Bone Reports 16 (2022) 101595

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Case Report

Spontaneous reshaping of vertebral fractures in an adolescent with osteogenesis imperfecta

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ARTICLE INFO

Keywords:
Vertebral fracture
Osteogenesis imperfecta
Vertebral reshaping
Bisphosphonates
Osteoporosis
Bone mineral density

ABSTRACT

Background: Vertebral compression fractures (VFs) are a common and severe finding in patients with osteoporosis. In children, VFs have the unique potential to reshape and regain their original configuration. Spontaneous vertebral body reshaping (*i.e.*, medication-unassisted) has been reported in secondary osteoporosis. Here we describe a previously unreported spontaneous vertebral reshaping in an adolescent with osteogenesis imperfecta (OI) with multiple vertebral fractures.

Case report: A 17-year-old female was diagnosed with OI type I at 5 years of age caused by a novel frameshift variant in *COL1A1* (NM_000088.4: c.540delC; p.Met181TrpfsTer84). Due to parental reservations about medication, she had never received bisphosphonate or any other bone active therapy. A lateral spine X-ray demonstrated transparent bones and no VF. However, previous spine X-rays taken at age of 6 years at an external institution showed VFs in T5–7 (Genant semiquantitative method grade I-II). The two lateral spine x-rays, taken 11 years apart, demonstrate that substantial spontaneous vertebral reshaping occurred without bone active therapy during puberty.

Discussion: Vertebral reshaping is explained by the stabilization of bone mineral density (BMD) and the remaining growth capacity the children. We hypothesize that spontaneous reshaping may occur in milder forms of OI, and that puberty may be a key mediator of the phenomenon. In all children with OI and vertebral fractures, we nevertheless recommend bisphosphonate therapy since it improves bone mass, BMD, vertebral shape, physical activity and reduces fracture rates.

1. Introduction

Vertebral compression fractures (VFs) are a common and severe finding in patients with osteoporosis. In children, VFs are observed in both secondary osteoporosis, and primary osteoporosis such as osteogenesis imperfecta (OI) (Tournis and Dede, 2018). Secondary osteoporosis may be due to administration of glucocorticoids, chronic inflammatory diseases, such as inflammatory bowel disease, juvenile idiopathic arthritis, Duchenne muscular dystrophy, or leukemia (Lentle et al., n.d.; Cummings et al., 2015; Ma et al., 2015).

In children, VFs have the amazing and often unrecognized potential to reshape and regain their original configuration. VFs occur in 71 % of individuals with milder forms of OI (Ben Amor et al., 2013). Since the introduction of bisphosphonate (BP) therapy for the treatment of pediatric osteoporosis, this reshaping phenomenon has been extensively described in the literature and is regarded as a common and desired effect of BP therapy in children with VF (Saraff and Högler, 2015; Diacinti et al., 2021).

Abbreviations: VF, vertebral compression fracture; OI, osteogenesis imperfecta; BP, bisphosphonate; GSQ, Genant semiquantitative method; DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; BMC, bone mass content; BMAD, bone mineral apparent density.

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https://doi.org/10.1016/j.bonr.2022.101595
Received 3 March 2022; Received in revised form 18 May 2022; Accepted 1 June 2022
Available online 3 June 2022

Spontaneous vertebral body reshaping (*i.e.*, medication-unassisted) has also been reported in secondary osteoporosis, once the underlying cause has been removed and there is enough residual growth potential to allow reshaping (Ward, 2020). However, spontaneous VF reshaping is rarely observed in patients with primary osteoporosis due to their intrinsic defect in bone development and formation (osteogenesis).

Here we describe an unusual case of spontaneous vertebral reshaping in an adolescent with OI with multiple VFs. To our best knowledge, spontaneous vertebral body reshaping in OI naïve to BP therapy has not been reported to date.

2. Case report

A 17-year-old female first presented to our multidisciplinary pediatric bone service. She had been diagnosed with OI type I at the age of five due to multiple fractures and blue sclerae at an external institution. OI was genetically confirmed. A novel, heterozygous frameshift variant was detected in the *COL1A1* gene (NM_000088.4: c.540delC; p. Met181TrpfsTer84), resulting in a severely truncated protein and thus, in a reduction of type I collagen production.

She self-reported >40 fractures between the ages of 3 and 15 years, although only 12 fractures of long bones and vertebral bodies were documented in the available radiographs. These fractures occurred in the upper and lower extremities, bilaterally. In cases where detailed fracture history was available (4/12 fractures), the cause of the fracture was low impact trauma. No bone densitometry study was conducted prior to our first consultation. She received regular physiotherapy but, due to parental reservations about medication, never received BP or any other bone active therapy.

At the age of 17 years, her physical, pubertal, and cognitive development was normal. Menarche had occurred at the age of 12 years and since the age of 16 years, she had been taking the contraceptive pill (desogestrel).

At the time of the consultation, the patient had no recent fractures (last fracture at the age of 15 years), no back pain or pain in other body parts. On physical examination, her height was 161.7 cm (21st percentile), weight 53.6 kg (48th percentile). Tanner stage B4P4. She had blue sclerae, no dentinogenesis imperfecta but slight hypermobility

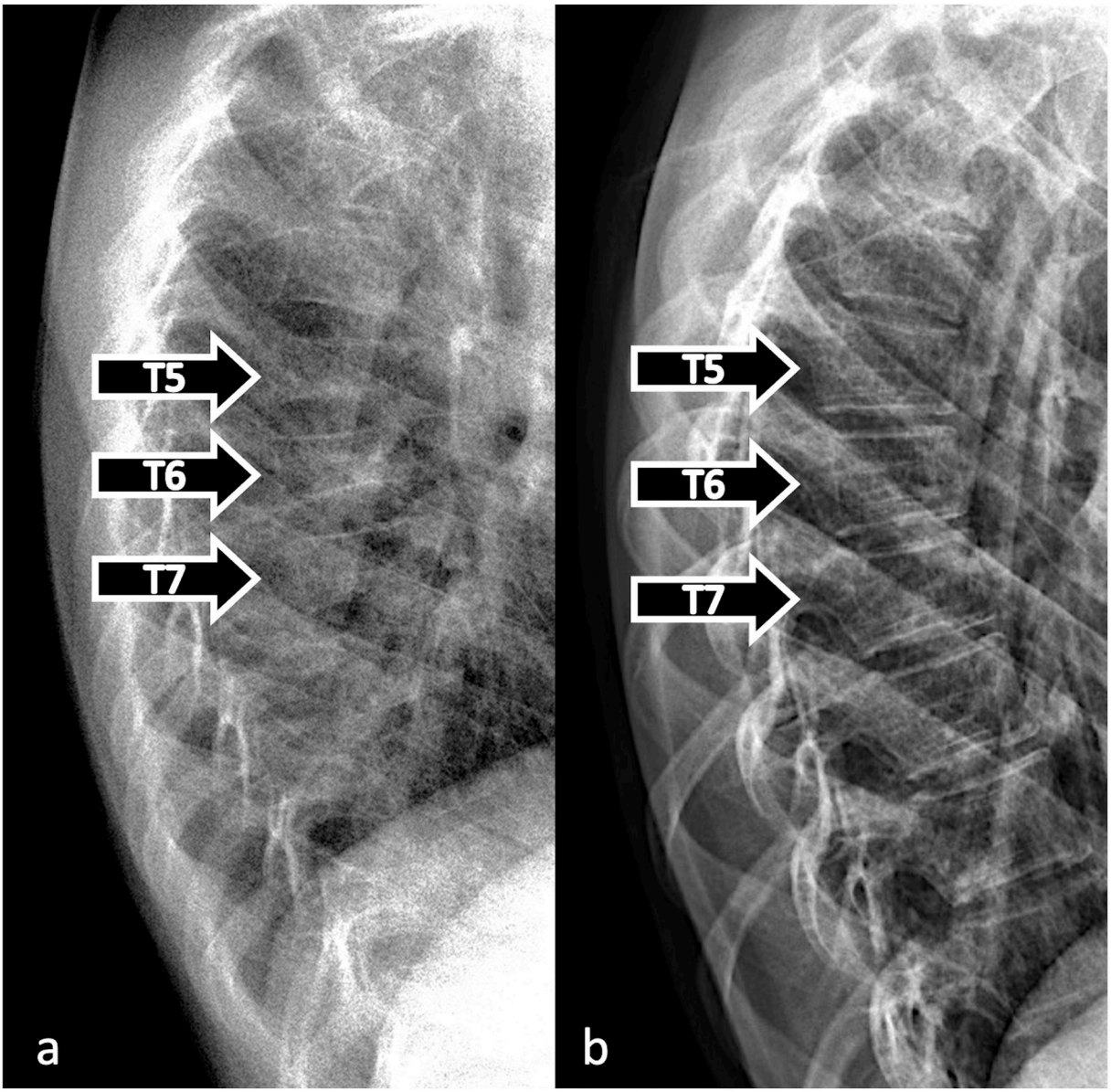

Fig. 1. Lateral spinal radiographs at the age of 6 years (a) and 17 years (b). At the age of 6 years wedging VF are visible at T5 (GSQ grade I) and concavity VF at T6 (GSQ grade II) and T7 (GSQ grade I). The fractures are in the known "hot spot" – the mid-thoracic region. All three VF had reshaped substantially by the age of 17.

of the fingers. There was no spine tenderness, but a slight right-convex scoliosis without other skeletal deformities.

A lateral X-ray of the spine was performed which demonstrated transparent bones. Vertebral fracture analysis was performed independently by two experienced pediatric radiologists using the Genant semiquantitative method (GSQ) (Ward, 2020; Genant et al., 1993). Three types of fractures were analyzed - wedging, concavity and crushing. Height reduction coefficients >20 % were interpreted as fracture (GSQ grade I (20–25 %), grade II (25–40 %), grade III (>40 %)). No vertebral wedging, concavity or crush fractures were demonstrated. Vertebra T5 showed a wedge deformity with a mild reduction in height; this deformity was not sufficient (<20 %) to be considered a VF. Dual-energy X-ray absorptiometry (DXA; Hologic QDR 4500 scanner) showed reduced total BMD Height-Adjusted-*Z*-score of −2.1, subtotal BMC for Height Z-score of −1.3 and lumbar spine bone mineral apparent density (BMAD) Z-score of −1.1.

When previous spine X-ray was reviewed, multiple VF were found at the age of 6 years. Despite the reduced quality of the image taken at an external institution, the radiography showed a fracture with wedge deformity at T5 (GSQ grade I), a moderate fracture with biconcave deformity at T6 (GSQ grade II) and a fracture with concave deformity at T7 (GSQ grade I). The available information from the medical records is insufficient to determine the indication for the X-rays. The patient's parents denied any major trauma that would justify such injuries at that age.

The two lateral spine X-rays, taken 11 years apart, demonstrate that substantial spontaneous vertebral reshaping occurred without bone active therapy during puberty (Fig. 1).

3. Discussion

We report spontaneous vertebral reshaping in a BP- naïve 17-year-old female patient diagnosed with OI type I. Comparison of lateral spinal X-rays showed a resolution of three VF. To date, vertebral reshaping in children with OI has been largely attributed to the effect of BP therapy in those children with sufficient remaining growth potential. This case report suggests that spontaneous reshaping of VF can also occur in BP-naïve patients with OI type I. To our best knowledge, this phenomenon has not been reported in OI.

Spontaneous vertebral reshaping is a common phenomenon in secondary osteoporosis. Once the underlying condition is successfully treated or cured, the VFs typically heal (demonstrated by the resolution of back pain, loss of edema on MRI); if there is sufficient residual growth potential, the vertebrae may also undergo vertebral reshaping and regain their original configuration. This spontaneous healing potential is attributed to healthy bone tissue with no intrinsic failure in bone formation and metabolism, following resolution of steroid-, inflammation- or immobility-induced forms of osteoporosis. The main factors, associated with a high likelihood of reshaping, are young age at disease onset with greater residual growth potential, catch-up growth, and absence of bone health threats (Lentle et al., n.d.; Ward et al., 2020). The degree of severity of the VF may also be a conditioning factor: the more severe the collapse, the more time will be needed for reshaping and the more residual growth potential will be required. The need for BP therapy in young patients with secondary osteoporosis who have overcome their underlying illness, or where illness is well controlled is currently under debate (Ward, 2020).

However, certain causes of secondary osteoporosis are not associated with spontaneous vertebral reshaping. In Duchenne Muscular Dystrophy, where the combination of high-dose steroid therapy and progressive muscle weakness cause a progressive, aggressive form of osteoporosis, no cases of vertebral reshaping have been described in absence of BP therapy (Ward et al., 2020; Högler and Ward, 2015).

Osteogenesis imperfecta is a rare heritable bone disorder, caused by qualitative or quantitative defects in collagen type I or the regulation of osteoblastic function. Its main manifestation is increased bone fragility caused by reduced bone mass and high material density, with multiple bone fractures and deformities (Tauer et al., 2019; Forlino and Marini, 2016). VFs are a typical finding. In some cohorts approximately 30 % of OI type I and 79 % of OI type III/IV had multiple VFs (Kok et al., 2003). VFs are an important component of morbidity and mortality in patients with OI. They predispose to the development of scoliosis and the "vertebral fracture cascade", causing reduced cardiorespiratory function, one of the main causes of death in OI (Folkestad et al., 2016).

Since the development of intravenous BP therapy, their use in patients with osteoporosis and VF has been established (Land et al., 2006; Plotkin et al., 2000). Historically, reshaping of VFs has been associated with BP therapy (Land et al., 2006; Plotkin et al., 2000). A recent publication reported increased BMD and reduced fracture incidence in children and adolescents with OI after therapy with zoledronate (3rd generation BP). They also found that the increase of lumbar spine BMD was an important determinant of vertebral reshaping (Li et al., 2019). This phenomenon has also been observed in other studies with different BPs (Palomo et al., 2015). In addition, initiation of BP therapy at an early age in patients with OI has been shown to improve physical activity in adulthood (Feehan et al., 2018).

Our patient had normal stature, no dentinogenesis imperfecta or bone deformities, typical for OI type I. In addition, DXA showed a spine BMD at the lower limit of normal, without previous BP therapy. Regarding genetic studies, segregation analysis showed that the variant occurred *de novo* in the proband. *In silico* prediction evaluated the variant as damaging (Landrum et al., 2014). The variant was not found in either the general population (GnomAD Database) or in mutation databases (ClinVar and LOVD) (Karczewski et al., 2020; Fokkema et al., 2011). At the same position, a duplication (c.540dup) has already been reported in two siblings with OI type 1 and open angle glaucoma (Wallace et al., 2014). Based on the guidelines of the American College of Medical Genetics and Genomics the novel variant was ultimately classified as the disease-causing variant (Richards et al., 2015). The novel truncating *COL1A1* variant results in haploinsufficiency, which would be compatible with a non-severe phenotype of OI.

The lack of spinal BMD assessments early on in life, as well as limited documentation prior to our consultation, hinders a more complete assessment of the evolution of the disease and a better explanation of the observed vertebral reshaping phenomenon. Of special interest in our case would be the exact timing of vertebral reshaping in relation to the timing of puberty. Estrogens possibly reduce the biomechanical threshold of osteocyte activation, favoring bone formation (Ward, 2020; Rauch et al., 2004). This hypothesis is supported by the fact that peak bone mineral accrual during puberty which coincides with menarche in girls (McKay et al., 1998), peak muscle mass accretion and growth velocity (Rauch et al., 2004). Undoubtedly, the ability for vertebral reshaping is associated with bone structural improvements during puberty. The reduction of fracture incidence towards the end of puberty in patients with OI is well known, even in the absence of BP therapy.

In summary, we hypothesize that the patient's remaining growth potential and pubertal hormones, physiotherapy and avoidance of trauma may have contributed to her exceptional spontaneous reshaping.

4. Conclusion

Spontaneous vertebral reshaping may be possible in OI with mild-to-moderate vertebral collapse. The lack of any reports on spontaneous reshaping in OI to date may be due to underdiagnosis in the past (vertebral imaging done infrequently, lack of experienced pediatric osteologist and radiologist) but more the routine commencement of BP therapy at diagnosis. Whilst our observation is of interest, we emphasize that this isolated report should not be used as an argument against BP therapy, which has been shown to be highly effective in numerous studies to improve bone mass and vertebral shape and reduce fracture rates. Initiation of BP therapy should not be delayed in OI patients with VFs, due to their large impact on morbidity and mortality.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Rodrigo Montero-Lopez: Conceptualization, Methodology, Writing – original draft. **Elisabeth Laurer:** Writing – review & editing. **Katharina Tischlinger:** Writing – review & editing. **Dóra Nagy:** Writing – review & editing. **Mario Scala:** Writing – review & editing. **Wolfgang Kranewitter:** Methodology. **Gerald Webersinke:** Methodology. **Thomas Hörtenhuber:** Writing – review & editing. **Wolfgang Högler:** Supervision, Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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