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ORIGINAL STUDY

Premature epiphyseal fusions in Beta Thalassaemia

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Thalassemia patients are now living longer due to better transfusion methods and diagnostic awareness. To see whether this longevity is associated with orthopaedic disability, especially physeal growth defects, we examined 105 patients aged between 5-25 years for evidence of clinically detectable premature epiphyseal fusions (PEF). Ours is a center focussed on transfusion dependent beta thalassemia (TDBT) patient management, and so detailed transfusion records related to age at first transfusion, regularity of transfusions and pre-transfusional haemoglobin (Hb) levels were available. Five (4.7%) patients had deformities or limb length discrepancies, which lead to the detection of PEF. All patients with PEF had pre transfusion haemoglobin levels of less than 8 gm/dL. On comparing with the literature, we found that the prevalence of clinically detectable PEF in TDBT patients has decreased with better blood transfusion regimes. Though the pathogenesis of PEF is yet to be conclusively established, it is apparent that better control of the disease to maintain pre-transfusional haemoglobin levels consistently above 8 gm/dL in the first decade, can decrease the occurrence of PEF.

Keywords : premature epiphyseal fusions ; thalassaemia ; deformity.

INTRODUCTION

Beta thalassemia is an inherited mendelian disorder characterised by severe haemolytic anaemia, due to deficient synthesis of the beta globin chain of haemoglobin A (*8*). Every year 100,000 infants are born with this disorder worldwide (*1*). The disease is clinically characterised by severe anaemia, peculiar haemolytic facies, greenish brown skin, and growth retardation ; skeletal disturbances are uncommonly discussed in detail and few reports exist highlighting the orthopaedic aspects of this disorder. One of the issues is that severe complications like iron overload, intercurrent infections, endocrine and cardiac disorders can occur and decrease the lifespan of these patients (*5,12*). Generally the treatment efforts in thalassaemia are aimed at supportive blood transfusion therapy, along with chelating agents to decrease the iron overload. Currently the emphasis of treatment is on hyper-transfusion

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regimen from an early age (*14*) and iron chelation (*2-4,14*). Newer methods, achieving therapeutic cure to varying levels, by either bone marrow or stem cell transplantation from HLA matched donors (*9*), are making the children live longer, and hence disability related to the skeletal system comes into focus.

Anatomic proximity of the growth plate to the active centres of haematopoiesis within the bone marrow, and interactions of bone, cartilage and synovium with the disease process lead to the manifestation of musculoskeletal problems (*14*), which include premature epiphyseal fusions (PEF) (*7,10, 11,16*), pathological fractures (*11*) and thalassaemic osteoarthropathy (*13*).

Premature epiphyseal fusions in the long bones can occur in up to 14%, with higher frequencies occurring in patients starting treatment above the age of ten (*7,10,11,16*). The sites of predilection with increasing order of frequency are the proximal end of the humerus (*7,10,11,16*) the distal end of the femur, and the distal and proximal tibia and fibula (*10,11*). Premature epiphyseal fusions may involve multiple long bones and can be bilateral, and there are no reports on involvement of any other bones other than the ones mentioned above (*11*). Premature epiphyseal fusions manifest clinically in the form of shortening and deformity of the affected bone (*10*). Not all PEF's are clinically obvious ; those involving the proximal humerus go unnoticed, and are often detected incidentally on chest or shoulder radiographs (*10,16*). Radiologically, PEF is detected as an area of bony sclerosis crossing the epiphyseal growth plate in an immature skeleton or in the form of deformities at the end of long bones in a mature skeleton. The association of PEF's with the severity of the disease or with the number of previous blood transfusions is yet to be established , however PEF is known to occur frequently in thalassemia intermedia patients who received few or no transfusions at all (*7,10,16*).

With improved blood transfusion regimes, and better patient longevity, we aimed to evaluate our patient population in an attempt to pick up the prevalence of clinically detectable PEF, its relation to age, sex, type of thalassemia, age at first transfusions, and average pre-transfusion haemoglobin status.

MATERIAL AND METHODS

Over a one-year period, 105 Transfusion Dependent Beta Thalassemia (TDBT) patients, attending the Thalassemia transfusion unit, at PGIMER, Chandigarh, for regular blood transfusions were evaluated on a one-time basis, to pick up the incidence of premature epiphyseal fusions. All children above the age of 5 years and both sexes were studied. There were 85 (81%) males and 20 females. The mean age of the study group was 12.1 years. Ninety-five patients were diagnosed to have thalassaemia major and the remaining 10 patients had thalassaemia intermedia.

In patients with thalassaemia major 70 patients (74%) were started on regular blood transfusion therapy from the first year of life and the remaining (25) 26% were started on regular transfusions from the second year of life. In patients with thalassaemia intermedia, all 10 patients were started on regular transfusion therapy after the age of 5 years. Throughout the treatment period 40% (42) of all patients had maintained average pre-transfusion haemoglobin levels above 8 gm/dl, while the remaining 60% (63) of patients had haemoglobin levels below 8 gm/dl. Generally, all TDBT patients were started on a hyper-transfusion regimen early in life and as these children grew older there were difficulties in maintaining transfusion regimen because of increasing blood demands and limited blood resources.

All patients included in this study were seen in clinic and the patients and their parents were interviewed to obtain detailed information regarding the onset, course and treatment of the disease. Case notes were studied for transfusion records and details regarding the initial transfusion, frequency of transfusion and pre- transfusion haemoglobin levels throughout the treatment period were noted. A note was also made of any documented musculoskeletal problems during this period. All patients were then clinically assessed for deformities, limp, and limb length inequalities. The patients identified to have deformities were further assessed by a detailed clinical and radiological examination. Patients with clinical evidence of deformity or limb shortening were evaluated radiologically for juxta-articular deformity (deformity at the level of the epiphysis) and/or bony sclerosis across the epiphyseal growth plate at the ends of long bones (fig 1).

The data collected was compiled and analysed to identify the prevalence of clinically detectable PEF in TDBT, and to evaluate its relation to age, sex, type of thalassemia, age at first transfusions, and to average pre-transfusion haemoglobin status.

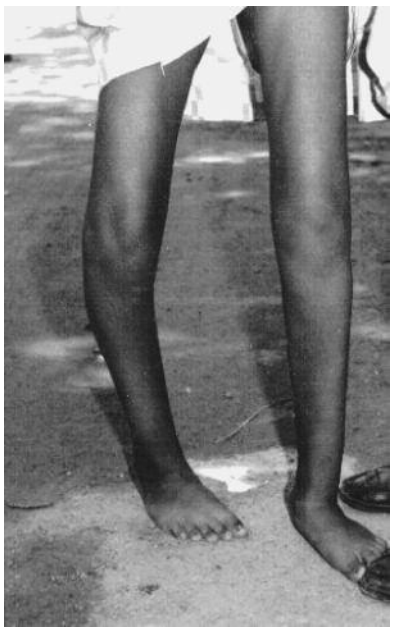

Fig. 1. — Clinical photograph showing genu varum deformity of the right knee and valgus deformity of the left ankle.

RESULTS

The details of PEF picked up by our evaluation are given in table I.

The overall prevalence of PEF in TDBT was 4.7% (10 premature epiphyseal fusions in 5/105 patients) ; in those over 12 years the prevalence of PEF was 7.3%. In female patients, three (15%) developed deformities, in males two (2.3%). In patients with thalassaemia major, three (3.1%) had deformities and all of them were on regular transfusion from the first year of life. In those with thalassaemia intermedia, two patients (20%) had deformities and both of them were started on regular transfusion at the age of 15 years. All patients with deformities had average pre -transfusion haemoglobin of less than 8 gm%, of whom 4 patients had Hb levels between 6-8 gm%, and one had a Hb level of less than 6 gm% throughout the treatment period. All 5 patients with deformities were among those who were under transfused, representing 8% (5/63) of this group. No deformities were observed in any of the patients maintaining an average pre-transfusional haemoglobin above 8 gm% throughout the disease period.

In four children with PEF, a history of fracture involving the same bone was present. All were diaphyseal fractures and none of the fractures involved the growth plate. All PEF's except one were located around the knee (fig 1 & 2) or the shoulder (fig 3.)

Table I. — Premature epiphyseal fusions in Beta thalassaemia

Serial No	Age (Yrs)	Sex	Type	PEF in Bones	Site of PEF	Fracture in the same bone	Deformity	First transfusion	Hb status (gm/dL)
1	25	M	TM	2	Right Proximal humerus and distal femur	Right distal humerus	Humeral head varus, Genu recurvatum	< 1 year	< 6
2	12	F	TM	1	Proximal humerus	-	Humeral head varus,	< 1 year	6-8
3	17	F	TI	5	Bilateral proximal tibia and distal femur, Left distal tibia.	Proximal tibia (Right)	Right Genu varum, left ankle valgus, Bilateral flexion deformity knee	15 years	6-8
4	19	F	TM	1	Distal femur	Shaft femur	Genu valgum	< 1 year	6-8
5	23	M	TI	2	Both Proximal tibiae	Both tibia shaft	Genu varum	15 years	6-8

Key : Hb : Haemoglobin ; F = female ; M = male ; TM = Thalassaemia major ; TI = Thalassaemia intermedia ; PEF = premature epiphyseal fusion.

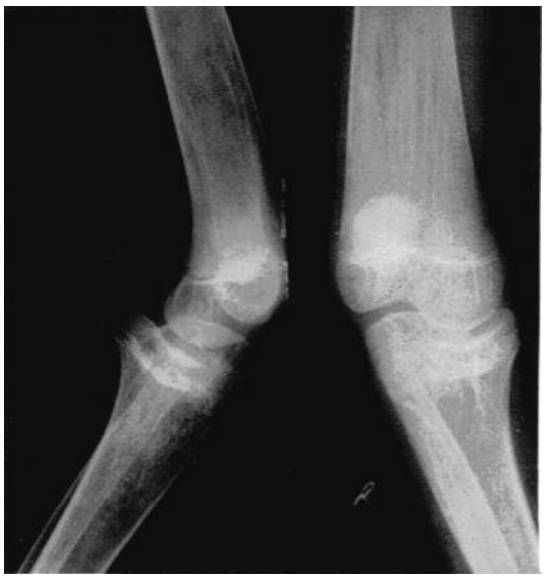

Fig. 2. — Anteroposterior and lateral radiographs of the right knee of the same patient showing genu varum deformity with hypoplastic medial tibial condyle and evidence of epiphyseal scar in tibia and distal femur.

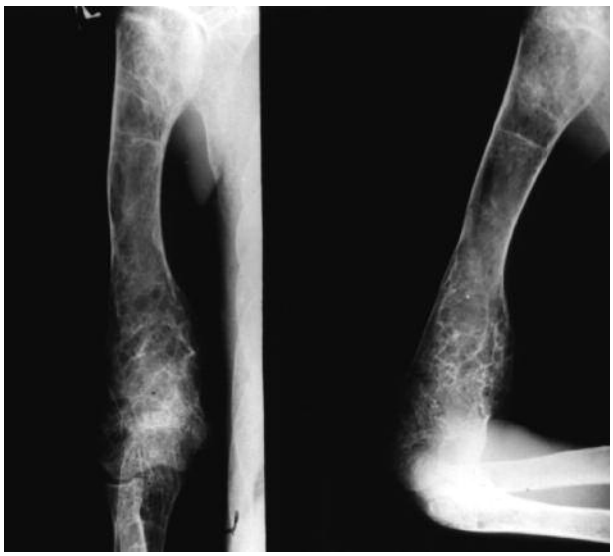

Fig. 3. — Anteroposterior and lateral radiographs of the right shoulder showing varus deformity of the humeral head due to PEF of the proximal humeral epiphysis. Note the severe osteoporosis and the honeycomb trabecular appearance of the distal humerus.

Radiographs in 4 out of the 5 patients with PEF's revealed evidence of severe osteopenia in the form of cortical thinning and increased trabecular pattern of the diaphysis and metaphysis of the long bones (fig 3).

DISCUSSION

The orthopaedic issues related to thalassaemia have come to light only with better longevity. Reynolds has described skeletal changes in beta thalassemia as early as 1927, and Baty described the occurrence of pathological fractures in 1932 (*6*). The problem is that this is a rare disorder, and the general experience of an average orthopaedic surgeon is limited. Our institute is a referral center, and the prevalence of this disease in our area is significant, reportedly due to descendants of Alexander's army settling here. This has lead to the development of a special clinic focussed on thalassaemia patients, which allows us to accumulate sufficient experience in this disease.

Currarino and Erlandson (*10*) and Colavita *et al* (*7*) reported an overall prevalence of PEF of 14% in patients with TDBT, and in those aged over 10 years the prevalence rose up to 23%. In our study group, the prevalence was 4.7%, and in those aged over 12 years 7.8%. We also observed that PEF was commoner in females (15%) as compared to males (2.3%).

A review of the literature suggests that PEF's are more common in thalassaemia intermedia than in thalassaemia major (*7,10*), which is consistent with our observation (20% in thalassaemia intermedia and 3.6% in thalassaemia major).

Thalassaemia intermedia patients become transfusion dependent towards the end of the first decade of their life, unlike thalassaemia major patients who become transfusion dependent in the first year of their life. While the aggressive intramedullary haematopoiesis continues in thalassaemia intermedia patients till they become transfusion dependent, this haematopoiesis process is well suppressed in thalassaemia major patients who have early and regular blood transfusions.

Colavita *et al* (*7*) have postulated that this increased intraosseous activity and hyperplastic bone marrow perforates the cortex and proliferates

subperiosteally at the level of the growth plate, leading to premature epiphyseal fusion. On the other hand, early and regular blood transfusions in thalassaemia major mitigate the anaemia and as a result the bone marrow is less aggressive, thereby reducing the occurrence of premature epiphyseal fusions and heterotopic bone marrow formation. This is also supported by the observations made by Pizzarelli *et al* (*17*) that premature epiphyseal fusion was significantly more common among patients who were started on an hypertransfusion regime after 10 years of age than those before 10 years of age and hence suggested that a hypertransfusion regime started early in life may prevent premature epiphyseal fusion.

Lawson *et al* (*16*) observed that none of their patients, who were hyper- transfused from an early age on, developed PEF and those who developed PEF were hypertransfused only after the age of 5 years. In the current study none of our patients with relatively well-controlled disease (Hb > 8 gm/dL), had clinical evidence of PEF and all patients who had clinically detectable PEFs were less well transfused (Hb < 8 gm/dL). These observations support the hypothesis that in well-controlled disease the occurrence of PEF can be minimized.

The lower incidence of PEF's recorded in our study is attributed to three factors. Firstly, an aggressive blood transfusion policy to maintain a pre-transfusional Hb > 8 gm/dL was pursued (*14*). It appears that in thalassaemic patients with well-controlled pre-transfusional haemoglobin levels, skeletal haematopoiesis is normally suppressed, and hence the absence of clinically detectable PEFs. A moderately controlled disease may lead to inadequate suppression of the bone marrow and cause extensive haematopoietic proliferation (*7,16*), which correlates well with the fact that all patients with PEF in the current study were under-transfused.

Secondly, a younger patient population was assessed in the current study (mean age 12.1 years) in comparison to other studies and the PEF occurrence is a depiction of the point prevalence of PEF in this study group. It is very well possible that some of the younger children may still develop PEF in the future. However the patients who developed PEF were all in their second decade of life, when the deformity was first detected. The age of the patients at the time of PEF detection was higher when compared to the mean age of the entire study group.

Thirdly, the higher incidence of PEFs in the study by Lawson *et al* (*16*) compared to the current study, is related to the radiological detection of PEF on chest radiographs of children, as an incidental finding. In our study, radiographs of the shoulder were taken only if the children had clinically detectable deformity or shortening of the arm.

Our observations of osteopenia and evidence of fracture in the same bone as PEF although at a different site, are supported by the observations made by Currarino and Erlandson (*10*). It remains unclear whether the growth plate had sustained any trauma/micro trauma at the time of injury, which could have initiated the events leading to premature epiphyseal fusion (*16*).

We found no relationship of PEF's to sex, severity of the disease, degree of osteoporosis and frequency of transfusions. Interestingly PEF was found more frequently in thalassaemia intermedia patients who had received few or no transfusions.

We conclude that although the site and the radiological pattern of PEF's have generally remained the same, our observations suggest that clinically relevant PEF's are less common. We infer that a hyper -transfusion regime from the first year of life to maintain consistently pre-transfusional haemoglobin levels above 10 gm/dl in the first decade, is probably the single most important factor in decreasing the prevalence of PEF.

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