■ Case vignette

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Epileptic Disorders

The epilepsy-movement disorder phenotypic spectrum and phenytoin-induced dyskinesia associated with *GABRB3* pathogenic variants

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VIDEO ONLINE

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Gamma-aminobutyric acid (GABA) A receptors are ligand-gated chloride channels responsible for maintaining inhibitory tone in the brain. Heterozygous pathogenic variants in *GABRB3,* encoding the β3 subunit of the $GABA_A$ receptor, have been implicated in several epilepsy syndromes [1]. Since $GABA_A$ receptors are critical for excitability regulation, deleterious loss-of-function pathogenic variants can result in GABAergic disinhibition, promote hyperexcitability, and lead to several genetic epilepsies [2]. Recently, the overlap between epilepsy syndromes and movement disorders has been widely recognized and numerous genes, including those that encode $GABA_A$ receptor subunits, such as *GABRB3, GABRA2, GABRG2,* and *GABRB2*, have been associated with both phenotypes [3]. We report a seven-year-old male patient, known for epilepsy due to a *de novo* pathogenic *GABRB3* variant, who developed dyskinesia after receiving a phenytoin load. Our case provides further support that GABRB3 dysfunction can be associated with movement disorders and suggests that a genetic predisposition may underlie phenytoin-induced dyskinesia.

Our patient is a seven-year-old male known for epilepsy, global developmental delay, mild to moderate intellectual disability and autism spectrum disorder secondary to a pathogenic *de novo GABRB3* variant (NM_021912.4: c.413_415dupACC; p.Asn138_Arg139insHis). He had an uncomplicated pregnancy and an induced vaginal delivery at 41 weeks. He was diagnosed with epileptic spasms at two months of age and was treated with vigabatrin and ACTH unsuccessfully. He developed other seizure types including eye convergence and nystagmus, head deviation, atonic head nods, and myoclonic jerks. EEG evolved into burst suppression. At the age of four months, topiramate was introduced with moderate effect and optimal seizure control was finally achieved with levetiracetam. Vigabatrin and levetiracetam were weaned successfully at nine months and 4.5 years of age, respectively.

At the age of seven years, during an attempted weaning of topiramate, the patient presented with brief bilateral tonic-clonic seizures appearing mostly during sleep. Reintroduction of topiramate did not resolve the seizures and the patient was hospitalized for status epilepticus requiring the use of IV phenytoin. Shortly after the phenytoin load, he developed dyskinesia of his face, arm and leg that lasted 24-48 hours *(see video sequence)*. The self-resolved dyskinesias were attributed to phenytoin toxicity with documentation of a phenytoin total blood level of 118 µmol/L (normal range: 40-80 µmol/L).

Pathogenic variants in genes encoding different GABA receptor subunits, such as *GABRG2, GABRA1, GABRD, GABRB2,* and *GABRB3*, have been associated with a broad phenotypic spectrum of epilepsies [1]. *GABRB3* pathogenic variants cause multiple epileptic syndromes

such as genetic epilepsy with febrile seizures plus, myoclonic astatic epilepsy, West syndrome, Dravet Syndrome, Lennox-Gastaut syndrome, epilepsy of infancy with migrating focal seizures and early infantile epileptic encephalopathy as well as developmental encephalopathy, intellectual disability and autism [1, 3–6]. *GABRB3* pathogenic variants alter $GABA_A$ channel gating by decreasing the probability of channel opening or by altering channel deactivation, leading to decreased GABA inhibition [1]. Furthermore, *GABRB3* pathogenic variants result in the impaired presence and clustering of $GABA_A$ receptors at synapses, especially inhibitory synapses [7].

Epilepsy-movement disorder phenotypes have been recently recognized in individuals with pathogenic variants of genes encoding GABA receptor subunits. Patients with *de novo GABRA2* or *GABRG2* pathogenic

▼ **Table 1.** Summary of clinical features in previously reported patients with *GABRB3* pathogenic variants and movement disorders.

	GABRB3 variant (NM_021912.4)	Inheritance	Age at seizure onset	Sex	Seizure type at onset	Other seizure types	Movement disorder	Developmental impairment	Reference
1	c.413_415dupACC; p.Asn138_Arg139insHis	*De novo*	2 mo	M	ES	GTCS, tonic, atonic, myoclonic, ES	Dyskinesia	Moderate ID	Current report
2	c.372A>C; p. Leu124Phe	*De novo*	7 wk	F	Clonic	Multiple types of focal seizures	Dystonia	Profound	Burgess *et al.*[4]
3	c.372A>C; p. Leu124Phe	*De novo*	2.5 mo	F	Clonic	Focal	Dyskinesia	Profound	Burgess *et al.*[4]
4	c.850C>A; p. Leu284Met (mosaic)	*De novo*	2 mo	F	Focal	Focal, tonic, ES	Dystonia, dyskinesia	Profound	Burgess *et al.*[4]
5	c.767T>A; p. Leu256Gln	*De novo*	1 d	M	NS	Focal, tonic, GTCS, ES	Hypotonia, dyskinesia	Profound ID	Moller *et al.*[1]
6	c.205G>A; p. Ala69Thr	*De novo*	8 mo	M	NS	ES, tonic, febrile seizure, GTCS	Ataxia, tremor	Moderate ID, regression	Moller *et al.*[1]
7	c.905A>G; p. Tyr302Cys	*De novo*	7 mo	M	Focal	Focal	Mild ataxia, hypotonia	Mild ID	Moller *et al.*[1]
8	c.902C>T; p. Pro301Leu	*De novo*	15 mo	F	Focal	Focal clonic, focal myoclonic	Ataxia, hypotonia	Mild ID	Moller *et al.*[1]
9	c.227C>G; p. Ser76Cys	*De novo*	9 mo	M	NS	Febrile seizure, GTCS, myoclonic atonic	Mild ataxia	Mild ID	Moller *et al.*[1]
10	c.694C>T; p. Arg232*	*De novo*	11 mo	M	NS	Febrile GTCS, dyscognitive, absence-like, tonic	Hand stereotypies	Severe ID, regression	Moller *et al.*[1]
11	c.758C>T; p. Pro253Leu (mosaic: 20%)	*De novo*	11 mo	M	NS	Dyscognitive, GTCS, atonic	Hand stereotypies, Rett-like	Severe ID	Moller *et al.*[1]

d: day; ES: epileptic spasm; F: female; GTCS: generalized tonic-clonic seizures; ID: intellectual disability; M: male; mo: month; NS: not specified; wk: week.

variants have been described presenting with early-onset epilepsy and varying movement disorders such as choreoathetosis, hand stereotypies, and hand posturing [3]. A handful of reports have described movement disorders in patients with *GABRB3* pathogenic variants, which are summarized in *table 1,* and include dystonia, dyskinesia and ataxia [1, 4].

Phenytoin-induced dyskinesia can occur at any time during the course of therapy and even at non-toxic concentrations. However, this side effect occurs more often with polytherapy and with toxic levels, which was the case in our patient [8]. Also, phenytoin-induced dyskinesia is frequently reported in children with epileptic encephalopathy and patients with pre-existing dyskinesias, suggesting the possible presence of underlying genetic susceptibility [8-10]. We theorise that the cause of the dyskinesia in our patient was multifactorial, including polypharmacy, increased phenytoin serum concentration and predisposition to movement disorders due to a *GABRB3* pathogenic variant.

In summary, this report provides further evidence suggesting that *GARBR3* is implicated in an epilepsy-movement disorder phenotypic spectrum, and suggests that genetic factors, such as *GABRB3* pathogenic variants, may represent a susceptibility to phenytoin-induced dyskinesia. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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The authors report no disclosures relevant to the manuscript.

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Legend for video sequence

Non-rhythmic, erratic, involuntary movements of the mouth, head and hands appearing shortly after the phenytoin load in a patient with a *GABRB3* pathogenic variant.

Key words for video research on www.epilepticdisorders.com
Phenomenology: non-epileptic paroxysmal event, dyskinesias (non-epileptic)
Localization: not applicable
Syndrome: non-epileptic paroxysmal disorder
Aetiology: non-epileptic paroxysmal disorder

TEST YOURSELF

(1) What is the main function of $GABA_A$ receptors in the brain and how are they implicated in causing epilepsy?

(2) What are the movement disorders reported in patients with pathogenic variants of genes encoding $GABA_A$ receptor subunits?

(3) Indicate whether the following statements about phenytoin-induced dyskinesia are true or false:

A. Phenytoin-induced dyskinesia can only occur when levels are at non-toxic concentrations.

B. Phenytoin-induced dyskinesia is more likely to occur in children with epileptic encephalopathy and patients with pre-existing dyskinesias.

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.