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Clinical Quiz

Osteogenesis imperfecta due to a possible new COL1A2 mutation; the importance of phenotyping and diagnostic challenges

Y.M. Papamerkouriou[1], A. Doulgeraki[2], Y. Gyftodimou[3], H. Athanasopoulou[2], E. Tsiridis[4], J. Anastasopoulos[5]

[1]Orthopaedic Department, Royal Hospital for Children, Glasgow,UK; [2]Department of bone and mineral metabolism, Institute of Child Health, "Agia Sofia" Chidren's Hospital, 11527, Athens, Greece; [3]Department of Genetics, Institute of Child Health, "Agia Sofia" Chidren's Hospital, 11527, Athens, Greece; [4]Aristotle University Medical School Thessaloniki, Papageorgiou General Hospital, Greece; [5]2nd Department of Paediatric Orthopaedics, "Agia Sofia" Chidren's Hospital, 11527, Athens, Greece

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Case

A 6 month-old boy fractured his right tibia, when he fell from a couch (50 cm height). One month later, he accidently kicked his leg against a desk. He was diagnosed with a fracture of the right femur. The following month, he again fell from a couch, sustaining a new fracture of the right femur. In addition to the fracture, his x-ray showed thin, osteopenic bones (Figure 1).

At the age of 11 months, the boy was assessed in our institution, in order to reach a diagnosis which would explain his three low-energy fractures. An eye check revealed blue sclera, heart sounds were normal, as were his teeth. His full metabolic bone profile (Table 1), showed low levels of procollagen type 1 C-terminal propeptide (PICP).

At 17 months, further laboratory tests were performed. The boy had microcephaly as well as generalised floppiness and delay in gross motor milestones (not sitting unsupported at 11 months, not walking independently at 17 months). His weight and head circumference were both below the 3rd centile for age and sex in all visits. Due to faltering height (initially

Figure 1. Anteroposterior x-ray of both femurs depicting fracture of right femur and thin osteopenic long bones.

Written parental consent was obtained prior to preparation of this manuscript. Authors Papamerkouriou YM, Doulgeraki A, Gyftodimou G, Athanasopoulou H, Tsiridis E, Anastasopoulos J, declare that they have no conflict of interest.

Corresponding author: Yvonne Papamerkouriou1 MD, MSc, Royal Hospital for Children, 1345 Govan Road, Glasgow, G51 4TS, UK
E-mail: ympapamerkouriou@yahoo.gr

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Table 1. Overview of the patient's diagnostic laboratory investigations.

Age	11 months	17 months	28 months (age- and sex-matched)	Reference values
Urea, electrolytes, liver function tests, *basic bone profile	normal	normal	normal	-
Bone formation markers				
§PICP (ng/ml)	**261**		**107**	>461 ng/ml
Osteocalcin (ng/ml)	28		29	10-30 ng/ml
Bone resorption markers				
SerumCTx (ng/ml)	-	-	2.4	1-4 ng/ml
UDPyr/Ucreat (mmol/mmol)	**62.63**		**46**	<40 mmol/mmol
Bone modeling marker				
IGF1(mcg/L)	166		88	80-250 mcg/L
25-(OH)-D (ng/ml)	33.5	20	32.2	20-100 ng/ml
PTH (pg/ml)	27	24	21.6	15-60 pg/ml
Complete blood count /ferritin	normal	normal	normal	-
Free T4/TSH	-	normal	-	-
Celiac screen	-	negative	-	-

*§PICP: Procollagen I C-terminal propeptide, CTx: C-terminal crosslinks, IGF-1: insulin growth factor 1, PTH: parathormone, TSH: thyroid stimulating hormone*Includes: Ca, P, Mg, ALP, creatinine, albumin, total protein, Ca/creat (urine), P/creat (urine).*

at the 50th centile, then at the 10th centile in the last visit), a failure to thrive work up was undertaken, which revealed no comorbidities (e.g. celiac disease, hypothyroidism).

Both parents were present during the assessment. The mother, who had been pregnant for the 3rd time, had had a miscarriage at 9 weeks. The father bore a striking resemblance to the child. He had a history of 5 fractures during adolescence and also reported multiple dental procedures as a child. His sclerae were also blue. His sister had sustained over 5 fractures during childhood and has been on treatment with IV bisphosphonates since the age of 25 years.

The clinical geneticist of our institution suggested a fibroblast biopsy of the patient, with a working diagnosis of OI. Also, DNA testing was performed on both the child and the parents.

Commentary

Sequencing of all coding exons (1-52) and all intron/exon boundaries of the COL1A2 gene was performed on the patient. A heterozygous COL1A2:c.4082G>T variant with unknown significance was found, which was identified in exon 52 of the COL1A2 gene. The substitution is a missense variant predicted to lead to the substitution of a glycine by a valine on position 1361 (COL1A2:p.Gly1361Val). The COL1A2:c.4082G>T was described as a novel variant not previously described in patients, nor in controls in the report of the lab which performed the analysis . It was not listed in the NHLBI Exome Variant database (~13000 alleles). It was classified as a variant with unknown significance according to the MutaDATABASE criteria although in silico predictions suggested pathogenicity.

Parental DNA tests revealed that the father was also a carrier of the same variant, whereas the mother was not. The father's sister did not consent to DNA testing.

We report the identification of a COL1A2 variant linked to the OI type 1 phenotype which had not been described at the time the testing was carried out. OI type I is usually due to mutations in the COL1A1 gene, resulting in the synthesis of approximately half the normal amount of functional pro-α1 chains, because of one null allele. Only a small subset of individuals with OI type 1 are found to have substitutions for glycine by small amino acids (cysteine, alanine and serine) near the amino terminal ends of the triple-helical domains of either COL1A1 or COL1A2 genes[1]. Therefore, a mutation in the COL1A2 gene, as discovered in our patient, is a more rare cause of OI type 1. Furthermore, COL1A2 may be linked to hip dysplasia or early onset scoliosis, which has not been the case so far in our patient.

At 28 months of age, the boy was prescribed cholecalciferol (600 IU/day). He is being reviewed every six months. A lateral x ray of the spine did not reveal any fracture. A DXA scan will be scheduled at the age of five years (pediatric software).

Of note, reaching a correct diagnosis for the child, led to the diagnosis of the father, whose bone mineral density was low (BMD Z-score L1-L4= -2.5) and he is now on oral alendronate.

Multiple fractures in an infant necessitate differential diagnosis between primary osteoporosis[2], OI being most com-

mon[3], and child abuse. According to a recent paper on fracture patterns in OI versus child abuse, infants and children with 3 or more fractures at the time of diagnosis represent only a small portion of children with OI[4]. In our patient, OI could have been assumed earlier, however there was no formal diagnosis of OI in the family, therefore abuse was initially suspected. In the same paper, it is argued that 72% of infants and children with OI can be readily diagnosed clinically[4]. A skin biopsy was performed on our patient because of the existing protocol at the time, but this is no longer necessary.

The phenotype of both the child and his father was typical of OI type 1. Macrocephaly is more common in these patients but evidently, OI type 1 can also be accompanied by microcephaly, as was the case with our patient.

Another interesting finding was the consistently low PICP of our patient. Although by no means diagnostic of OI, PICP is usually well below the reference range for age and sex in quantitative disorders of collagen, therefore a low value should raise suspicion of possible OI type I and this reflects the general experience of our institution (unpublished data).

We conclude that a thorough clinical examination of every patient with recurrent, low-energy fractures is mandatory. Special clues should be sought out i.e. blue sclerae, dentinogenesis imperfecta and the presence of generalized osteopenia, with very narrow bones. Additionally, both parents should be examined for further diagnostic clues and photos of other family members should be reviewed, since phenotype alone is often highly suggestive of a certain diagnosis[5]. Even though diagnosis can be made clinically, it is advisable to confirm it by genetic testing.

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Questions

1. What is the most common cause of OI 1?
A. Mutations in the COL1A2 gene
B. Mutations in the COL1A1 gene
C. A null allele of the COL1A2 gene
D. A null allele of the COL1A1 gene

Critique

A null allele of the COL1A1 gene resulting in the in the synthesis of approximately half the normal amount of functional pro-α1 chains is the most common cause of OI 1. A mutation in the COL1A2 gene, as discovered in our patient, is a more rare cause of OI type 1.
The correct answer is D.

2. All of the following are clinical features of OI1 except:
A. Multiple fractures
B. Microcephaly
C. Normal DXA Z-score
D. Blue sclerae

Critique

Multiple fractures and blue sclerae are common features of OI 1. It is usually accompanied by macrocephaly but microcephaly can also be seen as was the case with our patient. DXA Z-score is expected to be low.
The correct answer is C.

3. Children with OI are usually diagnosed:
A. Clinically
B. By genetic testing
C. By fibroblast testing
D. After having sustained at least 3 or more fractures

Critique

Infants and children with OI can be readily diagnosed without fibroblast or genetic testing. The vast majority of children diagnosed with OI are diagnosed based on clinical grounds. Infants and children with 3 or more fractures at the time of diagnosis represent only a small portion of children with OI.
The correct answer is A.

4. Laboratory tests in patients with OI may reveal:
A. Anemia
B. Abnormal thyroid hormone values
C. Low value of Procollagen I C-terminal propeptide (PICP)
D. Abnormal liver function tests

Critique

Usually OI patients have normal laboratory test values but a low value of Procollagen I C-terminal can be expected as was the case in our patient although this is not diagnostic.
The correct answer is C.