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Letter to the Editor Open Access

Cognitive Impairment can be a Manifestation of SLC25A4 Mutations

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Letter to the Editor

In an interesting article, Simoncini, et al. recently reported about a 74 year female with ptosis and ophthalmoparesis since age 64, mild quadruparesis, autoimmune hypothyroidism, and hypertrophic cardiomyopathy (hCMP) [1]. Her family history was positive for ptosis (mother, maternal grandmother, maternal aunt), heart disease (mother, brother), and sudden cardiac death (SCD) (father) [1]. The cause of this phenotype was the heterozygous mutation c.340G>C in the *SLC25A4* gene encoding for ANT1 [1]. We have the following comments and concerns.

We do not agree with the statement that "there are no data showing an association between ANT1 mutation and cognitive impairment" [1]. Cerebral involvement in patients carrying *SLC25A4* mutations is well established [2] and includes stroke, bleeding, seizures, white matter lesions, muscle hypotonia, hydrocephalus, insomnia, cerebral lactic acidosis, and headache, but also inattention [3] and mental retardation [4].

The MRI shows diffuse cortical atrophy, thinning of the corpus callosum, cerebellar atrophy, and non-specific white matter lesions [1]. Was the individual history positive for stroke, stroke-like episodes, or seizures in addition to the cognitive decline? Did she present with dysarthria or cerebellar ataxia? Though the presented patient had cerebral lactic acidosis on MR-spectroscopy no reference limits are provided to assess if cerebrospinal fluid lactate was elevated or not. Were the non-specific white matter lesions attributable to microangiopathy from arterial hypertension, smoking, diabetes, or hyperlipidemia? Was the EEG normal?

The family history was positive for ischemic heart disease in the mother and brother of the index case [1]. Was the history of these two individuals positive for myocardial infarction or coronary heart disease? Did the mother or brother undergo coronary angiography, stress testing, or myocardial scintigraphy? Which were the cardiovascular risk factors of these two individuals? Was there hypertension, hyperlipidemia, diabetes, or smoking? Did echocardiography show regional dyskinesia, hypokinesia, or akinesia? Was there myocardial thickening? Since *SLC25A4* mutations may be associated with hCMP it would be interesting to know if any features of hCMP were present. Since mitochondrial disorders (MIDs) are frequently associated with left ventricular hypertrabeculation / noncompaction, we should be informed if echocardiography was revised for this echocardiographic feature, which is associated with ischemic stroke, ventricular arrhythmias and SCD, and heart failure.

Since her family history was positive for SCD and since she was diagnosed with hCMP, we should be informed about the results of long-term ECG recordings, particularly if there were ventricular arrhythmias or atrial fibrillation. Was there ever implantation of an ICD considered to prevent her from possible SCD as well?

Though most of the phenotypic manifestations in the described patient were progressive, it is not mentioned if regular follow-up investigations were carried out. Particularly, did cognitive impairment deteriorate over time? Is the patient now demented requiring institutional care? Is she still ambulatory or has muscle weakness progressed to such a degree that she requires a walking aid or a wheel chair?

Overall, this interesting case could be more meaningful if the index case would be more extensively investigated, if close follow-up investigations would be carried out, if the patient would be prospectively investigated for multiorgan disorder syndrome, and if other family members would be genetically investigated as well.

Declarations

Both authors contributed equally, JF: design, literature search, discussion, first draft, SZ-M: literature search, discussion, critical comments. Both authors read and approved the final manuscript and there are no conflicts of interest.

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