Neurology Asia 2023; 28(3) : 775 – 779

Expanding the genotypic and phenotypic spectrum of the *SPTBN4* gene mutation: A new variant and dysmorphology

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Abstract

Congenital hypotonia and neuropathy caused by *SPTBN4* mutation are the core findings of a newly defined rare syndrome: Neurodevelopmental disorder with hypotonia, neuropathy, and deafness. Although hearing loss secondary to auditory neuropathy, dysmorphic findings, and epilepsy are distinctive features, they are not present in every patient, leading to a wide range of phenotypic spectrum. We report here a male patient with the *SPTBN4* gene mutation presenting with core symptoms but not hearing loss and epilepsy. There were also previously unreported dysmorphic findings such as prominent eyebrows, bilateral constant esotropia, microphthalmia, bitemporal narrowing, low hairline, low-set ears, broad nasal bridge, bulbous nose, anteverted nares, and high-arched palate, broadening the phenotypic spectrum even further. In conclusion, both genetic background and phenotypic features of the *SPTBN4* mutations were expanded in our report. After exclusion of spinal muscular atrophy in patients with congenital hypotonia and areflexia, the *SPTBN4* mutations should be considered.

Keywords: SPTBN4, spectrin, hypotonia, hearing loss, auditory neuropathy

INTRODUCTION

Spectrins are rod-shaped proteins located on the plasma membrane to form an important component of membrane architecture. As with erythrocytes, in which they were originally identified, spectrins are responsible for mechanical stabilization in axonal membrane.[1] Another significant function of spectrin is the regulatory role in clustering of Na+ and K+ channels, which are necessary for the initiation and propagation of the action potential in the axon.[2] Neurodevelopmental disorder with hypotonia, neuropathy, and deafness (OMIM #617519) is caused by homozygous or compound heterozygous variants in the *SPTBN4* gene, which encodes βIV-spectrin. Recently, the first human pathogenic variant in the *SPTBN4* gene was reported by Knierim *et al*.[3] Congenital myopathy, neuropathy, global developmental delay (GDD)/intellectual disability (ID) and deafness are considered as core symptoms, however, phenotypic spectrum has expanded over time.[4,5] As far as we know, only 21 patients from 17 families were reported in the literature.[3-10] Herein, we report a new pediatric patient to further detail the genetic background and clinical spectrum of this syndrome and review the literature briefly.

CASE REPORT

The male patient was born at term to healthy, first cousin Turkish parents. The pregnancy was uneventful, however, nonprogressive labor led to cesarean section. In the newborn period, he presented with general hypotonia and facial weakness with absent deep tendon reflexes. There were several dysmorphic features including prominent eyebrows, bilateral constant esotropia, microphthalmia, bitemporal narrowing, broad nasal bridge, anteverted nares, bulbous nose, low-set ears, high-arched palate, and low hairline (Figure 1). Early motor developmental milestones such as head control, rolling, sitting up, and crawling were never achieved. Social smile

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Date of Submission: 14 March 2023; Date of Acceptance: 21 March 2023

https://doi.org/10.54029/2023unk

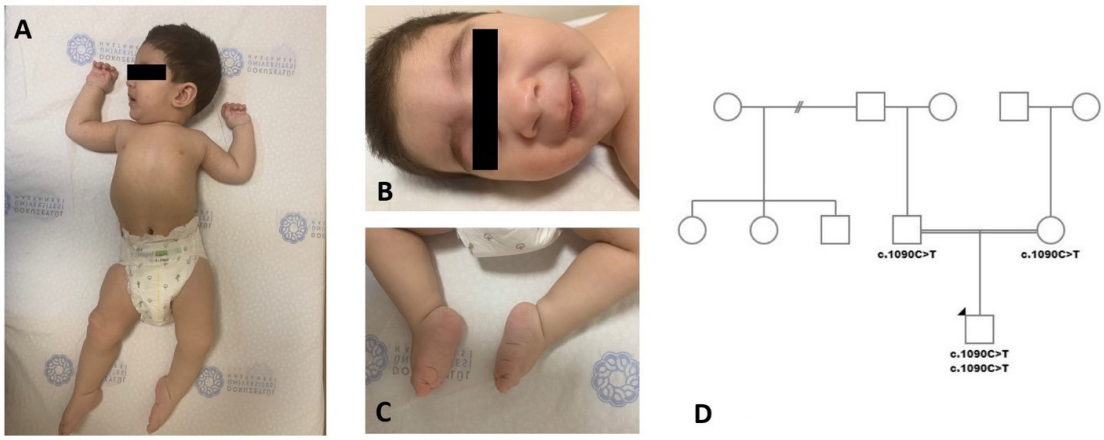

Figure 1. A. Frontal aspect of the patient. Please note prominent general muscular hypotonia with frog-leg posture. B. Dysmorphic features of the patients. Pay attention to prominent eyebrows, bitemporal narrowing, broad nasal bridge, anteverted nostrils, bulbous nose, and low set ears. C. Bilateral ankle contractions. D. Pedigree of the patient.

started at 2-3 months old. *SMN* gene analysis was inconclusive. Serum creatinine kinase levels were never elevated. Extensive metabolic tests were normal. Brain magnetic resonance imaging and echocardiography were normal. His ophthalmologic evaluation revealed blurred optic disc margins and mild hyperpigmentation of the macula with bilateral normoisochoric pupils and normal object tracking. At the age of eight month, he presented with severe muscle weakness, constantly opened mouth and ankle flexion contractures. Although height was normal for his age (-1.14 SDs), both weight and head circumference were below normal (-2.1 and -2.6 SDs, respectively). Tympanometry, otoacoustic emissions, and brainstem auditory evoked potentials in both ears were normal. Nerve conduction studies showed normal sensory and motor conduction velocities, with low-amplitude motor responses, demonstrating an axonal motor neuropathy. Electromyography revealed findings of both acute and chronic denervation including positive sharp waves, fibrillation potentials, neurogenic motor unit potentials with increased amplitude and duration, and decreased recruitment in proximal and distal muscles. There was neither pathologic decrement on repetitive motor nerve stimulation nor myotonic discharges. Whole exome sequencing revealed a homozygous nonsense c.1090C>T (p.Q364*) variant in the *SPTBN4* (NM_020971) gene. This variant has not been previously defined in the Human Gene Mutation Database and Clinvar mutation databases. Varsome and Franklin programs classify this change as "likely pathogenic" according to the American College of Medical Genetics and Genomics criteria. Sanger sequencing verified the variant and its segregation, in which both parents were heterozygous. At 12 months old, babbling and voice imitation started without any improvement in gross motor development. Severe dysphagia was also present. Parental consent for publication was obtained.

DISCUSSION

Congenital hypotonia without significant improvement over time and muscle weakness were reported in all patients, which is supported by our patient (Table 1). Motor developmental delay was reported in all patients, but minimal in only one patient, who was able to crawl and stand up with assistance at the age of 2 years and 5 months, but could not walk independently.[9] Head control can be rarely achieved.[3-10] Severe motor developmental delay including lack of head control in our patient corroborates the findings of a great deal of the previous patients. To date, severe ID was identified in all affected individuals except one patient with normal cognitive functions.[9] This feature, which significantly increases the phenotypic diversity of pathogenic variants in the *SPTBN4* gene, was also valid for our patient.

Despite its relatively lower rate compared to other characteristics, hearing loss is a remarkable finding of this syndrome since it is secondary to auditory neuropathy.[3,5] Moreover, the rate of hearing loss may be higher because an objective hearing test result could not be obtained in seven (39.1%) of the reported patients. Auditory evaluations of our patient were normal, reducing the rate in the literature to 36.4%.

Table 1: Brief literature review of the demographic, clinical, and radiological findings of the patients with the SPTBN4 mutations

	Reported cases	Present case	Total
Age last assessed	14 months-17 years (median: 5 years)	10 months	12 monhs-17 years (median 5 years)
Female	12/21 (57%)	Male	12/22 (54%)
Consanguinity	11/21 (52.4%)	+	12/22 (54%)
Neurological findings			
Congenital hypotonia	21/21 (100%)	+	22/22 (100%)
Neuromuscular weakness	21/21 (100%)	+	22/22 (100%)
Areflexia/Neuropathy	20/21 (95%)	+	21/22 (95.5%)
Language developmental delay	21/21 (100%)	Can not evaluate due to young age*	
Motor developmental delay	21/21 (100%)	+	22/22 (100%)
Intellectual disability	20/21 (95%)	-	20/21 (95%)
Facial weakness/Myopathic face	10/21 (47.7%)	+	11/22 (50%)
Joint contractures	8/21 (39.1%)	-	8/22 (36.4%)
Hearing loss	8/21 (39.1%)	-	8/22 (36.4%)
Visual impairment	7/21(33.3%)	-	7/22 (32%)
Seizures	5/21(24%)	-	5/22 (23%)
Scoliosis	5/21(24%)	-	5/22 (23%)
Nystagmus	3/21 (14.3%)	-	3/22 (13.7%)
Choreoathetoid movements	1/21(4.8%)	-	1/22 (4.5%)
Systemic/other findings			
Feeding difficulties	15/21 (71.4%)	+	16/22 (72.7%)
Respiratory difficulties	15/21 (71.4%)	-	15/22 (68.2%)
High-arched palate	6/21 (28.6%)	+	7/22 (32%)
Blue sclera	1/21(4.8%)	-	1/22 (4.5%)
Cardiomyopathy	1/21(4.8%)	-	1/22 (4.5%)
Abnormal Brain MRI	7/21(33.3%)	-	7/22 (32%)

MRI: magnetic resonance imaging.
*Babbling and sound imitation began at 12 months of age.

Details on anthropometric measurements in affected individuals have not been systematically noted; information of only three patients was available.[4,6,8] In one patient, Anazi *et al*.[6] reported that weight, height, and head circumference were below third percentile. One patient with normal height was reported to present low weight (-3.9 SDs) and microcephaly (-6.6 SDs), similar to our patient but more severely. We believe that careful follow-up of anthropometric measurements is especially important in determining nutritional supplements to prevent respiratory complications and improve quality of life.

Several nonspecific dysmorphic features such as myopathic facies, opened mouth, high-arched palate, hypertelorism, exophthalmos, and gingiva hyperplasia were reported.[3,4,10] The phenotypic spectrum of *SPTBN4* gene mutations was further diversified with the dysmorphic findings of our case. Vast majority of individuals with this disease, which is inherited with an autosomal recessive pattern, are homozygous except for compound heterozygosity in three patients (Table 2).[5,10] Including our patient, 18 different pathogenic variants -truncating (n= 12), missense (n= 4), multi-exon deletion (n= 1), and splice-site mutation (n= 1)- were identified.[3-10] The existence of a broad phenotypic spectrum can be justified by

Table 2: Literature review of genetic background and neuroimaging findings of the patients with the *SPTBN4* mutation

	Mutation locus	Zygosity	Parents status	Brain MRI
Knierim *et al*.[3] 2017	c.1597C>T (p.Gln533Ter)	Homozygous	Heterozygous	Mild hydrocephalus
Anazi *et al*.[6] 2017	c.3394del (p.His1132Thrfs*39)	Homozygous	NA	Diffuse T2 hyperintensity
Wang *et al*.[5] 2018	c.3820G>T (p.Glu1274*)	Homozygous	Heterozygous	NA
	c.3820G>T (p.Glu1274*)	Homozygous	NA	NA
	c.2709G>A (p.Trp903*)	Homozygous	NA	NA
	c.1511G>A (p.Arg504Gln) c.7303C>T (p.Arg2435Cys)	Compound heterozygous	NA	NA
	c.7453delG (p.Ala2485Leufs*31)	Homozygous	NA	NA
	c.1813C>T (p.Gln605) c.3829delC (p.Gln1277Argfs 4)	Compound heterozygous	NA	NA
Monies *et al*.[7] 2019	c.1665+2T>C	Homozygous	NA	Cerebral atrophy
	c.1217T>C (p.Leu406Pro)	Homozygous	NA	NA
	c.2535_2554del (p.Gly846AlafsTer13)	Homozygous	NA	NA
Pehlivan *et al*.[8] 2019	c.6433G>A (p.Ala2145Thr)	Homozygous	Heterozygous	Normal
Häusler *et al*.[9] 2020	c.3949-1G>A	Homozygous	Heterozygous	Delayed white matter myelination
	c.3949-1G>A	Homozygous	Heterozygous	NA
Belkheir *et al*.[4] 2021	c.6016C>T (p.R2006*)	Homozygous	Heterozygousity in mother Unavailable father DNA	Cerebral and cerebellar atrophy, thin corpus callosum
	c.6016C>T (p.R2006*)	Homozygous	Heterozygousity in mother Unavailable father DNA	Cerebral atrophy
Buelow *et al*.[10] 2021	c.3375_3393del (p.Asp1126Thrfs*39)	Homozygous	Heterozygous	Diffuse T2 hyperintensity
	c.3375_3393del (p.Asp1126Thrfs*39)	Homozygous	Heterozygous	NA
	c.737G>C (p.Arg246Pro)	Homozygous	Heterozygous	Normal
	c.1247del (p.Leu417Tyrfs*5)	Homozygous	Heterozygous	NA
	c.1149dup (p.Asn384Glnfs*17) chr19.g.(?_41,001,394)_(41,011,375_?) del	Compound heterozygous	Heterozygous	Normal
Present case	c.1090C>T (p.Q364*)	Homozygous	Heterozygous	Normal

NA: Not available. MRI: magnetic resonance imaging

these numerous different variants in the *SPTBN4* gene, each of which causes different localizations of βIV-spectrin in the neuronal membrane, thereby different membrane stability and clustering of ion channels.[5] Further studies including functional work-ups with more focus on variant-specific phenotypes may elucidate the certain underlying mechanisms, leading to molecular treatment strategies.

In conclusion, our report further broadens the variant spectrum and phenotypic presentations of the *SPTBN4* mutations. Once spinal muscular atrophy is excluded in patients with congenital hypotonia and areflexia, the *SPTBN4* mutations should be included in the differential diagnosis, particularly in the presence of hearing loss, dysmorphology and varying degrees of ID and epilepsy.

DISCLOSURE

Financial support: None

Conflict of interest: None

Ethics: The parents gave their informed consent for this publication.

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