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Incidental DEPDC5 variant in a child with sporadic hemiplegic migraine: a pitfall in clinical neurogenetics

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Introduction

Hemiplegic migraine (HM) is a rare subtype of migraine with aura characterized by reversible motor weakness associated with other focal neurological symptoms. Although pathogenic variants in genes such as CACNA1A, ATP1A2, and SCN1A are classically associated with HM, many sporadic cases remain genetically unresolved. The increasing use of broad next-generation sequencing panels has also led to the frequent identification of incidental variants in genes associated with cortical excitability disorders, posing challenges in clinical interpretation.

Case presentation

We report a 9-year-old boy with normal neurodevelopment and no family history of migraine or epilepsy who presented with three stereotyped episodes over one year. Each episode began with paresthesia in one hand, progressing to the ipsilateral arm and face, followed by transient weakness affecting the same limb. Subsequently, the patient developed contralateral pulsatile hemicranial headache associated with nausea and marked somnolence, while remaining arousable, oriented, and able to communicate appropriately throughout the episodes. Symptoms resolved completely after each attack, with alternating laterality between episodes. Interictal neurological examination, brain magnetic resonance imaging, and two prolonged electroencephalograms recorded during wakefulness and sleep were normal. A targeted migraine panel including CACNA1A, ATP1A2, ATP1A3, SCN1A, PRRT2, and PNKD revealed no pathogenic variants. An extensive epilepsy panel identified a heterozygous DEPDC5 variant (c.4115G>C; p.Cys1372Ser), classified as a variant of uncertain significance according to ACMG criteria. The variant was absent from large population databases and predicted in silico to be potentially deleterious.

Discussion

Despite the biological overlap between migraine and epilepsy, the patient did not exhibit clinical, electroencephalographic, or neuroimaging features suggestive of DEPDC5-related epilepsy. The case fulfills ICHD-3 criteria for sporadic hemiplegic migraine and illustrates the importance of phenotype-driven diagnosis and cautious interpretation of incidental findings generated by broad sequencing panels.

Conclusion:

This case highlights a potential pitfall in clinical neurogenetics, emphasizing that biologically plausible variants should not be overinterpreted in the absence of supporting phenotypic evidence.

Keywords:
Sporadic hemiplegic migraine
DEPDC5 variant
Epilepsy
Migraine

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