BRAIN
LETTER TO THE EDITOR

Reply: *De novo* mutations in *CLDN5*: alternating hemiplegia of childhood or not?

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We thank our colleagues Panagiotakaki *et al.*[1] for their interest in our recent work elucidating the functional relevance of the G60R mutation in the *CLDN5* gene in two unrelated cases of children presenting with alternating hemiplegia. Our study represents the first report of a dominant acting mutation in the coding sequence of the *CLDN5* gene and has, we believe, major implications for our understanding of blood–brain barrier (BBB) function and tight junction biology in general.[2]

In reference to queries from patients and patient groups, we would posit that mutations in *CLDN5* are most certainly not going to be a leading cause of alternating hemiplegia of childhood (AHC). However, while further research on BBB disruption and indeed the possibility of *CLDN5* variants being causative of hemiplegia is warranted, it would not be an arduous exercise to include *CLDN5* screening in any case of suspected hemiplegia or AHC in our opinion.

We appreciate that the on-going search for the genetic cause of AHC will present differential diagnoses that deviate from that of the 80% of cases attributed to the *ATP1A3* gene. In that regard, we would also stress that we certainly do not believe, nor have we stated in our study, that a large proportion of genetically undiagnosed patients will harbour the G60R mutation. We have no doubt that the remaining 20% of genetically undiagnosed cases likely represent multiple rare variants in a large cohort of genes similar to the two cases we described in our report.

In relation to the specific questions posed with regard to the clinical details of the patients reported in our study, both patients had recurrent episodes of alternating hemiplegia (different sides) over a period of years. These episodes had a duration over 24 h without seizures prior to the episodes. Resolution with sleep was not easily determined due to the different use of medications. We did conduct EEG analysis, and EEG tracing during the hemiplegic episodes did not show evidence of seizures with slow waves only.

Brain imaging in both patients excluded stroke like episodes (SLE), which are frequently associated with mitochondrial disorders. After admission, patients eventually recovered their previous neurological status with ataxia and mild cognitive impairment. Based on our clinical evaluation, we do support the idea that the clinical presentation is compatible with the AHC criteria of Aicardi.[3]

We are always willing to share our experience and expertise and would be delighted to expand this discussion along with our future plans exploring the role of the BBB in hemiplegia and AHC. We look forward to continued engagement with our colleagues.

Data availability

This is not applicable to this article as no new data were created or analysed in this study.

Competing interests

The authors report no competing interests.

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