KSS	+ [c]	nr	nr	nr
LS	nr	nr	nr	+ [i]
NS	nr	nr	nr	+ [j]
AHD	+ [d]	nr	nr	nr

NS non-syndromic MID, AHD Alpers-Huttenlocher disease, nr: not reported, a (Chinnery and Turnbull 1999), b (Kihira et al. 2004), c (Marie et al. 1999), d (Castro-Gago et al. 1999), e (Robeck et al. 1996) f (Maruyama et al. 1998), g (Pato-Pato et al. 2006), h (Parry-Jones et al. 2008), i (Yiş et al. 2009), j (Marrie et al. 2001)

the CNS and the variable immunogenicity of mutated proteins. Second, the family history was positive for MID, which makes it more likely that the phenotype was due to the mitochondrial defect as well. Third, immune-modulatory treatment did not prevent the progression of the disease. The low therapeutic effect, however, might be also attributed to the low compliance of the patient. Fourth, there are only few reports about patients with a MID who also developed MS or vice versa (Palace 2009; Parry-Jones et al. 2008). However, in a recent study on MS patients, complex I activity was found significantly reduced in fresh skeletal muscle (Kumleh et al. 2006). Fifth, the marked cerebral atrophy already at an early age favors the assumption of a single hereditary disease as the underlying cause. Definitely, however, the coexistence cannot be excluded.

Whether the respiratory chain defect was secondary to the immuno-suppressive treatment remains speculative. Arguments against such a speculation are that the disorder was most likely hereditary, that the disease progressed already before treatment, that the abnormalities persisted despite discontinuation of the treatment, that administration of immuno-suppressive medication was neither associated with a clinical nor instrumental deterioration, and that mitochondrial dysfunction secondary to immuno-suppressive therapy has not been reported in MS patients receiving such treatment. Arguments for a causal relation between the immuno-suppressive treatment and the development of an MID, however, are that steroids have been previously reported to deteriorate MIDs, that the development of critical

ill polyneuropathy may be triggered by steroids (Ahlbeck et al. 2009), that oxidation of mitoxantrone by SOD triggers the production of ROS in yeast (Reszka et al. 1986), and that beta-interferone blocks cytochrome-c (Kihira et al. 2004). These arguments suggest that immune-suppressive medication given for MS is potentially mitochondrion-toxic and if erroneously given to MID patients may contribute to their deterioration.

Even if CSF investigations or imaging studies suggest MS, differentials such as MIDs need to be excluded since immune-suppressive therapy given for MS is potentially mitochondrion-toxic. For diagnosing a MID the individual and family history, muscle enzymes, the disease course, the response to medication, and atypical findings on imaging should be additionally considered. Reduced tendon reflexes rather suggest MID than MS. Though MIDs are still frequently missed, the proportion of misdiagnosis is declining over the last years.

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