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Clinical Letter

Vigabatrin as a Targeted Treatment of $GABA_B$ Receptor-Related Epileptic Encephalopathy

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Loss of $GABA_B$ receptor function is associated with epilepsy,[1] epileptic encephalopathy,[2] and Rett-like neurobehavioral manifestations.[3] Although $GABA_B$ agonists (e.g., baclofen) partially rescue mutation-related epilepsy in a frog model,[3] these medications have not proven reliable human antiseizure medications,[4] and targeted treatment of $GABA_B$-related epilepsy remains elusive.

We report an infant with epileptic encephalopathy in the setting of partial $GABA_B$ receptor subunit deletion who had a robust response to vigabatrin treatment. He was born at term following an unremarkable pregnancy and delivery. He was healthy until age 2.75 months when he presented with focal seizures. On evaluation, he had frequent multifocal spikes and sharp waves (Fig 1A) with an unremarkable cerebrospinal fluid profile, brain magnetic resonance imaging, and metabolic testing. Single nucleotide polymorphism array identified a pathogenic deletion (arr[hg19] 9q22.33(101,401,471-102,128,509)x1) including a part of the $GABA_B$ receptor subunit gene *GABBR2*.

Seizures initially responded to levetiracetam but recurred despite loading doses of valproate and vitamin B_6. Seizures remitted with addition of phenobarbital, although electroencephalography remained highly abnormal (Fig 1B). He was discharged on levetiracetam 60 mg/kg/day and phenobarbital 5.9 mg/kg/day but continued to have breakthrough seizures.

He developed infantile spasms with hypsarrhythmia (Fig 1C) at age 4.5 months. He was started on prednisolone, which failed to stop clinical spasms. Vigabatrin was started and titrated up to a dose of 143 mg/kg/day over three weeks. Steroids were weaned, and levetiracetam and phenobarbital were maintained at previous doses.

He has (at age 11 months) been seizure free for 4.5 months after final titration at the time of writing. Repeat electroencephalography three days after titration was normal (Fig 1D). Developmental assessments at clinical encounters via gross motor milestones and the Capute Scales (Brookes, Baltimore, MD) demonstrated an initial regression in motor skills with onset of infantile spasms followed by rapid recovery of developmental trajectory following treatment optimization (Fig 2). Given sustained efficacy and tolerability as well as mechanistic plausibility, we intend to continue vigabatrin.

Missense variants in *GABBR2* are associated with autosomal dominant early infantile epileptic encephalopathy-59[2] and an autosomal dominant neurodevelopmental disorder with poor language and loss of hand skills,[3] although deletions have not been previously reported. Its gene product GABA-B_2 is a highly conserved core subunit of the $GABA_B$ G-protein-coupled receptor complex involved in receptor trafficking and activation,[1,5] and knockout in rodent models produces dramatically reduced ligand binding with an epileptic, learning-impaired phenotype. As vigabatrin increases GABA concentrations by inhibiting its degradation by GABA transaminase, it is possible that higher concentrations counteract effects of decreased binding and partially rescue $GABA_B$ complex signaling. The clinical response in this child

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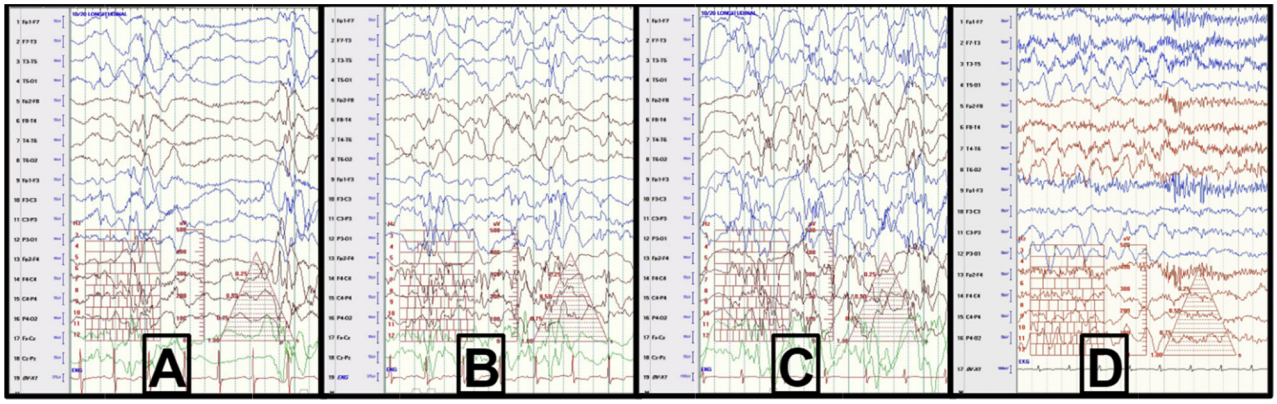

FIGURE 1. Electroencephalographic (EEG) findings. EEG at initial presentation (A) demonstrated frequent multifocal spikes and sharp waves that persisted on discharge (B) despite clinical response to levetiracetam and phenobarbital. Onset of infantile spasms coincided with expected hypsarrhythmia (C). EEG fully normalized (D) following uptitration of vigabatrin. The color version of this figure is available in the online edition.

suggests a potentially modifiable linkage between $GABA_B$ complex functioning and the neurodevelopmental phenotype. Experiments administering vigabatrin to animal models of $GABA_B$-related encephalopathy would help to validate effects and clarify mechanisms.

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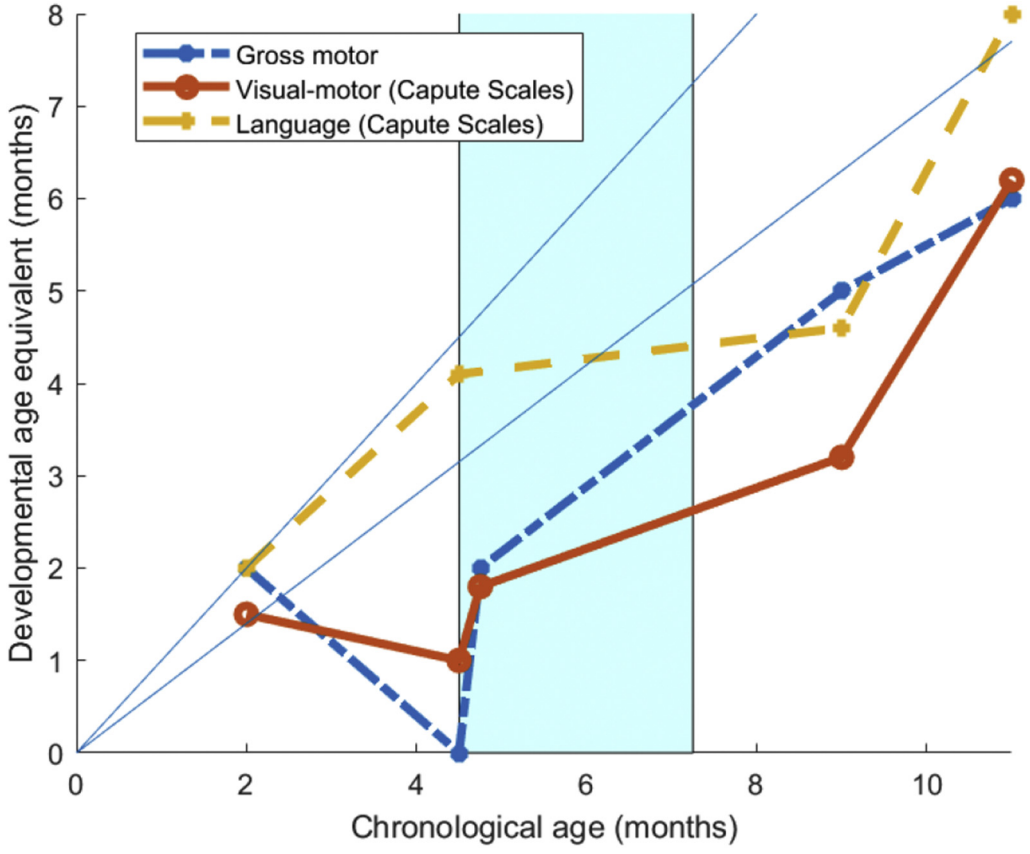

FIGURE 2. Developmental trajectory by domain. Bold lines represent developmental trajectory over time of gross motor (solid red), visual motor (alternate dashed blue), and language (dashed yellow) skills. Thin lines represent expected achievements from average (100% of typical) and borderline delayed (70% of typical) rates of development. The shaded area represents the time during which clinical infantile spasms were noted. Note significant regression of motor skills at onset of infantile spasms as well as resumption of typical rates of development (with persisting delays) following treatment optimization. The color version of this figure is available in the online edition.

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