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Case Report

Leriche Syndrome, As a Manifestation of a Mitochondrial Disorder

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Abstract: In case of a double trouble with a similar phenotype, one might prevent the other from being detected for years. In a 49yo and 149cm tall female with a history of calf muscle cramps since childhood, chronic recurrent abdominal pain, and slowly progressive triparesis with lower limb predominance since age 22y, panatherosclerosis, with stenosis of both internal carotid arteries, the renal arteries and occlusion of the abdominal aorta (Leriche syndrome) with excellent collateralisation were found at age 44 years. Risk factors for atherosclerosis were hyperlipidaemia, nicotine, the pill and malignant arterial hypertension since age 39y. Initially, the vascular abnormalities were made responsible for her complaints. Upon re-evaluation of the history, neurological examination, lactate stress testing, increased CSF-lactate, electromyography, and muscle biopsy, a second trouble, mitochondrial disorder (MID), was diagnosed and was made responsible for the neurological abnormalities. Though Leriche syndrome suggests to be responsible for slowly progressive paraparesis, it should not prevent from taking a neuromuscular disorder into consideration as a differential diagnosis. Leriche syndrome may be a primary manifestation of a MID.

Keywords: neuromuscular disorders, myopathy, atherosclerosis, arterial hypertension.

INTRODUCTION

Mitochondrial disorders (MIDs) may be due to acquired or genetic defects, leading to impairment of the oxidative phosphorylation system (OXPHOS). Genetic defects may include point mutations and large scale deletions in the mtDNA (primary or class I OXPHOS diseases) and mutations of nuclear genes encoding for respiratory chain assembly factors and respiratory chain polypeptides (secondary or class II OXPHOS diseases, predominantly neurodegenerative disorders) (Leonard, J.V., & Shapira, A.H.V. 2000a & Leonard, J.V., & Shapira, A.H.V. 2000b). A striking feature of MIDs is their clinical heterogeneity, ranging from single-organ involvement to multisystem disease, affecting the muscle, peripheral nerve, brain, eyes, ears, heart, gastrointestinal tract, endocrinium, bone marrow and kidneys (Leonard, J.V., & Shapira, A.H.V. 2000a & Leonard, J.V., & Shapira, A.H.V. 2000b). The same mutations or different mutations in the same gene may present with different phaenotypes while the same phenotype may be caused by the same mutation. Because of this clinical and genetic heterogeneity, MIDs are easily overlooked, particularly if there is a second trouble that mimics the MID phenotype, as in the following case report.

Case Report

A 49-year-old, HIV-negative women (height: 149cm) was admitted because of sudden lower limb paraparesis and a sensory transverse syndrome after a fall from the wheel chair, 11 days before admission. Her history was noteworthy for calf muscle cramps during and after exercise since childhood, chronic recurrent abdominal pain since 1960, weak lower limb pulses at a check-up in 1961, and inability to get up from the squat since 1973. In 1984 she developed allergenic asthma and consecutive emphysema after contact with a rabbit, being treated with corticosteroids, theophyllin and β2-mimetics since then. In 1985 muscle cramps spreaded towards the thighs and she developed slowly progressive gait disturbance. In 1986 she noticed inability to dance during a ball. In 1989 she was hospitalised for pulmonary embolism. In 1990 she was admitted for abdominal pain, being attributed to cholecystolithiasis, pneumonia, and arterial hypertension. The latter was detected for the first time and mostly inadequately treated since then. In 1991 she underwent cholecystectomy. Investigations prior to surgery revealed pangastritis, cholecystolithiasis, pancreatitis and a pancreatic cyst. After adequate therapy, her symptoms relieved, but abdominal pain

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recurred. After dismissal, she recognised paraesthesias of the left leg for the first time. Her walking distance was limited to 20m, after which she noted muscle cramps and exhaustion. In October 1995 she was admitted for nausea, vomiting and abdominal pain. She still complained about muscle cramps and her walking distance had decreased to <20m. Extensive investigations revealed general arterial occlusive disease with stenoses of the right internal carotid artery (60-70 %), the left internal carotid artery (75-80%), the left vertebral artery (50%), both renal arteries, of which the right one was stented with a Palmaz-stent, and a Leriche syndrome with occlusion of the infrarenal abdominal aorta and both common iliac and external iliac arteries but excellent collateralisation. Therapy with ticlopidine and clopidogrel respectively were not tolerated, why heparin was applied. Anticoagulation was rejected because of malignant arterial hypertension. In October 1997 she was hospitalised for increasingly tiring after only moderate exercise and abdominal pain, both attributed to a gastritis and the vascular abnormalities. Since May 1999 she recognised recurrent paraesthesias of both legs including the hips. Since September 1999 she recognised stocking-type numbness and dysaesthesias bilaterally. After vaccination against influenza in January 2000, she developed recurrent fever and chronic fatigue. At that time she was still able to walk a few meters by supporting herself on walls, chairs and tables. In March 2000 she was admitted because of a prolonged asthmatic attack during which she shortly lost consciousness. Because of prolonged dyspnoea and further asthmatic attacks, she was largely bound to bed, but still able to move her legs. Eleven days before admission to the neurological department she fell from the wheel chair after having shortly lost her consciousness again. Afterwards, she noted complete inability to move her legs. Between 1969 and 1996 she was smoking up to 80 cigarettes daily. She was regularly taking corticosteroids (since 1984), theophyllin (since 1984), antihypertensive drugs (since 1990) like prazosin, doxazosin, nifedipine, diltiazem, bisoprolol, valsartan, atenolol, enalapril, clonidin, lipid lowering drugs (since 1997), and the pill between 1970 and 1997. She had allergies against a number of molecules including penicillin. The family history was positive for stroke (mother) and pulmonary embolism (father).

Clinical neurologic examination on admission revealed double vision when looking to the right, slight hypacusis on the right side, hypaesthesia of the left face, slight deviation of the tongue to the right, and slight wasting of the right edge of the tongue. The neck muscles were sore. On the upper extremities there was slight weakness on the right side (Medical Research Council (MRC) grade 5-), bilateral postural tremor, exaggerated deep tendon reflexes. There was a sensible transverse syndrome at Th11, sore spinal muscles and saddle area numbness. On the lower extremities there was severe weakness bilaterally (MRC grade 1), hypotonia, clonic patella reflexes with left sided predominance, exaggerated Achilles tendon reflexes and stocking type sensory disturbances up to the knees. She had oedema of the feet and was unable to stay or walk.

Routine blood chemical investigations showed hyperlipidaemia, hyperuricaemia, slight hyperglycaemia and a glycosilised haemoglobin of 6.8% (normal: <6.0%). The ECG showed P-pulmonale, ST-elevation in V1 and biphasic respectively negative T-waves in V2-V6. Cerebral angiography via the right brachial artery, revealed stenosis of the left internal carotid artery (90%) and the right internal carotid artery (75%). Spinal angiography via the left brachial artery revealed occlusion of the abdominal aorta and quite a number of atypical spinal and abdominal arteries being interpreted as collaterals. CSF investigations showed elevated lactate of 1.8 mmol/l (normal <1.6 mmol/l) exclusively. MRIs of the cervical, thoracic and lumbar spine revealed degenerative alterations of the spinal colum, but normal spinal cord. Nerve conduction studies of the right median nerve were normal. Nerve conduction velocity of the right peroneal nerve were reduced to 45.9 m/s. Orthodromic nerve conduction velocity of the left sural nerve was reduced to 39.5 m/s. Electromyograms of the right brachial biceps (anterior tibial) muscles were myogenic with fibrillations at 2 (18) of 20 sites, a mean motor unit action potential duration of 9.2 (11.7) ms, 0 (5) % percent polyphasia and a dense low amplitude interference pattern. Visually evoked potentials gave a normal P100 latency, but an increased P100/N145 amplitude of 24 μV on the left and of 28.4 μV on the right side. Modified lactate stress testing (LST) by lifting weight with the upper limbs, was abnormal. Muscle biopsy from the right lateral vastus muscle showed myopathic features, ragged-red-fibres, which intensively reacted for NADH, deficiency of cytochrome-c oxidase, and abnormally shaped and structured mitochondria. Biochemical investigations of the muscle homogenate and screening for mtDNA mutations were normal.

DISCUSSION

The presented patient is interesting for suspected MID due to a respiratory chain defect upon immunhistology. MID was suspected for the following reasons: 1) There was a multisystem disorder with involvement of the skeletal muscle (myopathy with exercise induced cramps since childhood, double vision, triparesis and easy fatigability), the peripheral nerves (sensori-motor polyneuropathy with stocking-type sensory disturbances), the central nervous system (tremor, increased CSF-lactate, increased amplitude of the visually evoked potentials being attributed to cortical synchronisation effects, exaggerated deep tendon reflexes on the upper as well as lower limbs), the ears (hypacusis), the gastrointestinal tract (abdominal pain of undetermined cause, presumably

recurrent pancreatitis, pancreatic cyst), and the endocrinium (short stature, hyperlipidaemia, increased glycosilised haemoglobin, hyperhidrosis). 2) The modified lactate stress test was abnormal. 3) EMGs from the upper as well as from the lower limbs were myogenic. 4) Muscle biopsy was compatible with MID. Arguments against a MID in our patient are that, abdominal pain may derive from recurrent gastritis. tremor and hyperhidrosis may be due to the chronic medication, fatigability may be due to the long-standing chronic obstructive lung disease, hypacusis may be due to panatherosclerosis, biochemical, and mtDNA screening investigations were normal, and there were risk factors for a secondary myopathy (lipid lowering drugs, long-term corticosteroid treatment, and chronic muscle ischemia). Secondary vascular myopathy was excluded because of the excellent collateralisation and the muscle biopsy findings. Corticosteroid myopathy was excluded because of the distribution of weakness (predominant affection of the lower limbs), the muscle biopsy, and the fact that gait disturbance had already started before corticosteroids were given. Overall, it cannot be excluded that chronic administration of corticosteroids additionally affected the muscles. Myopathy due to lipid lowering drugs was excluded because they were not taken before 1997, long after weakness and gait disturbances had already developed. Again, it cannot be definitively excluded, that lipid lowering drugs enhanced the pre-existing muscular abnormalities.

That panatherosclerosis, including Leriche syndrome, was causative for the neurological abnormalities is unlikely for the following reasons: 1) Manifestations of the myopathy were present long before risk factors for atherosclerosis could be effective. 2) The patient never had typical claudicatio intermittens 3) There was at least slight weakness on the upper limb but no angiographically confirmed atherosclerosis of the right upper limb arteries. 4) Leriche syndrome usually does not lead to severe paraparesis (Velut, J.G. et al 1998; Yabe, M. et al 1996; Sugimoto, T. et al 1997; Genoni, M. et al 1994). 5) There was progression of the lower limb paraparesis without progression of the lower limb arterial occlusive disease. Concerning the pathogenesis of atherosclerosis, it remains unclear, if it was due to hypertension, hyperlipidemia, diabetes, an inborn vascular abnormality, the contraceptive therapy, nicotine, or even a previously undescribed manifestation of MID. Supposing, occlusive arterial disease was present already at age 10 years, its pathogenesis remains unclear, because of absent risk factors, unless it is speculated that juvenile atherosclerosis was one of the initial manifestations of MID. However, no previous reports are available about an increased prevalence of atherosclerosis in patients with MID but it is meanwhile well established that MIDs also manifest in the arteries (Finsterer, J., & Zarrouk-Mahjoub, S. 2016). Most likely, panatherosclerosis was multifactorial with some contribution of each of the above mentioned factors. Whether arterial hypertension was primary or secondary, remains unclear, although the renovascular abnormalities suggest hypertension to be secondary. However, there are meanwhile reports, which suggest that arterial hypertension may be a primary manifestation of a MID (Lin, L. et al 2019). At least, hyperthyroidism, hyperaldosteronism, hyperreninism and phaeochromocytoma were excluded as causes of secondary hypertension.

Symptoms and signs attributable to the vascular abnormalities are the acute deterioration of the lower limb paresis with development of a sensible transverse syndrome. This acute deterioration of the lower limb paresis may be attributed to steel phenomena within the collaterals or even acute occlusion of a strategic artery after the fall from the wheel chair. However, there was no indication for spinal cord ischaemia on repeated spinal MRIs and CSF-investigations for inflammation, tumour or immunological disorders were negative. Furthermore, it cannot be excluded that the deterioration was interpreted as acute only by the patient, but was actually slowly progressive due the prolonged immobilisation. The sensory transverse syndrome and paraesthesias of the lower limbs, but not stocking type sensory disturbances, may be attributed to the vascular abnormalities, since they developed not before 1991, when there was already evidence for panatherosclerosis. However, it cannot be definitively excluded, that paraesthesias were also a manifestation of the polyneuropathy.

It is concluded that Leriche syndrome may prevent unmasking an underlying MID, particularly if the latter also manifests predominantly in the lower limbs. Though Leriche syndrome suggests to be responsible for slowly progressive paraparesis, it should not prevent from taking a neuromuscular disorder into consideration as a differential diagnoses. Lastly, it cannot be excluded that Leriche syndrome was a primary manifestation of the MID.

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