New *MECP2* variant associated with Rett syndrome, generalized and focal seizures, and Chiari malformation: a case report.

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Background on Rett Syndrome (RTT):

RTT is an X-linked dominant neurological disorder (OMIM #312750) caused by loss of function mutations in the methyl-CpG-binding protein 2 (*MECP2*) gene. With a higher incidence in females, it is characterized by normal development during the first 6-18 months of life followed by regression. Typical clinical manifestations include delayed developmental progress, loss of speech and motor skills, repetitive hand movements and neurological issues, such as seizures.[1]

Case Presentation:

Birth & Development:

Patient is a 9-year-old female born at 41 weeks to a 21-year-old G2P1 mother and 24-year-old father. It was a normal spontaneous vaginal delivery and uncomplicated pregnancy. Birth weight and length were 3.6kg (55th percentile) and 53.3cm (75th percentile). The patient smiled at 3 months, rolled over at 6 months, sat alone at 7-8 months, crawled before 12 months, walked at 12 months, and spoke at 3.5-4 years.

Past medical history:

Patient history is significant for developmental delay, autism spectrum disorder, bilateral intermittent esotropia, midline hand-wringing movements, ataxia, seizures: focal and generalized, segmental syringohydromyelia from C4 to T9, and Chiari malformation type I with 10mm herniation of the cerebellar tonsils.

Genetic Evaluation:

Sequence analysis and duplication/deletion testing revealed heterozygous in-frame deletion in the *MECP2* gene (c.918-926del) translating to a three-amino acid deletion (p.Lys307-Arg309del). Patient had a normal microarray, and both parents tested negative for the variant, suggesting a de novo mutation.

Figure 1: Chiari malformation type I

Figure 2: Syringohydromyelia

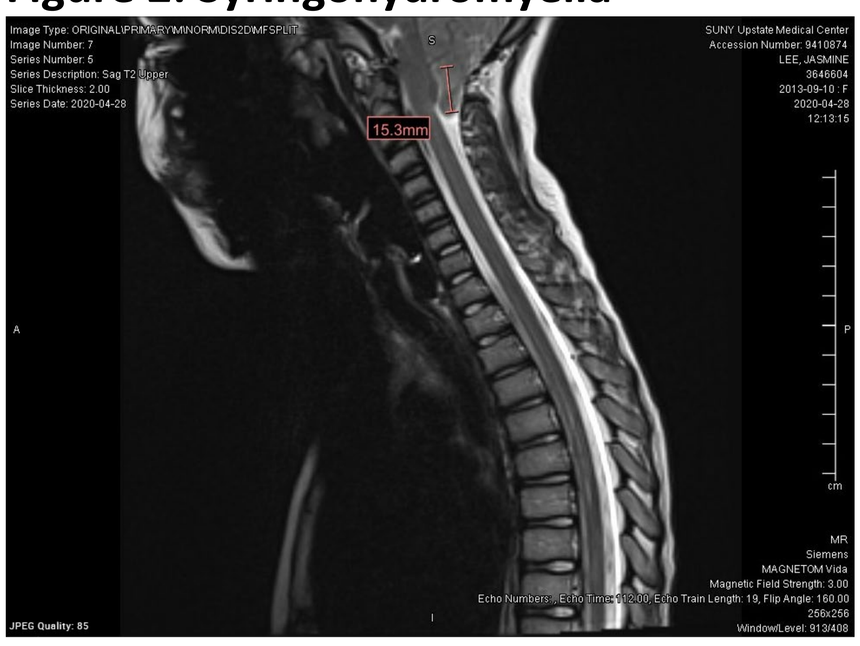

Figure 3: Samples of Epileptiform Activity

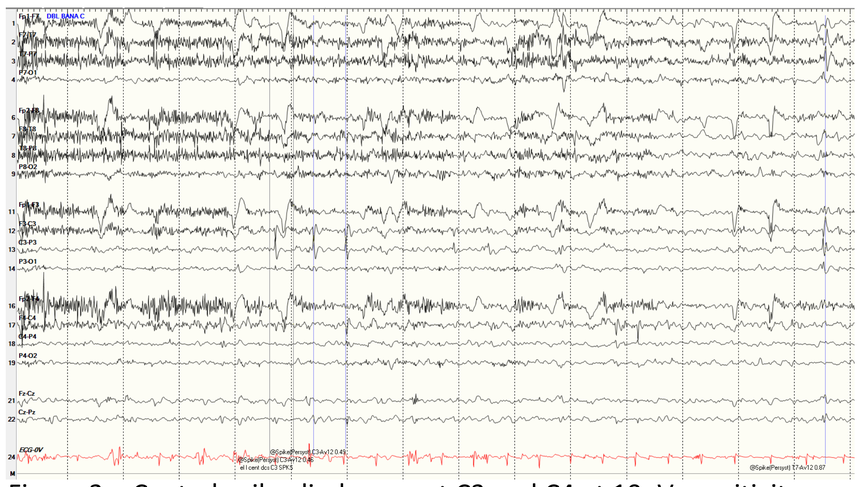

Figure 3a: Central spike discharges at C3 and C4 at 10uV sensitivity.

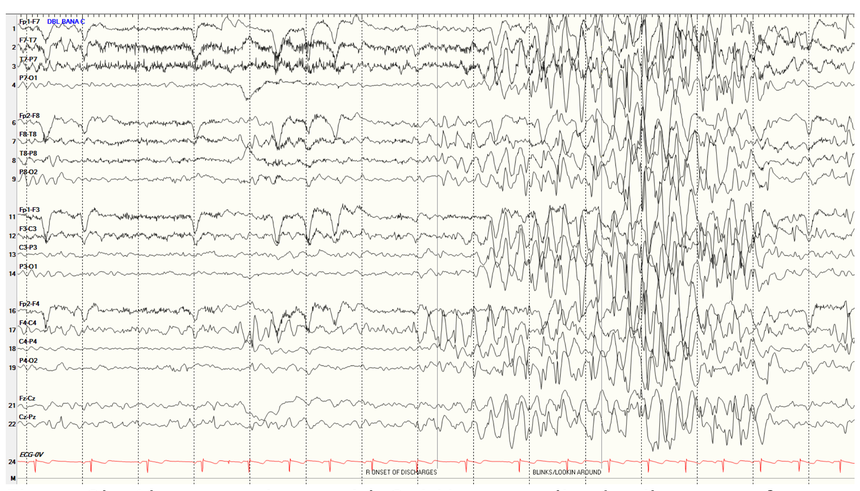

Figure 3b: Absence seizure with 3-4 Hz generalized spike waves from central leads at 15uV sensitivity.

Discussion:

This case reveals a novel in-frame pathogenic *MECP2* variant associated with RTT. This patient displays unique neurological characteristics including focal and generalized refractory epilepsy, Chiari malformation type I (Figure 1), and syringohydromyelia (Figure 2) in addition to typical clinical manifestation. Seizures include behavior arrest and impaired awareness with both focal and generalized features as well as rare tonic seizures (Figure 3). There has been one other reported case of atypical RTT with Chiari malformation, but the mutation in this patient was in the methyl binding domain (Q128P), whereas our patient has a mutation in the transcriptional repression domain.[2]

Conclusion:

The three-amino acid in-frame deletion (p.Lys307-Arg309del) variant has not been previously reported in the literature as contributing to RTT. However, this variant interrupts the Arg309 residue, and other variants with a disruption of this residue have been shown to be pathogenic, but with atypical Rett features.[3,4] This suggests that the disruption of Arg309 may play a significant role in the pathogenesis of RTT. Additionally, the unique clinical presentation of syringohydromyelia and Chiari malformation type I demonstrates further variability in the RTT clinical phenotype.

References:

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