Decreased Bone Density in Carriers and Patients of an Israeli Family with the Osteoporosis-Pseudoglioma Syndrome

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Abstract

Background: The osteoporosis-pseudoglioma syndrome is a rare autosomal recessive disorder characterized by severe juvenile-onset osteoporosis and congenital or early-onset blindness. Other manifestations include muscular hypotonia, ligamentous laxity, mild mental retardation and seizures. The gene responsible was recently identified to be the low density lipoprotein receptor-related family member *LRP5* on chromosome 11q11-12.

Objective: To measure bone density in two siblings with the OPPG syndrome as well as in their family members (parents and siblings).

Methods: Bone mineral density was determined in the lumbar spine (antero-posterior), femoral neck, two-thirds distal forearm (> 95% cortical bone) and ultradistal forearm (predominantly trabecular bone) by dual-energy X-ray absorptiometry.

Results: The studies revealed osteoporotic changes both in the patients and the carriers.

Conclusion: The findings demonstrate that OPPG carriers have reduced bone mass, which is a risk factor for development of early osteoporotic changes.

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Osteoporosis-pseudoglioma syndrome is a rare autosomal recessive disorder characterized by severe juvenile-onset, generalized osteoporosis leading to bone deformity and pathologic fractures and congenital or early-onset blindness, associated with progressive vitreoretinal degeneration and phthisis bulbi [1,2]. Using the positional candidate approach, the gene responsible for OPPG was recently identified: a low density lipoprotein receptor-related family member *LRP5* on chromosome 11q 12-13 [3].

In contrast to other heritable childhood disorders that affect bone strength, patients with OPPG do not have identifiable defects in collagen synthesis, anabolic and catabolic hormones, calcium homeostasis, endochondral growth, or bone turnover [4–8]. It was recently shown that carriers of the OPPG are prone to have reduced bone density [3].

We performed bone density studies in two patients with OPPG, as well as in their parents and siblings. We demonstrated that obligate carriers of mutant *LRP5* genes indeed have significant diminution of bone density when compared to age and gender-matched controls.

OPPG = osteoporosis-pseudoglioma

Family history

The parents are healthy, consanguineous (the father is the mother's uncle) Tunisian Jews. They have seven children: two suffer from osteoporosis-pseudoglioma syndrome (patient 1 and 2), two daughters and a son are healthy (siblings 3, 4 and 5), a son who was born with tracheal atresia later developed spastic diplegia after food aspiration and asphyxia (sibling 6), and a daughter who was involved in a car accident at the age of 3 years is ventilated and bedridden (sibling 7).

Patient 1

A 21 year old male was the term product of an uneventful pregnancy and delivery. The neonatal period was unremarkable. At age 4 months, the parents first noticed that the baby did not visually track. Gradual deterioration of vision and complete blindness became evident by age 6 years. Reportedly, the boy had normal psychomotor development. At age 4 years, the patient had febrile convulsions followed by recurrent non-febrile complex partial seizures. The seizures were controlled with phenobarbital, which he has been taking ever since. At age 10, as part of an evaluation for persistent back pain, he was radiologically diagnosed as having severe generalized osteoporosis. Calcium and vitamin D supplementation was started. No history of fractures was reported.

At age 17 he was reexamined because of an episode of generalized seizures. Antiepileptic treatment with phenobarbital and carbamazepine was beneficial. Electroencephalogram, computed tomography scan and magnetic resonance imaging were normal. Examination at age 20 showed normal growth parameters (head circumference 55 cm, 40th percentile). No dysmorphic features or skin lesions were noted. He had a pigeon-chest deformity and kyphosis. A bone density study revealed severe osteoporosis [Table 1]. An ophthalmologic examination showed bilateral microphthalmia, nystagmus, complete opacification of the cornea and total blindness. A neurologic examination showed no abnormalities. Cognitive functions were normal.

Patient 2

This 15 year old is the brother of patient 1. Pregnancy and delivery were uneventful. At age 3 months, the parents noticed the absence of eye-tracking. He was diagnosed as blind at the age of 8 months. When he was 4 years old he had a single non-febrile generalized seizure. He was treated with a short course of phenobarbital. EEG

Table 1. Bone mineral density in patients and family members

		Lumbar spine	Femoral neck	1/3 distal forearm	Ultra-distal forearm
Patient 1, age 21	BMD (g/cm^2)	0.540	0.437	0.611	0.272
	T score	-5.0	-4.9	-3.7	-4.2
	Z score	-5.0	-4.9	-3.7	-4.2
Patient 2, age 15	BMD (g/cm^2)	0.427	0.343	0.492	0.246
	T score	-6.0	-5.8	-5.8	-4.7
	Z score	-5.2	NA	NA	NA
Father, age 47	BMD (g/cm^2)	0.761	0.703		
	T score	-3.0	-2.5		
	Z score	-2.7	-1.5		
Mother, age 42	BMD(g/cm^2)	0.899	0.724		
	T score	-1.3	-1.7		
	Z score	-1.0	-1.2		
Sibling 3, age 20	BMD (g/cm^2)	0.736	0.739		
	T score	-2.8	-1.6		
	Z score	-2.6	-1.6		
Sibling 6, age 14	BMD(g/cm^2)	0.353	0.562		
	T score	-6.7	-3.8		
	Z score	-5.1	NA		
Sibling 7, age 8	BMD (g/cm^2)	0.272	0.157		
	T score	-7.1	-7.4		
	Z score	-4.5	NA		

NA = not available

and CT scan were normal. Radiologic examination of the spine at age 4 was normal. No fractures were reported. Physical examination at age 13 showed a head circumference of 53 cm (25th percentile). Findings of the eye examination were similar to those of his brother. No other physical abnormalities were observed. Neurologic and cognitive examination were normal. A bone density study revealed severe generalized osteoporosis [Table 1].

Methods

Bone mineral density studies were performed in the two affected brothers, in the parents, in one healthy sister, and in two siblings with neurologic disability. Bone mineral density was determined at the lumbar spine (antero-posterior projection) and the femoral neck by dual-energy X-ray absorptiometry (QDR 4500 Acclaim densitometer, Hologic, Waltham, MA, USA). The two patients also had a BMD study at the third distal forearm (cortical bone) and ultradistal forearm (predominantly trabecular bone). The densitometer measures an integral (cortical and trabecular) bone mineral content and divides it by the scanned area to obtain an "areal" BMD (g/cm^2). Expressed as coefficient of variation (mean SD x 100), the precision of the measurement at the various sites is in the order of 1–3%. The deviation of the measurement result from the mean of the gender-matched control group is calculated in units of standard deviations and is expressed as either T score (comparison with peak BMD in young healthy adults) or Z score (comparison with BMD in an age-matched control population).

BMD = bone mineral density

According to the World Health Organization criteria, osteoporosis is diagnosed by a T score < -2.5, while a T score of (-1) to (-2.5) defines osteopenia. In growing individuals it is more prudent to use Z scores. The reference data used are those provided by the manufacturer. For subjects under the age of 20 years reference data were available for the lumbar spine only.

Genetic mapping of *LRP5* on chromosome 1 was done as described in the article in the *American Journal of Human Genetics* [8].

Results

BMD data are presented in Table 1. Both patients have severe generalized osteoporosis, at the axial as well as the appendicular skeleton, affecting both cortical and trabecular bone compartments. The two children with neurologic disability (siblings 6 and 7) have severe osteoporosis as well. The father and the sister (sibling 3) have definite osteoporosis at the spine and osteopenia at the femoral neck. The BMD values in the mother were consistent with osteopenia.

Patients 1 and 2 are homozygous for a genetic change in the *LRP5* gene. The exact mutation is still being deciphered. Based on linkage analysis, the parents and siblings 3 and 6 are carriers. We have not yet received the results on the other siblings.

Discussion

Osteoporosis-pseudoglioma syndrome is a rare genetic disorder with a variable clinical picture. The presenting clinical symptom is usually abnormal vision. Complete blindness has a variable onset; some patients are reported as congenitally blind while others become blind during the first years of life [1]. Microphthalmia appears to be associated with total visual loss. Abnormalities of the globe are typical and include microcornea, corneal opacities, absent anterior eye chamber, iris atrophy, posterior sinechiae and opacities. A histologic examination in two cases showed pseudogliomatous tissue [9]. Pseudoglioma can also be found in Norrie disease, which is an X-linked recessive disorder characterized by congenital blindness and in some cases mental retardation and deafness. The gene associated with Norrie disease was identified in 1992 [10]. Osteoporosis is not a part of this disease.

A second cardinal feature of this syndrome is osteoporosis or osteopenia [3]. The severity of skeletal complications (fractures and deformities) appears to be quite variable. Disproportionate length of the trunk compared to the lower limbs, leading to short stature, has sometimes been observed. Some degrees of ligamentous laxity and muscle weakness have been noticed in a number of patients. Histologic analyses of bone biopsies from affected patients reveal deficient trabecular bone volume, but normal surface density and appearance of osteoblasts and osteoclasts on bone surfaces [4]. Muscle biopsies have not shown any sign of myopathy or denervation [5]. Mild mental retardation has been reported in some patients, although it is not a usual feature. In the cases presented here, the patients had seizures but normal intelligence.

OPPG is inherited by an autosomal recessive trait; both sexes are affected, and parents of affected individuals have been considered phenotypically normal. Linkage analysis and homozygosity mapping assigned the OPS locus to chromosome 11q12-13

Table 2. Lumbar spine Z scores in the present family compared to published data [3]

Subjects	Published lumbar spine BMD Z score Mean (SD) [3]	Individual lumbar spine BMD Z scores of the present family members
OPPG patients	-4.7 (0.9)	-5.2, -5.0
Parents	-1.3 (1.4)	-2.7, -1.0
Siblings: healthy carriers	-2.3 (0.3)	-2.6
Siblings: immobilized carriers	Not available	-5.1, -4.7

[8]. Recently, using the positional candidate approach, the gene responsible for OPPG was identified as being the LDL receptor-related family member *LRP5* [3]. As was hypothesised before, the gene identified encodes a matrix protein expressed in bone and eye, and is important during eye and bone development [3,11].

Two additional Mendelian bone density-related disorders – autosomal dominant high bone mass and autosomal recessive osteopetrosis – have been linked to 11q12-13. This finding led scientists to evaluate whether a locus or loci in this region influences BMD in the normal population. Identification of the *LRP5* gene and the other causal genes for these traits and their protein products will enable determination as to whether a single gene with different alleles could provide insights regarding common osteoporotic conditions [12,13].

Pathologic fractures and severe osteoporosis in heterozygotes was first described in 1986 [14]. Gong et al. [3] showed that obligate carriers of the mutant *LRP5* gene have reduced bone mass when compared to age and gender-matched controls. They conclude that while the recessive effect includes a severe reduction in bone mass and ocular pathology, the dominant effect appears to be reduced bone mass in obligate carriers.

We performed bone density tests in patients and family members (parents and three siblings) and found substantially low BMD in all. Spine BMD Z scores could be compared with the most comprehensive study of OPPG recently published by Gong et al. [3], showing remarkable similarity in the patients and the healthy siblings [Table 2]. Additional factors that could adversely affect bone density in this family include long-term use of anticonvulsants in patient 1, and complete or partial immobilization along with insufficient exposure to sunlight in siblings 6 and 7. The extent of osteoporosis in the two immobilized siblings approached that of the patients!

In conclusion, severe osteoporosis is a hallmark of patients with OPPG, representing failure of bone accrual that results in very low peak bone mass. However, carriers of OPPG are also prone to develop diminished peak bone mass, in particular when combined with coexisting medical conditions that can adversely affect bone density. Recently, it was shown that intravenous bisphosphonate therapy appears safe and beneficial in patients with OPPG and may prevent progressive vertebral deformity [15]. Bone density studies should therefore be obtained in all heterozygotes in order to reveal osteoporotic changes at the earliest stage and permit appropriate intervention.

LDL = low density lipoprotein

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