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Exploring the Phenotypic Spectrum of KCNB1: A Case Series of Two Unique Presentations

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Abstract

Background and Purpose: We present two cases exemplifying the broad phenotypic spectrum associated with pathogenic changes in *KCNB1* protein. Our case series highlights the variability of the outcomes of this genetic condition.

Methods: This is a descriptive retrospective review of medical histories of two patients under the age of 18 years with *KCNB1* related neurodevelopmental disorder. We performed a literature review from published articles in PubMed indexed journals.

Brief Report: A 9-year-old girl with developmental delay and autism found to have a pathogenic mutation in the *KCNB1* gene presented with regression in her language, staring spells, and EEG findings suggestive of Electrographic Status Epilepticus in Sleep (ESES). She is maintained on Clobazam and continues to make gains in her milestones.

A 16-year-old boy with a heterozygous mutation in the *KCNB1* gene presented with mild intellectual disability and attention deficit hyperactivity disorder. His EEG showed frequent bursts of generalized, sharply contoured theta activity - a finding of uncertain clinical significance. However, no clinical seizures were mentioned. He is maintained on valproic acid for mood stabilization.

Conclusion: The phenotype associated with *KCNB1*-related neurodevelopmental disorders is variable and includes epilepsy, intellectual disabilities, and psychiatric diagnoses. While our first patient had typical manifestations of the condition, treatment with anti-seizure medication was seen as beneficial. Our second patient had no clinical seizures, and his case highlights the importance of assessing the risk-benefit ratio of anti-seizure medication. It is important to understand the spectrum of the disease in order to identify clinical manifestations and perform early testing for a better prognosis.

Keywords: Neurodevelopmental disorder; *KCNB1* protein; Pediatric neurology

Introduction

KCNB1 encephalopathy is caused mostly by de novo heterozygous likely pathogenic and pathogenic variants in the *KCNB1* gene. The mutational spectrum of this gene includes multiple variant types, with missense reported most frequently followed by truncating variants [2]. It has been proposed that truncating variants located in the C-terminus region of the gene are associated with a less severe epilepsy presentation [3]. The *KCNB1* gene codes for the KV2.1, an ion channel that helps drive potassium out of the cell and plays a role in maintaining and transmitting electrical signals [1]. *KCNB1* encodes the alpha subunit

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of the Kv 2.1 voltage gated potassium channel which is highly expressed in the mammalian brain and may play a role in regulating neuronal excitability [5]. *KCNB1* is a potassium channel gene on chromosome 20q13.3. The protein encoded by *KCNB1* is a 96kDa core protein with 858 amino acids forming the alpha subunit of the voltage gated potassium channel subfamily 2 (Kv2.1). Each alpha subunit has 6 transmembrane helices (S1-S6) that include the voltage sensing domain (S1-S4) and a pore domain (S5-P-S6). These channels are expressed throughout the Central Nervous System (CNS) in proximal dendrites and initial segments of the neuron [1]. The voltage-sensor S4 helix contains a series of positively charged amino acids that senses the change in the membrane potential leading to channel opening and closing [6]. The selectivity filter of the pore is formed by the TVGYG amino acid motif located in the re-entrant pore loop between S5 and S6. In addition, Kv2.1 voltage-gated potassium channels have an N-terminal cytoplasmic region that modulates homotetramerization as well as heterotetramerization with other families of channel-forming subunits, such as the silent alpha subunits Kv6 (KCNG), Kv8 (KCNV) and Kv9 (KCNS) [9].

Given the pivotal role of voltage-dependent potassium channels in moderating neuronal excitability, it is these channels responsible in the pathogenesis of epilepsy. [1,2]. While this condition is characterized by global developmental delays, behavioural problems and various developmental and epileptic encephalopathy. (OMIM). They present with a broader phenotypic spectrum which includes early psychomotor developmental delay, mild-profound ID, autism, impulsivity [1,2].

Studies have shown that among the patients with the condition, 80-85% develop epilepsy with a median age of onset 17 months. More than 50% patients present with Autism spectrum disorder or other behavioural problems such as ADHD and aggression. Poor language development is seen in 20-50% patients and manifests as being non-verbal, using single words or only short sentences [2].

We identified two patients with KCNB1 related neurodevelopmental disorder. Patient 1 had the -H313Y variant which resulted in developmental delay, speech delays and clinical seizures. This pathogenic variant has fewer reported cases. Patient 2 had the R306C variant which resulted in developmental delay earlier in childhood, ADHD and mild ID. We describe the variation in the phenotype associated with KCNB1 related disorders and to add to the existing gene database

Methods

This is a descriptive retrospective review of medical histories of two patients. In addition we performed a narrative review using PubMed the index to *KCNB1* and the index to clinical spectrum was searched from 2012 to 2023 using search terms*: KCNB1* Variants, Developmental spectrum, phenotypic relevance, potassium channelopathies. Verbal Consent was obtained from parents and patients.

Results

Case 1

A 9-year-old girl with diagnosis of developmental delay and Autism presented for the first time to a tertiary care centre with a de novo heterozygous likely pathogenic variant on trio whole exome sequencing, KCNB1 (NM_004975.2) c.937C>T p.(H313Y). Prior to this she had staring spells starting at the age of 2 years. She was evaluated locally for syncopal spells at the age of 9 years. She also had language regression and stopped communicating in sentences, appeared more forgetful and was not learning at school which prompted referral to our tertiary neurology centre. Routine EEG captured several episodes of electrographic seizures described as generalized spike slow wave, at 2 - 3 Hz correlated with behavioural arrest and inability to recall a test word. A total of 9 electrographic seizures were captured. Other predominant findings included: Lack of well sustained/modulated Posterior dominant rhythm, lack of well-organized anterior to posterior gradient, moderate background slowing and abundant sleep activated/fragmented burst of irregular generalized spike slow wave discharges, with shifting predominance. Levetiracetam was initiated and prolonged EEG recording was obtained and revealed findings consistent with ESES (Electrical status epilepticus during slow-wave sleep). She was tried on oral diazepam and was later started on Clobazam. ESES improved on subsequent monitoring. Improvement was also noted in her language ability including ability to follow commands (receptive language) and communicate in 2–3-word sentences (expressive language). Family reported an increase in ability to learn new things in her school. Patient continues on Clobazam (0.8 mg/kg/day) and continues to make gains in her development and academic performance.

Case 2

A 16-year-old boy born at 36 weeks gestation due to preterm Premature Rupture of Membranes (PPROM) with Hashimoto Thyroiditis, Attention Deficit Hyperactivity Disorder (ADHD) and mild Intellectual Disability (ID) originally presented to neurology clinic at age 12 years for evaluation of developmental delays, behaviour problems, and abnormal EEG results. He had never had a clinical seizure. His developmental delays were primarily in social and communication development. Early development was appropriate with first words at 9 months of age (mama, dada used specifically to refer to his parents) and combining two words into phrases at age 18 months and receptive language remained intact throughout the developmental years. However, by 3 years he was not forming more complex sentences. His social development was also delayed, and he was noted to have difficulty interacting with peers but enjoys playing with other children, especially his sisters. He also had classic features associated with ADHD including inattention, restlessness, and impulsivity. There is no family history of seizures, developmental delays, or autism spectrum disorder. This patient was found to have a heterozygous pathogenic variant in KCNB1 on an autism/intellectual disability panel, KCNB1 (NM_004975.2) c.916C>T p.(R306C). We do not know if parental testing was performed. The 40-minute EEG at that time showed frequent, brief bursts of irregular, frontally predominant, generalized spike and slow wave complexes with moderate background slowing. He was started on a valproic acid titration to 250 mg twice daily for seizure prevention and mood stabilization. Magnetic Resonance Imaging (MRI) of the brain revealed a small right choroid fissure cyst, thought to be an incidental finding of limited significance and was otherwise within normal limits for age. Repeat EEGs have demonstrated frequent, sleep potentiated frontal epileptiform activity and slow, poorly sustained posterior dominant rhythm for age. His most recent EEG demonstrated frequent bursts of generalized, sharply contoured theta activity - a finding of uncertain clinical significance.

Today he is 16 years old and has never had a clinical seizure. He is maintained on valproic acid 250 mg in the morning and 500 mg in the evening as well as 62.5mcg daily of levothyroxine

for his diagnosis of Hashimoto Thyroiditis. He is in school with an individualized education plan and enjoys baseball. His motor exam is normal.

Discussion

Epileptic encephalopathies embody a group of age-dependent syndromes, which can be characterized by refractory seizures, severe Electroencephalography (EEG) abnormalities, and psychomotor developmental delay or decline. Approximately 40% of new-onset epilepsies before the age of 3 years can be attributed to epileptic encephalopathy [1,2]. The term Developmental Encephalopathy (DE) has been proposed to designate disorders where developmental delay emerges before the presence of epileptic activity or in the presence of infrequent epileptic activity [2,4].

Interestingly, patient 2 did not present with any clinical seizures, unlike the 85% of the patients with this variant that present with seizures [1,2,] and does not fit the clinical criteria for DEE [21]. While it is not uncommon for the KCNB1 variants phenotypically to present without seizures [12,16].

Mutations can be present in the pore domain or transmembrane segment of the voltage sensing domain. Studies suggested that pore vs voltage sensor influences penetration and severity of electroclinical and seizure phenotypes while neurodevelopmental delay is present in all cases to date [19].

Previously reported cases were all located in the pore domain [14,18,20]. There have also been studies describing mutations in the voltage sensing domain which was also functionally characterized [7]. Both our patients have missense variants located on the transmembrane segment, S4, which is the voltage sensor domain, yet their clinical presentation is very different. This highlights the need for additional research into genotype-phenotype correlation in the future.

Our descriptive study also seeks to highlight the phenotypic variation in patients carrying the R306C variant.

Patient 2 in our study, with the (R306C) variant showed phenotypic expression which was unique from other reports.

Reports characterized findings in a patient with the R306C variant in a seven-year-old male who presented with developmental delay. Onset of seizure at age 1 (spasm, tonic clonic, myoclonic and focal with head deviation at 2 yrs.) EEG findings showed generalized discharges of high amplitude spikes-waves and polyspikes at 2 yrs 11 months refractory to therapy. Additionally, no hypotonia, severe ID (no words), started walking at 2 yr 3 months and no MRI findings. Genetic mutations at this location suggest that they affect Kv2.1 voltage sensing. While this showed more damaging and severe phenotypes with earlier onset seizures, heterogenous, drug-resistant seizures, infantile spasms, and myoclonic, tonic-clonic seizures and focal seizures [14].

Reports of a patient with Jeavons syndrome, harbored the c.906C>T (p.Arg306Cys) missense variation, located on the S4 segment of the voltage sensor domain of the protein. also showed functional characterisation of developmental delay, with generalized epilepsy with myoclonic seizures with eyelid myoclonia with photosensitivity [11].

In contrast, our patient 2 had the same R306C variant presented with no clinical seizure, but positive for developmental delay, EEG findings.

Describing patient 1, while phenotypically was like other *KCNB1* variant cohorts and presented clinically with developmental delay, language delay and epilepsy, ESES, the variant harbored, is lesser known among the *KCNB1* cohorts.

Management of these patients is long term and requires them to follow up with a neurologist. Patient 1 showed significant improvement with clobazam and continued to make developmental progress and improve speech. Patient 2 continues to be maintained on valproic acid. It is known that valproic acid has been beneficial in treating epilepsy caused by the *KCNB1* variants [10]. The rationale for maintaining patient 2 on Valproic acid is to maintain behaviour as well as prophylactic for seizures considering the *KCNB1* variant.

Our study highlights two patients with different pathogenic variants in the *KCNB1* gene leading to varied clinical presentation associated with the diagnosis known as *KCNB1* related neurologic and developmental disorder. We demonstrate the importance of further research to better understand the genotype-phenotype relationship so as to provide better prognostic guidance for patients and families and more comprehensive and effective treatment options for providers managing these patients' neurological conditions.

Author Statements

Declaration by Authors

All authors have read and approved the final manuscript.

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