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Letter to the Editor

Multisystem mitochondrial disorder is more prevalent than *BGC1* variants in patients with Fahr's syndrome

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With interest we read the case report by Dembele et al. about a 26yo male with Fahr's syndrome, who also developed multisystem disease during the disease course, which started at age 10y with seizures, followed by recurrent movement disorder, cataract, gait disturbance, myopathy, cerebellar ataxia, and cognitive impairment [1]. The patient was treated symptomatically for all the various clinical manifestations [1]. The report has a number of shortcomings.

The main shortcoming of the study is that a mitochondrial disorder (MID) was not considered as a differential of the clinical presentat6ion. Since the patient obviously had multisystem disease [1], which cannot be explained simply by hyperparathyroidism, we strongly suggest to investigate the index patient for MID. Clinical manifestations started with generalised tonic clonic seizures, followed by movement disorder (chorea), surgery for bilateral cataracts, gait disturbance, proximal myopathy, ataxia, and cognitive impairment [1]. The patient had hyperparathyroidism and symmetric intra- and supratentorial calcifications. We should know if myopathy was attributed to hyperparathyroidism, which has been previously reported [2] or if work-up provided another cause. Concerning myopathy, we should know if muscle groups other than the limb muscles, particulary the extra-ocular, the axial, the facial, or the respiratory muscles were clinically or subclinically additionally affected.

The multisystem nature of the phenotype is a strong argument for MID. A further argument for MID is the in-effectivity of phenobarbital (PB). From a number of anti-seizure drugs (ASDs) it is known that they are potentially mitochondrion-toxic [3], why they should be given only with caution for mitochondrial epilepsy [3]. These include valproic acid (VPA), phenytoin (PHT), carbamazepine (CBZ), and PB [3]. We should know if PB induced any side effects or was only in-effective with regard to epilepsy. We should also know if VPA was effective or if it caused any side-effects or deterioration of the phenotype. The cortex was not affected by the calcifications, why causes other than calcifications are more likely explanations for generalised epilepsy.

Another shortcoming is that the patient was not prospectively investigated for clinical or subclinical multisystem involvement. Organs of particular interest with regard to the differential MID are the ears, heart, intestines, kidneys, bone marrow, cartilage, and the skin [4]. Investigating the heart in patients with a neuromuscular disorder (NMD) is crucial as the myocardium is frequently additionally affected if there is skeletal myopathy. Involvement of the heart may strongly determine the outcome of these patients and is potentially treatable. This is why recording of a standard and long-term ECG and echocardiography are the minimum of investigations that should be done. Cardiac investigations are also crucial in the light of hyperparathyroidism since low calcium levels (the patient had hypocalcemia) may determine the excitation and conduction along cardiomyocytes and may predispose for ventricular arrhythmias [5].

Further shortcomings are that height and weight were not reported, that serum and CSF levels of lactate were not determined, that no MR-spectroscopy had been carried out, that it was not delineated if hyperCKemia was due to seizure activity or due to limb myopathy, that no explanation was provided why movement disorder disappeared spontaneously one year after onset, that the term “cortical irritation syndrome” was not specified, that it is not explained why haloperidol was administered, that outcome, effect, and tolerability of ASDs (VPA, clonazepam) was not reported, and that no genetic work-up had been initiated. Is it conceivable that movement disorder disappeared following the initiation of PB?

Overall, this interesting case report has a number of shortcomings, which should be addressed before, final conclusion are drawn. The case has a strong didactic potential which should be exploited by a thorough and extensive work as outlined above.

Author contribution

JF: design, literature search, discussion, first draft, critical comments.

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