Osteoporosis-pseudoglioma syndrome (OPPG): Improvement of osteoporosis on bisphosphonate therapy

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BACKGROUND

Osteoporosis-pseudoglioma syndrome (OPPG) is a rare autosomal recessive condition characterized by juvenile osteoporosis, bone deformities, neuromotor retardation, and congenital blindness. This syndrome is caused by biallelic loss of function mutations in *LRP5* (Low-density lipoprotein receptor-related protein 5). Here we report four cases from three families with OPGG who benefited from bisphosphonate therapy for osteoporosis.

CASE REPORTS

Four patients were followed-up at medical genetics, neurology and ophthalmology clinics due to congenital blindness and neuromotor retardation, and were referred to our clinic for assessment of osteoporosis. At presentation, cases 1 and 2 had already suffered fractures after mild trauma, case 3 had no fracture and in case 4, fractures were noted in further follow-up. Except case 1, height SDS of the patients were within target height SDS range. Clinical features of cases are summarized in Table 1 and 2. At presentation and during follow-up, biochemical parameters (serum calcium, phosphorus, creatinine, alkaline phosphatase), parathormone (PTH), 25 OH vitamin D and L1-L4 bone mineral density (BMD) measurements using dual energy X-ray absorptiometry (DXA) (Hologic 4500W) were performed annually in all cases. Modified BMD z-score according to height was calculated. Fractures were detected by X-ray of vertebrae and extremities. The diagnosis confirmed in all cases by detecting biallelic mutations in *LRP5*. These mutations segregated in accordance with autosomal recessive inheritance pattern within the families. At presentation and follow-up, biochemical parameters, 25 OH vitamin D and PTH levels were found to be within normal ranges. All patients were given vitamin D (600 U/day) and oral calcium (500 mg/day) together with pamidronate infusion (6-9 mg/kg/year) varying from 3 to 6 month intervals. Bisphosphonate therapy resulted in a significant improvement in BMD z-scores.

Table 1: Clinical features of patients at presentation

	Case 1	Case 2*	Case 3*	Case 4
Age (yrs)	6.5	7.0	2.8	2.6
Gender	F	F	M	M
Consanguinity	5th degree	1st degree	1st degree	1st degree
Birth weight gr/(SDS)	3500/(+0.4)	3025/(-0.6)	3250/(-0.5)	3630/(+0.4)
Weight kg/(SDS)	22/(-0.1)	25/(+0.6)	19/(+2.2)	10.5/(-2.5)
Height cm/(SDS)	108.6/(-2.2)	111.9/(-1.8)	96.2/(+0.3)	86.5/(-1.6)
Target height cm/(SDS)	156.7/(-1.0)	158/(-0.8)	171/(-0.8)	168.5/(-1.1)
Final adult height cm/(SDS)	148/(-2.6)	-	-	-
Clinical Findings				
• **Eye**	Blindness, Retinal detachment, Leukocoria, Microphtalmia	Blindness, Retinal detachment, Leukocoria, Microphtalmia	Blindness, Retinal detachment, Leukocoria, Microphtalmia	Blindness, Retinal detachment, Leukocoria, Microphtalmia
• **Neurological symptoms**	Mild intellectual disability, Stereotypic movement, Seizures	Mild intellectual disability, Seizures	Intellectual disability, Stereotypic movements, Autism	Mild intellectual disability, Stereotypics movement
• **Skeletal system**	Fractures, Bone deformities (wheelchair bound)	Fractures, Kyphoscoliosis, Loss of vertebral corpus height, Hypermobility	Mild Scoliosis, Loss of vertebral corpus height, Hypermobility	Fractures, Loss of vertebral corpus height, Hypermobility
***LPR5* Gene analysis**	chtz [exon 14-16 del] / [c.43_60del (p.L15_120del 16)]	hmz c.3517C>T (p.Gln1173*)	hmz c.3517C>T (p.Gln1173*)	hmz c.731C>T (p.Thr244Met)
Follow-up duration (yrs)	12	3	3	3

** sibling, chtz: Compound heterozygous, hmz: Homozygous*

Table 2: Some clinical findings of patients at follow-up

	Case 1	Case 2	Case 3	Case 4
Duration of bisphosphonate treatment (yrs)	11	2	2	2
L1-L4 BMD z-score				
• **At Presentation**	-6.6	-6.4	-2.6	-4.3
• **Recent**	-1.8 (*modified*)	-3.4 (*modified*)	-1.8	-3.6
Last Follow-up Records				
Age (yrs)	18	9.4	5.2	6.0
Weight kg/(SDS)	51/(-1.1)	27.3/(-0.6)	25.4/(+1.9)	17/(-1.5)
Height cm/(SDS)	148 /(-2.6)	121.4/(-2.1)	113.3/(+0.4)	110.3 /(-1.2)
Pubertal stage (Tanner)	Adult	Prepubertal	Prepubertal	Prepubertal

CONCLUSION

- **Osteoporosis-pseudoglioma syndrome should taken into consideration in patients with osteoporosis accompanied by congenital ocular symptoms.**
- **Phenotypic variability may be seen even in members of the same family.**
- **Osteoporosis is an expected condition of OPPG which can be treated with bisphosphonates.**