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Clinical letter

Epileptic encephalopathy and brain iron accumulation due to WDR45 mutation

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We present the case of a 10-year-old Chinese boy with profound developmental delay, spastic quadriparesis, and intractable epilepsy with tonic and atypical absence seizures. He was first noted to have a delay at 9 months. When evaluated at 17 months he had diffusely decreased tone, was only able to roll over but could not sit, hold his head, crawl or communicate. His seizures started at age 2 and consisted of atypical absence (hypomotor) and generalized tonic seizures occasionally preceded by myoclonic jerks. He remained globally intellectually impaired with absent speech or eye contact, truncal hypotonia and limb spasticity He had an extensive work-up of his epileptic encephalopathy including whole exome sequencing that showed a de novo p. V66E (c.197 T > A) mutation in autophagy gene WDR45. He was admitted to our epilepsy monitoring unit in December 2017 to assess the burden of his seizures. Brain MRI done in 2014 at age 6 had shown signs of abnormal iron accumulation in the Globus Pallidus Interna and Externa, and Substantia Nigra on susceptibility weighted imaging (SWI) (Fig. 1).

These changes were not seen on his prior imaging done at 1 year old. His MRI also showed moderate brain parenchymal volume loss with lack of supratentorial white matter myelination (not visualized here). Video EEG showed features of epileptic encephalopathy: Interictal EEG showed abundant generalized spike wave complexes occurring in organized runs, maximum in frontal and parasagittal regions that wax and wane without overt clinical signs, intermittently replaced with rhythmic slowing and some sharp components. Spike wave complexes were abundant in wakefulness and sleep. Brief axial tonic seizures were recorded with a diffuse ictal pattern (Fig. 2).

He was previously on Lamotrigine and Ethosuximide. During his last admission, Valproic acid was started, Lamotrigine decreased by 50% and Ethosuximide discontinued. Clonazepam was later added; parents and teachers reported fewer seizures which were also milder in intensity.

1. Discussion

WDR45 at Xp11.23 comprises 12 exons and codes for WD40 repeat protein interacting with phosphoinositides 4 (WIPI4) with a characteristic structure resembling a seven-bladed propeller that is implicated in the autophagy pathway which delivers cytoplasmic material to lysosomes for degradation [1].

This mutation causes a non-conservative amino acid substitution that is associated with X-linked dominant form of neurodegeneration with brain iron accumulation (NBIA) called beta-propeller protein-associated neurodegeneration (BPAN), also known as static encephalopathy of childhood with neurodegeneration in adulthood (SENDA) [2]. This phenotype was almost exclusively found in females as its presence in males was associated with lethality. The distinct pattern on brain MRI is T1-weighted signal hyperintensity in the substantia nigra with a central T1-weighted hypointensity band and T2-weighted signal hypointensity, suggesting iron deposition in the globus pallidus and substantia nigra [1].

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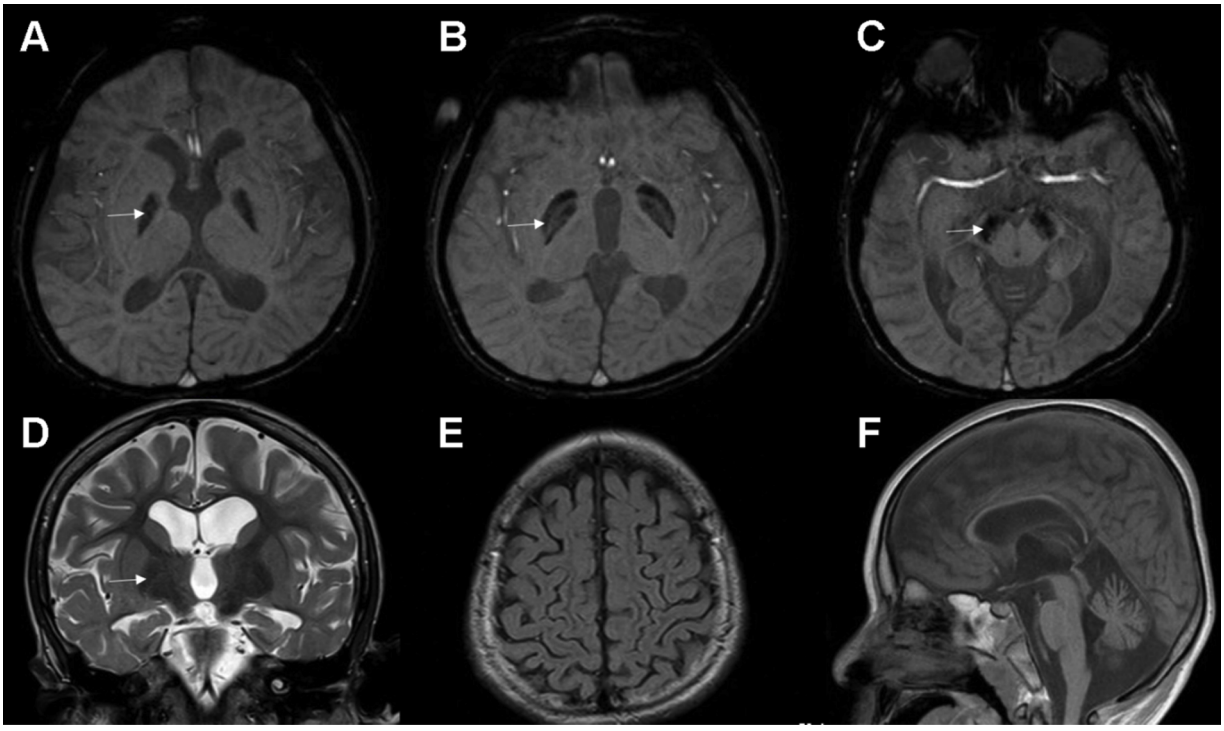

Fig. 1. Brain MRI shows striking iron accumulation, abnormal for age, in the globus pallidus interna and externa, (A, B) and substantia nigra (C), seen as hypointense signal on SWI susceptibility weighted image) sequences. The findings are less striking on T2 weighted images (D). Diffuse cerebral atrophy (D, E), and thin corpus callosum (F) were also noted.

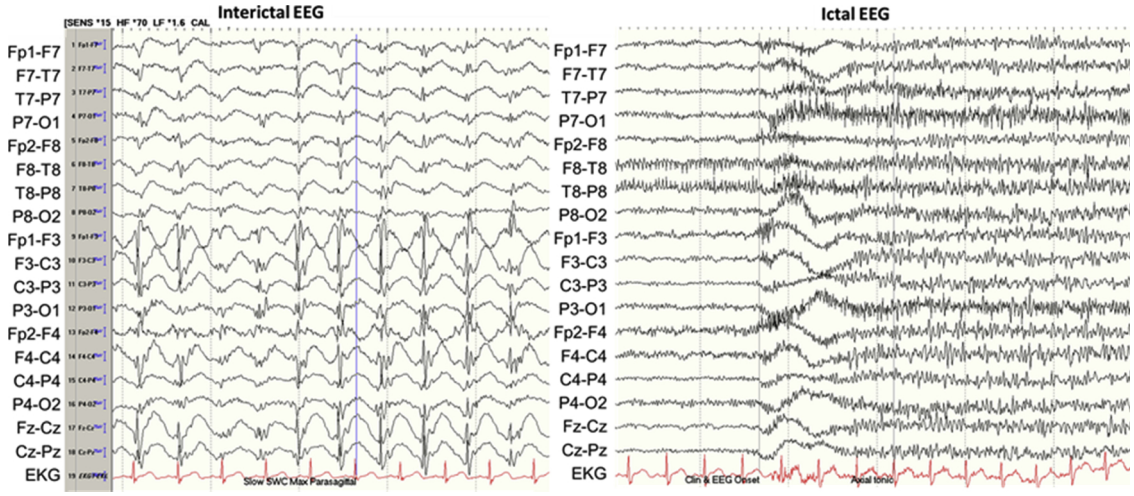

Fig. 2. Interictal EEG showed abundant generalized spike-wave complexes at 2–2.5 Hz, maximum in frontal and parasagittal regions, occurring in organized runs, constituting 40–50% of awake periods, intermittently replaced with diffuse rhythmic slowing (not shown). Ictal EEG showed diffuse fast activity during the generalized tonic seizure.

Epileptic encephalopathy of infantile onset has been recognized as a phenotype variant of WDR45 mutation [3]. Most described cases had early-onset intractable seizures, profound intellectual disability and developmental delay. Seizure phenotypes included West syndrome, focal onset impaired awareness seizures, atonic, myoclonic, atypical absence.

Disclosures

None for all authors.

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