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DNAJC30 variants can also manifest phenotypically as Leigh/ /LHON overlap syndrome

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To the Editors

We were interested to read the article by Dzwilewski et al. about a 12-year-old boy who had been suffering from a progressive gait disorder, ataxia and dystonia of the limbs since the age of four, which was attributed to the homozygous variant c.152A > G (p.Tyr51Cys) in DNAJC30, the phenotype of which was classified as Leigh syndrome [1].

Despite oral treatment with idebenone (900 mg/d), the phenotype progressed and the patient developed dysarthria and dysphagia, quadruparesis and quadrudystonia, which is why idebenone was discontinued after 18 months [1]. The study is convincing, but some points should be discussed.

The first of these is that we disagree with the diagnosis of Leigh syndrome. Leigh syndrome is characterised on imaging by symmetrical lesions of the basal ganglia, thalamus, brainstem, cerebellum, or dorsal columns [2]. The index patient had only unilateral lesions in the midbrain, caudate nucleus and putamen [1]. As the presented cerebral MRI was not typical for Leigh syndrome, the patient might also have been diagnosed with non-syndromal mitochondrial disorder (MID). As the patient also exhibited optic atrophy, it is also conceivable to classify the phenotype as Leber's hereditary optic neuropathy (LHON) plus, rather than as Leigh syndrome. In addition to visual impairment, the index patient also had ataxia, left-sided hemiparesis and limb dystonia [1]. LHON plus with dystonia has been reported previously [3]. Ataxia has also been described as a manifestation of LHON plus [4].

Our second point is that it was not reported whether the patient had only optic atrophy or also features of LHON such as severe visual impairment, colour vision defects, central scotoma, loss of retinal nerve fibres, loss of macular retinal ganglion cells, microangiopathy, or telangiectasia [5]. The results of the ophthalmological examination, including optical coherence tomography (OCT), should be reported.

The third point is that Leigh syndrome is usually characterised by epilepsy [6]. The index patient had no history of epilepsy, nor was he taking antiepileptic drugs (ASD) regularly. Therefore, we should know whether the patient had ever had an electroencephalogram (EEG) recorded, and if so whether epileptiform discharges were ever seen on any of the EEGs.

The fourth point is that the design of a single case report is not suitable for assessing whether a particular drug is useful or not. To assess whether idebenone really helps in patients with DNAJC30 variants, a double-blind, placebo-controlled, multi-centre design would be desirable. However, due to the rarity of DNAJC30 variants, such an approach is challenging to achieve.

Our fifth and final point is that the cause of gait disturbance was not clarified. Was gait impairment due to ataxia or dystonia, or both? Did the patient also develop muscle weakness? Myopathy can be a feature of Leigh syndrome. There has also been one report of a DNAJC30 mutation carrier who presented with a neuromyelitis optica spectrum disorder (NMOSD)-like disease [7].

Overall, this interesting study has limitations that relativise the results and their interpretation. Addressing these limitations could strengthen the conclusions and support the study's message. DNAJC30 variants may phenotypically also manifest as Leigh/LHON overlap syndrome.

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