

FAMILIAL HEMIPLEGIC MIGRAINE TYPE 2 IN AN ITALIAN FAMILY: A COMPLEX PHENOTYPE WITH FOCAL EPILEPSY AND NEURODEVELOPMENTAL DISORDERS

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Background. Familial hemiplegic migraine (FHM) is a monogenic subtype of migraine with aura, characterized by transient motor weakness associated with other reversible aura symptoms. FHM is genetically and clinically heterogeneous, and is associated with pathogenic variants in CACNA1A, ATP1A2, and SCN1A. ATP1A2-related FHM (FHM2) may be associated with a broader neurological phenotype. Here, we report an Italian family carrying an ATP1A2 variant and presenting with a complex phenotype of hemiplegic migraine, focal epilepsy, and cognitive and neurodevelopmental features.

Methods. We describe a 41-year-old woman with recurrent hemiplegic migraine evaluated at the Headache Center, Department of Neuroscience "Rita Levi-Montalcini", University of Turin. Personal and family history were reviewed, focusing on neurological manifestations, cognitive and neurodevelopmental features, and genetic counselling.

Results. The patient reported recurrent migraine with visual aura beginning at 6 years of age. During the disease course, attacks evolved to include right-limb paresthesias and weakness, expressive aphasia. Symptoms lasted 30 minutes and were followed by right-sided temporal headache associated with nausea/vomiting, photophobia, and phonophobia. One prolonged episode of limb weakness lasting several days occurred, with negative neuroradiological investigations. Recently, she developed disabling migraine without aura. Her history included focal epilepsy and mild intellectual disability. Serial brain MRI showed no progressive abnormalities. Family history revealed hemiplegic migraine in her mother and maternal aunt. One sister had autism spectrum disorder, while another deceased sister had severe intellectual and motor disability. Genetic testing identified the heterozygous ATP1A2 variant NM_000702.4:c.2723G>A (p.Arg908Gln), shared by affected family members, confirming FHM2. This variant affects a conserved residue in the C-terminal transmembrane region and has been shown to impair α2 pump function. Chromosomal analysis and FMR1 premutation testing were normal. Triptans were avoided; prophylaxis was attempted with lamotrigine and then topiramate.

Conclusions. To our knowledge, this is the first Italian family carrying the ATP1A2 p.Arg908Gln variant, previously reported in one patient with sporadic hemiplegic migraine and in two unrelated German and Russian families with FHM2. The co-occurrence of hemiplegic migraine, focal epilepsy, intellectual disability, and neurodevelopmental disorders further supports the broad phenotypic spectrum of FHM2.