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A Rare Case of Boucher-Neuhäuser Syndrome in a Child with PNPLA6 Mutation: Expanding the Pediatric Phenotype

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ABSTRACT

Background: Boucher-Neuhäuser Syndrome (BNS) is a rare autosomal recessive neurodegenerative disorder characterized by the triad of cerebellar ataxia, hypogonadotropic hypogonadism, and chorioretinal dystrophy. Mutations in the PNPLA6 gene, which encodes neuropathy target esterase, have been implicated in the pathogenesis of this condition.

Case Presentation: We report a 15-year-old male, born to consanguineous parents, who presented with progressive difficulty in walking since the age of 5 years. Clinical examination revealed characteristic features including cerebellar ataxia, chorioretinal dystrophy, and hypogonadotropic hypogonadism. Additionally, the patient exhibited short stature, coarse facies, hirsutism with trichomegaly, brachydactyly with hypoplastic nails, micropenis, bilateral pes cavus, and motor axonal polyneuropathy. Neuroimaging demonstrated cerebellar atrophy with subcortical white matter hyperintensities. Genetic analysis confirmed a homozygous mutation in the PNPLA6 gene, establishing the diagnosis of Boucher-Neuhäuser Syndrome.

Management and Outcome: The patient was managed with a multidisciplinary approach including neurorehabilitation, low vision aids, and hormone replacement therapy. Genetic counseling was provided to family members.

Conclusion: This case highlights the importance of early recognition of BNS, particularly in pediatric patients presenting with progressive ataxia combined with visual impairment and delayed puberty. While no definitive cure exists, timely interventions through a multidisciplinary approach are crucial for improving quality of life and delaying functional decline in affected individuals.

Keywords: *Boucher-Neuhäuser Syndrome, PNPLA6 mutation, cerebellar ataxia, hypogonadotropic hypogonadism, chorioretinal dystrophy, pediatric phenotype, neurodegenerative disorder, consanguinity, multidisciplinary management*

1. INTRODUCTION

Boucher-Neuhäuser Syndrome (BNS) is a rare autosomal recessive neurodegenerative disorder characterized by a triad of hypogonadotropic hypogonadism, cerebellar ataxia, and chorioretinal dystrophy. First described by Boucher and Neuhäuser in the late 20th century[1] BNS belongs to the spectrum of Poretti-Boltshauser syndrome and has been linked to mutations in the **PNPLA6** gene, which encodes neuropathy target esterase (NTE), a critical enzyme in neural function[2]. The disorder

presents in childhood or adolescence, progressively affecting coordination, vision, and hormonal development, leading to significant functional impairment over time[3].

The clinical presentation of BNS varies, but its hallmark features typically emerge sequentially, with cerebellar dysfunction being one of the earliest manifestations. Patients often present with gait ataxia, dysarthria, and ocular motor abnormalities, followed by progressive visual impairment due to chorioretinal dystrophy. Hypogonadotropic hypogonadism may manifest with delayed or absent puberty, affecting both males and females[4].

Due to its rarity and overlapping features with other neurodegenerative and endocrine disorders, BNS is frequently misdiagnosed or diagnosed late. Neuroimaging, particularly brain MRI, often reveals cerebellar atrophy and may aid in early recognition[5]. Molecular genetic testing remains the gold standard for confirming the diagnosis.

In this case report, we describe a patient with BNS, detailing the clinical course, diagnostic approach, and genetic findings to contribute to the expanding literature on this rare condition. Our objective is to highlight the importance of early recognition, multidisciplinary management, and genetic counselling for affected individuals and their families.

2. CASE DETAILS

A 15-year-old male, born to third degree consanguineous parents, presented with progressive difficulty in walking since the age of 5 years. He had an unremarkable perinatal history and mild delay in early developmental milestones. However, at the age of 11 years, the child began experiencing progressive difficulties in coordination and balance, along with stiffness in both lower limbs eventually leading to frequent falls and impaired fine motor skills. Family history was not significant except for the consanguinity.

On examination, the child exhibited: normocephaly, short stature, coarse facies, hirsutism with trichomegaly, brachydactyly with hypoplastic nails, micropenis (stretched penile length -2cm) and bilateral pes cavus. Secondary sexual characteristics were underdeveloped for the age and was prepubertal. Fundus examination demonstrated chorioretinal dystrophy with changes of pigmentary retinopathy. Neurological examination showed wasting of distal lower limb muscles and spasticity in both lower limbs and exaggerated deep tendon reflexes. Upper limb tone and reflexes were normal. Cerebellar signs were positive. Spine examination was normal. Rest of the systemic examination was normal.

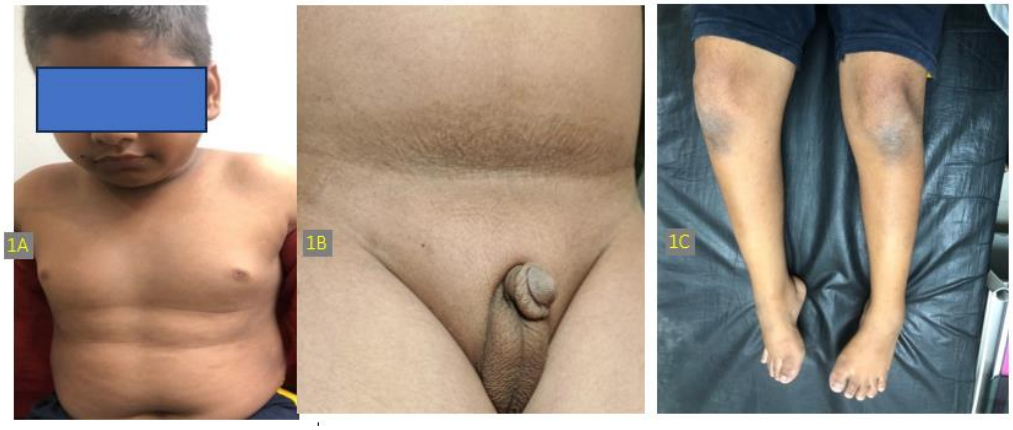

Image 1 (1A-C) – Clinical images: 1A - showing the facial dysmorphism with bulbous nose, thick eyebrows, trichomegaly.; 1B - micropenis with bilaterally undescended testes.; 1C - Wasting of leg muscles with pes cavus with flexion contractures at knee and equinus contractures at ankle.

Endocrine evaluation confirmed hypogonadotropic hypogonadism, evidenced by low levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Thyroid function test was normal. Echocardiography revealed no structural cardiac abnormality. MRI brain demonstrated cerebellar atrophy with subcortical white matter hyperintensities. Nerve conduction study revealed motor axonal polyneuropathy pattern. Genetic analysis with whole exome sequencing revealed a homozygous mutation in the **PNPLA6** gene, confirming the diagnosis..

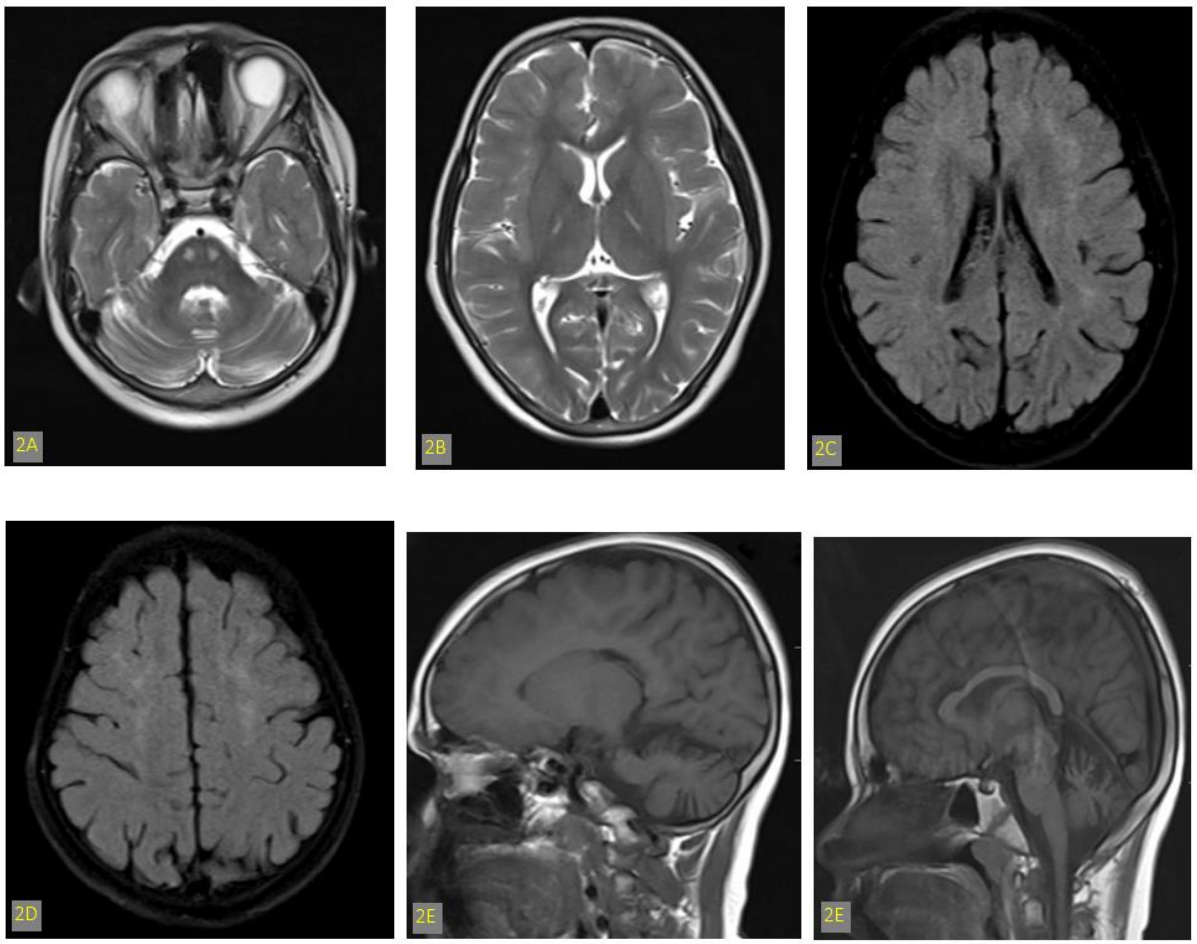

Image 2 (2A-F) – MRI Brain images : 2A – Axial T2 weighed image – symmetric hyperintensity over central tegmental tract along the pons; 2B – Axial T2 weighed image – symmetric hyperintensity over bilateral posterior limb of internal capsule; 2C and 2D - – Axial FLAIR image – periventricular and centrum semi-ovale white matter hyperintensity ; 2E and 2F – Sagittal T1 weighed image – cerebellar hemispheric atrophy, kinking of corpus callosum anteriorly.

The patient was managed with a multidisciplinary approach. Child was started on neurorehabilitation, low vision aids for progressive visual impairment and Pediatric endocrinology reference for hormone replacement therapy for hypogonadism. Genetic counselling for family members, were also provided.

3. DISCUSSION

The PNPLA6 gene, also known as the patatin-like phospholipase domain-containing protein 6 gene, encodes an enzyme that plays a crucial role in various cellular processes, particularly in lipid metabolism and membrane dynamics. Mutations in the PNPLA6 gene are associated with a broad spectrum of neurodegenerative disorders, including spastic paraplegia type 39, Gordon-Holmes syndrome, and Boucher-Neuhäuser syndrome, Laurence-Moon syndrome and Oliver-McFarlane syndrome.[6,7,8]

Boucher-Neuhäuser syndrome is characterized by variable combinations of cerebellar ataxia, chorioretinal dystrophy, hypogonadotropic hypogonadism, and other systemic manifestations. This triad was first defined by Limbert et al[9] from the case descriptions of Boucher and Neuhäuser. There is no sex predilection[10,11] and the inheritance pattern is autosomal recessive. The age of onset of symptoms is usually in childhood/adolescence but is variable, ranging from 4 to 40 years for ataxia and 1year to 48 years of age for visual disturbances[10].

The commonest symptom reported at onset is cerebellar ataxia which is usually slowly progressive[10,11]. It begins axially with unsteadiness of gait and then progresses to incoordination of extremities, tremors and frequent falls[11]. Our patient symptomatology started with progressive ataxia with frequent falls and incoordination. Other findings include dysarthria, pyramidal tract signs (spasticity), peripheral polyneuropathy and mild to moderate cognitive dysfunction[6,10,11]. These features

were in the index case too with lower limb spasticity, moderate cognitive dysfunction as well as evidence of peripheral neuropathy with distal lower limb muscle wasting, pes cavus and motor axonal neuropathy in nerve conduction study. Another classic clinical feature is chorio retinal dystrophy which leads to slowly progressive loss of vision which was present in our case as well. The onset and course of visual symptoms are variable and therefore, patient may have intact vision and no visual complaints or have severe vision impairment/blindness at the time of presentation. Visual field defects (scotomas), pigmentary deposits and impaired colour vision are also present in many. Endocrine abnormality noted is hypogonadotrophic hypogonadism with low testosterone, LH and FSH and underdeveloped secondary sexual characteristics with delayed puberty (9). Our case also had hypogonadism with low FSH and LH levels. Other uncommon features include short stature, pes cavus[1,10,12] and movement disorders such as focal dystonia and chorea[13]. So, a detailed ophthalmologic evaluation, endocrinological assessment including sexual maturity scoring and hormonal assessment should be carried out in all patients with cerebellar type of ataxia, especially if family history for neurological or ophthalmological disorders is present.

Neuro-imaging has consistently reported diffuse cerebellar atrophy of the cerebellar hemispheres and of vermis, particularly the superior and dorsal vermis[10,11]. Brainstem atrophy, mild cerebral cortical atrophy, T2 weighted white matter hyperintensities in basal ganglia structures and in periventricular regions of cerebral cortices were also reported in some cases[10,11]. The present case also had cerebellar atrophy with periventricular white matter hyperintensity.

The management of Boucher Neuhäuser is multidisciplinary. Hypogonadism is responsive to supplementation[11] with testosterone in males and an oestrogen/progesterone combination in females and consequently successful pregnancies. In addition to hormonal substitution, prescription of visual aids, physical therapy and assistive devices for balance and mobility, speech therapy, pharmacotherapy for tremors and movement disorders, genetic and psychosocial counselling remain integral in improving quality of life.

4. CONCLUSION

This case highlights the importance of early recognition of BNS, particularly in patients presenting with a combination of ataxia, chorioretinitis and hypogonadism with delayed puberty. The progressive nature of the disorder necessitates timely interventions to improve the quality of life and delay functional decline. While no definitive cure exists, a multidisciplinary approach involving neurologists, endocrinologists, ophthalmologists, and rehabilitation specialists is crucial for optimal management.

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