CASE REPORT

Mutation of *TBC1* Domain containing kinase (*TBCK*) with associated intellectual disability and hypotonia

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

Abstract

Infantile Hypotonia with Psychomotor Retardation and Characteristic Facies-3 (IHPRF-3) Syndrome is a rare pathology occurring due to mutations in the TBC1 domain containing kinase (*TBCK*). This is a neurodevelopmental disorder presenting with a neurological and dysmorphic feature including intellectual disability, limb and craniofacial abnormalities. We present a case of *TBCK* mutation of the variant (p.Gln164*), present on Exon 6; this sequence change creates a premature translational stop signal (p.Gln164*) in *TBCK*, creating a disrupted protein leading to a loss of function. This variant has not yet been reported in genetic databases. We need to establish a better understanding of this disorder by reporting these novel genetic mutations so that these complex patients can be successfully managed by multidisciplinary teams.

Keywords: Infantile hypotonia, Intellectual disability, Gene mutation.

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Introduction

Infantile Hypotonia with Psychomotor Retardation and Characteristic Facies (IHPRF) Syndrome are a group of severe heterogeneous infantile encephalopathies, clinically recognised in 2008, and genotyped in 2016. Out of its multiple types, IHPRF-3 is an ultra-rare disease, of which only 33 cases have been reported and studied in the world.[1] IHPRF-3 presents with intellectual disability and hypotonia and a distinctive phenotypical triad of craniofacial anomalies and limb and brain malformations. Originating from pathogenic variants in the TBC1 domain containing kinase (*TBCK*), it presents with an array of neurological abnormalities and has been coined as *TBCK*-related intellectual disability syndrome.[2] *TBCK*, which exists within an encoded protein[3] is a GTPase-activating protein (GAP), from the Rab (G protein) family which plays a crucial role in cell proliferation, growth[4] and regulation of the mTOR (mammalian target of rapamycin) pathway[5] helping in differentiation of the Schwann cells, contributing to myelination. In this report, we describe the case of a female who presented with typical findings of a *TBCK* pathogenic variant not yet reported in well-recognised genomic databases.[2] Due to limited genetic testing in South Asia and high statistics of consanguineous marriages, there are greater chances of biological relatives being a carrier for or being at risk for *TBCK*-related conditions.

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

Case Description

The patient was a six-and-half-year-old female, daughter to a healthy, consanguineous Afghani couple. Pregnancy and prenatal period were unremarkable. Delivery occurred on term, however, due to foetal distress caesarean section had to be performed. Neonatal history was un-eventful; however, during the first few years of her life, she developed poor feeding, causing frequent regurgitation episodes, which were followed by coughing and bouts of cyanosis. As their child began to grow, parents noticed low tone, bilaterally in her upper and lower limbs along with decreased movement and delayed global milestones including standing, walking, and chewing. Neck holding and sitting with support was achieved at three years of age. Fine motor skills such as finger grip were also delayed. The patient remained nonverbal. She also developed febrile seizures and was managed on sodium valproate, for two years. Upon presentation to the paediatric neurology clinic, at Aga Khan University Hospital, Karachi, Pakistan, in January 2021, her weight was 18.3 kg (10th percentile), while her height was undetermined. On examination, she had hypotonic facies (figure 1), generalised decreased tone and floppiness with diminished deep tendon reflexes in bilateral limbs. Valgus deformity was also noted on physical examination.

The patient was advised Electromyography (EMG), which gave insignificant findings, that is, observation of reduced motor unit activation; however, these may be due to decreased voluntary effort by the child. Previously done MRI showed periventricular leukomalacia. A genetic condition was suspected and the patient was advised genetic testing. Next-Generation Sequence (NGS) Cerebral Palsy Spectrum Disorders Panel was performed. The result

identified two pathogenic variants—*TBCK* and *GLB1*. First defect was noted in c.490C>T (p.Gln164*) (homozygous) in *TBCK*, Exon 6, which is an autosomal recessive gene. This sequence change creates a premature translational stop signal (p.Gln164*) in *TBCK*, creating a disrupted protein product leading to a loss of function. This variant has not yet been reported in population databases.[2] *GLB1* was identified as a likely pathogenic variant, c.1769G>A (p.Arg590His). The *GLB1* gene is associated with autosomal recessive GM1 gangliosidosis and mucopolysaccharidosis. However, the likelihood of this condition being caused by the first genotypic disruption is highly suspicious.

Discussion

IHPRF-3 is a neuro-genetic disorder, caused by disease-causing variants in *TBCK*, on chromosome 4q24. Bhoj in 2016, identified nonsense pathogenic variants of *TBCK* with mutational hotspots between exons 7 and 22, all characterised with severe presentation of phenotype. Our patient, belonging to a consanguineous Afghani family, showed homozygous *TBCK*, c.490C>T (p.Gln164*) variant, on Exon 6 which is neither present in population databases, until now, nor has it been reported in the literature.[2] The most consistent characteristics of IHPRF-3, as categorised by previous studies, are dysmorphic features, neurological signs and findings on MRI of the head.[1] The most common dysmorphic facial features, as identified by Aldana 2019[1] in their review of all 33 cases of IHPRF-3, are bitemporal narrowing, deep set eyes, tented upper lip vermilion, and macroglossia.[1] On examination our patient appeared to have hypotonic facies without coarseness and slight bitemporal narrowing (Figure 1). The neurologic signs such as profound global developmental delay, severe hypotonia and pharmaco-resistant seizures were commonly identified in cases of IHPRF-3.2 A variety of reflexes have been observed on neurologic examination, dominantly showing absent stretch reflexes and hypo/hyper reflexia.[1] Our

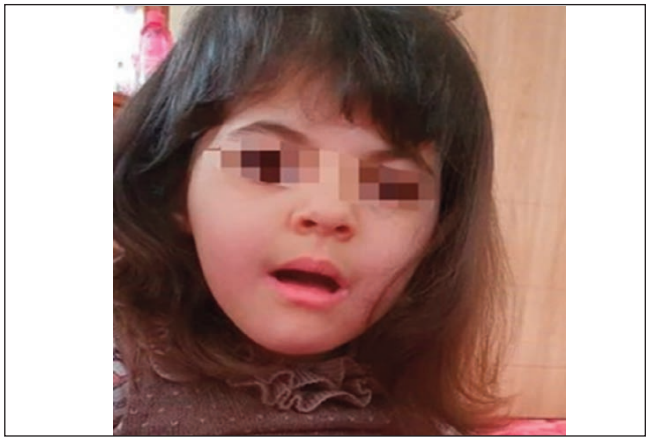

Figure-1: Slight Dysmorphism including lip vermilion, bitemporal narrowing and hypotonic faces.

Figure-2: Global motor delay.

patient also had global motor delay (Figure 2), generalised floppiness and hypotonia along with diminished deep tendon reflexes.

Disease-causing variants in *TBCK* decrease the transcription of mTOR complex proteins leading to down-regulation of mTOR signalling[2] which helps in the differentiation of the Schwann cells contributing to myelination. This dysregulated mTOR signalling can explain the abnormal reflex patterns observed in the reported cases[1] and in the current case. These disorders are also characterised by seizures, disorganised cortical lamination, and cytomegaly[6] out of which, this patient too demonstrated pharmaco-resistant seizures. As reported in 2016 by Bhoj,[2] it was observed that addition of leucine was able to increase the mTOR signalling in affected individuals by using increased phosphorylation of proteins. This shows that there is a *TBCK*-independent pathway for leucine to stimulate the mTOR pathway, which could be utilised for therapeutic effect in these individuals.[2] Leucine supplementation is already clinically available for certain metabolic disorders and has a wide therapeutic range.[2] Most common brain malformations reported in patients with IHPRF-3 are atrophy of the cerebellar region and thinning of the corpus callosum.[1] The MRI of the head shows non-specific findings, such as periventricular leukomalacia dilation of the lateral ventricles and white-matter changes.[7] Our patient's MRI also showed biventricular periventricular leukomalacia.

This disease has spread throughout many geographic regions, and has affected individuals with diverse ethnic backgrounds.[2] Genetic heterogeneity leads to vast variances in clinical presentation and, hence, is a major obstacle in establishing a working molecular classification of neurological disease.[8] A distinctive typical gestalt does not really exist for IHPRF-3[9] and there is paucity of literature

identifying the role of *TBCK*. Early recognition of this disorder will provide doctors with a more precise prognostic information which will be crucial for guiding decisions about invasive treatments, such as tracheostomy and gastrostomy in neonates and young children.[7] Furthermore, distinguishing *TBCK*-related encephalopathy from the rest will ensure accurate counselling regarding risk of recurrence and reproductive planning.[10]

Conclusion

This report provides a comprehensive description of the presentation and natural course of the disease through an additional case with novel disease-causing variants and a detailed review and case summary of the literature.

Recommendations:

Until a better understanding of this disorder and possible treatments are realised, the management of these complex patients is best placed in a multidisciplinary team framework that includes nutritional support, occupational and physical therapy, monitoring of their development, seizures control, and proper genetic counselling.

Ethics Approval: for publishing the case report was provided by the Ethics Review Committee of the Aga Khan University Hospital, Karachi, Pakistan.

Consent to publish the case report of the infant was provided by the parents.

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Conflict of interests: None.

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