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Mitochondrial disorder mimicking ocular myasthenia

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Abstract

Objectives: Ocular myasthenia (OM) and mitochondrial disorder (MID) may be easily mixed up, if the MID presents with similar manifestations as OM and if MID manifestations progress only slowly.

Case report: In a 69yo Caucasian female OM was diagnosed at age 54y. Six years after onset the diagnosis was challenged, because the response to cholinergic medication was weak, acetyl-cholin-receptor antibodies were only marginally elevated, creatine-kinase was slightly elevated, and because the patient's mother had developed dementia. Resting lactate was normal but the lactate-stress-test was highly abnormal. Muscle biopsy was indicative of a MID and biochemical investigations revealed a complex I defect.

Conclusions: MID may be easily mixed up with OM, particularly at onset of a MID with only mild manifestations. The diagnosis of OM should be challenged if untypical clinical features develop or clinical manifestations do not respond to cholinergic medication.

Key words: Encephalomyopathy; neuromuscular disorder; metabolic myopathy; mitochondrial disorder; seizures; epilepsy; stroke-like episode.

Introduction

At onset mitochondrial disorders (MIDs) may manifest clinically only with mild symptoms, such as ptosis or easy fatigability (1). Since such discrete manifestations may also occur in other diseases, such as ocular myasthenia (OM) (2), these two entities may be easily mixed up, particularly at onset of manifestations, as in the following case.

Case report

The patient is a 69 yo, HIV-negative, Caucasian female, height 159 cm, weight 59 kg, with a history of migraine between age 18 to 20 y, pyelonephritis at age 25 y, cholecystectomy at age 31 y, hysterectomy with consecutive sepsis at age 42 y, right-sided hypacusis since age 42 y, hyperlipidemia since at least age 49 y for which she received various types of lipid lowering agents, and borreliosis at age 54 y, who developed bilateral ptosis since age 54 y. At that time neurological diagnostic work-up resulted in the diagnosis of OM in the absence of a thymoma. The diagnosis was based on the clinical presentation, a beneficial response to edrophonium, an abnormal decremental response to repetitive nerve stimulation, and slightly elevated acetyl-cholin-receptor (AchR)-antibodies. The patient underwent an adequate therapy with pyridostigmine during the next six years. Azathioprine was given during a few months but was discontinued because of nausea.

At follow-up visits 6 y after onset the diagnosis of OM became questionable for the following reasons: AchR-antibodies remained always only slightly elevated, repetitive nerve stimulation became normal although ptosis persisted, creatine-kinase was slightly elevated, the index patient's mother developed dementia, and ptosis in the index patient only marginally resolved upon administration of pyridostigmine. Re-evaluation for MID at age 60 y revealed normal creatine-kinase and normal resting lactate (1.6 mmol/l (n, < 2.0 mmol/l)). Lactate stress testing under a constant workload of 30 W during 15 minutes on a bicycle ergometer according to an established protocol was abnormal, showing values of 1.6, 2.5, 3.1, 3.6, and 3.1 mmol/l. Echocardiography was normal. Muscle biopsy revealed type 1-predominance, ragged-red fibres, reduced SDH and COX staining, and, on electron microscopy, morphologically abnormal mitochondria. In the surroundings of these mitochondria lipid droplets and glycogen masses were located. Biochemical investigations revealed a complex-I-defect. Double strand sequencing of the mtDNA failed to detect a causative mutation but revealed the polymorphism 8348A>G in the tRNALys gene. MID was diagnosed and the

cholinergic therapy discontinued without deterioration of her complaints.

The further course was dominated by the following history: since age 56 y she developed chronic sinusitis; since age 62 y slowly progressive, permanent weakness of the limb muscles became apparent; at age 62 y she developed abdominal pain from choledocholithiasis, cholangitis, and pancreatitis, which required papillotomy at age 63 y and age 67 y; at age 65 y she underwent re-constructive surgery for bilateral ptosis with transient effect; since age 65 y a mild bilateral coxarthrosis was diagnosed and she complained about lumbalgia since age 66 y; she also developed a cataract bilaterally and a glaucoma on the right side. She never experienced double vision or ophthalmoparesis thus far. During the last years resting lactate was elevated only once. She is actually on a therapy with triazolam 0.25 mg/d, midodrin drops for arterial hypotension, esomeprazol 20 mg/d, and ezetimib 10 mg/d. Various combinations of antioxidants and cofactors have been tried without significant effect.

Discussion

Clinical manifestations MID and OM may have in common are ptosis, ophthalmoparesis, easy fatigability and an abnormal response to repetitive nerve stimulation (3, 4). Particularly at onset, a MID may present with ptosis as the sole clinical manifestation and may thus mimic OM (3, 4). This is why at this stage the correct diagnosis may be difficult to establish. Features, which delineate both disorders more clearly are the more pronounced, beneficial response to cholinergic medication and immuuno-suppression in OM patients (Table 1). In the majority of the cases clinical manifestations of OM resolve under application of cholinergic medication or immuno-suppression (5). On the contrary, MID patients do not profit from immuno-suppression. Upon the response to steroids the entities cannot be clearly distinguished since single MID patients may also profit from steroids (6, 7). MID and OM may be definitively delineated by muscle biopsy findings, biochemical investigations of the respiratory chain complex activity, or most clearly, by demonstration of a mtDNA or nDNA mutation, which can be made responsible for the MID phenotype.

Why MID was misinterpreted as OM for six years in the presented patient has several reasons. First, many physicians are not aware that MID is a differential diagnosis of OM and vice versa. This is why MIDs are not considered as differentials of OM. Second, the negative response to cholinergic medication was not carefully appreciated and recognised. The effect of cholinergic medication may be particularly intriguing since some MID patients report at least a transient beneficial effect to cholinergic medication. Particularly, the edrophonium test may be false positive in MIDs. Third, manifestations, such as short stature and migraine, present already at onset of the clinical neurologic manifestations, were not considered as possible manifestations of a MID. Fourth, AchR-antibodies were slightly elevated and thus suggestive of OM. Other manifestations of the MID, such as cataract, and weakness and wasting were not present at onset. On the contrary, OM may be misinterpreted as MID if AchR-antibodies are absent, which is the case in about 10% of the patients.

Table 1

Similarities and differences between MID and OM

Feature	MID	OM
Reaction to cholinergics	+	+++
Beneficial effect of steroids	++	+++
Beneficial effect of immuno-suppression	-	+++
Decremental response	+	+++
Elevated AchR-antibodies	(+)	+++
Presence of thymoma	-	++
Beneficial response to edrophonium	+	+++
Short stature	++	(+)
Cataract	++	(+)
Family history suggestive of a MID	++	-
Abnormal muscle biopsy	+++	-
Reduced respiratory chain complex activity	+++	-
Presence of a mtDNA mutation	++	-
Hyperhidrosis	++	+
Hyper-CK-emia	+++	+

Not earlier than six years after onset of the clinical manifestations these points were addressed and re-assessment of the diagnosis initiated. What made the treating physician suspicious after six years were the absent response to the cholinergic medication, the only slightly elevated AchR-antibodies, the short stature of the patient, the occurrence of mild hyper-CK-emia with CK-values up to 198 U/l (n, < 140 U/l), that the mother of the patient had developed dementia, that she had a history of migraine, and that she had no thymoma. Establishing the correct diagnosis after 6 y was further supported by the development of slight, slowly progressive but permanent weakness in all limb muscles and wasting of the thigh muscles. Decreased SDH activity on immunehistochemistry was explained as a secondary effect of a yet unidentified mtDNA or mtDNA mutation. The presence of RRFs not necessarily implies a mtDNA mutation as causative but has been also described in OPA1 and twinkle mutations (8, 9).

This case shows that a MID may be easily mixed up with OM, particularly at onset when a MID presents with only mild manifestations. Misinterpretation of a MID as OM may be abated upon slightly elevated AchR-antibodies, a false positive edrophonium test, and an abnormal decremental response to repetitive nerve stimulation. The diagnosis of OM should be challenged if untypical clinical features develop and if clinical manifestations do not respond to cholinergic medication.

REFERENCES

1. Zeviani M. Mitochondrial disorders. Suppl Clin Neurophysiol. 2004;57:304-12.
2. Antonio-Santos AA, Eggenberger ER. Medical treatment options for ocular myasthenia gravis. Curr Opin Ophthalmol. 2008;19:468-78.
3. Finsterer J, Oberman I, Reitner A. Respiratory chain complex-I defect mimicking myasthenia. Metab Brain Dis. 2002;17:41-6.
4. Juel VC, Massey JM. Myasthenia gravis. Orphanet J Rare Dis. 2007;2:44.
5. Hart IK, Sharshar T, Sathasivam S. Immunosuppressant drugs for myasthenia gravis. J Neurol Neurosurg Psychiatry. 2009;80:5-6.
6. Rossi FH, Okun M, Yachnis A, Quisling R, Triggs WJ. Corticosteroid treatment of mitochondrial encephalomyopathies. Neurologist. 2002;8:313-5.
7. Letuve S, Druilhe A, Grandsaigne M, Aubier M, Pretolani M. Critical role of mitochondria, but not caspases, during glucocorticosteroid-induced human eosinophil apoptosis. Am J Respir Cell Mol Biol. 2002;26:565-71.
8. Amati-Bonneau P, Valentino ML, Reynier P, Gallardo ME, Bornstein B, Boissière A, Campos Y, Rivera H, de la Aleja JG, Carroccia R, Iommarini L, Labauge P, Figarella-Branger D, Marcorelles P, Furby A, Beauvais K, Letournel F, Liguori R, La Morgia C, Montagna P, Liguori M, Zanna C, Rugolo M, Cossarizza A, Wissinger B, Verny C, Schwarzenbacher R, Martín MA, Arenas J, Ayuso C, Garesse R, Lenaers G, Bonneau D, Carelli V. OPA1 mutations induce mitochondrial DNA instability and optic atrophy 'plus' phenotypes. Brain. 2008;131:338-51.
9. Kiechl S, Horváth R, Luoma P, Kiechl-Kohlendorfer U, Wallacher-Scholz B, Stucka R, Thaler C, Wanschitz J, Suomalainen A, Jaksch M, Willeit J. Two families with autosomal dominant progressive external ophthalmoplegia. J Neurol Neurosurg Psychiatry. 2004;75:1125-8.

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