Aseptic meningitis as a manifestation of a mitochondrial disorder

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Myopathy is usually a disorder with muscle weakness, muscle wasting, abnormal electromyography, or abnormal muscle biopsy (electromyography – EMG) [1]. Occasionally, however, myopathy may either occur without symptoms or with only mild clinical manifestations, or even without symptoms and only elevated creatine kinase (CK) [2]. Electromyography is frequently normal or even shows neurogenic features. Muscle biopsy can be normal. If systems other than the muscle are additionally affected, myopathy is only a collateral feature in a multisystem disease or the patient suffers from a double or triple etc. trouble. Here we report a patient with a multisystem disease including myopathy, which is most likely attributable to a common cause.

The patient is a 45-year-old, Caucasian woman, height 166 cm, weight 60 kg, with a history of recurrent aseptic meningitis (no causative organism was detected) at age 24 years, at age 43 years, and at age 45 years. These episodes always started with sudden, prickly, holocranial headache, followed by > 40° fever and vomiting. After the first meningitis she developed residual headache lasting 1 year. Despite pleocytosis up to 393/3 cells, a causative agent was never detected. Each time the condition resolved completely without permanent sequelae under antibiotic treatment. Interestingly, the second aseptic meningitis was associated with aseptic pancreatitis. At age 43 years multiple cavernomas located in the frontal regions bilaterally, the pons, parahippocampally, and the occipital regions bilaterally were detected (Figure 1). From age 42 years she additionally recognised extreme fatigability and rapid exhaustion when carrying out simple daily activities. At age 43 years she experienced pontine bleeding being attributed to a cavernoma, for which she underwent gamma-knife therapy 1 month later. Shortly after gamma-knife, hyper-CK-aemia with a maximal value of 1582 U/l (n, < 170U/l) was diagnosed. From the same time, she also experienced generalised weakness and wasting of the entire musculature with a weight loss of altogether 17 kg. Though she was able to attend a fitness centre 3 times/week, she experienced muscle aches each time after exercising. For years she also had polydipsia with a fluid intake of up to 3 l/day. Her history was further noteworthy for nephrolithiasis, renal insufficiency, hyperlipidaemia, cholecystolithiasis, surgery for varicosities, haemorrhoids, recurrent syncopes as an adolescent, pneumonia as a child, left-sided habitual patella luxation requiring surgery, a rape at age 22 years, of which she did not notify the police, and depression since her best girlfriend passed away and more intense since gamma-knife therapy. Her first child was born in a breech presentation.

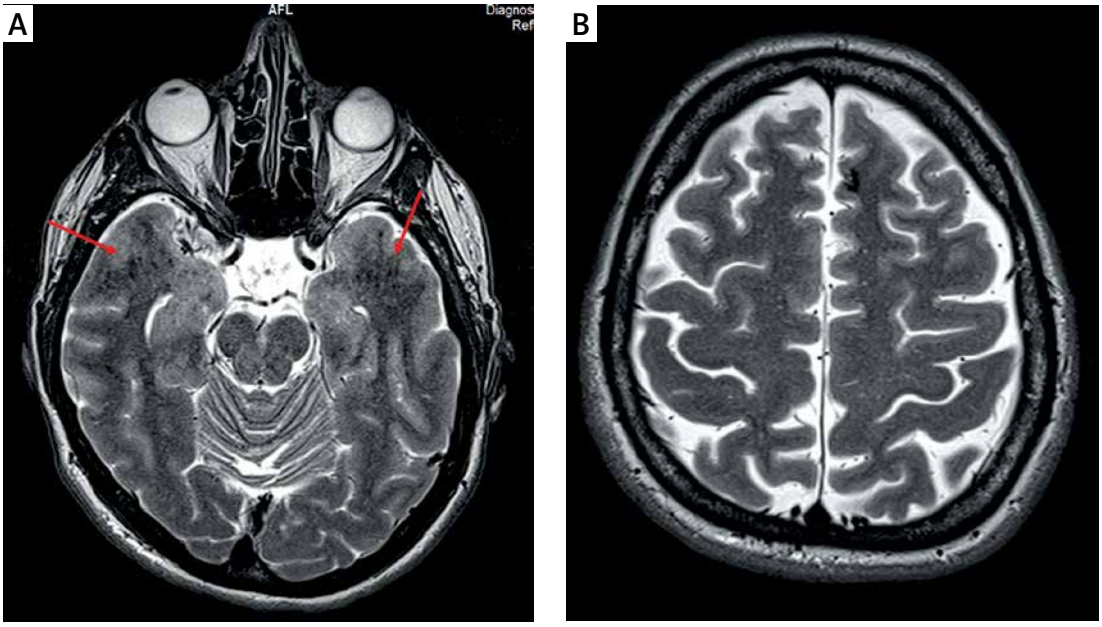

Figure 1. MRI T2-weighted images showing hypointensities in the temporal poles bilaterally, the midbrain, and the frontal lobe on the left side being interpreted as cavernomas

Her family history was positive for polydipsia (sister), multiple cavernomas of the skin (father, grandmother from the mother's side), hypothyroidism (mother, sister), hyper-CK-aemia (mother), diabetes (father, mother, grandfather from the mother's side), easy fatigability (mother, sister), blindness (grandmother from the father's side), depression (mother, grandmother from the mother's side), schizophrenia (sister of father, cousin from the father's side), psychiatric abnormality (female cousin), left-sided habitual patella luxation (daughter, sister), prostate cancer (father's brother), and astrocytoma (cousin from the father's side).

Clinical neurologic examination at age 45 years was normal except for sore neck muscles and myopia. Antibodies against viruses in the serum and CSF and *Toxocara canis* were negative. Nerve conduction studies, needle EMG, and echocardiography were normal. She did not consent to muscle biopsy or genetic work-up. She regularly took only bupropion (300 mg/day).

The presented patient is interesting for several aspects. First, the patient had exercise intolerance and hereditary hyper-CK-aemia without stigmas on clinical examination or EMG (Table I). Nonetheless, she experienced easy fatigability, muscle soreness after exercise, general weakness, wasting, weight loss, and there was constant hyper-CK-aemia at least since age 42 years. Since other organs were additionally involved (pancreas, kidneys, cerebrum, bones), the condition was regarded as a multisystem disease. The most frequent among the multisystem diseases with myopathy include myotonic dystrophies, respiratory chain defects, β-oxidation defects, choline kinase beta chain defects, Danon dis-

Table I. Results of blood chemical investigations in the described patient

Parameter	RL	19.07.99*	17.01.11	28.06.14	09.07.14	22.12.14	5.03.15	23.04.15
CK	26–145 U/l	52	114	**248**	112	**297**	**272**	**216**
GOT	< 35 U/l	8	19	**149**	19	23	ND	ND
GPT	0–35 U/l	8	24	**176**	**52**	24	ND	30
GGT	0–40 U/l	7	16	**360**	**349**	15	ND	19
Amylase	28–100 U/l	32	ND	380	36	32	ND	ND
Lipase	13–60 U/l	ND	ND	1700	46	42	25	ND
Creatinine	0.5–0.9 mg/dl	1.0	0.68	0.88	**0.97**	**0.98**	0.89	**1.04**
GFR	> 90 ml/min/ 1.73 m^2 BS	ND	> 60	ND	ND	ND	**69**	**57**

*RL – reference limits, *reference limit at that time was < 70 U/l, CK – creatine kinase, GOT – glutamate oxalate transaminase, GPT – glutamate-pyruvate transaminase, GGT – γ-glutamyl transpeptidase, GFR – glomerular filtration rate, ND – not done, BS – body surface.*

Table II. Differential diagnoses of aseptic meningitis

Differential	Reference
Viral meningitis	[8]
Mollaret's meningitis	[9]
Tuberculous meningitis	[30]
Kikuchi Fujimoto disease	[10]
Intracerebral hypotension	[33]
Drug-induced	[31]
Viral (with or without agent)	[8]
IgG4-related	[11]
Tsutsugamushi disease (scrub typhus)	[12]
Leptospirosis	[13]
Mitochondrial disorder	[14]
Giant leaking colloid cyst	[15]
Heat exposure	[16]
Systemic lupus erythematosus	[17]
Sjögren syndrome	[18]
Intrathecal morphine infusion	[19]
Extramedullary spinal teratoma	[20]
Kawasaki disease	[21]
Congenital apex cholesteatoma	[22]
Still's disease	[23]
IgG3 subclass deficiency	[24]
Macroprolactinoma	[25]
Sarcoidosis	[26]
Cerebral aneurysm	[27]
Wegener granulomatosis	[28]

ease, McLeod syndrome, and Barth syndrome. Myotonic dystrophy was excluded upon the clinical presentation and the normal EMG. Barth syndrome was excluded based on the fact that the patient was female. Danon disease was excluded due to absence of hypertrophic cardiomyopathy and intellectual decline. McLeod syndrome was excluded in the absence of anaemia, dementia, seizures, acanthocytes, and female gender. The most likely cause was an mitochondrial disorder (MID). Arguments for an MID in addition to myopathy are the cerebral manifestations, short stature, aseptic pancreatitis, renal insufficiency, nephrolithiasis, hereditary hyper-CK-aemia, polydipsia, hyperlipidaemia, unilateral habitual patella luxation, and the family history. The multisystem condition of the presented patient and of some of her relatives is noteworthy and suggests a mitochondrial multiorgan disorder syndrome (MIMODS) [3–7].

Second, the patient had recurrent aseptic meningitis of unknown aetiology, despite intensive work-up for various differentials (Table II) [8–28]. A viral cause was excluded upon repeated negative search for antibodies against viruses and for virus DNA. Mollaret's meningitis was excluded because of a negative HSV2 test [29]. Tuberculous meningitis [30] was excluded since the patient was not severely ill, since the course was of long duration without marked deterioration, and since the QuantiFERON blood test and PCR for *Mycobacterium tuberculosis* were negative. Drug-induced meningitis [31] was excluded since she was not regularly taking ibuprofen, zaltoprofen, carbamazepine, trimethoprim, ergot alkaloids, immunoglobulins, tumor necrosis factor (TNF)-α, ipilimumab, amoxicillin, or cetuximab [32]. Acute intracerebral hypotension [33] mimicking aseptic meningitis was excluded since the patient developed fever each time and since stigmas of low cerebrospinal fluid (CSF) pressure syndrome were absent on MRI. There was also no indication for a paraneoplastic origin of recurrent pleocytosis. Additionally, it is unclear whether aseptic meningitis truly resolved upon antibiotic treatment or spontaneously. Arguments for aseptic meningitis as a manifestation of an MID are that pancreatitis has been reported once in association with aseptic meningitis [34], that the currently presented patient had pancreatitis during the second aseptic meningitis, and that in a single patient aseptic meningitis was associated with vasoconstriction syndrome, also a rare manifestation of an MID [35].

Third, it remains speculative whether the multiple cavernomas are a manifestation of the suspected MID or a second trouble due to another cause. Both possibilities are conceivable. Arguments for a common cause of the condition are that features of an MID and at least cutaneous cavernomas were also present in other family members, that vascular involvement is well established as a manifestation of MIDs [36], and that cyst formation in the liver, pancreas or kidney may also indicate an MID. Arguments against a common cause of the cavernomas and the MID are that cavernomas have not been reported in patients with a MID so far, that cavernomas of the skin and the cerebrum may have a different aetiology, and that aseptic meningitis has been reported in association with cavernomas only once [37]. In this patient with at least 9 episodes of aseptic meningitis a single cavernoma was accidentally found on cerebral MRI [37].

In conclusion, this case shows that myopathy with multisystem involvement suggests an MID, that the MID may manifest as aseptic meningitis and multiple cavernomas, and that myopathy in the MID may manifest with muscle symptoms and hyper-CK-aemia but normal clinical examination and EMG.

Conflict of interest

The authors declare no conflict of interest.

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