Multiple repetitive fragility fractures in young patients- differentiation between osteogenesis imperfecta, osteomalacia (secondary to vitamin D deficiency) and domestic abuse

Cristina Capatina¹⁺, Mara Carsote¹, Corneliu Capatina², C. Poiana¹, M. Berteanu³

Abstract: Fragility fractures (i.e. fractures occurring in abnormal bones, caused by minimal or no trauma) during childhood are infrequent and secondary to rare metabolic or bone diseases. The presence of multiple fractures should also raise the suspicion of inflicted injury (abuse), which is much more frequent, thus it is extremely important to distinguish between genuine fragility fractures and traumatic fractures.

We report the case of a 20 years old male with a history of multiple unexplained fractures of the long bones during the entire childhood and adolescence. In this patient a diagnosis of both osteogenesis imperfecta and severe vitamin D deficiency was made on the basis of the clinical picture, biological data and radiographic findings. We provide a brief overview of the most important elements to be sought for in the differential diagnosis between fractures caused by induced trauma and fragility fractures secondary to either osteogenesis imperfecta or defective bone mineralisation due to vitamin D deficiency.

Key Words: fragility fractures, osteogenesis imperfecta, vitamin D deficiency, domestic abuse.

Pathological (fragility) fractures (i.e. fractures occurring in abnormal bones, caused by minimal or no trauma) are infrequent in young patients and they are caused by the abnormal bone structure secondary to rare metabolic or bone diseases. Among the most frequent of these are nutritional rickets or osteomalacia (bone mineralization disorders secondary to nutritional vitamin D deficiency) and osteogenesis imperfecta.

Osteomalacia and rickets are disorders of bone mineralization, most frequently caused by longstanding vitamin D deficiency; osteomalacia occurs in adults while rickets is the corresponding disorder affecting the epiphyseal growth plates in children [1]. Osteogenesis imperfecta (OI) is a rare genetically- inherited connective tissue disorder predisposing the affected individual to multiple fragility fractures and bone loss [2]. Multiple fractures in children, adolescents and young adults should therefore prompt a thorough investigation aiming at the detection of such rare etiologies.

However, the increased awareness of child abuse in the last decades has led to the more accurate recognition of this complex problem. The incidence of child abuse is not negligible, being estimated in the USA between 15 and 42/1000 annualy [3] and fractures are the second most common consequence of abuse after soft tissue injuries [4]. As child abuse is significantly more prevalent than the rare bone diseases leading to multiple unexplained fractures, many families with a young member affected by one of these conditions are initially subjected to unfounded suspicion of child abuse [5]. It is therefore mandatory, in order to

1) "Carol Davila" University of Medicine and Pharmacy, Department of Endocrinology, Bucharest, Romania
* Corresponding author: Assist. Prof. of Endocrinology, Tel.+40724 679 504, Email: cristina.capatina@yahoo.com
2) "Mina Minovici"National Institute of Legal Medicine, Bucharest, Romania
3) "Carol Davila" University of Medicine and Pharmacy, Department of Physical and Rehabilitation Medicine, Bucharest, Romania
increase the likelihood of a correct differential diagnosis between inflicted trauma and the pathological conditions associated with iterative fractures, to perform a thorough history, careful clinical examination (looking simultaneously for both phenotypic signs of the bone or metabolic diseases and for additional signs suggestive for abuse or neglect), biological and radiological assessments [3].

**CASE REPORT**

We report the case of a young male with a history of multiple fracture of the long bones. At the time of his first presentation in our department the patient was 20 years old but the pathological history began as early as 6 months of age when the patient presented on several occasions with severe dehydration and vomiting and a diagnosis of idiopathic mild hypercalcemia, hypercalciuria and nephrocalcinosis was made.

Later in life, until the first presentation in our department, the calcium level was consistently normal; the nephrocalcinosis was stable, without associated impairment of the renal function.

The first fragility fracture of the left femur was diagnosed at 7 years of age; this was treated by intramedullary osteosynthesis. In the next years, more than 10 different pathological fractures of either the femoral bone or the osteosynthesis implants occurred, bilaterally. The pathological examination of a bone sample from one fracture area revealed many areas of sclerohyalinosis and spotted infiltration with both fibroblasts and fibrocytes.

The physical development was severely delayed; at the age of 18 years the patient's stature was more than 4 SD (standard deviations) below the mean (150 cm) and his weight was about 5 SD below the mean (36 kg). At that time a very severe vitamin D deficiency was also diagnosed (25OHD 6.7 ng/mL).

The clinical examination of the patient at presentation revealed severe short stature, severe scoliosis, marked asymmetry between the length of the legs, spontaneous adduction and internal rotation of the left thigh. The patient complained of muscle pains but he did not perceived any bone or joint pains. The clinical examination was otherwise unremarkable; in particular no changes of the sclerae or teeth were present.

No family history of childhood fractures, multiple fractures, phenotypic stigmata suggestive of osteogenesis imperfecta could be elicited.

The laboratory tests revealed increased concentrations of both bone resorption and formation markers, vitamin D deficiency, increased alkaline phosphatase (ALP), normal values of calcium in both serum and urine, normal parathyroid hormone levels –see table. Osteodensitometry (DEXA method, GE Lunar Prodigy machine) revealed severe osteoporosis.

The radiographical examination of the pelvis and lumbar spine revealed marked distortion of the normal bony architecture, severe scoliosis – see Fig. 1. The bones were extremely gracile and osteoporotic. The osteosynthesis implant on the left side was obviously fractured at the level of the inferior nail, the implant on the right appeared intact. Discrete osteolysis areas in both femoral neck areas were also described. – see Fig. 1. The skull base had homogeneously increased density. – see Fig. 2.

A clinical diagnosis of osteogenesis imperfecta was made and treatment with intravenous bisphosphonates and vitamin D was initiated.

**DISCUSSION**

Multiple unexplained fractures in children are a rare occurrence and the evaluation of the patient should look carefully for any sign of concern related to possible non-accidental injury while still bearing in mind that rare bone or metabolic diseases might be present. Among the most frequent pathological conditions associated with repetitive fractures in the young age are osteogenesis imperfecta and nutritional rickets or osteomalacia.

Osteogenesis imperfecta (OI, so-called “brittle bone disease”) is a genetically transmitted connective tissue disorder, caused by mutations in the type I collagen gene, with many clinical forms described, from very mild to lethal ones. Most patients suffer multiple fragility fractures or, in the mildest forms, premature severe bone loss [2]. Family history can aid in formulating the suspicion of a diagnosis

<table>
<thead>
<tr>
<th>Biological parameter</th>
<th>Result</th>
<th>Reference values</th>
</tr>
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<tbody>
<tr>
<td>Calcium</td>
<td>9.5 mg/dL</td>
<td>8.5-10.2 mg/dL</td>
</tr>
<tr>
<td>Calciuria</td>
<td>0.12 g/24h</td>
<td>0.07-0.3 g/24h</td>
</tr>
<tr>
<td>ALP</td>
<td>298 IU/L</td>
<td>38-129 IU/L</td>
</tr>
<tr>
<td>PTH</td>
<td>51.51 pg/mL</td>
<td>15-65 pg/mL</td>
</tr>
<tr>
<td>Beta crosslaps</td>
<td>2.21 ng/mL</td>
<td>0.14-0.58 ng/mL</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>292.60 ng/mL</td>
<td>24-70 ng/mL</td>
</tr>
<tr>
<td>25hydroxi vitamin D</td>
<td>22.88 ng/mL</td>
<td>30-100 ng/mL</td>
</tr>
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**Table 1. Biological parameters in the case presented (increased ALP and bone markers, vitamin D deficiency)**
but it is not always positive as some cases are the result of spontaneous genetic mutations or are the offspring of a very mildly affected undiagnosed parent.

Among the most frequent manifestations are: short stature, numerous pathological fractures, severe scoliosis, abnormalities of the skull base, possibly causing neurological manifestation by nerve compression, abnormalities of the sclerae (which have a bluish tint) and teeth (dentinogenesis imperfecta: translucent or discolored teeth), hearing loss [2]. Easy bruising is a quite common clinical manifestation related to the underlying connective tissue disorder [2]; the presence of bruising in association with repetitive unexplained fractures lead in many cases to the suspicion of inflicted trauma, exposing the affected families to an additional emotional burden. Although the medical team should be aware of this risk, child abuse should always be suspected, especially if no other phenotypic markers of the disease (teeth or sclerae abnormalities, severe scoliosis) are present or the family history is negative, mainly because child abuse is many times more common in the general population than OI [6]. As pointed out below, biological, radiological and densitometric data can usually clarify the differential diagnosis.

The usual biochemical tests panel is generally normal in OI with the exception of possible elevations of the alkaline phosphatase (ALP) or bone markers indicative of high bone resorption as in our case; however ALP concentration may be high as a result of the fractures themselves. Hypercalciuria is not infrequent in children with OI children [7] and it is correlated with a more severe phenotype but, just as in our case, it usually does not compromise the renal function to any significant extent [8].

The diagnosis is best confirmed by genetic testing; however, due to the fact that approximately 10% of the affected individuals test genetically negative for OI [9] and the lack of universal availability of the technique, the diagnosis is frequently made on clinical and biochemical grounds [10], as it was the case with our patient.

As we underlined, even if there is strong suspicion of child abuse, for a correct differential diagnosis a full biochemical panel including all the tests detailed above should be ordered. Vitamin D serum concentration is a useful adjunct because markedly decreased 25OH-vitaminD levels, possibly hypocalcemia with hypocalciuria and increased ALP serum levels are highly suggestive of nutritional vitamin D deficiency [11], another condition that can explain repetitive fractures in the young patient.

Severe longstanding vitamin D deficiency is manifested as rickets in children (causing slow growth, impaired bone mineralization, characteristic radiographic findings) and osteomalacia in adults (manifesting as bone pain, waddling gait, fractures, reduced bone density). Fractures may occur with little or no trauma, typically involving the ribs, vertebrae, and long bones. Severe untreated cases associate various deformities of the thorax, pelvis or spine [12]. The diagnosis is usually made on clinical and biochemical grounds only and does not require bone biopsy with tetracycline labeling (which classically reveals disorganized bone, with increased osteoid and prolonged mineralization lag time) [13].

Severe nutritional deficiency leading to osteomalacia is associated with characteristic radiographic findings [14]. Low bone density and thin cortices are usually noticed on radiological examination of these patients. Pseudofractures (Looser zones) are rarer but characteristic and they appear as clear narrow lines perpendicular to the cortical margins of the bone (mostly femur) - see Figure 3. Despite having severe vitamin D deficiency, our case did not cave any radiologic signs of rickets and did not meet any of the histologic criteria suggestive of osteomalacia. However, because vitamin D deficiency was also associated with impaired fracture healing [15] in our case, vitamin D deficiency might have contributed to the history of the disease.

The measurement of bone mass by DXA osteodensitometry is very useful in differentiating conditions with abnormal bone from child abuse (in the last case a normal result is expected). A low bone mass is not pathognomonic for a specific bone or metabolic disease in the young pa-

Figure 2. Plain skull radiograph showing in both anteroposterior (a) and lateral incidence (b) an increased density of the skull base. No wormian bones (sometimes found in OI) were identified.
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Atient but it strongly decreases the likelihood of abuse [16].

Summary of the key points in the evaluation of multiple unexplained fractures in children or young adults

In the setting of a child or young adult with multiple iterative fractures, the differentiation between OI, rickets/ osteomalacia and abuse can be difficult, and relies on a very detailed clinical evaluation. Characteristic elements of OI include a positive family history, short stature, scoliosis, hearing loss, teeth abnormalities, wormian bones, blue sclerae, present variably in affected individuals. Bone and muscle pain, waddling gait should suggest osteomalacia and a wide biochemical array of tests including vitamin D (25OHD) and bone markers should be ordered.

Clinical features that should raise the suspicion of inflicted trauma include any discrepancy between the injuries and the history, characteristic bruising patterns suggestive of abuse, delay in obtaining medical care [17]. In these cases, especially if there are clinical elements to suggest also the possibility of OI, genetic consultation for OI should be considered (it must also be borne in mind that the two can even coexist in the same case). Also, the diagnosis of reduced bone mineral density (which does not occur in child abuse) can be very helpful in the differential diagnosis.

ConClusions

Domestic abuse, rickets/osteomalacia and osteogenesis imperfecta are among the most frequent causes underlying repetitive fractures in the young age. Careful examination of the patient is of paramount importance for obtaining useful clues for the differential diagnosis and usual biological, radiological and bone mass testing can assist in making the correct diagnosis.

References