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Growth and development in thalassaemia major patients with severe bone lesions due to desferrioxamine

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Abstract Nine transfusion-dependent β-thalassaemia major patients (seven males and two females), aged 4–15 years, with growth retardation and severe rickets-like radiological lesions due to continuous subcutaneous chelation therapy with desferrioxamine (45–75 mg/kg body weight, 6–7 times/week), were seen in our centre during the last 8 years. Serum ferritin levels ranged from 976 to 4115 μg/l. There was a progressive decline in growth velocity in these patients 2–3 years before the appearance of rickets-like radiological lesions. All patients underwent surgery to correct genu valgum and/or slipped capital epiphyses. The final height was below the 3rd percentile in six patients (SDS: from –2.9 to –5.2). The short stature was mainly due to a disproportion between upper and lower segments. Six of the patients had an associated sensorineural hearing loss.

Conclusion Our data emphasize the importance of an accurate surveillance of the toxic effects of desferrioxamine treatment and warn of the risk of overtreating patients with low iron overload and also suggest a possible individual idiosyncrasy to the adverse effects of chelation therapy.

Key words Growth · Development · Thalassaemia major · Desferrioxamine · Bone lesions

Abbreviations *DFX* desferrioxamine · *IRMA* immunoradiometric assay

Introduction

In the late 1970s desferrioxamine (DFX, Desferal; Ciba-Geigy, Basel-Switzerland) was for the first time administered by continuous subcutaneous infusion over 10–12 h to patients with thalassaemia major to reduce tissue iron stores [9]. The data available in the literature indicate an improvement in survival of patients treated from early childhood using this method of administering DFX as an iron chelating treatment [14].

In recent years, however, various adverse effects have been described in transfusion-dependent anaemic patients who have received chelation therapy with DFX [1, 2, 4, 6, 7, 10, 15].

We report for the first time an analysis of data on the growth from childhood throughout adolescence into young adulthood in a group of thalassaemic patients with severe rickets-like radiological lesions due to continuous subcutaneous chelation therapy with DFX.

Patients and methods

Between April 1986 and November 1994, nine transfusion-dependent β-thalassaemia major patients (seven males and two females), aged 4–15 years, with short stature and/or reduced growth velocity who underwent surgery for genu valgum or slipped capital of femoral head, were seen in our centre. Three were prepubertal (Nos. 1, 3 and 9) and six (Nos. 2, 4, 5, 6, 7, and 8) were in the early to middle stage of puberty (Table 1). One patient was regularly followed in our centre (No. 7) and the remaining eight were referred

Table 1 Main laboratory data in thalassaemic patients with bone lesions due to DFX

Patient No	Sex	Age at first transfusion (m)	Annual blood consumption (ml/kg/year)	Dose of DFX (mg/kg/d)	Peak of serum ferritin level (μg/l)	Serum ferritin level at first signs of bone lesions (μg/l)	Urinary iron excretion (mg/24 h)	Liver enzymes[a]	
								ALT (IU/l)	γ GT (IU/l)
1	M	6	137	60	1665	976	–	8	10
2	F	10	189	45	1300	1300	16	36	8
3	M	3.5	136	65	3825	1590	10.2	62	12
4	F	14	153	50	2850	2185	8	361	7
5	M	13	190	50	4115	4115	15.2	57	11
6	M	2	–	60	3700	1700	–	29	11
7	M	22	170	75	1400	1000	13	8	11
8	M	11	145	55	2300	390	6.2	37	41
9	M	48	195	65	–	2995	9.4	277	26

[a] Normal range of serum alanine transaminase activity (ALT): 0–40 IU/l; and of serum gamma glutamyl transpeptidase activity (γ GT):7-50 IU/l

Table 2 Main clinical data, and description of surgery and associated complications in thalassaemic patients with bone lesions due to DFX (*ECP* chronic persistent hepatitis, *ECA* chronic active hepatitis; *SHL* sensorineural hearing loss)

Patient No	Age when chelation therapy started (years)	Age at diagnosis of bone lesions (years)	Age at surgery (years)	Surgery and associated complications
1	2.2	4	5	Bilateral femoral epiphysiodesis. Mild SHL
2	4	10	10	Fixture of the right femoral head. Mild SHL
3	2	7.3	13.6	Bilateral femoral epiphysiodesis
4	4	11.3	11.3	Bilateral femoral epiphysiodesis. ECP
5	2	12.8	13.4	Left femoral and bilateral tibial epiphysiodesis
6	2	13	16.2	Fixture of the right femoral head and left femoral epiphysiodesis. Severe SHL
7	2	15.6	16.4	Femoral and tibial epiphysiodesis bilateral. Mild SHL
8	6	13.6	15.11	Femoral and tibial epiphysiodesis bilateral. Mild SHl
9	3.6	10	10.11	Bilateral fixure of femoral head. Mild SHL. ECA

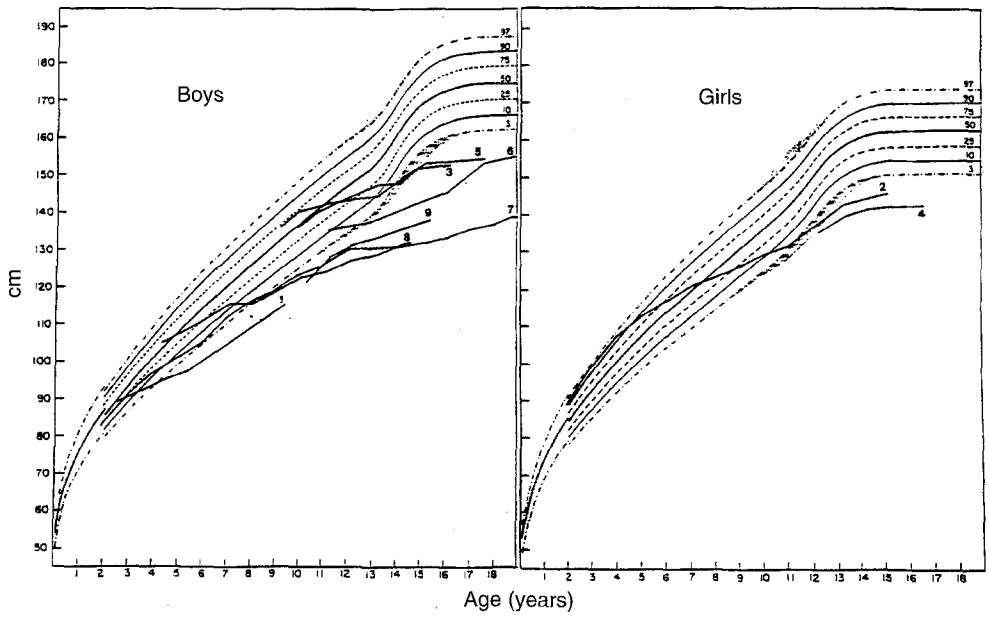

Fig. 1 Linear growth in seven males and two female thalassaemic patients with bone lesions due to DFX (numbers refer to the patients)

Table 3 Anthropometric data and pubertal maturation in thalassaemic patients with bone lesions due to DFX

Patient No	Height at diagnosis of bone lesions[a] (cm)	Age at onset of puberty (years)	Height at onset of puberty[a] (years)	Final standing height[a] (cm)	Final sitting height[a] (cm)	Parental target height[a] (cm)
1	95 (–1.5)	*	*	–	–	–
2	129.5 (–1.1)	10.6	134 (–0.8)	144.8 (–2.9)	71.6 (–5.4)	165.2 (–0.9)
3	113 (–1.7)	12.9	144.5 (–1)	153.2 (–3.3)	72.9 (–6.2)	175 (0.1)
4	135.1 (–2.8)	12.3	135 (–2.8)	143.6 (–3.1)	70.9 (–5.4)	158.7 (–0.6)
5	144.5 (–0.7)	12.3	144 (–0.7)	153 (–3.3)	73.1 (–6.1)	166.8 (–1.2)
6	141 (–1.7)	14	139 (–3.3)	154.7 (–3.1)	76.2 (–5.2)	168.5 (–1)
7	144.6 (–4)	14.4	129.8 (–5.2)	140.2 (–5.2)	71.6 (–6.6)	163.5 (–1.7)
8	131.9 (–6.2)	13.8	128.5	–	–	–
9	129 (–2.8)	14.7	134.5	–	–	–

[a] Numbers in parenthesis indicate the height standard deviation score (SDS)
* = prepubertal

to us for stunted growth or for a second opinion on their bone lesions. The diagnosis of β-thalassaemia major had been made on the basis of clinical and laboratory findings [19].

All patients had been transfused regularly with packed red cells from the first months of life until the present maintaining the pretransfusional haemoglobin level between 9.5 and 10.5 g/dl. None of them had splenectomy during the course of follow up. Blood consumption calculated according to Rebulla and Modell [16] varied from 145 to 195 ml pure red cells/kg per year (mean 164 ml/kg/year). The mean blood requirement in non splenectomized thalassaemic patients is below 180 ml/kg/ per year [16].

Clinical findings, linear growth and development

The major clinical features were short trunk with disproportion between upper and lower segments (mean ratio sitting height in boys 0.48 and in two girls 0.49), moderate sternal protrusion, genu valgum of variable severity and swelling of wrist and knees. There were also painful symptoms in the hips and/or feet with difficulty in walking, back pain and limited movements.

Six patients had mild or moderate sensorineural hearing loss and one had chronic active hepatitis, documented by liver biopsy (Table 2).

Over the whole period a progressive decline in growth velocity was observed in our patients (from 0 to 3.5 cm/year; mean 2.4 cm) 2–3 years before the clinical and/or radiological appearance of rickets-like radiological lesions (Fig. 1).

From the data available in five patients (Nos. 2, 3, 6, 8 and 9), we did not find any significant variation in linear growth after chelation therapy was reduced to between 30% and 50% of the initial dose or temporarily interrupted in the year following the appearance of bone lesions.

During the study there was evidence of spontaneous puberty in all patients who reached pubertal age. In the boys, the mean age at the appearance of a testicular volume of 4 ml was 13.6 years (range 12.3–14.7 years). Onset of puberty (Tanner stage II breast development) was observed at 10.6 and 12.3 years in the two girls whose menarche was at 13.4 and 13.5 years respectively. Total height increment reached from Tanner stage 2 to 5 varied from 9.7 to 13 cm in boys and was from 8.8 to 12 cm in girls.

The mean SDS final standing and sitting height was –3.4 and –5.8 respectively and the parental target varied from 0.1 to 1.7 SDS (Table 3) [18]. The mean SDS final height of the patients (–5.82 ± 0.56) was less than expected for the SDS parental target height (–0.89 ± 0.6; $P < 0.01$).

Bone lesions and X-ray findings

Bone lesions resembled those observed in rickets (Fig. 2). These lesions, multiple and symmetrical, were characterized by an increase in the thickness of the growth cartilage with enlargement and disfigurement at the cup of the metaphysis which had irregular features. The subchondral bone was of irregular thickness with small pseudocystic cavities with a small sclerotic border, more evident on the metaphyseal side. These lesions were more common in boys than in girls.

A marked platyspondylosis of the vertebral bodies in the dorsal and lumbar tract, a femoral genu valgum of variable severity and a diffuse osteopenia were also observed. Reviewing retrospectively the X-rays we saw that in some patients the wrists and/or knees were the first sites of the bone lesions.

In five patients (Nos 3, 6–9) it was possible to follow the metaphyseal lesions over time. The features were progressive and

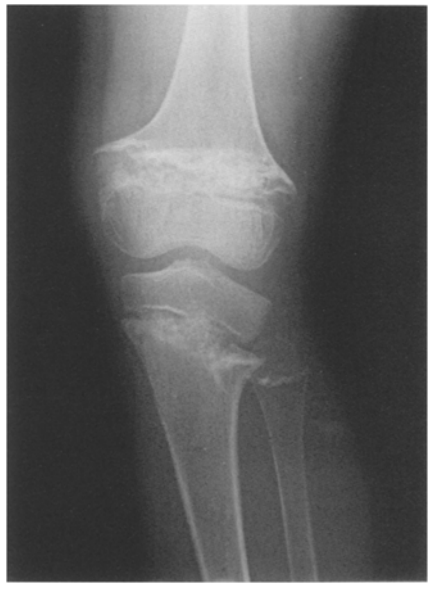

Fig. 2 Typical rickets-like radiological changes in a male thalassaemic patient who had been on high dose DFX

tended to extend to the diaphyses even if there was temporary interruption or reduction of the chelating dose (varing from 30% to 50% of the initial dose).

Due to the severity of metaphyseal bone changes all patients underwent surgery to correct genu valgum and/or slipped capital epiphyses (Table 2). During the follow up, six patients who had undergone femoral and/or tibial surgery showed metaphyseal osteosclerosis and partial fusion of growth cartilage.

Iron overload

The peak serum ferritin level in our patients ranged from 1400 to 4115 μg/l (mean 2644 μg/l), and at the time of diagnosis of the bone lesions, ranged from 976 to 4115 μg/l (mean 1805 μg/l). In four patients the serum ferritin concentrations were below 1500 μg/l and in two patients (Nos. 4 and 5) greater than 2000 μg/l. In both the latter patients a daily dose of DFX of 50 mg/kg day (6–7 days a week) was administered. Two patients (Nos 4 and 9) with serum ferritin levels over 2000 μg/l had elevated serum liver enzyme activities (Table 1). Urinary iron excretion ranged from 6.2 to 16 mg/24 h (mean 11.1 mg/24 h). The mean serum ferritin level in 36 thalassaemic patients (18 prepubertal and 18 pubertal) without bone lesions was 1957 and 2287 μg/l respectively.

Discussion

DFX chelation therapy is essential to prevent the harmful effects of iron overload in the heart, liver and endocrine glands [3, 20].

In the last 12 years a wide range of toxicities not previously described have been associated with DFX doses in excess of 50 mg/kg, and were of particular interest when standard doses were administered to patients with low iron load [1, 10, 15]. These adverse effects mainly include: cataracts, retinal damage with decreased vision, ototoxicity with sensorineural hearing loss and tinnitus and growth retardation with or without rickets-like radiological lesions [2, 5, 7, 13].

In this study we have shown a progressive decline in growth velocity from early childhood throughout adolescence in thalassaemic patients who developed severe bone lesions during DFX treatment. Growth failure was more pronounced 2–3 years before the radiological appearance of rickets-like radiological lesions and during the pubertal growth spurt. A significant reduction in standing height from diagnosis of bone lesions (mean SDS –2) to final height (mean SDS –3.4) was also observed in our patients. Lack of spinal growth was the main contributing factor to the reduction in growth potential and final height.

It is difficult to give an explanation for this. An adverse effect of chelation therapy in the aethiopathogenesis of short stature found in these patients seems to be confirmed by the fact that the only significant data which emerged from their examination were the presence of a discrete platyspondylosis of vertebral bodies similar to that observed in thalassaemics with bone lesions known to be from DFX [7, 9, 15].

The pathogenesis of toxic lesions resulting from DFX and affecting growth and bones is not clear. Different mechanisms may be postulated: chelation of trace elements [7], inhibition of cellular proliferation [17] and a direct adverse effect of the drug and its metabolites on bones, as a consequence of slow DFX clearance [11].

Although, in this study, we have not observed an improvement in severe rickets-like radiological lesions on linear growth after a temporary interruption or reduction of the DFX dose, evidence of healing and filling in of bone at the periphery of knee metaphyses after 9 months of reduction of DFX doses was reported by Brill et al. [2] and an improvement in growth velocity has been reported by Elena et al. [8].

In some of our patients bone lesions occurred despite a relatively high serum ferritin level. In particular, in two patients with a serum ferritin concentration greater than 2000 μg/l (2185 and 4115 μg/l) the standard daily dose of 50 mg/g per day caused DFX toxicity and therefore it seems that there is an individual idiosyncrasy to the adverse effects of DFX as it has been thought that DFX toxicity is only seen where there is minimal iron overload or as the result of large DFX doses [12].

The results of our study and the data reported in the literature emphasize the importance of an accurate surveillance of the toxic effects of DFX-treatment and warn of the risk of overtreating patients with low iron overload, and also suggest that there is no clear uniform threshold of DFX dose at which this severe metabolic bone disease might be predicted for an individual.

Growth should be monitored routinely at every follow up visit in order to detect any decline in growth velocity and to establish an appropriate protocol for investigations and treatment. Metaphyseal bone changes in wrists and/or knees may be detected at an early stage. From the practical point of view the recognition of the X-ray findings is important since it would enable us to identify patients who need accurate and regular follow up in order to prevent the progression of bone lesions. When they are found the nightly dose of DFX should be reduced to the lowest level that results in a negative iron balance or temporarily stopped, followed by reintroduction at a much reduced dose.

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