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CHILD WITH DEVELOPMENTAL DELAY AND PATHOLOGICAL MYOPIA: PORETTI–BOLTSHAUSER SYNDROME

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ABSTRACT

Poretti–Boltshauser syndrome is rare genetic disorder of brain malformation with ocular findings due to mutation in LAMA1 gene. We report a case of five years old girl who presented with high myopia, delayed language and motor development with otherwise normal neurological examination. Brain imaging findings were consistent of Poretti–Boltshauser syndrome with cerebellar dysplasia and cyst (CDC). However, cerebellar ataxia and retinopathy were not found in our index case.

Keywords: Cerebellar malformation, Developmental delay, High myopia

INTRODUCTION

Poretti–Boltshauser syndrome is a rare inherited disorder of brain malformation, ophthalmological problems and intellectual disabilities.¹ Its inheritance pattern is autosomal recessive and is due to LAMA 1 gene homozygous or compound heterozygous mutation. LAMA1 gene has important role in morphogenesis of cerebellum and retina via encoding laminin subunit. Laminins connect basal membrane with extracellular matrix and this maintains basic tissue structure. This gene has also studied in causing congenital muscular dystrophy group disease.² Patients present with variable clinical manifestations including language delay, intellectual disability of variable severity, non-progressive cerebellar ataxia, high myopia and retinal dystrophy.³ Brain imaging findings includes cerebellar dysplasia with cyst formation and hypoplasia of cerebellar vermis.

CASE PRESENTATION

A five-year-old female child, born to consanguineous parents, delivered via spontaneous vaginal delivery at term with uneventful antenatal and perinatal period. Other siblings were not affected. Child had significant developmental lag with no neck holding by five months

and parents noticed development of squint in the left eye. They took ophthalmological consultation initially and child was found to have high myopia for which she was advised glasses and further follow ups. At eight months, when child did not achieve significant milestones, neurology consultation was advised. There was no history of seizures, abnormal movements, and focal deficits, any skin hair changes or specific body odor. Examination showed a playful child with good socialization skills, having normal tone, power and reflexes. There were no neurocutaneous stigmata. Apart from squint, there was no sign of nystagmus or any other ocular finding. Child was planned for developmental rehabilitation in all domains and regular ophthalmological and neurological review.

Child had delay in achieving developmental milestones i.e. neck holding at eight months, sitting at one year and walking at two and half years. Language milestones were also delayed as first real word was appreciated by parents after three years of age. Developmental rehabilitation was started for this global developmental delay and child improved significantly.

Regarding the serial ophthalmological review, child had significant abnormalities as elaborated in Table 1.

Table 1 Age-related ophthalmological findings:

| Ophthalmological findings | 5 months | 1.5 years | 4 years | |
|-----------------------------------|----------|-----------|-----------------------|----------------------|
| Myopia | High | High | High | |
| Astigmatism | Present | Present | Present | |
| Spherical | -3.5 | -7.0 | -11 | |
| Cylindrical | | | -2.00 with axis 90 | |
| Axial length (Normal: 20-22mm) | | | Right eye- 25.75mm | Left eye- 25.75mm |
| Bilateral cornea and media | Clear | | | |

These eye findings were consistent with pathological myopia and progressive worsening over years with current ophthalmological findings depicted in Figure 1. For eye problems patient is on follow-up of ophthalmology department. Myopia is being managed by glasses and 0.01% atropine solution.

Brain imaging was performed at 1.5 years as MRI brain and findings were abnormal cerebellar foliation, multiple small cortical and sub cortical cysts of variable sizes, enlargement and square like fourth ventricle, and hypoplasia of cerebellar vermis. Few T2/FLAIR hyper intense signals in bilateral centrum semiovale and periventricular region were noted. All these radiological findings were consistent with Poretti-Boltshauser

syndrome. (Figure 2a, b, c) Electroencephalogram (EEG) was performed which showed no epileptic discharges. Considering developmental delay, pathological myopia and cerebellar malformation clinic-radiological diagnosis was consistent with Poretti-Boltshauser syndrome.

Anthropometric measurements were head circumference of 44.5 cm, weight 13 kg and height of 100 cm, all below 3rd centile. There were no cerebellar signs. Child could run, go up and down stairs independently. In language domain child could make complete sentences. She had normal response to voice, interactive play and schooling was started.

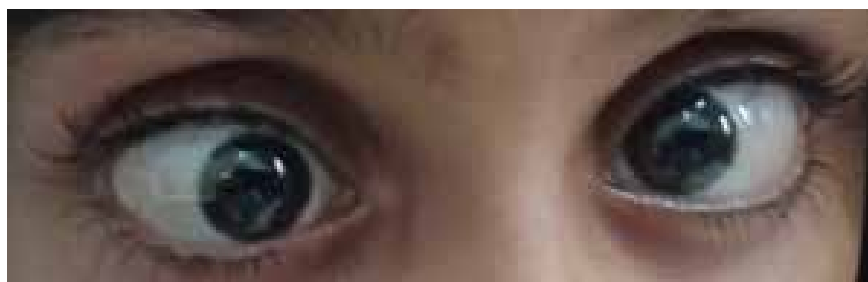
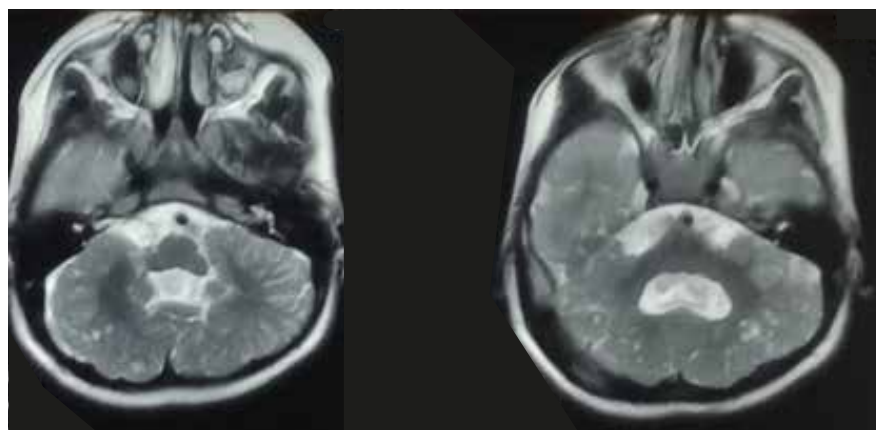
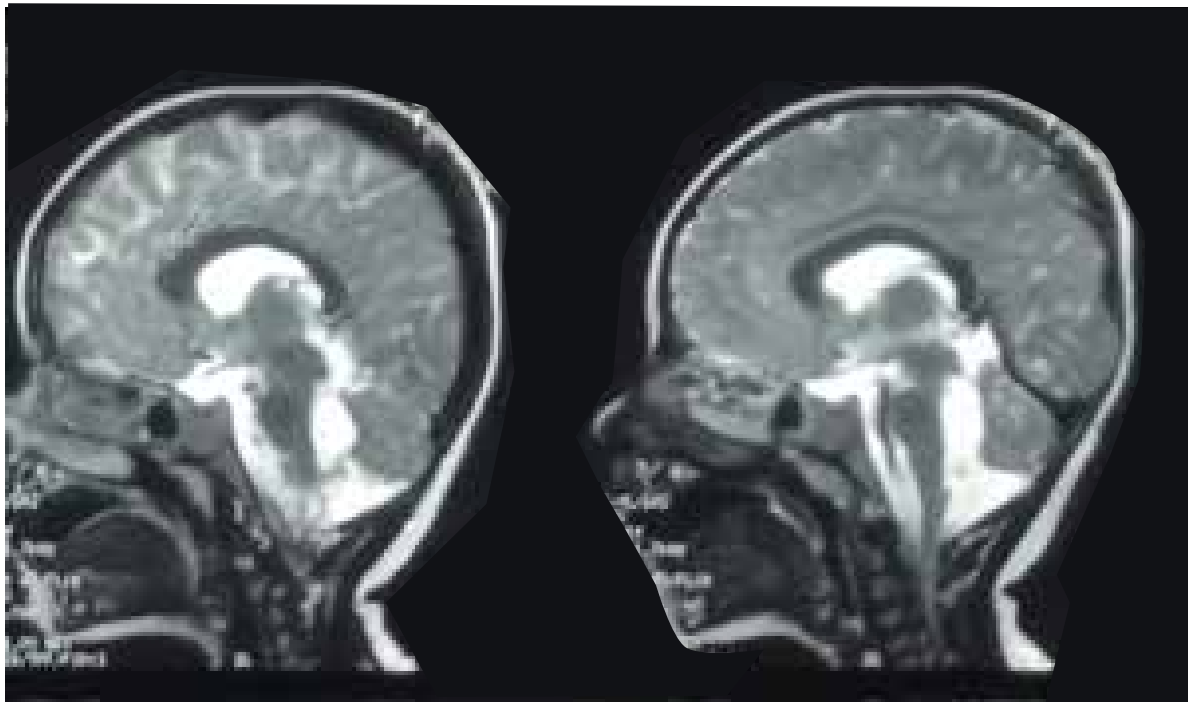


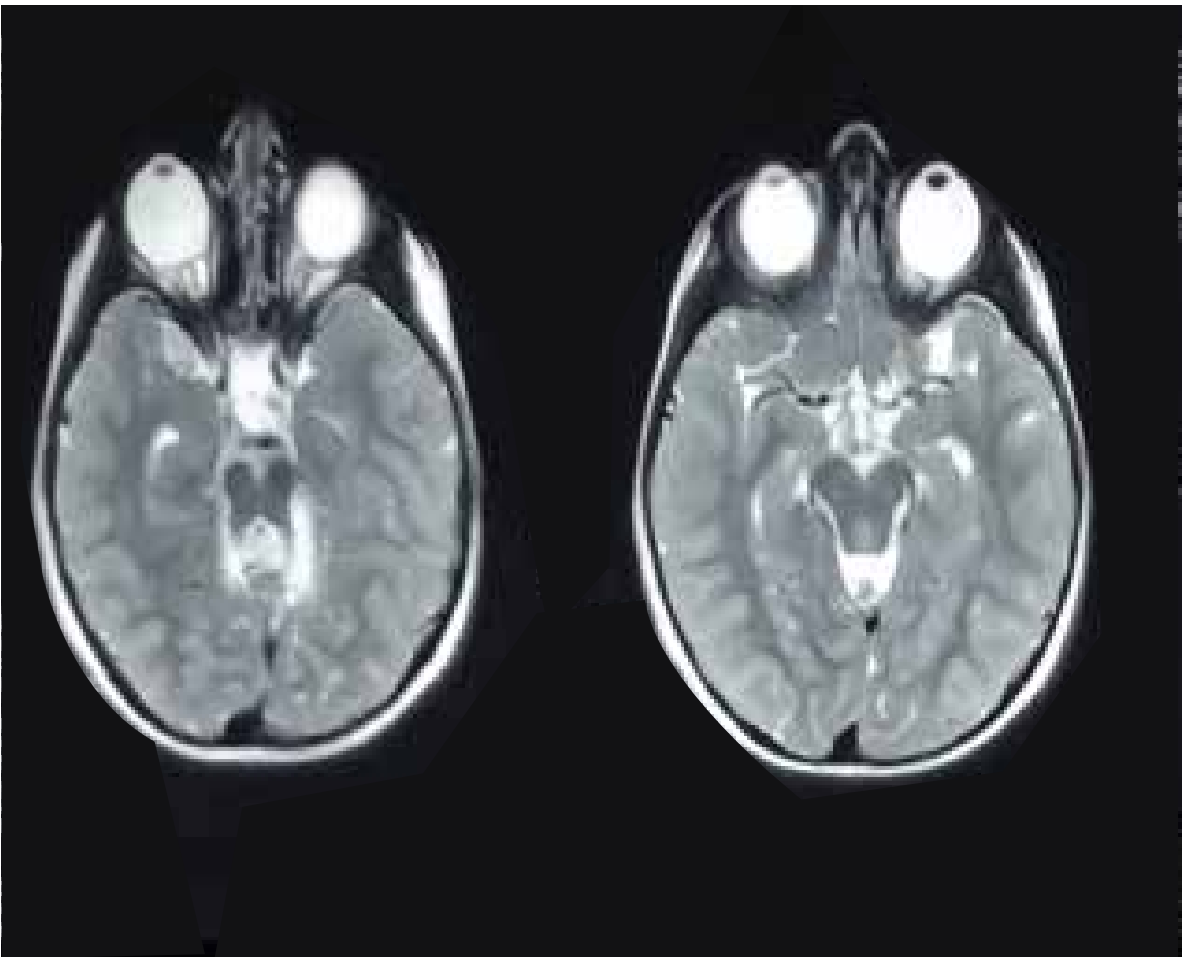
Figure 1: Strabismus and large eyes



(a)



(b)



(c)

Figure 2 (a, b, c): MRI findings of cerebellar cortical and sub cortical cysts, abnormal foliation, vermis hypoplasia

DISCUSSION

Poretti–Boltshauser syndrome is rare genetic syndrome with cerebellar malformation and abnormal eye findings. To best of our knowledge 42 cases of this syndrome have been reported in literature and no case report has been published from Pakistan.⁴ LAMA1 gene encoding laminin protein adheres basal membrane with extracellular matrix and its mutation leads to this syndrome. This rare disorder has been reported recently in 2014 involving seven children with underlying LAMA1 mutation.⁸ Later Elmas M reported twin boys with this syndrome having variable findings. In twin one, besides having consistent radiological findings and cerebellar ataxia, also had dysmorphic facial features including narrow face, pointed chin, smooth philtrum and thin upper lip vermillion. Another unusual thing was normal fundus examination and vision. Second twin had encephalocele, facial dysmorphism as of first sibling. Eye examination showed pale optic disc and no vision in both eyes. These were genetically conformed cases of LAMA1 gene mutation.⁴ Cai et al. reported a LAMA1 gene mutation positive case of three years old child having refractive error of 16.50 diopter in both eyes and retinal changes including reduced choroidal thickness. Our index case also had similar refractive error but retinal changes were not appreciated.⁵

Alahmadi et al. also reported similar case in two- and half-year female child. Important findings were delayed crawling and walking, myopia with cycloplegic refraction of -15 diopter bilaterally and severe retinal thinning.⁶ Micalizzi et al. reported clinical manifestations of

strabismus, nystagmus myopia, retinopathy, cognitive and language delay. Initial presentation was within first six months of life with developmental delay and abnormalities in eye movements. Cerebellar ataxia was noted at eight years of age. Ballistic movements were also observed in these patients. Imaging findings were cortical-subcortical cerebellar cysts and cerebellar dysplasia as reported in our case.⁷ With advent of next generation sequencing (NGS) genetic diagnosis has been made easy and cases have been reported in literature.⁸

Poretti–Boltshauser syndrome is a rare genetic inherited disorder and although genetic testing was not done in our case, but clinic-radiological findings aided us in diagnosing this rare inherited disorder where genetic testing was not readily available because of resource issue. Unique thing about this case is the follow-up data from five months to five years of age which led us to identify the evolution of disease with significant developmental delay and progressive ophthalmological findings, although without cerebellar signs, which may appear in future as the disease evolves.

CONCLUSION

Aim of reporting such rare condition is to amplify already known facts and broadening our horizon as regards evolution of Poretti–Boltshauser syndrome. Moreover, diagnosing rare genetic conditions can help us in relieving parental anxiety as well as offering genetic counseling for future pregnancies.

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Arshad Mehmood; concept, case management, manuscript writing

Javeria Raza Alvi; case management, manuscript writing

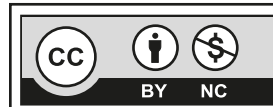
Ahmad Bilal; case management, manuscript writing

Sameen Qureshi; case management, manuscript writing

Shaila Ali; case management, manuscript revision

Tipu Sultan; case management, manuscript revision

All the authors have approved the final version of the article and agree to be accountable for all aspects of the work.



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