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CASE REPORT

Opsismodysplasia and Dilated Cardiomyopathy: a case report

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ABSTRACT

Background: Opsismodysplasia (OPSMD) is an extremely rare and severe autosomal recessive skeletal dysplasia that is under the category of severe spondylodysplastic dysplasia. It is characterized by delayed bone maturation, and affected patients are identified by a peculiar craniofacioskeletal dysmorphism in the form of wide anterior fontanelle, depressed nasal bridge, anteverted nares, and short limbs and feet. Radiologically, they are characterized by severe platyspondyly, squared metacarpals, delayed skeletal ossification, and metaphyseal cupping.

Case Presentation: We present the clinical and radiological features of a 14-month-old boy with a homozygous, likely pathogenic variant in *INPPL1* gene *c.2627dup (p.Pro977Thrfs*7)* consistent with the diagnosis of OPSMD. He also has dilated cardiomyopathy.

Conclusion: OPSMD is an uncommon form of skeletal dysplasia that should be suspected in the context of short stature with characteristic radiological features. Up to now, no definitive therapeutic measures are available, and hence preventive measures are essential in the management of families with affected members.

Keywords: Opsismodysplasia, hypophosphatemic chondrodysplasia, osteodystrophy, cardiomyopathy, case report.

Introduction

Skeletal dysplasias are a diverse group of disorders characterized by a genetically determined bizarre and erratic osteocartilaginous growth and development (1).

Opsismodysplasia (OPSMD: OMIM# 258480) is an extremely rare and severe autosomal recessive form of skeletal dysplasia that is characterized mainly by delayed bone maturation. This disorder belongs to a group of skeletal dysplasias termed as severe spondylodysplastic dysplasias or group 14, which in addition to OPSMD, includes achondrogenesis type 1A, Schneckenbecken dysplasia, spondylometaphyseal dysplasia and Sedaghatian type, as well as fibrochondrogenesis (2). Patients presenting with OPSMD are identified by a characteristic craniofacioskeletal dysmorphism in the form of wide anterior fontanelle, depressed nasal bridge, anteverted nares, and short limbs and feet. Radiologically, associated features are severe platyspondyly, squared metacarpals, delayed skeletal ossification, and metaphyseal cupping (2,3).

We hereby report one case of OPSMD with dilated cardiomyopathy (DCM) in a male child from Saudi Arabia.

Methodology

A retrospective chart review of the patient's medical records was conducted. CARE "CAse REport" guidelines (available in the public domain at https://www.care-statement.org) were followed.

Case Presentation

We hereby present a 14-month-old boy who was a product of full-term uneventful pregnancy and delivered by caesarian section because of face presentation, with neonatal intensive care unit admission for 20 days during

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which he required mechanical respiratory support due to respiratory distress. He was diagnosed with DCM after birth, for which he was started on Captopril and Digoxin.

The proband was referred to the Medical Genetics clinic as a case of short limbs with cardiomyopathy. He was significantly delayed in the acquisition of gross motor and expressive linguistic developmental milestones. The proband was merely able to roll over since the age of 8 months and was only capable of mumbling some incomprehensible sounds alongside with a single word since the age of 10 months, otherwise he was able to recognize his parents, and had developed separation anxiety and strangers' anxiety at 6 and 9 months, respectively. He was born to first-cousin, healthy, Saudi parents with an unremarkable family history of similar conditions. There was no history of reported early neonatal deaths prior to the birth of the proband, or any neurological, developmental, metabolic, or genetic conditions in the family (Figure 1).

At the time of evaluation, at 14 months of age, his weight, length and head-circumference were 5.8 kg, 56.3 cm and 44.3 cm, respectively, and all of which lied below the 3rd percentile for his age group. His facial features were coarse, with micromelic upper and lower limbs, in addition to a short trunk. His left eye examination showed a pendular nystagmus in association with generalized truncal and appendicular hypotonia on complete neurological examination. Other systemic and neurologic examinations were unremarkable.

The skeletal survey of the patient (Figure 2a-e) obtained at 14 months of age showed a relatively large cranial vault with a small skull base and narrowed foramen magnum, in addition to a frontal bossing with a depressed nasal bridge (midfacial retrusion). There was also a progressive decrease in the interpedicular distance in the lumbar spine with widening of intervertebral discs and anteroposterior narrowing of the ribs. The pelvis was small and trident in shape with a champagne glass type pelvic inlet, small-squared iliac wings, and short sacroiliac notches. The acetabular roof was distinctively horizontal suggestive of a narrowing of the acetabular angle. The radiographs of the limbs showed metaphyseal flaring with rhizomelic shortening of the femora and both humeri, along with a symmetric shortening of the metacarpal and metatarsal bones, as well as the proximal phalanges.

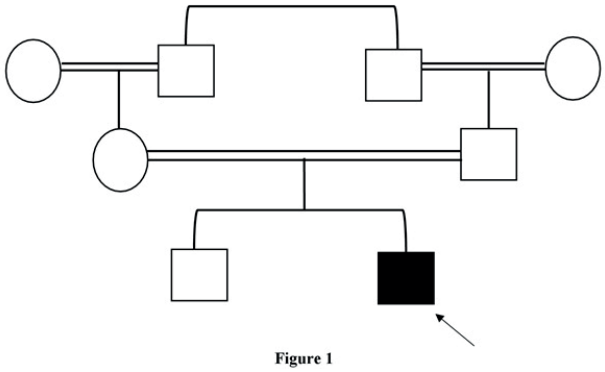

Figure 1. *Pedigree of the patient presented in this report.*

Laboratory evaluation revealed a high urinary phosphate excretion of 23.36 mmol/l (1.45-2.1 mmol/l), urinary creatinine of 1.2 mmol/l (0.0265-0.0619 mmol/l), urinary phosphate/creatinine ratio of 19.4 mmol/l (< 0.21645 mmol/l), total vitamin D level of 91 nmol/l (75-350 mmo/l), ionized calcium level of 2.67 mmol/l (2.25-2.75 mmol/l), and plasma phosphate level of 1.79 mmol/l (1.45-2.1 mmol/l).

Initially, achondroplasia was suspected, but *FGFR3* sequencing was negative. Subsequently, a skeletal dysplasia genes panel was sent and it came back positive for a homozygous likely pathogenic variant in *INPPL1 c.2627Dup (p.Pro977Thrfs*7)*. Parents were carriers of the same variant.

Discussion

OPSMD was described for the first time in 1977, and a few years later, the term "OPSMD" came to light by Maroteaux et al. in 1982 as a description of a disorder characterized by late bone maturation. The gene responsible for this condition (inositol polyphosphate phosphatase-like 1) (*INPPL1*) was identified in 1995, and it is highly expressed in skeletal and cardiac muscles among other tissues (2).

This gene is molecularly mapped to 11q13.4. The protein product of this gene is allegedly implicated in endochondral ossification via its role in postranslational modifications (phosphorylation or ubiquitination) and/or its interaction with specific protein network. It is, indeed, believed that it functionally takes part in a plethora of sub-cellular mechanisms involved in cells adhesions and cytoskeletal organization. Mutations in *INPPL1* presumably subject the growth plate to severely delayed ossification. Recently, S. Gosh et al. showed that *INPPL1* null cells showed impairment in cellular signaling which has secondarily led to the impairment of cellular migration and adhesion precluding endochondral ossification (3,4).

Patients affected by such a condition display a highly variable clinical and radiological manifestations, as well as prognosis which spans a wide range of outcomes extending from a poor one in which patients would pass away earlier in life, or even prenatally, due to respiratory complications, to a good one in which patients survive up to the second decade but with severe skeletal deformities. Such complications include, but are not limited to, atlantoaxial dislocation with or without severe scoliosis and hydrocephalus (5).

This variability has resulted in a major overlap between OPSMD and other forms of platysma dysplasia, such as Sedaghatian disorder; this disorder is, however; distinctively differentiated from other forms by the lack

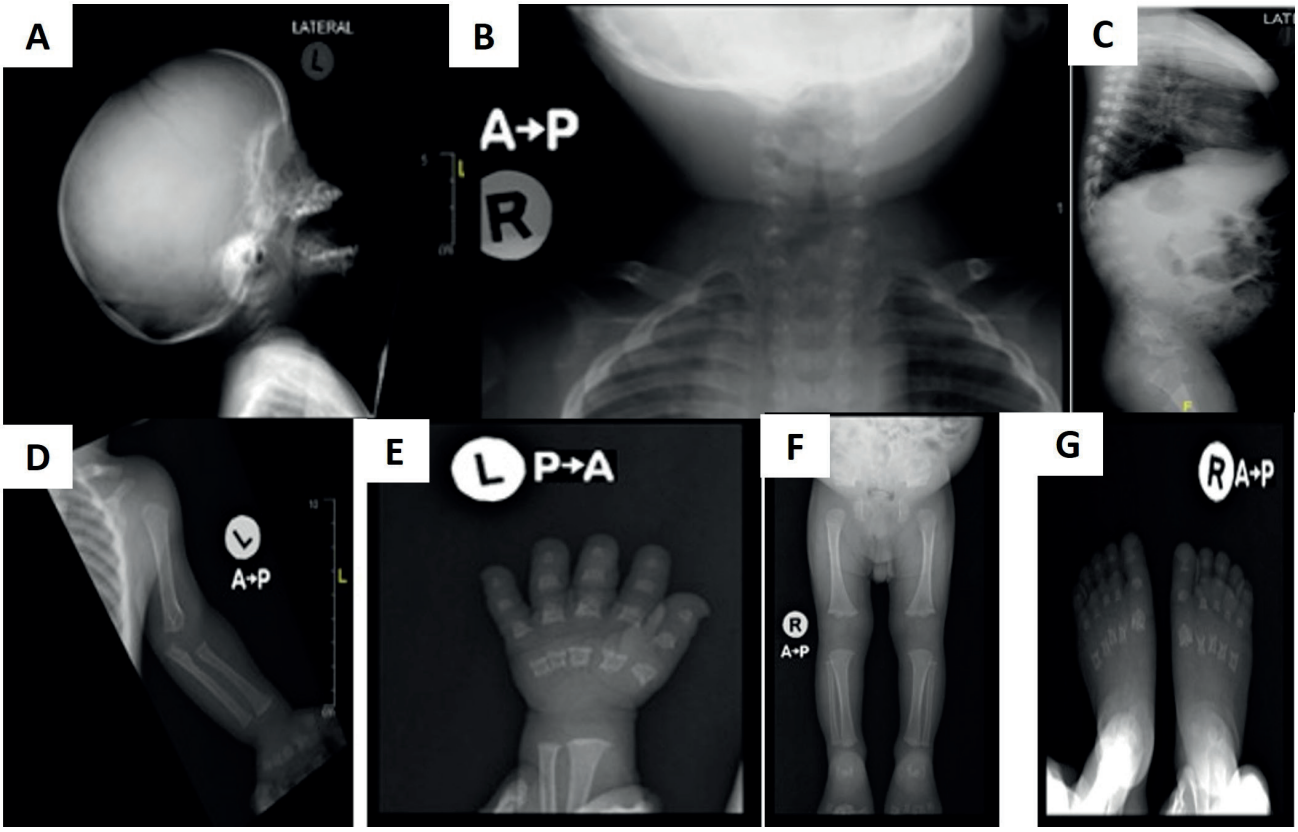

Figure 2. *(a) A lateral view of the skull and c-spine shows a relatively large cranial vault with a small skull base frontal bossing, a depressed nasal bridge (midfacial retrusion), and narrowed foramen magnum; (b) anteroposterior view of the c-spine and chest shows narrowing of the ribs; (c) lateral view of the thoracic and lumber spines shows a progressive decrease in the interpedicular distance in the lumbar spine with widening of intervertebral discs; (d-e) anteroposterior view of the left upper extremity shows rhizomelic shortening of the humerus with a metaphyseal flaring. The metatarsal bones as well as the proximal phalanges are short and of similar length (similar findings were radiologic evident in the right upper extremity as well); (f-g) anteroposterior view of the pelvis and lower limbs shows a horizontal acetabular roof (decreased acetabular angle), with a small squared iliac wings, small trident pelvis, champagne glass-type pelvic inlet and short sacroiliac notches, along with a rhizomelic shortening of the fumeri bilaterally, metaphyseal flaring, and shortening of the metatarsals and proximal phalanges.*

of intracranial anomalies and cardiac arrhythmias which are quite commonly reported in Sedaghatian disorder. On the other hand, less severely delayed ossification, alongside milder platyspondyly, in light of a reportedly unremarkable intrauterine growth, are distinct hallmarks in patients with Sedaghatian disorder (6,7).

The patient we presented was also found to have high urinary phosphate levels. This finding is believed to be a direct result of excess urinary phosphate losses and has been reported among patients diagnosed with OPSMD in the context of a biallelic loss-of-function variants, and it is commonly complicated by hypophosphatemic rickets. In one case report, Khawaja et al. reported a probably better clinical and bone density outcome among two siblings with OPSMD presenting with phosphaturia upon the administration of bisphosphonates, denoting a promising therapeutic role of bisphophonates in patients with OPSMD (8).

There has been only one reported case of cardiac involvement in patients presenting with OPSMD (6). We obtained a DCM panel on our patient and he was found to have variants of unknown significance in *TTN* (c.89711G>A (p.Arg29904His) and c.97099C>T (p.Arg32367Cys)) and *MYH6* (c.824T>A (p.IIe275Asn) and c.4505 G>A (p.Arg1502Gln)). The father is a carrier of the two *TTN* variants, while the mother is a carrier of the two *MYH6* variants found in the proband. These facts make these variants less likely to be disease causing, but actually do not completely rule out the pathogenicity of these variants given the incomplete penetrance. Also, DCM is not always a monogenic disorder. Therefore, it is not clear if DCM in our patient is a coincidence or a new association with OPSMD, as the full spectrum of OPSMD is yet to be fully understood, especially with a previously reported case of DCM in an OPSMD patient.

Conclusion

OPSMD is an uncommon entity of osteodystrophy and should be suspected in the context of short stature among

children belonging to consanguineous parents. Up to now, no definitive therapeutic measure is available, and hence preventive measures are essential parameters in the management of families with affected members.

List of Abbreviations

OPSMD Opsismodysplasia
DCM Dilated cardiomyopathy

Funding

None

Declaration of conflicting interests

The authors of this report have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Consent for Publication

No informed consent was needed in order to publish this study, as no details or pictures are shown, exposing the patient's own information.

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