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Behr's syndrome mimicking a case of hereditary spastic paraparesis

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Dear Editor,

Behr's syndrome is an infrequent genetic disorder affecting young children, presenting with progressive spastic paraparesis, ataxia, optic atrophy, peripheral neuropathy, and cognitive decline. Children presenting with difficulty in walking can be attributed to weakness, spasticity, dystonia, or mechanical deformity of the foot. Here, we discuss the clinical profile of two brothers in their childhood presenting with progressive difficulty in walking who were diagnosed with Behr's syndrome.

1. Case description

1.1. Case-1

A 9-year-old boy presented with insidious onset gradually progressive difficulty in walking since childhood. Initially, there was knee buckling, followed by toe-walking and problems getting up from the squatting position. There was no history of upper limb weakness, sensory complaints, bowel/bladder symptoms, falls, cognitive impairment, seizure, headache, diplopia, change in voice, or difficulty swallowing or hearing. There is no history of trauma, fever, cough, or weight loss. His birth history was uneventful. There is a similar history in his younger brother, who is seven years of age. There is history of consanguinity in his parents.

His general examination was unremarkable. Nervous system examination showed normal mental function and cranial nerve examination, including vision, fundus (except for bilateral temporal pallor), pupils, and eye movements. Motor examination in upper limbs is normal, while there was grade 4 power across all the joints in the lower limbs along with spasticity, brisk deep tendon reflexes, and extensor plantar response bilaterally. He used to stand with a wide base, requiring support, and walk unstably with difficulty turning. (Video-1) His sensory examination was normal except for a positive Romberg Sign. (Video-1) The rest of the nervous system examination was normal. Other system examinations were unremarkable.

His blood investigations for hemogram, renal profile, liver function, thyroid profile, and electrolytes were normal. Serological tests for HBsAg, Anti-Hepatitis C, and HIV-1,2 were negative. His vasculitis profile, Erythrocyte sedimentation rate, and C-reactive protein were normal. The spine and brain's magnetic resonance imaging (MRI) was normal. The nerve conduction study (NCS) demonstrated motor axonal polyneuropathy in both lower limbs. The visual evoked potential study showed increased P100 latency in both eyes (left eye 142.5 milliseconds and right eye 145.3 milliseconds).

He was suspected of suffering from hereditary spastic paraparesis initially; however, some points were against it, like a broad base unstable gait without evidence of scissoring of lower limbs while walking, Romberg sign, and abnormal NCS. The exome sequencing study was advised, which revealed a homozygous variant (NM_130837.3:c*4_*5 + 2del) in exon 30 of *OPA1* gene in chromosome 3: 193409918 showing splice junction loss suggesting a 'likely pathogenic' variant of uncertain significance in Behr syndrome. He was advised gait training, oral baclofen, and limb physiotherapy.

1.2. Case-2

His younger brother, who was seven years old, presented with similar motor complaints since childhood. He also had toe walking with difficulty getting up from a squatting position. His nervous system examination was similar to his brother's. He walked similarly.(Video-2) His vision was normal with normal fundus(except for temporal pallor), ocular movements, and pupil. His blood hemogram, biochemical tests, and serological tests were normal. MRI of the spine and brain were normal. His nerve conduction study showed axonal motor neuropathy in lower limbs and the VEP study was abnormal (P-100 latency in the left eye was 112 milliseconds in the left eye and 104 milliseconds in the right eye; normal <108 milliseconds). He was advised gait training, oral baclofen, and limb physiotherapy. A genetic study was not done on this child.

2. Discussion

Behr's syndrome (MIM 210000) is a classical phenotypic presentation of childhood-onset neurological symptoms, including optic atrophy, ophthalmoparesis, nystagmus, spastic paraparesis, ataxia, peripheral neuropathy, and learning difficulties. A German ophthalmologist Carl Behr first described it as "complicated hereditary infantile optic atrophy" in 1909 in six boys [1]. There is genetic heterogeneity in Behr's

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Table 1
List of causative genes for Behr's syndrome.

Serial Number	Gene	Chromosome Number	Inheritance	Mutation	Function of encoding protein	Clinical Phenotype
i	*C12orf65*	12q	Autosomal recessive	Homozygous (nonsense)[4]	Mitochondrial translation.	Childhood-onset optic atrophy, followed by spastic paraparesis, distal weakness, motor neuropathy and ophthalmoparesis
ii	*OPA1* *OMIM number* *605290.0003* *605,290.0018* *605,290.0020* *605,290.0021* *605,290.0022*	3q	Autosomal recessive	Compound heterozygous (missense), (splice site) [3]	Mitochondrial stability, energy production and cytochrome *c* sequestration.	Early-onset optic atrophy, ataxia, myopathy, neuropathy, and spasticity
iii	Concurrent *OPA1* + chromosome 3q deletion	3q	Autosomal recessive	Homozygous (missense) *OPA1* and de novo heterozygous 3975 kb micro-deletion in 3q[5]	Mitochondrial stability, energy production and cytochrome *c* sequestration.	Early-onset and progressive optic atrophy, peripheral neuropathy, and developmental delay

Note: q, long arm; kb, kilo-base; [4], Pyle et al.; [3], Marelli et al.; [5],Zeng et al. .

syndrome, with the majority being sporadic, followed by autosomal recessive and lesser autosomal dominant inheritance [2]. The expressivity of these genes is variable; hence, there can be diversity in clinical symptoms. The causative genes include *C12orf65* mutations, *OPA1* mutation and chromosome 3q deletion [3–5].(Table 1) The exact pathophysiology of Behr's syndrome is not certain. Histo-pathologically, central optic nerve atrophy and disarray of the typical structure of the lateral geniculate nuclei have been described [6]. While the optic atrophy in these patients remains stable, and despite the presence of optic atrophy, visual functions are relatively good, and blindness is quite exceptional [7]. These neurological syndromes can progress during childhood to become disabling in young adulthood.

We present two young siblings suffering from chronic progressive spastic paraparesis with ataxia, peripheral neuropathy, and optic nerve involvement diagnosed as Behr's syndrome. The clinical manifestations of the disease are usually evident between 1 and 9 years, as in our case (in ages of 9 and 7 years in case 1 and case 2, respectively). They did not have visual symptoms, but there was evidence of increased P-100 latency and temporal pallor in fundus examination. There is only a few case report of Behr's syndrome in India [8]. Many cases might be misdiagnosed as Hereditary spastic paraparesis (HSP)due to clinical overlap [9,10]. The other differentials include talipes, equinus deformity, leucodystrophy, spastic cerebral palsy, and corpus callosal atrophy. HSP is a group of clinically and genetically diverse disorders presenting primarily with progressively severe weakness and spasticity of lower extremity in children and young adults [11]. Differentiating HSP from Behr's syndrome is challenging, and genetics can help. However, definitive treatment is lacking in these genetic disorders as of now. The strength of this case discussion is the clinical and laboratory work-up of the cases along with genetic testing of the prominently affected child. The limitation of our study is that a parental genetic trio-analysis was not performed which could have been better to understand the extent of the mutation within the family.

3. Conclusion

A careful examination can guide towards a correct suspicion in children with spastic paraparesis. The element of ataxia, peripheral neuropathy, optic atrophy can suggest a syndromic genetic diagnosis, as in this case. Awareness about this genetic disorder can be helpful.

4. Bullets

- Behr's syndrome is an important cause of childhood-onset paraparesis, optic neuropathy, ophthalmopathy, nystagmus and ataxia.
- Hereditary spastic paraplegia is a common differential.
- Genetic exploration can help in differentiating these clinical syndrome and determine the exact diagnosis.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ensci.2024.100494.

CRediT authorship contribution statement

Rajesh Verma: Writing – review & editing, Conceptualization. **Rajarshi Chakraborty:** Writing – review & editing, Visualization.

Declaration of competing interest

None.

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