Studia Medyczne Akademii Świętokrzyskiej tom 4
Kielce 2006

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GROWTH AND ENDOCRINE COMPLICATIONS IN THALASSAEMIA: THE FERRARA EXPERIENCE

SUMMARY

Patients with thalassaemia are now surviving into their fifth decade of life; however, many show problems with growth and sexual development in their adolescent years. In this review the clinical manifestations and management of growth and endocrine complications in these patients are presented.

Key words: thalassaemia, growth, endocrine complications.

INTRODUCTION

The haemoglobinopathies (thalassaemias and sickle-cell disease) are the most commonly inherited genetic disorders world wide with some 240 000 infants born annually with major haemoglobinopathies and at least 190 million carriers world wide. They are all inherited in a mendelian recessive manner so the person with the carrier or trait state is healthy.

PATHOPHYSIOLOGY

The basic genetic defect results in the destruction of the thalassaemic red cells before the erythroblasts are well haemoglobinized; this is a consequence of the imbalance between the production of the α- and β-globin chains. This results in ineffective erythropoiesis leading to severe anaemia, increased production of erythropoietin and expansion of the bone marrow by 15 to 30 times the normal. This marrow expansion results in distortion and fragility of the bone and an increased blood volume. The reticuloendothelial cells become congested by these abnormal red cells and consequently hepatosplenomegaly develops.

TREATMENT

The recommended treatment for thalassaemia is regular blood transfusions and chelation therapy, maintaining the overall mean haemoglobin level of about 12 g/dl. Pre-transfusion haemoglobin should be 9.5 g/dl whereas post-transfusion haemoglobin should be a maximum of 14-15 g/dl. The aim is to transfuse 10-20 ml/kg body weight of packed filtered red cells over a period of 2-3 hours throughout life. This ensures that erythroid marrow suppression preserves excellent health and normal development. The effectiveness of blood transfusion can be measured and frequency calculated from the rate of haemoglobin fall. In a splenectomized patient the fall is 1.0 g/dl of haemoglobin a week, in a non-splenectomized patient it is 1.5 g/dl.

COMPLICATIONS OF THALASSAEMIA MAJOR

Most of the complications are attributable to iron overload which may be the result of economic circumstances (expense of the chelation therapy), late onset of chelation therapy or poor compliance with the desferrioxamine treatment. Compliance is the major problem in Europe and North America. In iron overload, excess iron deposited in the tissues causes damage. Toxicity starts when the iron load in a particular tissue exceeds the tissue or blood-binding capacity of iron, and free non-transferrin iron appears. The 'free iron' is a catalyst of the production of oxygen species that damage cells and peroxidize membrane lipids leading to cell destruction.

We report our personal experience on growth and endocrine complications in 165 patients with b thalassaemia major (their mean age is 26.5 ± 6.1 years – range 7-41 years) regularly followed in our Centre. All patients are treated with regular blood transfusions to maintain a mean haemoglobin level of 10 g/dl. Chelating therapy with desferrioxamine (DFX) (Desferal, Novartis) was given intramuscolarly, until 1978 and thereafter by the slow subcutaneous route. Initially the dose of DFX was 20 mg/kg b.w. (3-4 times/week) and from 1984 was 40-55 mg/kg b.w. (5-6 times/week). At present they receive a mean DFX dose of 38 mg/kg b.w. Compliance to treatment was good from 1987 in 80% of patients.

Growth

Over the years, many causes have been put forward to explain the short stature in thalassaemics. However out of specific well recognized pathologies the etiopathogenesis is still an intriguing problem [1].

In the past, the growth retardation has been mainly attributed to iron overload in the tissues and endocrine glands, chronic anaemia, hypersplenism, folic acid deficiency, delayed or absent puberty. In 1988, a direct toxic effect on the bones has been observed in patients, before puberty, receiving continuous s.c. chelation therapy [2].

Because modern chelation therapy was introduced 25 years ago the group of patients attending our clinic have had different length chelation therapy and transfusional regimes. Height above the 10th centile was achieved in 50% of males and 64% of females. A decanalization of growth due to reduced growth spurt has been observed in a retrospective analysis of our patients who were regularly transfused and chelated from the age of 2 years or later.

It is difficult to give an explanation for this. An individual idiosyncrasy or an adverse effect of chelation therapy in the etiopathogenesis 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 platyspondilosis of vertebral bodies similar to that observed in thalassaemics with bone lesions known to be from DFX. In few cases a marked body disproportion was observed in our adult patients who had been only poorly chelated i.m. before reaching adult height [3, 4]. In few cases a marked body disproportion was observed in our adult patients who had been only poorly chelated i.m. before reaching adult height.

In the severe form of desferal 'toxicity' the growth velocity/year is markedly reduced or absent. The clinical picture of these patients is charactherized by short trunk, moderate sternal protrusion, swelling of wrist and knees and genu valgum of variable severity. In some patients back pain, bone pain and limitations in movement are also present [1, 5, 6].

In recent years we have observed similar signs in 12 thalassaemic patients, aged from 3 to 16 years. Five patient had surgery of the femoral and/or tibial epiphyses ant two had fixture of the femoral head for a marked genu valgum or slipped capital epiphyses. Reviewing retrospectively the X-rays of these patients we saw that the distal ends of the ulna and radius were usually the first site of the bone lesions. Initially the affected metaphyses appeared concave and widened and later they became cupped. Subsequently, the changes proceded from the metaphysis to the diaphysis and metaphyseal line of variable gravity.

From the practical point of view the recognition of these findings is important since it would enable us to identify the patients who need an accurate and regular follow-up in order to prevent the progression of bone lesions. During follow-up we saw evidence of marked stunting of growth in all such patients who reached their final stature.

Using microradiography and X-ray diffraction (XRD), we found in thalassaemic subjects a reduced and irregular mineralization of the bone (compared with controls). Bone tissue microhardness was also significantly reduced. Nevertheless, bone apatite lattice was unalterated and no 'foreign' crystallographic phase was recorded by XRD [5].

Abnormal chondrocytes, alteration of cartilage staining pattern, irregular columnar cartilage, and lacunae in the cartilaginous tissue were revealed histologically. Osteoid thickness was either normal or slightly increased. Some bone trabeculae had microfractures and some had cartilaginous oases. In some cases, iron deposition was detectable by Perls' Prussian Blue staining [6].

Treatment of bone lesions from DFX

The first patient came under our care from another centre at the age of 6y 10m. His weight – 23 Kg and height – 121 cm were at 50th centile (c). Since then he has continued to be treated with transfusions on an average every 21 days at 10-15 ml/kg. Pre-transfusion Hb was between 9.2 ± 0.5 g/dl and 11.3 ± 0.5 g/dl and post-transfusion Hb was between 10.8 ± 0.8 g/dl and 13.1 ± 0.6 g/dl with an annual consumption of red blood cells per Kg varying from 120 ml to 140 ml (mean 126 ml). Iron chelation until the age of 12y 4 m was with subcutaneous DFX. The average dose per year varied from 37 mg/Kg/d to 44.6 mg/Kg/d with serum ferritin values varied from 836 ng/ml to 3595 ng/ml.

Over the years he had a progressive decrease in growth velocity between the ages of 7y 2m and 12y 2m, from –0.9 to –3.1 Standard Deviation Score (SDS), with decline of the growth curve from 50th c (+0.5 SDS) to 10th c (–1.1 SDS). The sitting height between the ages of 10y 2m and 12y 2m showed a decrease in SDS from –1.4 to –2.6.

An X-ray of the vertebral was done and a flattening of the vertebral bodies (platyspondilosis) at the dorsal-lumbar region was demonstrated. For assessment of the growth defect an endocrine evaluation was performed at the age of 11y 8m (GH, thyroid function, hypotalamic-pituitary gonadal function). All results were normal.

The bone age, assessed by Tanner and Whitehouse, corresponded to chronological age. Pubertal development started spontaneously at the age of 12y 2m and was followed 4 months later by the appearance of a marked genu valgum with rickets-like radiological lesions typical of DFX toxicity.

An X-ray and MRI of the knees showed richets-like radiological lesions, bilaterally. It was decided to stop the chelating therapy with DFX and start with the oral chelator deferiprone (L1) at a dose of 75 mg/Kg/d. X-rays and/or MRI of the knees were done 1y and 2y after the start of L1 chelation therapy and showed a progressive improvement of the bone lesions which had disappeared by 2y. Clinically we witnessed a marked reduction of genu-valgum of the knees and an increase in the growth velocity (from –3.1 to –0.3 SDS). However, the sitting height had decreased further (from –2.6 to –3.6 SDS), confirming the irreversibility of platyspondilosis, so affecting the final standing height which was at the bottom of the potential genetic target.

The second thalassaemic female patient (9 years old) developed short stature and osteochondrodystrophic lesions during therapy with desferrioxamine (DFX). Healing was noted after the dose of DFX was decreased for 3 years. Unfortunately the spinal cartilage abnormalities did not change suggesting an irreversibility of the ossification process [7]. In few cases a marked body disproportion was observed in our adult patients who had been only poorly chelated i.m. before reaching adult height.

Growth hormone and insulin-like growth factor axis (GH-IGF1 axis)

Although GH secretion appears to be normal in many thalassaemic patients with short stature, there is evidence indicating a dysfunction of the GH-IGF1 axis in some of them (3.1% of 598 Italian thalassaemia major patients, personal observations) [4]. Several mechanisms have been suggested to cause disorders of GH secretion:

- Neurosecretory dysfunction,
- Hypothalamic GH releasing hormone deficiency,
- Pituitary GH deficiency,
- Increased somatostatin activity.

Eight prepubertal thalassaemic patients: 6 males and 2 females, ranging in age from 9.2 to 11.7 years, were treated with rechGH. The criteria for study inclusion were:

a) height below the 3rd centile,
b) reduced GH response (less than 10 ng/dl) to two stimulation tests,
c) growth velocity less than 10th percentile for bone age, in the last 12 months of observations.

The serum ferritin level ranged from 900 to 3840 ng/ml. RechGH in a dose of 0.6 UI/kg per week was given subcutaneously in 6 divided doses for 4 years. Bone age was determined at the start and after one year of treatment. Venous blood samples were taken periodically to monitor biochemical, haematological and endocrinological parameters.

After the first 12 months of rechGH treatment a significant increase of growth velocity was observed in 6 patients who doubled growth velocity before basal value (4 cm or more), 2 patients had a partial response (growth increment between 2 and 4 cm/year above the basal value). A better growth response was observed in patients with serum ferritin levels < 2000 ng/ml. One patient developed during the study an abnormal oral glucose tolerance test.

In the following 3 years all thalassaemic patients had a partial response to the treatment with rechGH. None of the patients had a significant advancement in bone age during the treatment.

In conclusion, despite somewhat reduced sensitivity to rechGH, compared to GH deficiency children, there is evidence indicating that thalassaemic patients may benefit from rechGH treatment.

These data also indicate that higher doses of rechGH may be required to obtain an improvement in growth velocity. Glucose tolerance must be controlled in these patients as they are at risk to develop an abnormality of glucose tolerance [4].

A practical approach to clinical evaluation and treatment of thalassaemic patients with short stature [7, 8] is reported in table 1 and 2.

Table 1. Clinical and laboratory evaluation in well treated and chelated thalassaemic patients with short stature

1. Auxological examination and pubertal staging a. Birth data b. Standing height c. Sitting height d. Height measurement of both parents e. Calculation of mid-parental percentile f. SPAN g. Tanner's stage: pubic hair (PH 1-5) breast (B 1-5) testicular volume (ml)
2. Assessment of skeletal maturity
3. Routine biochemical analysis
4. Plasma zinc
5. Antigliadin antibodies
6. Thyroid function and hypothalamic-pituitary gonadal axis (if necessary)
Notes: *Interpretation of results*: the normal range of plasma zinc concentration using atomic absorption spectrophotometry is 11-19 µmol/l. In mild deficiency it is between 7-10 µmol/l, in severe deficiency it is less than 7 µmol/l.

Table 2. Prevention and treatment of skeletal dysplasia due to desferrioxamine (DFX) in patients with thalassaemia major

1. DFX doses should be established on the basis of iron balance and dose response curves
2. DFX administration should be initiated only after iron accumulation is established
3. A dose of DFX greater than 50 mg/kg of body weight should not be used
4. The dose of DFX should be reduced in patients with reduction in growth velocity and serum ferritin consistently below 1500-1000 ng/ml
5. A temporary withdrawal of chelation therapy followed by deferiprone (L1) therapy or a reintroduction with low DFX dose should be undertaken in thalassaemic patients with severe toxic lesions from DFX.

Endocrine complications

Hypogonadism is the commonest endocrine complication [1, 3]. Thalassaemic girls who reach menarche have increased progressively from 1970. At the same time, however, we have observed a parallel increase of the percentage of thalassaemic girls who develop SA. There is an adverse correlation between age at menarche and length of menstrual activity. This can be due to the fact that menarche is more delayed in thalassaemic with more severe endocrine impairment. SA is mainly due to damage of pituitary gland.

Failure of pubertal development has been observed in 43% of patients over the age of 16 years. In some patients, this was thought to be primary gonadal in origin, whereas in others it was postulated to be secondary to pituitary insufficiency or to a combination of both primary and secondary hypogonadism.

The anterior pituitary glands is particularly sensitive to free radical oxidative stresses and exposure to this. Magnetic resonance imaging (MRI) shows that even a modest amount of iron deposition within the anterior pituitary can interfere with its function.

Hystologically a reduced number of cells and moderate siderosis of the parenchymal cells of the anterior pituitary have been found in these patients. Testicular biopsies show various degrees of interstitial fibrosis and hyperpigmentation of undifferentiated seminiferous tubules and a decreased number of Leydig cells. Tickened stroma of ovaries with occasional iron-containing macrophages and a reduced number of primordial follicles have been reported [1].

Other possible cause of hypogonadism in b thalassaemia major include liver disorders, chronic hypoxia, diabetes mellitus and zinc deficiency [3]. In our experience SA and hypogonadism carry a bad prognosis with a little change of spontaneous recovery.

The treatment of pubertal disorders consists of hormone replacement therapy with sex steroids. Successful induction of spermatogenesis and ovulation have been reported after hormonal stimulation with gonadotrophins. These results are good and should encourage further thalassaemics to comply with their chelation therapy.

The significant improvement in the prognosis for length of survival of these patients, the high incidence of hypogonadism and the association with other pathologies raise a number ethical and clinical questions. In particular, what should be our attitude to a patient with multi-organ damage when asking for induction of ovulation or spermatogenesis? We think that this aspect should be discussed in an ethical committee and their recommendation should be followed. What is the life expectancy of these patients? It is difficult to give a definitive answer to this. The condition of some of our patients with thalassaemia major is good 10 years after pregnancy and their compliance towards chelating therapy is excellent.

Hypogonadism causes osteopenia and osteoporosis, therefore a measurement of bone density should be performed using a dual-rays absorpiometry (DEXA) in all

patients. A bone density below normal was observed in 81% of patients. A negative correlation between the degree of osteopenia, weight and height and a positive correlation with the osteopenia, osteoporosis, duration of amenorrhea and age have been observed in our thalassaemic patients. In well established osteoporosis therapeutic option include the use of bisphosphonates.

Hypothyroidism

This endocrine complication is common in patients who are anaemic and/or poorly chelated (17%) but is rare in patients who are well treated [1].

Three types of thyroid dysfunction have been recognised: *pre-clinical* – the classical symptoms of hypothyroidism are absent; the serum FT4 is normal; TSH marginally increased and TSH response to TRH is increase; *mild hypothyroidism* growth retardation, tiredness and dry skin may be present, serum FT4 is marginally low whilst TSH is elevated and TSH response to TRH is exaggerate. In *severe hypothyroidism* short stature, decreased activity, dry skin, cardiac failure and pericardial effusion may be present. The serum FT4 is low, TSH elevated and TSH response to TRH is exaggerate.

Treatment depends on the severity of the organ failure [3]. For severely affected patients gradual replacement with L-thyroxine is recommended. In mild hypothyroidism the decision to treat depends on each individual case. Preclinical hypothyroidism requires only careful follow-up. In these cases we have observed that a good compliance to chelation therapy in iron overloaded patients may improve the thyroid function. In 52% of thalassaemic patients with preclinical hypothyroidism the thyroid function was restored to normal following intensive s.c. chelation therapy.

Carbohydrate homeostasis

Impaired glucose tolerance and diabetes mellitus are frequently observed complications in patients with thalassemia. The incidence varies between 5-15% in the Mediterranean countries [1]. The onset of diabetes in the majority of patients occurs after the age of ten. There is no obvious difference between the sexes. The onset of diabetes in the majority of patients occurs after the age of ten.

Impaired glucose tolerance and diabetes mellitus may be the consequence of beta cell destruction secondary to iron overload, chronic liver disease, viral infection and genetic factors. In the pancreas iron deposition in the interstitial cells results in excessive collagen deposition and defective in micro-circulation. Impaired oxygen supply eventually leads to insulin deficiency. Insulin-dependent diabetes in thalassaemia shows unusual characteristics compared with type 1 diabetes:

– ketoacidosis is rare presenting symptoms,
– renal glucose threshold is rare,

– islet cell antibodies are negative,
– there is no association with HLA haplotypes.

Whilst impaired glucose tolerance is asymptomatic, diabetes mellitus itself presents with the classical symptoms, accompanied by ketosis. Biochemical diabetes may be reversible.

Hypoparathyroidism

Hypoparathyroidism is a late complication of the iron overload and/or anaemic thalasseamia patient. The incidence of this complication is 3.6%. The majority present after the age of 16 years and both sexes are equally affected [1].

Hypoparathyroidism is thought to be the consequence of iron deposition in the parathyroid glands or the suppression of parathyroid secretion induced by bone reabsorption resulting from increased haematopoiesis secondary to the chronic anaemia. The majority of patients have a mild disease with paraesthesia only while in the more severe, tetany seizures or cardiac failure may occur.

Laboratory findings are: low serum calcium, increased serum phosphate, low or inappropriately normal parathyroid hormone for the serum calcium level and low levels of 1,25 dihydroxy-vitamin D. Twenty-four-hour urinary calcium and phosphate excretions are reduced. Radiological changes in the bones include osteoporosis with trabecular destruction and cod-fish deformities of the vertebrae. Treatment is with oral vitamin D or one of its analogues.

CONCLUSIONS

These results suggest that an ideal therapeutic regime, which avoids the toxic effects of iron overload and of continuous s.c. chelation therapy has not yet been found, and therefore further studies and long term observations on the effects of s.c. chelation therapy are needed before this intriguing puzzle is solved.

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