Poretti-Boltshauser Syndrome: A Novel Variant of *LAMA1* Gene

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ABSTRACT

Poretti-boltshauser syndrome (PBS) is a rare autosomal recessive (AR) disorder that occurs due to a mutation in the *LAMA1* gene. Clinically and radiologically, PBS is described as a disorder associated with ophthalmological problems, developmental delay, cerebellar dysplasia, cerebellar cyst, and intellectual disability. Herein, we report an 18-month girl with a novel variant of the *LAMA1* gene. To the best of our knowledge, this is a novel variant in the *LAMA1* gene that has not been reported previously in the literature.

Key Words: *LAMA1 gene mutation, Cerebellar dysplasia, High myopia, Developmental delay.*

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INTRODUCTION

Poretti-boltshauser syndrome (PBS) is a rare genetic syndrome, transmitted as autosomal recessive (AR) trait due to mutations in the *LAMA 1* gene (Laminin subunit protein-coding gene). Laminins are heterotrimeric glycoproteins that connect the basal membranes and extracellular matrix to the cells and their role is to provide strength to the tissues. One of these genes is the *LAMA1* gene encoding laminin alpha-1. Greets *et al*. has reported that homozygous or compound heterozygous mutations in this gene cause PBS.[1]

PBS is associated with ophthalmological problems, which include high myopia, retinal dysplasia, oculomotor apraxia, cerebellar malformations, developmental delay, and intellectual disabilities. The *LAMA1* gene plays an important role in the development of the cerebellum and retina. Patients with *LAMA1* gene mutations manifest varying clinical features which include delayed cognition and motor development, language delay, non-progressive ataxia, and myopia, with or without retinal dysplasia. Neuroimaging results are distinct and help in the diagnosis of PBS.[2,3]

In this report, we aim to present the clinical and radiological findings of a novel variant of the *LAMA1* gene.

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CASE REPORT

This is a case of an 18-month girl who was born at term *via* normal spontaneous vaginal delivery without any antenatal or perinatal complications. She was a product of a consanguineous marriage. She was referred from the ophthalmology department with developmental delay for evaluation. Her parents observed that she had been nodding her head a lot since she was of eight months. Her speech and motor skills were also delayed. When she was one year of age, her parents also noticed that she was struggling to follow the object. She also used to experience abnormal ocular deviation to one side. After a thorough evaluation, ophthalmologists diagnosed her as having high myopia and recommended spectacles. There was no significant family history of any neurological disorder.

Her physical examination revealed that she was microcephalic (OFC 43 cm) without any dysmorphic features. However, head nodding was observed with a deviation of ocular gase persistently towards one side. There was no social development because no response was noticed upon interaction. Her ophthalmological examination revealed poor visual attention and an inability to fixate on a moving toy. Her pupils were symmetrical, and equally reactive to light. Motor system examination revealed central hypotonia with a normal bulk of muscles and normal deep tendon reflexes. The fundoscopic examination was already done by an ophthalmologist who reported normal optic disc, macula, and retinal vessels. MRI brain showed dysplastic cerebellum, vermial hypoplasia, and a cerebellar cyst (Figure 1). Whole exome sequencing (WES) was performed, which confirmed a novel variant of the *LAMA1* gene. The *LAMA1* variant, c.3333del p. (Cys1111 Trpfs* 56) creates a shift in the reading frame starting at the codon 1111 in exon no. 23 of 63.

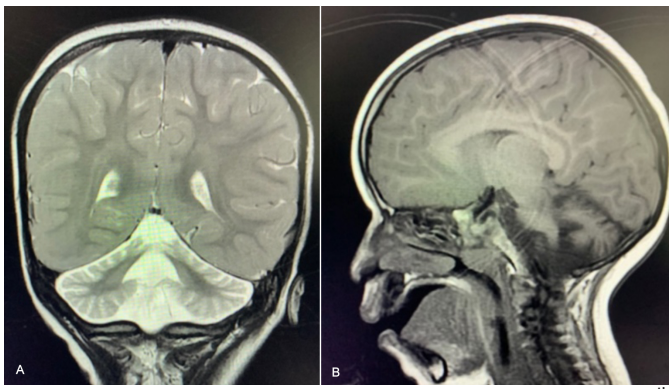

Figure 1: MRI brain (A) Coronal section T2 FLAIR showing enlarged 4th ventricle, vermial hypoplasia with small midline cyst. (B) T1 sagittal section showing cerebellar atrophy.

DISCUSSION

PBS is a rare neuro-ophthalmological disorder, clinically identified by the cerebellar ataxia, developmental delay, intellectual impairment, and language delay. Eye abnormalities include myopia, retinal dystrophy, amblyopia, strabismus, and oculomotor apraxia. Neuro-imaging identifies developmental cerebellar abnormalities. Intellectual disability may vary from normal to severe cognitive impairment.[2,3] This case report is a novel variant in *LAMA1* gene confirmed by the WES study, which is to the best of our knowledge, not previously reported in the literature.

Poretti *et al*. reported clinical presentations and features of seven children from different families who were discovered to have cerebellar cysts on brain MRI. The most eminent clinical characteristics were ataxia, intellectual impairment, and speech delay. Among them, five patients were diagnosed with oculomotor apraxia and severe myopia.[4]

Al-dinger *et al*. described the same number as reported by Poretti *et al*. These patients also belonged to different families with the same phenotype, reminiscent of that described by Poretti *et al*. All of these patients presented with motor developmental delay but only two among them had delayed speech.[2] Brain MRI of all patients revealed cerebellar dysplasia and only two had cerebellar cysts. All seven patients also exhibited ophthalmological abnormalities, including oculomotor apraxia, retinal dystrophy, and retinal atrophy. Three patients had central hypotonia on clinical assessment.[2,5,6]

Al-Ahmadi *et al*. reported a patient with similar clinical, ophthalmological, and radiological findings.[7] Mehmood *et al*. also reported a five-year girl who presented with delayed language and motor development with cerebellar dysplasia and a cyst on neuro-imaging.[8]

Another report of two genetically confirmed cases of PBS described by Turange *et al*. discovered cortical dysplasia (polymicrogyria and lissencephaly) on neuroimaging in two patients who presented with developmental delay and seizures. They suggested possible phenotype expansion of PBS. They also mentioned that there is an increased risk of developmental delay and seizures in PBS with cortical abnormalities.[9]

The present case report highlights the novel variant in *LAMA1* gene which has not been described in the literature before.

Although PBS is a rare neuro-ophthalmological disorder, clinicians should contemplate PBS in the differential diagnosis in younger children who present with developmental delay, especially when associated with ophthalmological abnormalities. We believe that PBS is underdiagnosed due to the lack of availability of genetic testing.

PATIENT'S CONSENT:

Verbal consent was taken from the parents of the patient for the publication of this case report.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

MS: Diagnosis, study, and design.
MS: Literature searching, drafting, and proofreading.
MAS: Critical revision.
SAT: Study and genetic literature.
BGAA: Conception and proofreading.
All authors approved the final version of the manuscript to be published.

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