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A 12 Years Old Boy with Osteogenesis Imperfecta Type VI in South Western Saudi Arabia - A Case Report

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Abstract

Osteogenesis imperfecta (OI) comprises a group of connective tissue disorders characterized by bone fragility and reduced bone mineralization density. The disorder is clinically and genetically heterogeneous. Here, we present a case of 12 years old boy who was presented to the pediatric emergency department of Al-Qunfudah general hospital at southwestern Saudi Arabia with multiple repeated fractures due to trivial trauma. He got his first fracture of the femur at the age of 6 years and within a short period, due to the multiple and repeated fractures that involved his long bones and vertebrae, he became handicapped, depending on a wheeled chair in his movement. Genetic testing confirmed that the boy has a homozygous pathogenic variant in the *SERPINF1* gene, consistent with the genetic diagnosis of autosomal recessive OI type VI. Both parents showed the familial heterozygous pathogenic variant in the *SERPINF1* gene confirming a carrier state. Here we are going to present the case and follow up its diagnosis by biochemical bone profile and genetic analysis. We conclude that OI-type VI is a rare, recessively inherited bone mineralization disorder that has no cure yet, but a challenging multidisciplinary management approach is warranted.

Keywords: Osteogenesis imperfect • *SERPINF1* • OI-type VI • Autosomal recessive • Homozygous

Introduction

Osteogenesis imperfecta (OI) is a rare group of genetic disorders of connective tissue occurring at a rate of about 1/20,000 worldwide and is characterized by bone fragility "brittle bone disease" with multiple and recurrent fractures [1]. People with OI have a genetic defect that impairs the body's ability to make strong bones. Severely affected patients have childhood spontaneous or minor trauma-related multiple fractures, however, the most seriously affected cases die shortly after birth [2]. Classically, OI occurs due to mutations in the collagen, type I, alpha 1 and collagen type I alpha 2 genes, which encode the alpha 1 and the alpha 2 chain of type I procollagen, respectively. The majority of OI cases are caused by a dominant mutation in a gene coding for type 1 collagen [3], however, autosomal recessive forms have been reported [4,5]. The phenotype is variable, ranging from osteoporosis presenting in adulthood to lethality in children. The major clinical manifestation of OI is skeletal fragility with/without skeletal deformity, joint and ligamentous hyper-laxity, beading of the ribs, arthritis, back pain, scoliosis, and tendon ruptures [6]. Additional extra skeletal manifestations may be present, such as blue/gray sclera, otosclerosis with hearing loss, high arched palate, dentinogenesis imperfecta (DI), and growth retardation. Moreover, some other OI-associated conditions were also, reported such as hypercalciuria, aortic root dilatation, vascular, pulmonary complications and neurologic conditions such as macrocephaly, hydrocephalus, and basilar invagination [7].

Diagnosis of OI can be established clinically and by history taking in addition to the radiographic and laboratory investigations including biochemical bone profile, collagen analysis of skin fibroblast culture or blood deoxyribonucleic acid analysis. Lack of good understanding of OI health concerns, difficulties in its diagnosis, optimal treatment, and recent progress about the disease could potentially result in problems for physicians, such as missed diagnosis, diagnostic error, or litigation [8].

There is no cure for OI but multidisciplinary management approach involving surgery, physiotherapy and rehabilitation is the optimal intervention. However, medical treatment, especially with bisphosphonate have shown promising results [9]. In 1979, David Sillence classified OI clinically into four types (types I to IV)3 and recently the classification is broaden to involve from (Type I to Type XV type) [8].

The most clinically relevant characteristic of all types of OI is bone fragility, which manifests as multiple spontaneous and recurrent fractures. OI type I is mild, type II is lethal, type III is severe, type IV and V are moderate. OI type I is non-deforming with normal height or mild short stature, blue sclera, and no DI. Patients with type II present multiple rib and long bone fractures at birth, marked deformities, broad long bones, low density on skull X-rays, DI and dark sclera. The main signs of type III include very short stature, a triangular face, severe scoliosis and grayish sclera. Patients with type IV have moderately short stature, mild to moderate scoliosis, grayish or white sclera, and DI. Type V is characterized by mild to moderate short stature, dislocation of the radial head, mineralized interosseous membranes, hyperplastic callus, white sclera,

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and no DI. Other genetically different types have been observed (types VI to IX) but they are not clinically different from types II-IV [10].

All the first five clinical types (95% of cases) of OI classification are caused by autosomal dominant mutations in the *COL1A1* and *COL1A2* genes while autosomal recessive forms of OI are also observed and are caused by mutations in the P3H1, CRTAP, and PPIB genes. Autosomal recessive forms are always severe with marked hypotonia. The rare autosomal recessive OI Type VI, is a form of the disease that can be caused by a homozygous mutation in the gene *SERPINF1* on chromosome 17p13.3, causing a defect in mineralization of the cartilage with Distinctive "fish–scale" appearance to bone when viewed under the microscope [11].

In Saudi Arabia, the most common skeletal dysplasia is OI (16%). Worldwide, OI is known to be an autosomal dominant disorder; however, in Saudi Arabia, 64% of OI cases are-autosomal recessive and 85% of cases are de novo disease causing variants in collagen genes [12]. In contrast to other countries, novel genes e.g., WNT3A, PAN2, RIN1, and DIP2C have been described in the Saudi population [13].

Recently, a 12 years old boy had been presented to the pediatric emergency department, Al-Qunfudah general hospital in the Southwestern region of Saudi Arabia, with multiple repeated fractures due to trivial trauma. Within a short period and due to the multiple and recurrent fractures that involved the long bones and vertebrae, he became handicapped, depending on a wheeled chair in his movement. Here, we are presenting this rare case and follow up its diagnosis by biochemical bone profile and genetic analysis.

Case Report

We present a case report of 12 years old boy with OI type VI, who was diagnosed at Al-Qunfudah general hospital, at Al-Qunfudah governorate, located in Southwestern, Saudi Arabia. He is the second-born boy of a consanguineous marriage after a normal uneventful pregnancy with normal antenatal care, and delivered by uncomplicated spontaneous normal vaginal delivery (Figure 1). He had an average weight and height with no limb deformities or other abnormalities and no history of admission to the neonatal intensive care unit (NICU). He grew normally, fed on breast milk until the age of 2 years and continued nutation by taking his meals with family, and reached normal milestones according to age. He received his vaccinations regularly according to the Saudi expanded program on immunization. At the age of 6 years, he had the first fracture of his right femur after receiving a minor trauma while playing soccer with his friends. Shortly afterwards, he got a fracture of his left femur following a minor trauma followed by a re-fracture of his right femur. He used to complain of chronic back pain and developed a compression fracture of his lumber vertebrae without a history of trauma. Due to these multiple fractures, by the age of 8 years, he became wheel-chaired. All his admissions to the hospital since his age of 6 years were due to orthopedic complaints and fixation of his long bone fractures by orthopedic surgeons, (Figures 2a-2d). There is a history of having umbilical hernia that was operated on when he was just at the age of 7 months.

On clinical examination, he had white sclera, normal teeth-appearance with normal hearing and vision, though he had mild scoliosis. His biochemical bone profile results were within normal range; (Ca+ 2.4 mmol/L (2.1-2.55), P+ 1.4 mmol/L (0.8-1.45), PTH 35 pg\mL (17.3-72), ALP 200 U/L (126-340), VIT-D 47.3 ng/mL (30-100). Other laboratory findings revealed a normal renal function; BUN 8.1 mg/dl (7-20), creatinine 20.7 umol/L (58-110), Na+ 141.2 mg/dL (135-145), K+ 5 mg/dL (3.5-5.5), and a normal liver function; AST 14 U/L (15-41), Albumin 43 g/L (35-50), T-Bilirubin 13.4 umol/L (6.8 - 34.2 umol/L). He had normal thyroid function with free T4 21.9 pmol/L (10-28.2) and TSH 3.37 uU/mL (0.46-4.68). DXA scan showed low bone mineralization density (BMD) with Z-score -3.3.

In order to rule out other causes of osteoporosis CK-MB, IgA and stool analyses were performed. CK-MB level was elevated 39.3 U/L (0 -10), but with normal CK 164 U/L (55-170). IgA level was 2.55g/L (0.58-3.58), IgATTG (tTg-IgA) was 9.2 U (0-20). He had a normal complete blood picture, a normal stool analysis and culture, and normal stool for calprotectin. Bone X-ray showed osteopenia and compression fractures of the lumber vertebrae.

Genetic test of the boy's blood sample showed a homozygous pathogenic variant in the *SERPINF1* gene. This result is consistent with the genetic diagnosis of autosomal recessive OI type VI (Table 1).

Genetic test of the parents' blood samples showed the familial heterozygous pathogenic variant in the *SERPINF1* gene. Biallelic pathogenic variants in the gene are associated with autosomal recessive OI type VI. The result is consistent with a carrier status for the pathogenic variant identified in the *SERPINF1* gene and the boy is not at risk of developing the disorder. This result together with the results of the boy's parents confirms the homozygous state of this variant in their affected child and indicates a 25% probability of having a child affected with *SERPINF1* gene related autosomal recessive disorder in each pregnancy. A pedigree is shown in Figure 1. Both parents agreed and gave full consent for treatment of their child according to the recommended treatment protocols and guidelines of Al-Qunfudah general hospital. A separate consent for genetic testing and publication of the results and the case report was also obtained from the parents of the body.

Methodology

In this case report, a 12 years old boy attended at the outpatient clinic of Al-Qunfudah general hospital complaining of recurrent fractures due to minor traumas that suggest a bone-related disorder. To get a confirmed diagnosis of the case, a thorough clinical, family, past and present history of the patient were obtained. Bone X-ray, DXA scan and biochemical bone profile were performed according to the manufacturers recommended procedures.

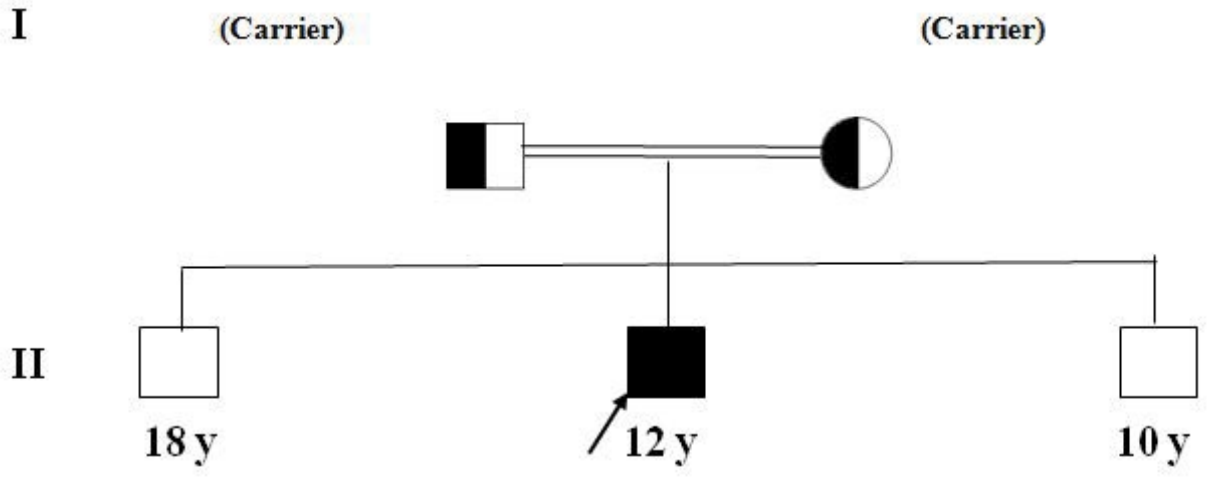

Figure 1. Pedigree of the family of osteogenesis imperfecta boy, showing the unaffected parents (carrier state).

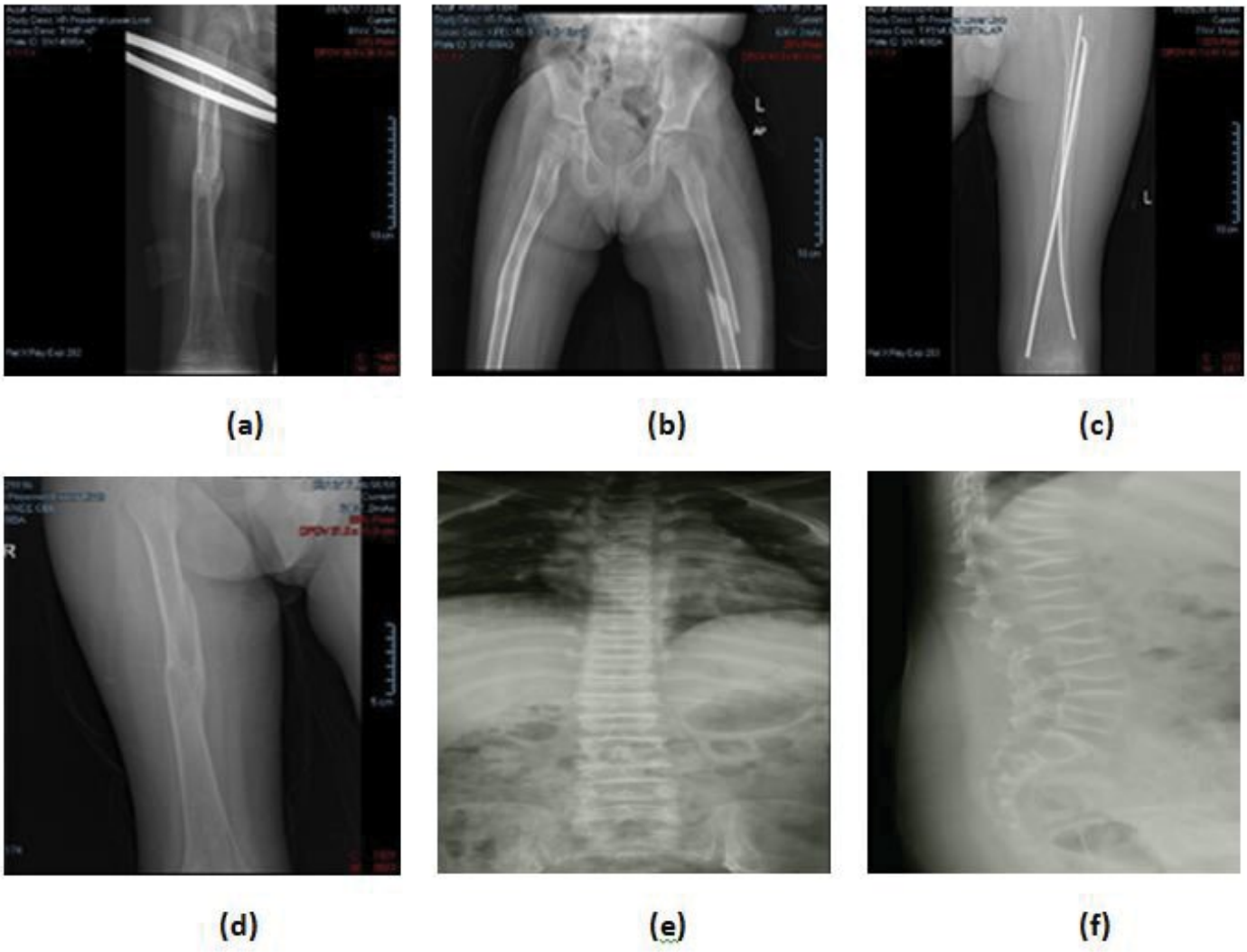

Figure 2. X-rays showing fractures and re-fractures of the boy's long bones (right and left femur) and lumbar vertebrae.

Table 1. Genetic results of the boy's sample showing the pathogenic variant.

Gene	Variant Coordinates	Amino Acid Change	SNP Identifier	Zygosity	In Silico Parameters*	Allele Frequencies**	Type and Classification***
SERPINF1	NM_001329903.1:c.653del	p.(Val218Glufs*22)	rs398122520	Homozygous	PolyPhen: N/A Align-GVGD: N/A SIFT: N/A MutationTaster: N/A Conservation_nt: N/A Conservation_aa: N/A	gnomAD: - ESP: - 1000 G: 0.000077 CentoMD: 0.000066	Frameshift Pathogenic (class 1)

Variant annotation based on OTFA (using VEP v94). * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations.

Genetic testing for the child and his parents were performed for differential diagnosis of the case. After obtaining the parents' consent for genetic testing, blood samples were collected from both parents and their son, labelled and sent to Saudi Diagnostic Laboratory - SDL Lab Takhasousi street 11211 Riyadh Saudi Arabia, then it was sent to CENTOGENE GmbH • Am Strande 7 • 18055 Rostock • Germany.

CentoXome® Solo (including next generation sequencing (NGS)-based CNV analysis) was requested to confirm the homozygosity and genetic counselling whenever needed.

Double stranded DNA capture baits against approximately 36.5 Mb of the human coding exome (targeting >98% of the coding RefSeq from the human genome build GRCh37/hg19) are used to enrich target regions from fragmented genomic DNA with the Twist Human Core Exome Plus kit.

All variants with minor allele frequency (MAF) of less than 1% in genomAD database, and disease-causing variants reported in HGMD®, in ClinVar or in CentoMD® as well as all potential modes of inheritance patterns were considered.

In addition, provided family history and clinical information are used to evaluate identified variants with respect to their pathogenicity and causality. Variants are categorized into five classes (pathogenic; likely pathogenic; VUS; likely benign; benign). All variants related to the phenotype of the patient are reported. CENTOGENE has established stringent quality criteria and validation processes for variants detected by NGS.

Limitations

The genetic results are interpreted in the context of the provided clinical

findings, family history, and other laboratory data. Only variants in genes potentially related to the boy's medical condition are reported.

Ethical Considerations

Prior to reporting and investigating this OI case, an informed consent was obtained from the parents of the OI affected boy after explaining the purpose of presenting this paper to the scientific community. The authors confirmed to the boy's parents that all data and information related to this case will be de-identified and considered confidential and will never be used for purposes other than the scientific ones. An approval for presenting this case report was obtained from the Ethical Reviewing board of Umm Al-Qura University, with a registration number in the National committee of Bio Ethics: HAPO-02-K-012.

Discussion and Conclusion

The present case report was clinically, laboratory and genetically confirmed as OI type VI. Generally, most of OI cases (95%) are caused by dominant mutations affecting the synthesis and/or structure of type I procollagen or by recessively inherited mutations in genes responsible for the post-translational processing/trafficking of type I procollagen.

Unlike these mechanisms, OI type VI is rare and recessive constituting approximately 4% of cases [2]. OI type VI is unique among OI types in that it has a pathognomonic histological finding that distinguishes it from other forms of OI, which is the large amount of un-mineralized osteoid; thereby suggesting a distinct disease mechanism [1].

The loss of function mutations in serpin peptidase inhibitor, clade F, member 1 (*SERPINF1*) is one of the candidate genes that was detected as a cause of OI type VI comprising a novel mechanism for OI with involvement in bone mineralization. OI type VI shows reminiscent of osteomalacia, despite normal vitamin D levels and normal calcium and phosphorus serum levels, coupled to the disorganization of the bone matrix, where the lamellar pattern is replaced by a distinctive microscopic fish scale appearance [4,14].

In Saudi Arabia, 64% of OI cases are-autosomal recessive and 85% of cases are de novo disease causing variants in collagen genes and others [12] such as *WNT3A, PAN2, RIN1*, and *DIP2C* [13].

In the present case report, no mutations were detected in all the suggestive genes whereas, the genetic analysis of the boy and both of his parents showed a mutation in the *SERPINF1*, c.653del p.(Val218Glufs*22). This variant creates a shift in the reading frame starting at codon 218. The new reading frame ends in a stop codon 21 positions downstream. According to HGMD Professional 2020.3, this variant has previously been described as disease causing for OI, autosomal recessive by Shaheen et al., 2012 (PMID: 23054245) [15], Maddirevula et al., 2018 (PMID: 29620724) [13]. ClinVar lists this variant as pathogenic (clinical testing, Variation ID: 41894) [16].

The boy has been improved upon using bisphosphonates and a supplemental treatment of vitamin D and calcium gluconate. However, management of OI is challenging, and he needed orthopedic surgery for treatment of his long bone fractures. Surgery is the main way for treating OI in addition to the supportive physiotherapy, physical and emotional rehabilitation. However, a long history of experimental systemic interventions exists. Attempts to treat OI started with using combinations of phosphorus, cod-liver oil, fresh air and exercise. Hormonal therapy including, androgens, estrogens, calcitonin, pituitary, thyroid and parathyroid hormones; as well as supplemental trials with vitamins and minerals including; vitamins A, C and D with mineral agents such as strontium, aluminum, fluoride, magnesium and citrate of sodium hydroxide have been used [17]. Medical interventions used a successful naturally occurring agent, Bisphosphonates (diphosphonates), which can slow down or stop the process of bone resorption, increase bone mineral density and strength, reduce the risk of fracture and increase height and weight of children [9,18]. Further trials combining bisphosphonate with growth hormone produced a better result in terms of bone mineral density, lumbar spine projected area and growth velocity than bisphosphonate alone [19].

Bone marrow transplantation is an alternative approach for OI treatment since, the bone marrow mesenchymal cells can differentiate into a variety of tissues including bone and cartilage improving the bone mineral content and increasing the bone strength with reduction in fracture rate [20]. One of the most important goals for interventions in treating OI is to safe guard the affected patients against the secondary complications that affect various internal organs, leading to major or minor secondary problems. These include: vulnerability to lung problems e.g., asthma and pneumonia [21], heart valves problems [22], variable degrees visual difficulties and hearing loss [23], periodontitis [24], macrocephaly or hydrocephalus [25], increased vascular fragility, reduced clotting factors VIII and abnormal platelet function [26].

Therefore, OI patients necessitate regular checkups for early detection of such various complications in its early stages with early intervention and proper management for prevention of complications and deterioration of their health status.

We conclude that OI-type VI is a rare, recessively inherited bone mineralization disorder that has no cure, however, multidisciplinary management is warranted. Surgery, physiotherapy, palliative treatment, rehabilitation, vitamins, minerals, bisphosphonates, bone marrow transplantation and gene therapy are the main options for management of OI. Increasing bone mineralization density and strength, reducing the rate of fractures, preventing deformities of long bone and spines and improving the well-being of the affected individuals are the ultimate goals of OI management.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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Data availability Statement

The authors confirm that all the clinical, laboratory investigations, X-rays and other radiological investigations as well as the genetic testing results for the boy and both his parents are available for any revision requests.

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