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Letter to the Editor

Before a Beneficial Effect of High-Dose Riboflavin in Complex-I-Deficiency can be Postulated, It must be Demonstrated through Appropriately Designed Studies

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Letter to the Editor

We read with interest the article by Ferrera *et al*. regarding a retrospective observational study on the effects of high-dose riboflavin in two patients: a female patient (19 years old) with a mitochondrial disorder caused by compound heterozygous variants c.2083T>C and c.2084A>G in the NDUFS1 gene (classified as likely pathogenic) and a male patient (18 years old) with the homozygous variant c.547G>A in the NDUFV2 gene (also assessed as likely pathogenic) [1]. Both patients received riboflavin at a dosage of 10 mg/kg/day combined with coenzyme Q (5 mg/kg/day) for several years [1]. Within one year of starting riboflavin therapy, the clinical neurological and neuropsychological deficits resolved almost completely in patient-1 and completely in patient-2 [1]. While the study is informative, it warrants discussion.

The first point concerns the retrospective nature of the study. Retrospective study designs have numerous disadvantages [2]. Crucial variables may be missing, inconsistent, or recorded with varying accuracy by different personnel, as the data are typically collected for clinical or administrative reasons rather than for research purposes [2]. Determining the exact sequence of events can be difficult, leading to temporal ambiguities. Comparison groups are often selected using convenience sampling, meaning they are not representative of the general population [2]. Since retrospective studies are usually observational, they are susceptible to hidden confounders and provide a weaker basis for establishing causality [2].

The second point concerns the study design (case series) [1]. Case series have several disadvantages. They lack statistical power and cannot establish definitive cause-and-effect relationships. Due to the absence of control groups, it is impossible to determine whether a specific intervention was directly responsible for the treatment outcome or whether the result was attributable to chance or confounding factors. The findings are often specific to an individual patient's anatomy, genetics, or environmental conditions, making them non-generalizable to the broader population [1]. Furthermore, authors of case series are susceptible to selection and observer bias, as only successful cases may be reported and data could be interpreted subjectively to support a preferred hypothesis [3]. Publication bias is also a possibility, as journals tend to publish positive or unusual results, which can lead to a skewed assessment of the drug's efficacy. The small number of patients precludes the determination of reliable data regarding incidence and prevalence.

A third point is that the two patients did not receive riboflavin alone; after 14 months (Patient 1) and a few weeks (Patient 2), respectively, they were also administered coenzyme Q [1]. Consequently, it cannot be ruled out that the observed long-term effect of riboflavin was actually due to the combination of both agents rather than riboflavin alone. Additionally, it should be stated whether either patient received other medications alongside riboflavin and coenzyme-Q. Knowledge of the complete medication regimen is crucial, as other individual drugs or combinations of agents could potentially have produced a positive effect in these patients.

A fourth point is that spontaneous recovery - at least of certain abilities - has been reported in patients with complex-I deficiency [4]. In a study of 130 patients with complex-I deficiency, motor skills recovered spontaneously in at least some of the affected individuals [4]. Spontaneous recovery is also known to occur in patients with Leber's hereditary optic neuropathy (LHON), a rare mitochondrial disorder characterized by partial or complete vision loss during adolescence. Although spontaneous restoration of visual acuity is rare in LHON patients, it has been observed, particularly in patients with the m.14484T>C mutation [5]. Spontaneous recovery of vision has also been reported in carriers of the m.11253T>C variant in the MT-ND4 gene. It is interesting to note in this context that LHON is also classified as a complex-I disorder.

Finally, the pathogenicity of the described variants has not been sufficiently established [1]. Classifying the variants as "likely pathogenic" based on in silico methods is insufficient to confirm their pathogenicity. Pathogenicity should be verified through the following steps: checking whether the variant is extremely rare or absent in a large, healthy control group; examining family members to determine whether the variant is co-inherited with the disease; and conducting functional studies using laboratory experiments on cells or animal models.

In summary, the beneficial effect of high-dose riboflavin in complex-I deficiency remains to be demonstrated through appropriately designed studies - such as randomized, double-blind, placebo-controlled crossover trials. Given that complex-I deficiencies are genetically and phenotypically heterogeneous, it is also essential that the cohorts examined in such studies be homogeneous with respect to genotype and phenotype.

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