CASE REPORT

Variable Expressivity and Response to Bisphosphonate Therapy in a Family with Osteoporosis Pseudoglioma Syndrome

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Background: Osteoporosis pseudoglioma syndrome (OPPGS) is a rare autosomal recessive genetic disorder characterised by congenital blindness and osteoporosis, caused by biallelic mutations in the *LRP5* gene. **Case characteristics:** A consanguineous family with four OPPGS-affected members with variable expressivity. **Observation:** A novel homozygous missense pathogenic variant (c.3709C>T) was identified in the *LRP5* gene. Good response to biphosphonate therapy was observed in all affected members. **Message:** This case highlights the importance of screening for osteopenia in a case of familial exudative retinopathy, for early institution of bisphosphonate therapy.

Keywords: *LRP5 gene, Osteopenia, Retinopathy.*

Osteoporosis pseudoglioma syndrome (OPPGS) is a rare autosomal recessive genetic disorder characterised by congenital- or infantile-onset blindness and severe osteoporosis [1,2]. It is caused by loss-of-function biallelic mutations in the *lipoprotein receptor-related protein 5* (*LRP5*) gene. We describe a family from southern India with four members affected with OPPGS, wherein a novel homozygous missense pathogenic variant was identified in the *LRP5* gene. Significant variability in the phenotypic severity was noted in the affected family members, which is unusual for an autosomal recessive genetic disorder. Initiation of bisphosphonate therapy resulted in significant clinical improvement in the two severely affected members over a 6-month follow-up period.

CASE REPORT

The index patient (IV.3), a 4-year-old female child, the third offspring of 3rd degree consanguineous parents (***Fig.* 1**) who presented with a referral diagnosis of osteogenesis imperfecta, had history of multiple fractures (five fractures involving bilateral lower limbs and right upper limb) since early infancy and complete blindness of both eyes since birth. Her antenatal and perinatal periods had been uneventful. Though developmentally normal in all other spheres, she had attained the ability to stand with support by 3 years but had never been able to walk, even with support. There was no history of hearing loss, other focal neurological deficits or any other systemic symptoms.

On examination, the proband's anthropometric measurements were as follows: height 90 cm (5th centile), weight 10 kg (-2 to-3 SD) and head circumference 43 cm (-4 to -5 SD). She had bilateral microcornea with corneal opacities, with white sclerae. The craniofacial dysmorphic features noted included microcephaly, enophthalmos, mildly low set ears, prominent zygomatic arches and bulbous tip of nose (***Web Fig.* 1**). Bowing of both thighs and legs was present. The neurological examination was normal except for complete loss of vision in both eyes and mild hypotonia in both the lower limbs. No abnormality was found on examination of the cardiovascular, respiratory and abdominal systems.

A detailed family history was elicited which revealed similar symptoms in one maternal uncle (III.3), one maternal aunt (III.5) and one elder female sibling (IV.2) as indicated in the pedigree in ***Fig.*1(*a*)** and in ***Table* I**. Examination of these other three affected family members revealed similar findings, but with variable severity. The uncle (III.3) had short stature (height 145 cm; -3 to -4 SD), normal head circumference (54.5 cm), bilateral microphthalmia with corneal opacification, no other significant facial dysmorphism, widely spaced and eroded teeth, swollen and tender knee joints and bilateral anteriorly bowed tibiae. The affected aunt (III.5) had a normal height (143 cm; 5th centile) with no skeletal deformity, microcephaly (head circumference 50.5 cm; -2 to -3 SD), bilateral microcornea with corneal opacities, enophthalmos, low-set ears and bulbous tip of nose. The

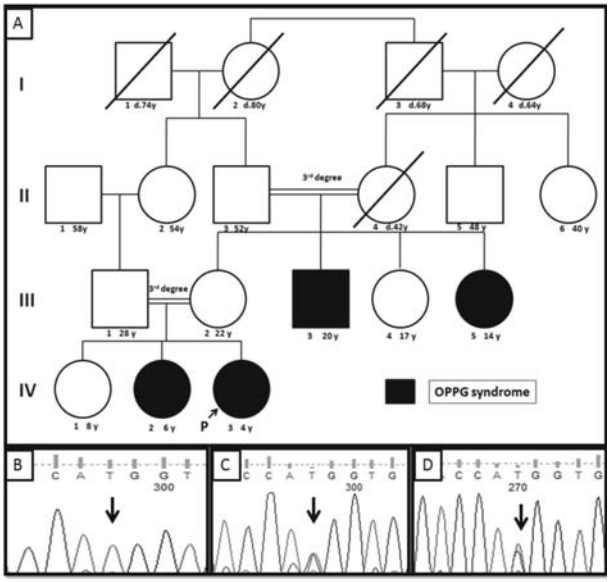

***Fig.* 1** *(a)Pedigree of the reported family; (b) Sanger sequence chromatogram of the proband showing homozygous c.3709C>T (marked by black arrow) variant in the LRP5 gene; (c & d) Sanger sequence chromatograms of the proband's father and mother respectively showing the heterozygous c.3709C>T (marked by black arrow) variant in the LRP5 gene.*

affected sister (IV.2) had short stature (height 101 cm; -2 to -3SD), microcephaly (head circumference 46 cm; -3 SD), the same eye and facial dysmorphic findings as the proband, and no skeletal deformities.

Radiographs of the spine, pelvis, femur and knee in the proband and the other three affected family members were suggestive of diffuse osteopenia. The proband additionally had vertebral compression (***Web Fig.* 1**). Serum calcium, phosphorous, alkaline phosphatase and total vitamin D3 were within normal limits. Ophthalmological examination revealed evidence of foveal exudative vitreoretinopathy with phthisis bulbi in all four individuals.

Based on the above findings, a provisional diagnosis of Osteoporosis pseudoglioma syndrome was made and sequencing of the *LRP5* gene was done. A novel homozygous c.3709C>T (p.Arg1237Trp) missense sequence variant was identified in the proband in exon 17 of the *LRP5* gene (***Fig.*1*b***) through targeted gene panel testing using the Illumina sequencing platform (Illumina Inc., San Diego, California, United States) and further validated through Sanger sequencing using the ABI 3130 automated genetic analyzer (Life Technologies, Thermo Fisher Scientific Corporation, Foster City, California, USA). This sequence variant was not present in the dbSNP, 1000 Genome and Exome Aggregation Consortium (ExAC) databases. The pathogenicity of this variant was inferred based on the results of the variant prediction software Polyphen-2, Mutation Taster, and

TABLE I CLINICAL FEATURES IN THE AFFECTED MEMBERS OF THE REPORTED FAMILY DEMONSTRATING VARIABLE EXPRESSIVITY OF THE DISEASE

Clinical features	*Affected uncle (III.3)*	*Affected aunt (III.5)*	*Affected sister (IV.2)*	*Proband (IV.3)*
Fractures	+ (5 episodes)	+ (1 episode)	-	+ (5 episodes)
Age at 1st fracture	9 years	12 years	-	Infancy
Blindness	Complete	Partial vision in one eye	Complete	Complete
Motor developmental delay	-	-	+	+
Microcephaly	-	+	+	+
Short stature	+	-	+	-
Hearing loss	+	-	-	-
Vertebral compression	-	-	-	+
Dysmorphic features				
Deep set eyes	+	+	+	+
Asymmetric palpebral fissures	-	-	-	+
Sparse lateral third of eyebrows	+	+	+	-
Prominent zygomatic arches	+	+	+	+
Bony prominence over lateral supra orbital margin	-	-	+	-
Bulbous nasal tip	+	+	+	+
Thick lips	+	+	+	+

SIFT. Targeted mutation analysis of the other family members was done through Sanger sequencing; the affected uncle (III.3), affected aunt (III.5) and elder sister (IV.2) of the proband were confirmed to be homozygous for the c.3709C>T variant and the parents (III.1 and III.2) and maternal grandfather (II.3) were confirmed to be heterozygous carriers for the same (***Fig.* 1*c*** and **1*d***).

The proband and her affected elder sister were started on intravenous Pamidronate therapy at a dose of 1mg per kg body weight for three consecutive days, once every 3 months and the affected uncle and aunt were started on oral bisphosphonate therapy (oral Alendronate in the dose of 1mg per kg body weight once a week) with daily calcium supplementation. The proband was followed up after 3 months and 6 months, by which time she showed remarkable clinical improvement with no fractures reported during the period and had attained the ability to walk with one hand held over a distance of up to 2 metres. The severely affected uncle also reported a marked clinical improvement with cessation of pain, ability to stand by himself without support and ability to walk with the help of a walking stick.

DISCUSSION

The LRP5 protein is believed to play a role in determining bone mineral density through the Wnt signalling pathway and in retinal vascularisation through Norrin/ Frizzled 4 signalling [3-6]. Loss-of-function mutations in the *LRP5* gene are therefore associated with osteoporosis and exudative vitreoretinopathy. Variable expressivity and intra-familial variability, though usually associated with autosomal dominant disorders, may occur with autosomal recessive conditions. There was marked intra-familial variability of the OPPGS disease-phenotype in the reported family.

Many short-term studies on bisphosphonate therapy in OPPGS have reported beneficial effects, which include reduction in bone pains, increased bone mineral density, decreased fracture rate and subsequent improvement in the quality of life [7,8]. However, long-term follow-up data pertaining to the use of bisphosphonates in OPPGS is limited. A recent study [9] reported that though there is significant improvement in the areal bone mineral density (aBMD) in bisphosphonate-treated OPPGS patients, the trabecular volumetric BMD (vBMD) remains low and therefore in the long term there is no significant improvement in the bone fragility.

Further studies in such cases to look for causes of variable expressivity may throw a light on novel disease/ phenotype modifying genes and genomic variants. This case also highlights the importance of screening for osteopenia in cases of familial exudative vitreoretinopathy for early intervention.

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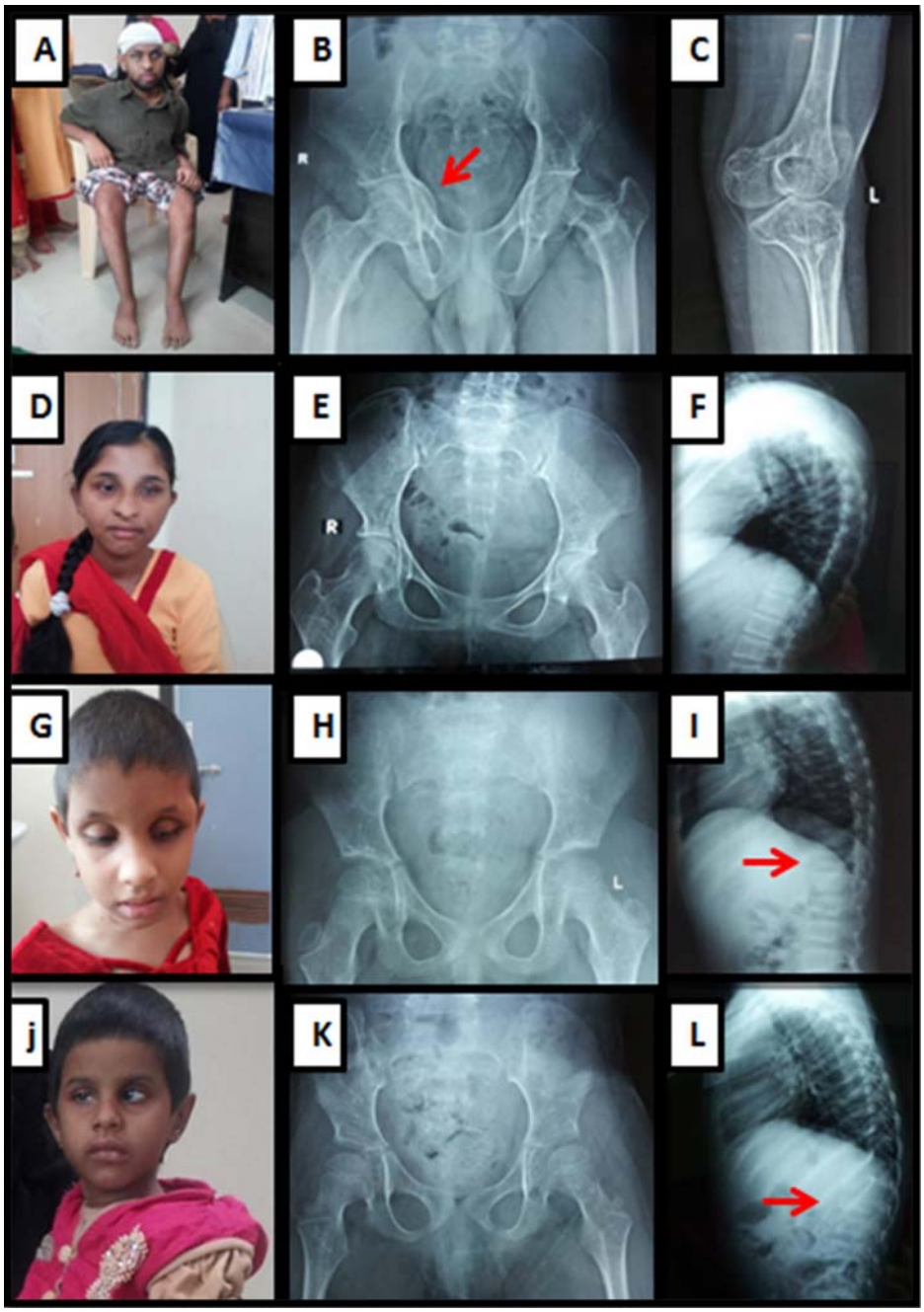

Web Fig*. 1:** ***A: *Clinical photograph of proband's uncle showing the deep set eyes, prominent zygomatic arches, low set ears, swollen bilateral knee joints and anteriorly bowed tibiae.* ***B:*** *Radiograph of the pelvis of the proband's uncle showing osteopenia and protrusio acetabulae (marked by red arrow).* ***C:*** *Radiograph of the left knee of the proband's uncle suggestive of osteopenia.* ***D:*** *Clinical photograph of proband's aunt showing microcephaly, deep set eyes, corneal scarring of left eye, prominent zygomatic arches and low set ears.* ***E:*** *Radiograph of the pelvis of proband's aunt showing osteopenia.* ***F:*** *Radiograph of the thoracolumbar spine of proband's aunt showing relatively milder degree of osteopenia and exaggerated thoracic curve.* ***G:*** *Clinical photograph of proband's sister showing microcephaly, deep set eyes, prominent zygomatic arches, bony prominence over the left lateral supra orbital margin and low set ears.* ***H:*** *Radiograph of the pelvis of proband's sister showing osteopenia.* ***I:*** *Radiograph of the thoracolumbar spine of proband's sister showing a relatively milder degree of vertebral compression.* ***J:*** *Clinical photograph of proband showing microcephaly, deep set eyes, asymmetric palpebral fissures, squint, prominent zygomatic arches and low set ears.* ***K:*** *Radiograph of the pelvis of proband showing marked osteopenia.* ***L:*** *Radiograph of the thoracolumbar spine, lateral view of proband showing osteopenia and vertebral compression (marked by arrows).*