

Letter to the Editor

## BENIGN SYMMETRIC LIPOMATOSIS WITH AXONAL NEUROPATHY AND ABNORMALITIES IN SPECIFIC MITOCHONDRIAL tRNA REGIONS

RESPONSE TO ZUBER M, PITTASCH D, BENIGN SYMMETRIC LIPOMATOSIS (LAUNOIS-BENSAUDE SYNDROME) - A RARE CAUSE OF MUSCULAR WEAKNESS, EUR J MED RES. 2006 APR 28;11(4):174-7

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### Abstract

Benign symmetric lipomatosis, also called Madelung's disease, is characterized by lipomata and fatty infiltrations. Involvement of the nervous system has occasionally been described, mitochondrial dysfunctions have been suggested. We report a 55 year old male suffering from benign symmetric lipomatosis with associated axonal neuropathy and hyperlipoproteinemia. He showed a remarkable phenotype of neuropathy i.e. no sensory disturbance, ubiquitous fasciculations and muscle cramps, furthermore reduced COX activity and abnormalities in specific mitochondrial tRNA regions.

*Key words:* Madelung's disease, Neuropathy, mitochondrial tRNA, Hyperlipoproteinemia

*Abbreviations:* MD = Madelung's disease

Sirs,

benign symmetric lipomatosis, also called Madelung's disease (MD), is characterized by lipomata and fatty infiltration and was first described by Brodie [1]. Mitochondrial dysfunction has been suggested [2]. Involvement of the nervous system has been described [3, 4].

The 55 years old male first noted symptoms at the age of 33 with crampi and fasciculations which spread from the distal lower extremities to proximal limbs. Additionally, the patient suffered from MD. Lipomas were found in the neck and the upper and lower limb girdle. Otherwise neurological examination was unremarkable, apart from ubiquitous fasciculations and reduced deep tendon reflexes. There was no evidence for muscular weakness or atrophy, no sensory disturbance.

Electromyography and nerve conduction velocities demonstrated a predominantly motor axonal neuropathy. Laboratory investigation showed hyperlipoproteinemia of Fredrickson type IV and increased CK level (669 U/l). There was no history or clinical evidences for alcoholism. The familial history showed crampi of the calves in his 28 years old daughter, but no evidence for MD. He showed no other causes for neuropathy.

Caused by increased CK-level a muscle biopsy was performed, the analysis revealed myopathic changes with increased myonuclei and connective tissue, as well as ragged red fibers and histochemically COX-negative fibers. Biochemically a reduced COX activity was found, plotted to the percentual Citrate-Synthase activity (COX: 68.9, range 78-127). Spectrin and Lamin immunohistochemistry and electron microscopy were normal. Mitochondrial gene-analysis showed abnormalities in tRNA Ser(UCN) SSCP and tRNA Lys SSCP, but neither MELAS 3243 nor MER-RF 8344.

The patient showed typical features of MD. Electrophysiological studies showed axonal neuropathy. Enzi [5] initially noted the association between MD and neuropathy and reported a variety of motor, sensory and autonomic disturbances. The precise relationship between MD and the axonal neuropathy has been clouded by the frequent incidence of alcohol consumption in patients reported in the literature [5]. Chalk et al. [6] argued that there is evidence that the neuropathy associated with MD is not a consequence of alcoholism. There are only few nonalcoholic MD patients with axonal neuropathy, like our patient. Stoll et al. reported a family with MD and polyneuropathy as an inherited dominant condition [7]. Pollock et al., [8] mentioned 3 patients with history of alcoholism but argues that the nerve pathology in their case differs from that expected in alcohol neuropathy. It is unclear whether the relationship between MD and axonal damage reflects the action of a single gene affecting both nerve and adipose tissue, or the neuropathy is a consequence of altered lipid metabolism. Previous authors discussed the possibility of defective mobilization of stored triglycerides in MD. Busetto et al. reported the occurrence of a characteristic metabolic pattern of high HDL-cholesterol and low LDL-cholesterol [9]. Our patient showed hyperlipoproteinemia type IV and abstinence from alcohol. He showed a remarkable phenotype of MD associated neuropathy i.e. no sensory disturbance, ubiquitous fasciculations and muscle cramps. Zuber et al. mentioned that benign

symmetric lipomatosis is a rare disorder of unknown origin and poorly understood pathophysiology. It is believed to be a disease of disturbed lipogenesis induced by catecholamines [10]. In our patient, a reduced COX activity was present, furthermore abnormalities in specific mitochondrial tRNA regions. We think that in every patient with Madelung's disease a mitochondrial gene analysis should be performed. This could be helpful to understand the complex pathophysiology of this seldom disease.

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#### REFERENCES

1. Brodie B. Lectures illustrative of various subjects in pathology and surgery. London: Longman, 1846, pp 275-276.
2. Klopstock T, Naumann M, Schalke B, Bischof F, Seibel P, Kottlors M, Eckert P, Reiners K, Toyka K, Reichmann H. Multiple symmetric lipomatosis: abnormalities in complex IV and multiple deletions in mitochondrial DNA. *Neurology* 1994;44:862-866.
3. Enzi G, Angelini C, Negrin P, Armani M, Perobon S, Fedele D. Sensory, motor and autonomic neuropathy in patients with multiple symmetrical lipomatosis. *Medicine* 1986;64:388-393.
4. Castro-Gago M, Alonso A, Pintos-Martinez E, Novo-Rodríguez MI, Blanco-Barca MO, Campos Y, Arenas J, Eiris-Punal J. Multiple symmetric lipomatosis associated to polyneuropathy, atrophy of the cerebellum and mitochondrial cytopathy. *Rev Neurol* 2003;6:1026-9.
5. Enzi G. Multiple symmetrical lipomatosis: an updated clinical report. *Medicine* 1984;63:56-64.
6. Chalk CH, Mills KR, Jacobs JM, Donaghy M. Familial multiple symmetric lipomatosis with peripheral neuropathy. *Neurology* 1990;40:1246-1250.
7. Stoll C, Alembik Y, Truttmann M. Multiple familial lipomatosis with polyneuropathy, an inherited dominant condition. *Ann Genet* 1996;39:193-6.
8. Pollock M, Nicholson GI, Nukada H, Cameron S, Frankish P. Neuropathy in multiple symmetric lipomatosis: Madelung's disease. *Brain* 1988;111:1157-1171.
9. Busetto L, Strater D, Enzi G, Coin A, Sergi G, Inelmen EM, Pigozzo S. Differential clinical expression of multiple symmetric lipomatosis in men and women. *Int J Obes Relat Metab Disord* 2003;27:1419-22.
10. Zuber M, Pittasch D. Benign Symmetric Lipomatosis (Launois-Bensaude syndrome) - A Rare Cause of Muscular Weakness. *Eur J Med Res.* 2006 Apr 28;11:174-7.

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