Recurrent encephalopathy and subsequent hemiplegic migraine and intellectual disability caused by a de novo mutation in ATP2A2 gene

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Background

- Hemiplegic migraine (HM) is a rare form of migraine with aura, in which the core symptoms are headache and an aura which is predominantly manifested by transient hemiparesis (1).
- HM can be sporadic (SHM) or familial (FHM) with autosomal dominant inheritance. The three genes that have been classically associated with MH are *CACNA1A, ATP1A2*, and *SCN1A* (1-2).
- The mutated gene is the cause of an altered neuronal excitability and reduced threshold value for cortical spreading depression (CSD) (3).
- While ATP1A2 mutation are known to cause HM, to our knowledge the association with intellectual disabilities and recurrent encephalopathies is not described in the literature.
- We present a case of ATP1A2 mutation presenting with recurrent encephalopathies, intellectual delay, and HM.

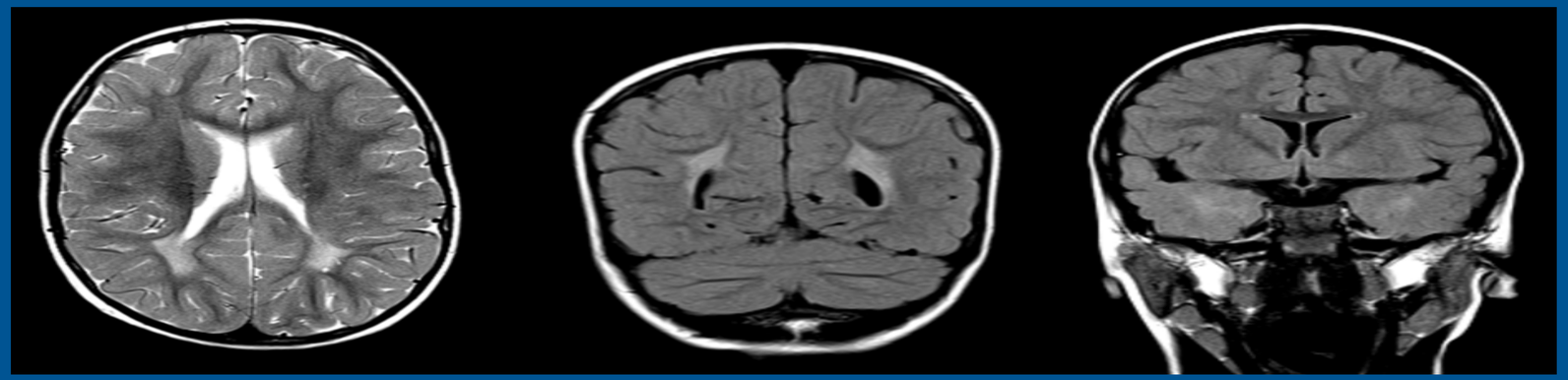

Figure 1: MRI done at 3 years of age

Case Presentation

- A thirteen-year-old male presented with a two-day history of progressive left-sided weakness, with altered consciousness, urinary incontinence, and dysarthria/aphasia.
- Lumbar-puncture, CT Brain, EEG, CSF studies, blood, and urine cultures, all were normal.
- Past history revealed similar episodes, with motor and intellectual delays, while the motor component recovers after each episode intellectual delay never resolved.
- The first episode was at 18 months of age, and occurred following an episode of head trauma. CT Head was normal. He was initially diagnosed with epilepsy and started on Valproate since age of four years. His episodes are triggered by emotional distress, as well as multiple episodes of head trauma.
- MRI done at the time of presentation and compared to previous MRI done at age of 3 years showed interval changes (Figures 1-2).
- Epilepsy genetic panel showed a *de novo* pathogenic heterozygous mutation of *ATP1A2* gene [Ex. 9 c.1133C>T (p.Thr378Ile)]. Both parents did not have a history of migraine or indeed any other neurological disorders.
- He was weaned of Valproate and started on Topiramate 25 mg twice daily, during the attack he was on Acetazolamide 250mg daily.
- His neuropsychological and intellectual assessment showed low scores in all domains including the overall general cognitive ability. The WISC-IV was done, it is a measure of intelligence that consists of 4 main domains.
- The patient scored extremely low in all domains including the overall general cognitive ability. His scores were FSIQ of 45, VCI of 56, PRI of 48, WMI of 47 and PSI of 49.

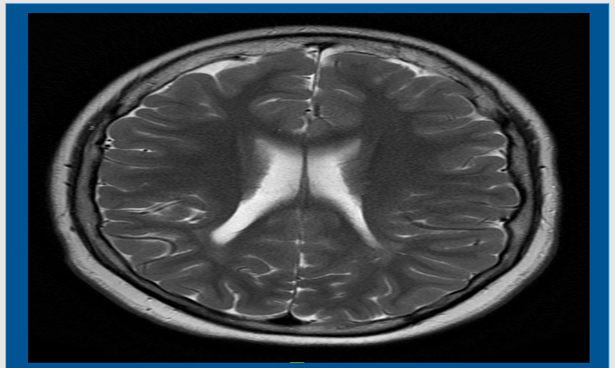

Figure 2: current MRI shoring interval changes

Discussion and Review

- HM is a complex monogenic disorder related to a mutation in genes encoding for ion transporters. The ATP1A2 gene encodes for cell membrane proteins regulating the electrochemical gradients of the sodium and potassium ions (4).
- It is mainly a clinical diagnosis, but genetic testing is necessary to find out the genetic subtype (4).
- The ATP1A2 gene is associated with autosomal dominant familial hemiplegic migraine, alternating hemiplegia of childhood (AHC), and autosomal dominant early infantile epileptic encephalopathy (5).
- AHC is typically distinguished from FHM by infantile onset, high prevalence of paroxysmal clinical signs (including dystonic posturing, choreoathetoid movements, tonic spells, nystagmus, and autonomic features), and progressive cognitive and neurological decline over time (5).
- These individuals are typically affected with early-onset, intractable epilepsy as well as variable degrees of intellectual disability and developmental delay. Individuals affected with early-onset epileptic encephalopathy have also been reported (5).
- Currently, management of HM relies on the control of triggering factors, abortive treatments have been shown to be effective when started early from disease onset.
- There is also little evidence for prophylactic treatment with verapamil and acetazolamide to reduce frequency and severity of migraine attacks (1).

References

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