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Effects of idebenone treatment in a patient with DNAJC30-associated Leigh Syndrome

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To the Editors,

Mitochondrial complex I (CI) is an essential component of the respiratory chain, playing a critical role in energy production. Pathogenic variants in genes encoding CI components can disrupt the cellular energetic state. Nerve tissue is particularly sensitive to disruptions in energy balance, thereby often rendering neurological symptoms as the sole indicators of underlying metabolic disturbances.

DNAJC30 (OMIM: 618202) is a nuclear gene that encodes a chaperone protein facilitating the proper exchange of CI subunits [1]. Recently, biallelic pathogenic variants in *DNAJC30* have been associated with autosomal recessive Leber hereditary optic neuropathy (arLHON) and Leigh Syndrome (LS) [1–4]. Interestingly, the Eastern European population has a high incidence of the c.152A>G,p.(Tyr51Cys) variant, probably due to the founder effect [1, 2, 4]. Although the vast majority of patients with *DNAJC30* mutations present isolated optic neuropathy, several cases with LS have been reported [2–4].

Idebenone is currently the only drug registered to treat mtDNA LHON and has been shown to be effective in the treatment of arLHON [1, 2]. However, there have been no reports on the benefit of idebenone in *DNAJC30*-associated LS.

We present a description of the first patient with LS and a homozygous pathogenic *DNAJC30* p.(Tyr51Cys) variant treated with idebenone therapy.

A 12-year-old male of Polish origin had been under neurological care since the age of four when he had begun to present progressive gait disturbance. Over the years, he experienced progressive optic neuropathy, ataxia, left-sided hemiparesis, and limb dystonia. Brain magnetic resonance imaging (MRI) revealed right-sided hyperintensities on FLAIR sequences in the midbrain and the right lenticular nucleus with an increased lactate peak (Fig. 1).

Trio exome sequencing (ES) and trio genome sequencing (GS) identified a homozygous pathogenic variantc.152A>G, p.(Tyr51Cys) in the *DNAJC30* gene. Re-analysis of GS and mtDNA sequencing data showed no other potential variants in genes linked with LS, LHON, or the respiratory chain enzyme complexes.

After written informed parental consent following the regulations for 'off-label' drug administration, the patient was given idebenone in a dose of 300 mg three times per day. However, no improvement in his neurological state was observed. On the contrary, his symptoms gradually deteriorated. The patient started to experience speech and swallowing difficulties, bilateral paresis, and dystonia of all limbs. Vision

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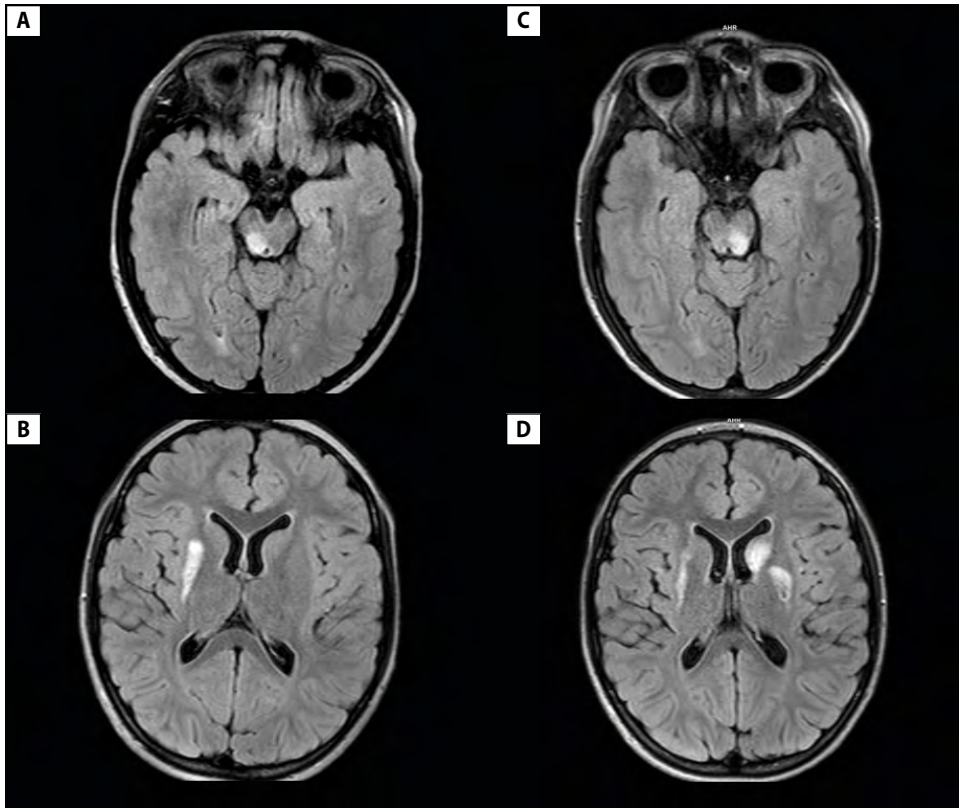

Figure 1. Brain MRI images from patient with DNAJC30-associated Leigh Syndrome treated with idebenone. Brain MRI axial views performed at baseline demonstrate signal intensity changes on FLAIR sequences in midbrain (**A**) and right lenticular nucleus (**B**). Control axial views performed after nine months of idebenone therapy show novel contralateral hyperintensities in midbrain (**C**), head of left nucleus caudate, and left putamen (**D**). Novel alterations show diffusion restriction corresponding to active lesions

Evoked Potentials indicated a significant bilateral progression of conduction disturbances. He was no longer able to walk independently. His cognitive functioning remained unimpaired. There was no correlation between deterioration of the patient's neurological symptoms and external factors such as infection or stress. Additionally, the patient was not receiving any medication known to cause mitochondrial toxicity, and had not experienced any trauma or serious infection requiring antibiotic therapy or hospitalisation. Control brain MRI after nine months of therapy revealed novel contralateral hyperintensities in the midbrain, the head of the left nucleus caudate, and the left putamen (Fig. 1). The parents decided to cease medication after 18 months of treatment.

As evidenced in our case, idebenone did not halt progression of the disease, nor induce any neuroprotective effect apparent in neuroimaging. Neurological deterioration, typically occurring in stepwise decrements, is a natural consequence of this disease, inevitably resulting in severe neurological impairment.

Our findings are in contrast with the literature, which reports high responsiveness to idebenone therapy among patients with arLHON, homozygous for the p.(Tyr51Cys) allele. Two studies involving 18 and 30 idebenone-treated subjects with arLHON, all of whom harboured the p.(Tyr51Cys) variant, reported recovery rates of 80.6% and 77% in treated eyes respectively [1, 2].

This raises the question as to why idebenone is effective in arLHON but showed no improvement in our LS patient, despite them sharing the same genetic variant. Firstly, there might be another undetected variant associated with CI dysfunction, which together with *DNAJC30* induces the additive effect, resulting in the manifestation of idebenone-resistant LS. This phenomenon has indeed recently been reported, where the combination of *DNAJC30* biallelic variants and a heterozygous variant in another gene encoding a CI subunit was responsible for LS phenotype [2–4]. Moreover, a digenic co-occurrence of the m.11778G > A LHON-related variant with heterozygous variants in nuclear genes encoding CI subunits was recently described in six individuals with LS [5].

The inability to detect a 'second hit' allele in our patient could be attributable to several factors such as the technical limitations of next generation sequencing methods or the presence of a 'second hit' variant in a gene not yet associated with mitochondrial disease. It's important to note that analysis of ES and GS focuses on rare variants, potentially leaving more common, incompletely penetrant variants undetected. The limited benefit of idebenone

may also result from unspecified molecular/cellular differences between arLHON and LS phenotypes. Phenotypic heterogeneity in individuals carrying identical disease-causing variants is shared among other mtLHON/LS subtypes [6].

In conclusion, despite the significant efficacy of idebenone in arLHON, its benefit in LS remains uncertain. Further studies on a larger group of patients are necessary to evaluate the effect of idebenone in *DNAJC30*-associated Leigh Syndrome.

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