

Wrist Deformity in Children and Adolescents with β -thalassemia on Oral Iron Chelation Therapy

RASHID H MERCHANT¹, AMEYA KULKARNI², PEZAD N DOCTOR¹, AMITKUMAR CHOUDHARI² AND DEEPAK P PATKAR²
From Departments of ¹Pediatrics and ²Radiology, Nanavati Super Speciality Hospital, Vile Parle East, Mumbai, Maharashtra, India.

Correspondence to: Dr Pezad N Doctor, Department of Pediatrics, Nanavati Super Speciality Hospital, Mumbai, India.

pezaddoctor@gmail.com

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Objective: To describe a novel wrist deformity in β -thalassemia major patients, and their radiographic and magnetic resonance imaging findings. **Methods:** 30 patients with β -thalassemia major who were noticed to have ulnar deviation at wrist joint were evaluated for previous history of medications, serum ferritin levels, presence of pain and swelling at the wrist joint, and the duration of iron chelation therapy. Radiographs of wrist and limited magnetic resonance imaging (MRI) sequences were obtained in 30 and 15 patients, respectively. **Results:** Radiographs revealed varying severity of distal ulnar shortening, distal radial slanting and presence of soft tissue distal to the ulna. MRI showed similar deformities along with abnormal marrow signal at distal ulnar ends; in 8 patients, a soft tissue distal to the distal end of ulna was noted. **Conclusion:** Varying severity of radiological abnormalities, predominantly affecting the distal ulna, are present in children and adolescents with β -thalassemia receiving oral chelation therapy.

Keywords: Arthropathy, Bone deformity, Deferiprone, Growth plate.

Iron overload in β -thalassemia major patients due to repeated blood transfusions requires administration of iron chelation therapy in the form of parenteral Desferioxamine (DFO) or oral iron chelators such as Deferiprone (DFP) or Deferasirox (DFX). Mild arthropathy occurs with the use of DFP that usually resolves either on its own, with the use of non-steroidal anti-inflammatory drugs, or by temporary withdrawal of therapy [1-3]. The long-term outcome of DFP-related arthropathy is not known, and is not adequately documented in literature [4,5]. We aimed to describe radiographic findings in children who were receiving DFP at some point during their treatment course.

METHODS

At a thalassemia day care center in Mumbai, during the period from February 2014 to March 2017, records of 155 β -thalassemia major patients were evaluated. Thirty of these patients, aged 12 to 18 years, were noted to have bilateral wrist deformity with ulnar deviation (**Fig. 1**). Iron chelation therapy had been initiated after receiving 20 units of packed red blood cells (PRBCs) or when serum ferritin levels were above 1000 $\mu\text{g/L}$. Change in drugs for chelation therapy was made when serum ferritin exceeded 2500 $\mu\text{g/L}$, intolerance to the drug, or non-response to a single agent.



FIG. 1 Bilateral ulnar deviation at wrist joint in a 13-year-old boy with β -thalassemia receiving oral iron chelation.

These 30 patients with asymptomatic wrist joint deformity were further evaluated with reference to their bony abnormality. Informed consent was obtained from the parents for radiological investigations and clinical photographs. Ethical approval for the study was obtained from Ethics Committee of Dr Balabhai Nanavati Hospital, Mumbai, India.

Radiographs of wrist of all 30 children were

evaluated by a single reader (AK) who was not blinded to the clinical deformity. MRI coronal T-1 and T-2 weighted sequences of wrist were obtained using a 3 Tesla, Discovery 750W scanner (GE healthcare, Milwaukee, USA). MRI findings were evaluated by two readers (AC and DP). Serum calcium, phosphorous, alkaline phosphatase and 25-hydroxy Vitamin D3 levels were done along with serum ferritin levels in all patients.

RESULTS

In 30 patients (21 boys) noted to be having bone deformity, the median (IQR) age was 15 (2.25) years, and the duration of deferiprone therapy ranged from 1.5 to 16 years with a median (IQR) of 8.25 (5.75) years. There was no history of trauma, skeletal dysplasia, prior surgical intervention of the wrist joint or any other skeletal deformities.

The median (IQR) serum ferritin level when the wrist deformity was diagnosed was 2350 (1690) ng/dL. The serum calcium, phosphorous, alkaline phosphatase and 25-hydroxy Vitamin D3 were normal in all patients. All children had received DFP in doses ranging from 75-100 mg/kg/day at the initiation of iron chelation between ages of 2 to 8 years. Twenty of these were presently on oral DFX in doses ranging from 30-40 mg/kg/day as a single agent, four were receiving a combination of DFX and DFP, four were receiving injectable DFO in doses 30-40 mg/kg/day and DFP, while two were on DFO and DFX. Ten patients on DFP developed severe arthralgia in knee joint with no wrist pain, necessitating shift of therapy to DFX. At the time of evaluation, only eight

were receiving DFP in combination with another iron chelator.

Radiographic changes observed included shortening of distal ulna at wrist in 17 (**Fig. 2**), shortening of ulna with rotation of scaphoid, and distal radial slant in 4, shortening of ulna with deformity at wrist along with degenerative changes at radio-carpal joint and abnormal shortening of ulnar third of the radial epiphysis in 7, and shortening of ulna with rotation of scaphoid and scapho-lunate dislocation with a positive Terry Thomas sign in 2 [6]. No patient had pain, swelling or restricted movement of the wrist joint or any other joint swelling or deformity.

MRI coronal T-1 and T-2 weighted images obtained in 15 randomly selected patients showed similar deformities as those seen on radiographs along with abnormal marrow signal at distal ulnar end. In eight cases with significant ulnar shortening, there was a soft tissue present distal to the distal end of ulna, likely to be due to abnormal fibrous tissue in the region of distal radio-ulnar joint (**Fig. 3**). Osteonecrosis of scaphoid was seen in one case.

DISCUSSION

We noted the radiographic wrist deformity affecting the distal ulna in children with β -thalassemia major, which predominantly showed lucency and thinning of the ulnar metaphysis, deformed small ulnar epiphysis and impaired growth of the physal cartilage leading to ulnar shortening. The clinical wrist deformity was more apparent in older children as impaired physal growth of the ulna may have resulted in progressive shortening of



FIG. 2 Radiograph of both wrist shows shortening of distal ulna. Scaphoid bones show abnormal orientation bilaterally with scapho-lunate dislocation (arrow).

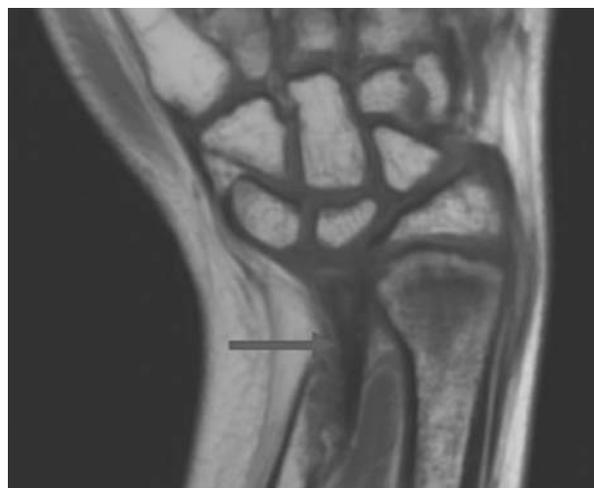


FIG. 3 Coronal T1-weighted MRI of right wrist shows shortening of distal ulna resulting in wrist deformity. Arrow points to a hypo-intense tissue distal to the distal end of ulna, which is likely to be fibrous tissue in relation with the distal radio-ulnar joint.

WHAT THIS STUDY ADDS?

- X-ray and MRI changes in the wrist joint are seen in a subset of children and adolescents with β -thalassemia major who received oral iron chelation therapy with deferiprone.

the ulna in comparison to the radius. In addition, MRI provided further information regarding marrow signal and soft tissue involvement.

The study evaluated a population of patients visiting our centre with wrist deformities after being on iron chelators for variable duration of time. The major limitation was that it was a cross-sectional observational study, and there was no long-term, longitudinal followed up to document the progression of this deformity. The cumulative doses of iron chelators used were not calculated and compared as they varied with age, weight and serum ferritin levels of the children.

DFO therapy can result in skeletal dysplasia with metaphyseal widening of long bone, rachitic changes, shortening of the vertebrae, distal ulnar metaphyseal and occasional epiphyseal sclerosis and thinning [7,8]. The mechanism of skeletal dysplasia may be either due to the binding of zinc or the anti-proliferative effect of DFO [8]. Only six of our patients received DFO for a prolonged period of two years or more after the age of ulnar epiphysis formation, and thus DFO is unlikely to be the cause of ulnar deformities in our series of patients. DFP can also cause chondromalacia, and is toxic to growing tissues such as bone marrow [7,9]. DFP causes an arthropathy that usually involves the knees [10]. However, Sharma, *et al.* [5] reported abnormal wrist X-rays findings in 13 out of 40 patients receiving deferiprone; clinical ulnar deviation at the wrist joint was noted in 4 patients in their series. There are no earlier reports describing MRI findings of wrist in patients receiving iron chelation therapy.

The exact etiology of the arthropathy associated with DFP remains uncertain; however, it has been hypothesized to be due to the toxic effects mediated by free iron radicals, resulting from the formation of 1:1 or 2:1 Deferiprone-iron complexes rather than the usual, inert, 3:1 complexes [10,11]. These unstable complexes catalyze the formation of free oxygen and hydroxyl radicals, damaging the distal epiphysis and metaphysis of ulna.

Sharma, *et al.* [5] previously postulated that the anti-proliferative effect of DFP may explain the toxic effects on the growth cartilage. They further explained the propensity for ulnar changes as ulnar epiphysis develops approximately between four to six years of age

[12], the age at which all their patients had been receiving deferiprone. Prospective cohort studies might help us understand the progression of this deformity and the associated disability. Large controlled studies with different iron chelators are required to assess the causal relationship of this deformity with DFP.

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