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Letter to the Editor

Kearns-Sayre Syndrome is not Associated with *POLG1* Variants

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Letter to the Editor

We read with interest the article by Rivas *et al*. Regarding a 28-year-old man with Kearns-Sayre syndrome (KSS) attributed to a variant in POLG1, presenting phenotypically with ophthalmoplegia, hearing loss, vestibular dysfunction, ataxia, and cardiomyopathy [1]. The cardiomyopathy manifested as heart failure and bifascicular block. Treatment involved cardiac resynchronization therapy and orthotopic heart transplantation (HTX) [1]. The post-HTX course was complicated by a CMV infection, which led to a worsening of neurological symptoms [1]. The authors concluded that CMV can contribute to morbidity in patients with mitochondrial disease [1]. While the article is noteworthy, certain aspects warrant discussion.

First, POLG1 variants do not cause KSS. KSS is typically caused by single mtDNA deletions [2]. Were long-range PCR, real-time PCR, or Southern blot analyses performed to determine whether the KSS phenotype was indeed caused by an mtDNA rearrangement?

Second, the specific POLG1 variant considered causative was not reported [1]. To establish a genotype-phenotype correlation, it is essential to know which specific POLG1 variant was identified and whether it was a novel mutation or one previously described.

Third, the diagnostic criteria for KSS were not listed [1]. A diagnosis of KSS requires onset before the age of 20, ophthalmoplegia, and pigmentary retinopathy. In addition, at least one other feature (conduction defect, cerebellar symptoms, or elevated CSF protein) must be present. There is no mention of whether the index patient actually exhibited pigmentary retinopathy. This suggests that he does not meet the criteria for a diagnosis of KSS.

A fourth point is that the hypothesis of a generally impaired immune system in KSS is unsubstantiated [1]. There is no mention of whether immunoglobulins were determined, lymphocyte flow cytometry was performed, vaccine titers were measured, or complement analyses were conducted. Until immune system impairment has actually been demonstrated, any statement regarding immune system involvement in KSS remains purely speculative.

A fifth point is that the cause of the somnolence was not elucidated [1]. Given that CSf analysis was unremarkable and imaging yielded no diagnostic clues, adverse effects of administered medications or non-convulsive status epilepticus should have been considered. Glucocorticoids are known to impair consciousness [3]. Tacrolimus [4], mycophenolate mofetil [5], and cyclosporine can also compromise the level of consciousness. Was the EEG unremarkable?

A sixth point is that no information regarding family history was provided [1]. Did the POLG1 variant arise de novo, or was it inherited from the father or the mother? Since POLG1 variants can be inherited in either an autosomal dominant or an autosomal recessive manner, both the father and the mother should have undergone genetic testing for the index patient's specific POLG1 variant.

In summary, this interesting study has limitations that affect the results and their interpretation. Addressing these limitations could strengthen the conclusions and reinforce the study's key message. Further evidence should be presented before suggesting that the immune system is generally impaired in KSS.

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