CASE REPORT

Potassium voltage-gated channel subfamily H member 1 (KCNH1) missense mutation causing epileptic encephalopathy and autistic behaviour

Prem Chand[1], Asna Sulaiman[2], Salman Kirmani[3]

Abstract

The phenotypically similar genetic diseases Zimmermann-Laband syndrome (ZLS) and Temple-Baraitser syndrome (TMBTS) cause neurodevelopmental problems. Mutations in the gene coding for potassium voltage-gated channel, primarily KCNH1, cause these symptoms. An uncommon mutation in KCNH1 (p.Arg357Trp) present on Exon 7, reported to replace arginine with tryptophan at codon 357 of the KCNH1 protein c.1069C>T, caused pharma coresistant seizures and autistic behaviour in a 2.7-year-old boy. This mutation causes problems with protein modelling and has yet to be documented in any genetic databases around the world. This mutation was overlapped with GPHN gene, c.828+1G>A, in our patient, causing GPHN-related spectrum disorder (autosomal dominant) along with molybdenum cofactor deficiency (autosomal recessive) leading to a neuropsychiatric presentation including autistic behaviour, making diagnosis and management even more complicated.

Keywords: Zimmermann-Laband syndrome, Temple-Baraitser syndrome, Autism, KCNH1 (p.Arg357Trp).

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Introduction

Mutations in the potassium voltage-gated channel subfamily H member 1 (KCNH1) are linked to syndromic neurodevelopmental problems. Zimmermann-Laband syndrome (ZLS) and Temple-Baraitser syndrome (TMBTS) are two multi-systemic disorders that have been reported. To date, 23 cases of KCNH1-related encephalopathy have been reported,1 out of which the majority were diagnosed clinically.[1] Zimmermann-Laband syndrome (ZLS) and Temple-Baraitser syndrome (TMBTS) are characterised by a wide range of symptoms, including epilepsy, intellectual impairment, and developmental delay.[2] Other signs and symptoms include gingival hyperplasia, hypertrichosis, facial dysmorphism, and a variety of skeletal abnormalities.[3] The potassium voltage-gated channel subfamily H member 1 (KCNH1) gene encodes voltage-gated potassium channel that is abundant in neurons and tumour cell proliferation; however, its physiological functions are unknown.[3,4] This phenotypic heterogeneity, as well as the significant overlap between the two syndromes, suggests that Zimmermann-Laband syndrome (ZLS) and Temple-Baraitser syndrome (TMBTS) are related and a continuum of the same disease. We describe a similar presentation in our case report, contributing further to the limited understanding of this neuro-genetic disease.

[1,3]Department of Paediatric and Child Health, Aga Khan University Hospital, Karachi, Pakistan; [2]Department of Medical Education, Aga Khan University Hospital, Karachi, Pakistan.t
Correspondence: Prem Chand. e-mail: prem.chand@aku.edu
ORCID ID. 0000-0001-5401-4780

Case Report

The patient is a two years seven-month-old baby boy, born to a healthy, non-consanguineous Pakistani couple. At the age of one year, the patient presented to the emergency department at the Aga Khan University Hospital, Karachi, Pakistan, in April 2021, with infantile seizures. These were tonic-clonic in nature with up-rolling of eyes and frothing from mouth occurring in multiple episodes, without any loss of consciousness. To maintain his airway, the patient had to be intubated in the emergency room (ER). In his relevant history it was revealed that the pregnancy and prenatal period were unremarkable, except for some oligohydramnios observed in his prenatal scans. The delivery occurred on term, however, it had to be progressed to emergent lower caesarean section, due to cord around the neck. He had a family history of seizures, present in his maternal cousin and grandmother. Baseline metabolic workup was sent with plasma amino acids, homocysteine levels and urine organic acids which were normal. A CT scan of the head with contrast was done which showed mild diffuse cerebral oedema with effacement of sulci and gyri, without evidence of brain herniation, followed by brain imaging; Magnetic Resonance Imaging (MRI), was done, which was normal. Diffuse theta and delta slowing were seen on Electroencephalogram (EEG), along with excessive diffuse beta activity; these findings are suggestive of moderate encephalopathy. He was followed as inpatient by paediatric neurology and genetics teams for augmentation of management, and was started on Phenobarbital, followed by Levetiracetam and Phenytoin and was sent home. He

subsequently had breakthrough seizures, thrice, leading to multiple readmissions. Doses of antiepileptic medication were adjusted but his seizures could not be controlled. His growth progress was reviewed in the clinic; he was able to hold his neck at six months, was sitting at eight months, and walking at 14 months; however, his vocabulary was limited to only one to two words (nonspecific) at age two. On recent examination, the child was hyperactive, showed no response to his name, not socialising, and had no dysmorphic features; however, tone, power deep tendon reflexes were normal. Repeat EEG showed intermittent right fronto-centro temporal at times spreading to left central spikes, sharp and slow wave discharges. Brainstem Auditory Evoked Potentials (BAEP) was done, which was normal. A genetic condition was suspected due to resilient seizures, with poor response to anti-epileptics and the patient was subsequently advised genetic testing. Next-Generation Sequence (NGS) Epilepsy Panel was performed. NGS are a series of diagnostic tests that evaluate gene(s) for variants (genetic changes) associated with genetic disorders. Diagnostic genetic testing, when combined with family history determine the individual's risk for the disease and further support clinical diagnosis; hence, assisting with the development of a personalised treatment and management strategy. The result identified on May 2021 showed two pathogenic variants. Firstly, GPHN gene, c.828+1G>A (Splice donor), was identified which is associated with GPHN-related spectrum disorder (autosomal dominant) and molybdenum cofactor deficiency (autosomal recessive) presenting with intellectual impairment, seizures, and autism. Secondly, KCNH1 c.1069C>T (p.Arg357Trp) present on Exon 7 was identified which causes rare KCNH1-related conditions, i.e. ZLS and TMBTS. Missense variant was identified in this patient, which has not yet been reported in the literature in individuals with KCNH1-related conditions. The sequence change is known to replace arginine with tryptophan at codon 357 of the KCNH1 protein (p.Arg357Trp). This mutation disrupts the protein sequence causing hindrances in its structural and functional properties. Antiepileptic medications were further readjusted; Valproic acid was added along with Levetiracetam and Clobazam which were to be continued. He had last seizure episode in April 2021. He was started on occupational, behavioural and speech therapy over the suspicion of autism spectrum disorder. The rarity of this finding is being described in this case report after taking consent from the patient's parents and approval from the appropriate ethical review committee.

Discussion

Zimmermann-Laband syndrome (ZLS) and Temple-Baraitser syndrome (TMBTS) are a group of disorders marked by significant limits in intellectual function and adaptive behaviour that appear before the age of 18 and are accompanied by developmental delays. Overgrowth of the gum tissue (gingival hyperplasia), excessive hair growth (hypertrichosis), unique facial features (dysmorphism), and recurring seizures are all common signs of intellectual disability, which can range from mild to severe (epilepsy). However, despite having a harmful KCHN1 mutation, none of the physical symptoms described above were present in this patient, demonstrating the phenotypic heterogeneity of the condition. His main presenting complaint was neurological characteristics such as significant developmental delay and pharmacoresistant convulsions. Clinical characteristics make it difficult to distinguish between these two disorders.[5] As a result, mutations in KCNH1 are believed to induce a phenotypic continuum of neurodevelopmental diseases ranging from ZLS to TBS, with the most common symptoms being syndromic developmental delay and infantile seizures.[5] In our patient, a link was also made with the GPHN gene, which causes an GPHN-related spectrum disorder that includes seizures, autism, and intellectual disability; molybdenum cofactor deficiency was discovered to be likely pathogenic after genetic testing.[6] A metabolic disorder, molybdenum cofactor deficiency is characterised by neonatal intractable seizures and brain anomalies such as atrophy, cerebral oedema, and dysgenesis of the corpus callosum. Feeding difficulties, dysmorphic traits, and severe developmental delay are all symptoms of this condition.[6] At the age of two, our patient's autistic traits were identified, and supportive therapy was initiated. Overlap of GPHN and KCHN1 gene mutations results in a diverse phenotypic presentation, making clinical diagnosis challenging, and this was one of the difficulties encountered while dealing with this patient.

Potassium (Kv) voltage-gated channels are the most complicated type of voltage-gated ion channel and its subfamily H is KCNH1 gene encoded.[7] The alpha subunit of a voltage-gated non-inactivating delayed rectifier potassium channel (pore forming) is active at the beginning of myoblast differentiation and is widely present in both the brain and myoblasts.[7] The reinitiated hyper-activation of KCNH1 showed increase resorption and alterations in the cilia-mediated pathway which were, therefore, proposed to lead to skeletal and nail malformations.[1] In our patient, KCNH1 c.1069C>T (p.Arg357Trp) present on Exon 7 was identified which causes rare KCNH1-related conditions. This sequence change replaces arginine with and is caused by missense variant which is expected to disrupt KCNH1 protein function. This variant disrupts the p.Arg357 amino acid residue in KCNH1. This variant has not been reported in the literature in individuals with KCNH1-related conditions.

Conclusion

In summary, this study shows that the same KCNH1 mutation can lead to both ZLS and TMBTS. Due to the phenotypic variability, identification of such genes would be of great importance as it can be because of the presence of modifier gene(s). However, multiple genetic mutation can overlap to give rise to a new phenotype and hence a careful analysis of genetic polymorphisms in various loci should be taken into consideration for clinical diagnosis.

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Conflict of Interest: None.

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