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# Osteogenesis Imperfecta Type 1 with an incidental finding of bilateral radioulnar synostosis

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**Abstract**

Osteogenesis Imperfecta (OI) is a rare heritable connective tissue disorder that has varying degrees of severity. Over 85% of patients have pathogenic variants in the type 1 collagen genes (*COL1A1/COL1A2*). OI used to be previously classified into distinct sub-types based on clinical presentation and presence or absence of unique discerning clinical characteristics. Type 1 OI is generally classed as a milder form of OI and caused due to variants in *COL1A1* and *COL1A2*. Type V OI is associated with interosseous membrane calcification along with difficulty in supination and pronation and more recently been described in association with a recurrent c.-14C>T variant in *IFITM5*.

Here we report a female patient with genetically diagnosed type 1 OI with an additional finding of bilateral radioulnar synostosis which is thought to be a unique feature of type V OI. The synostosis was identified at three years of age following a fractured upper limb. On review, following cast removal, restriction in supination and pronation was identified and bilateral radioulnar synostosis was identified on skeletal imaging.

To our knowledge, a patient with genetically confirmed type 1 OI and bilateral radioulnar synostosis has never been reported previously. We report on this unusual combination of clinical characteristics and highlight the need to bear this association in clinical practice.

## Background

Osteogenesis Imperfecta (OI) is a rare connective tissue disorder with an estimated incidence of around 6-7/100,00 births worldwide and presents with varying degrees of severity (1-3). Type 1 is less severe and is associated with blue sclera. Characteristics of this type are fragility of the bone and hearing difficulties (1, 2). Type II is classified as lethal or very severe form of OI often presenting antenatally with short long bones, fractures and bowing deformities. Type III and Type IV OI are moderately severe forms of the condition with variable phenotype in terms of the fracture history and stature. Type V OI is classified by the presence of interosseous membrane calcification, which results in limited supination and pronation (1-4).

OI is a genetic condition, with most patients being affected by variants in genes known to be involved in the production or processing of type 1 collagen (1, 5). The genes most commonly associated with this are *COL1A1* and *COL1A2*, which follows an autosomal dominant (AD) pattern of inheritance (1, 4, 5). Over time, the number of genes recognised as part of OI has increased, including autosomal recessive variants (2, 5). Some cases of type II OI can be accounted for by recessive genes such as *CRTAP/ P3H1/ PPIB* and a recurrent variant in *IFITM5* has been associated with Type V OI (1-5). The treatment of OI relies on a multidisciplinary approach with bisphosphonates being the mainstay in terms of medical management (5). Education and support for families is essential for the child to optimise their quality of life.

We report a female patient who has been diagnosed with Type 1 OI and has developed bilateral radioulnar synostosis. To our best knowledge, this association has never been reported before apart from a case report in a patient with genetically unconfirmed type I OI previously reported by Lupu et al in 2015 (6).

## Clinical Report

A female baby was born at 38 weeks gestation weighing 2.8kg (-1.26 SD). There were no antenatal concerns and she is the first child of a healthy, non-consanguineous relationship. Her mother has three children from a previous relationship who are well. The patient was referred to the Endocrine Team due to a family history of Osteogenesis Imperfecta Type 1. Her father and paternal grandmother are affected. Her father also has a history of aortic regurgitation.

On her first review, at the age of three months, the patient was developing appropriately and gaining weight as expected. She was noted to have grey sclerae, but otherwise her examination was unremarkable. There were no dysmorphic features or obvious bony abnormalities. A hip ultrasound ruled out developmental dysplasia of the hip. Genetic testing confirmed a novel *COL1A1* c.578del, p.Pro193fs pathogenic variant confirming the clinical diagnosis of OI Type 1 as other frameshift variant in *COL1A1* are known to be associated with OI. This variant is predicted to result in a premature termination codon 72 acids downstream and is situated in exon 7 of *COL1A1*.

The patient appeared to have no concerns with her hearing or dentition. The patient went on to sustain multiple fractures and at two and half years of age she was started on treatment with Zoledronic acid.

At three years of age, the patient suffered from a left lateral condyle fracture, which was reviewed by the Orthopaedic team. It was noticed that the patient could only supinate to approximately ten degrees from neutral position post cast removal, but she had full pronation of the left arm (Figure 1). Interestingly, her x-rays at this time were reported to show fusion of her proximal radial and ulnar bones and synostosis (Figure 2). At this time, these findings

were not restricting the patient's daily activities and are likely to be why it had not been identified clinically.

## Discussion

We report a female patient who was genetically diagnosed with Type 1 OI with an incidental finding of bilateral radioulnar synostosis. Radioulnar synostosis is a rare condition that often has an unknown aetiology (7). A quarter of cases have a genetic cause and radioulnar synostosis can be associated with a variety of genetic conditions, for example Apert syndrome, arthrogryposis, Treacher Collins syndrome and Holt-Oram syndrome (7-9). It has been associated with OI previously, however it is typically seen in type V (4, 6). Fassier et al 2007 investigated the association between upper limb deformity and OI. In total, 489 upper limbs of paediatric patients were examined and radial head mal-alignment was found in 83 (10). This finding was significantly higher in patients with type V OI compared to the other types ($p<0.001$). The radial head mal-alignment was associated with calcification of the interosseous membrane when found in type V OI and not when found in the other types (10).

Following a literature search, there is one further case report of a child diagnosed clinically with OI type I and radioulnar synostosis in Romania in 2015; given the genetic aetiology was not identified the question remains as to whether this was a type V OI as this may be clinically indistinguishable early without specific radiological clues to the diagnosis (6).

Radioulnar synostosis is characterised by fusion of the proximal ulna and radial bones and is bilateral in approximately 60% of reported cases (7, 11, 12). There are two types of radioulnar synostosis, based on the location of the connection. In type 1, there is fusion involving two to six centimetres of the area between the radius and ulna bones and is more proximal to the elbow. With this type the radial head is absent (8). In type 2, the fusion is farther from the elbow and there is dislocation of the radial head (8).

Embryologically, upper limb development begins around day 25, with the elbow developing by day 34, and the radial bone and ulna by day 37 (13). Failure of segmentation of the long bones during the seventh week will result in fusion of the radius and ulna (7, 12, 13).

The main symptoms of radioulnar synostosis are restricted movement with respect to pronation and supination from the elbow (8, 12). This can vary greatly depending on the severity of the abnormality (8). It can be associated with pain if there is a dislocation of the radial head, which tends to occur in adolescents, particularly if undiagnosed or untreated. With our patient, her restriction had not been identified prior to her fractured arm. However, retrospectively, the parents reported issues with certain tasks such as eating and carrying large objects with both hands. This had previously been put down to her being 'clumsy' rather than due to restriction of movement.

Exercise and occupational therapy are encouraged to help strengthen other joints and muscles (12). Radioulnar synostosis may be treated surgically and Bakkalet et al, 2018 report two examples that surgery is indicated. Firstly, pronation fixed beyond ninety degrees and secondly, bilateral synostosis (7, 14). The aim of surgical treatment is to aid 'daily function activities' (7) and often only performed in severe cases (14). Complications do occur and include nerve damage and recurrence (12).

## Conclusion

Here, we report a female patient with confirmed type 1 OI with bilateral radioulnar synostosis diagnosed following a fracture which is more typical of type V OI. This patient was found to have restriction of supination and pronation, which had not previously been identified as she had learned to compensate for this. To date, this patient has not had any surgical intervention.

## References


1. Fratzl-Zelman N, Misof BM, Roschger P, Klaushofer K. Classification of osteogenesis imperfecta. Wien Med Wochenschr. 2015;165(13-14):264-70.
2. Van Dijk FS, Sillence DO. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. Am J Med Genet A. 2014;164A(6):1470-81.
3. Brizola E, Felix TM, Shapiro JR. Pathophysiology and therapeutic options in osteogenesis imperfecta: an update. Research and Reports in Endocrine Disorders. 2016;6:17-30.
4. Zhytnik L, Maasalu K, Duy BH, Pashenko A, Khmyzov S, Reimann E, et al. IFITM5 pathogenic variant causes osteogenesis imperfecta V with various phenotype severity in Ukrainian and Vietnamese patients. Hum Genomics. 2019;13(1):25.
5. Hoyer-Kuhn H, Netzer C, Semler O. Osteogenesis imperfecta: pathophysiology and treatment. Wien Med Wochenschr. 2015;165(13-14):278-84.
6. Lupu VV, Subotnicu M, Ignat A, Padararu G, Naumcieff I, Ciubara B, et al. Association of Bilateral Radioulnar Synostosis with Osteogenesis Imperfecta Type 1 - Case Presentation. Romanian Journal of Oral Rehabiliation. 2015;7(4):55-9.
7. El Bakkaly A, El Ghordaf I, Bouljrouf J, Amrani A, Dendane M, Alami Z, et al. Surgical Treatment of Congenital Radioulnar Synostosis in Children: A Case Report. International Journal of Surgery and Medicine. 2018;4(1):44-7.
8. Bauer M, Jonsson K. Congenital radioulnar synostosis. Radiological characteristics and hand function: case reports. Scand J Plast Reconstr Surg Hand Surg. 1988;22(3):251-5.
9. Dogra B, Singh M, Malik A. Congenital Proximal Radioulnar Synstosis. IJPS. 2003;36(1):36-8.

10. Fassier AM, Rauch F, Aarabi M, Janelle C, Fassier F. Radial head dislocation and subluxation in osteogenesis imperfecta. J Bone Joint Surg Am. 2007;89(12):2694-704.

11. Siemianowicz A, Wawrzynek W, Besler K. Congenital radioulnar synostosis - case report. Pol J Radiol. 2010;75(4):51-4.

12. Tsai J. Congenital radioulnar synostosis. Radiol Case Rep. 2017;12(3):552-4.

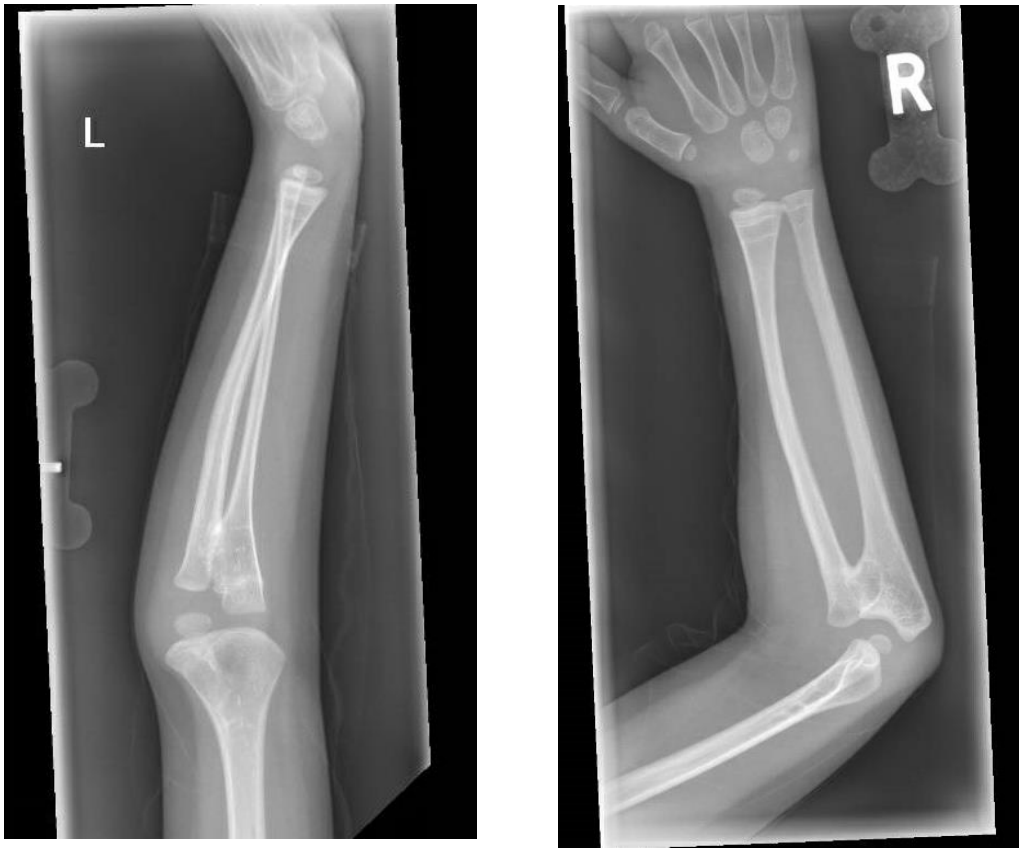
13. Mital MA. Congenital radioulnar synostosis and congenital dislocation of the radial head. Orthop Clin North Am. 1976;7(2):375-83.

14. ElSayed S. Derotation Osteotomy for Congenital Radioulnar Synostosis. Orthopaedic Journal. 2014;49(2):92-5.

**Figures:**

*Figure 1a and b: Extended forearm in patients demonstrating radioulnar synostosis*

*Figure 2a and b: X-ray of patient's forearm to demonstrate radioulnar synostosis radiologically*




**Contributions** Report was written by LA and SR. Supervised by MB and RR.

**Competing Interests** None.

**Patient Consent** Written consent obtained from parent.