

Familial diabetes suggests mitochondrial disease

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Letter to the Editor

In a recent, interesting article, Agarwal et al. report about a 62yo male with familial diabetes and a syncope due to familial AV-block-III [1]. We have the following comments and concerns.

We do not agree with the notion that autonomic neuropathy was the cause of AV-block-III [1].

1. Usually, patients with autonomic neuropathy from diabetes also have sensory and motor neuropathy [2]. but nothing is reported about affection of motor or sensory fibers in the index case [1]. Did the patient undergo electrophysiological investigations of motor and sensory nerves? Did the patient complain about sensory disturbances, neuropathic pain, weakness, or wasting? Was there weakness, wasting, or reduced tendon reflexes on clinical exam?
2. Diabetic neuropathy is usually accompanied by diabetic micro- or macro-angiopathy [3]. Micro-angiopathy may even play a role in the pathogenesis of diabetic neuropathy [3]. Since macro-angiopathy was excluded in the index patient (by coronary angiography?), presence of neuropathy is also rather unlikely.
3. Diabetes was well controlled (HbA1c 7.2), suggesting that complications like angiopathy or neuropathy seem rather unlikely.

More likely than due to diabetes, the clinical presentation was due to a maternally transmitted genetic disease, i.e. a mitochondrial disorder (MID) due to a mtDNA mutation. Did the grandmother from the mother's side present with any typical features of a MID? Arguments for a MID in the index case are that the family history strongly suggests maternal transmission, that the

patient had familial diabetes, that there was familial AV-block-III, that there was metabolic acidosis in the absence of hyperglycemia, and that he obviously had hyperlipidemia [1]. Diabetes is frequently associated with MIDs. Thus, patients with familial diabetes are suspect of MID. MIDs per se are frequently associated with cardiac disease, in particular cardiomyopathy and arrhythmias. Thus, conduction defects, such as complete AV-block-III or QT-prolongation and arrhythmias, such as atrial fibrillation or ventricular fibrillation, leading to sudden cardiac death, may be a primary and not a secondary manifestation of a MID. Metabolic acidosis could be due to lactic acidosis.

To confirm the suspicion of a MID, it is essential to extend the individual and family history, and the clinical exam, to carry out instrumental investigations, including morphological and biochemical studies of the muscle, and to sequence the mtDNA. More widespread investigations may reveal mildly manifesting or subclinical manifestations of a mitochondrial multiorgan disorder syndrome (MIMODS) [4]. Were there indications from the clinical and instrumental investigations for cataract, hypoacusis, epilepsy, migraine, hypothyroidism, hypogonadism, pancreatitis, hepatopathy, renal disease (insufficiency, stones, cysts), anemia, osteoporosis, or diverticulosis?

Concerning the syncope, epilepsy, other cerebral abnormalities, and carotid artery stenosis need to be excluded.

Overall, this interesting case could be more meaningful if more extensive clinical and instru-

mental investigations would have been carried out in the index case and his first-degree relatives, not to miss mildly manifesting or subclinical MI-MODS, and if the suspicion of a MID would have been confirmed genetically. If genetic investigations are not affordable, histological, histochemical, and biochemical investigations of the muscle should be carried out.

References

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