Thalassemia major. A report of two cases with severe skeletal involvement

A. Lešić1, A. Bogdanović2, V. Sudjić1, N. Suvajdžić-Vukovic2, HDE Atkinson3, M. Bumbaširević1

1Institute for orthopaedic surgery and traumatology, CCS, School of Medicine, Belgrade
2Institute for hematology, CCS, School of Medicine, Belgrade
3North London Sports Orthopaedics, Department of Trauma and Orthopaedics, North Middlesex University Hospital, London, UK.

Learning objective: To present two cases of severe skeletal involvement in thalassemia major.

INTRODUCTION

Thalassemia is a genetic disease which affects the production of one or more globin chains (alpha, beta, gamma and delta), resulting in a depletion or loss of hemoglobin function. The disease has several clinical entities including thalassemia minor (a mild heterozygous trait/carrier state), thalassemia intermedia (a severe heterozygous disease), and thalassemia major (homozygous disease), the most severe.

Beta thalassemia major is rare in Serbia. Previously incurable, affected patients now live to adulthood with regular blood transfusions. The improvement in supportive treatment over recent decades has given rise to many more patients suffering from the associated metabolic complications of anaemia and iron overload, such as osteopenia and other skeletal changes. We present two patients with severe beta thalassemia major from early childhood, who encountered pathological long-bone fractures during the clinical course of their disease. One suffered a distal femoral diaphyseal fracture, and the second a distal tibia fracture. Both fractures occurred in osteopenic bone and were managed non-operatively due to the patients’ general medical condition. Despite intense medical intervention, both patients died from disease progression within one year of their fractures, aged 23 and 24 years. As life expectancy rises it is anticipated that an increasing number of patients suffer from the secondary metabolic effects of the disease, including osteoporosis and its related fractures.

CASE REPORTS, MATERIAL AND METHODS

First patient, VP born in 1981, was diagnosed with beta thalassemia major and the Lepore hemoglobin variant at the age of 18 months. He was treated with intermittent blood transfusions and subcutaneous deferoxamine infusions, and underwent splenectomy at the age of 9 years. His early childhood development was not significantly affected. In 1999 he was referred to our Institute because of a deteriorating condition. On examination he was found to have many clinical features of secondary hemosiderosis, including bronze skin hyperpigmentation, hepatomegaly 10 cm below the right costal margin (RCM), hypogonadism, and diabetes. Laboratory analyses demonstrated severe anemia with leukoerythroblastic differential and signs of liver decompensation due to secondary hemosiderosis (AST 95U/L, ALT 60U/L, AP 130U/L, gGT 35U/L, LDH 598U/L) with markedly elevated ferritin 7420 mcg/L (normal limit 500 mcg/L). The patient was commenced on regular transfusions of filtrated red blood cells (PRBC) and chelating agents (deferoxamine), the survival of patients improved. However, an increasing number of patients suffer from the secondary metabolic effects of the disease, including osteoporosis and its related fractures.

Key words: Beta thalassemia major, osteopenia, long-bone fracture
In August 2004 the patient suffered a spontaneous stress fracture of the distal femoral diaphysis. There had been no prodromal symptoms or prior clinical skeletal problems. The patient had delayed bony union and ongoing pain following conservative management in plaster cast (Figures 1, 2). Radiographs showed rarefaction of the cancellous bone, loss of cortical thickness and widening of the intramedullary canal (Figure 3). Similar osseous changes were also noted in both humeri. The lumbar spine was osteopenic and the L2 vertebra had loss of height.

The patient’s condition continued to deteriorate, with a more prominent anemia and increased transfusion demands, with further deterioration in liver function. The patient died in July 2005 at the age of 23 from progressive hepatic failure.

Second patient, ZV born in 1976 had the Yugoslav-defined beta thalassemic homozygous mutation and the Hemoglobin Lepore variant, and was diagnosed with beta thalassemia major at the age of 2. She underwent splenectomy at the age of 16 in an attempt to reduce the number of hemolytic crises, and was included in the 1996 trial with hydroxyurea (350mg/d) and sodium butyrate.

She was referred to our Institute in 2000 at age of 24, with a severe deterioration in her general health, signs of hepatic insufficiency and severe endocrine dysfunction (insulin dependent diabetes mellitus and amenorrhea). The patient had also recently developed severe bony pain in the axial skeleton and in all four limbs from bone marrow hyperplasia (Figure 4), and had sustained a fracture of the distal tibia immediately prior to hospital admission. The fracture was treated with manipulation and plaster cast immobilization, but failed to show any signs of bony union by 3 months. On admission her Karnofsky index was 30% and ECOG performance was 3. She had severe hemolytic anemia as a part of the thalassemia syndrome with leukoerythroblastic differential. Ferritin levels were not determined due to technical reasons, and transferrin saturation was 81%. She also had hepatomegaly 7cm below the RCM, with deranged liver tests, ALT 32U/L, AST 55U/L, AP 97U/L, LDH 650U/L. She developed a deep vein thrombosis in her injured leg shortly after admission, despite thromboprophylaxis, and died from hepatic insufficiency at the age of 24.

Both patients had small stature, and were below the 5th centile for height. Neither had trophic changes or legs ulcers, or a prior history of skeletal problems, and both had erythroblastosis without particularly marked rises in alkaline phosphatase.

**DISCUSSION**

The underlying mechanisms of skeletal involvement in thalassemia are complex. Patients suffer hemolysis and subsequent tissue hypoxia, as a result of their globin dysfunction. As other regulatory mechanisms are preserved, patients develop intramedullary bone marrow hyperplasia in reaction to this hypoxia. It is now recommended that patients be transfused to hemoglobin levels of 110-120 g/L to decrease tissue hypoxia and erythropoietin secretion. Splenectomy is also indicated in severe forms of hemolysis.

Hemosiderosis of the hypophysis, pancreas and other organs, secondary to hemolysis and multiple PRBC transfusions, leads to many endocrine and metabolic changes. These endocrine changes affect the process of ossification and lead to delays in bone maturation, premature epiphyseal fusion, a decrease in cortical bone thickness, abnormalities in remodeling and arthralgia. Some have suggested treating thalassemic osteopenia with dietary supp-
lements such as 1200mg calcium daily (in the adolescent population), vitamins D, B6, B12, and K together with physical exercise and training\textsuperscript{3,4}. Hormonal treatment (estrogen, testosterone) is indicated where there is hypogonadism, and calcitonin and bisphosphonates when treating osteoporosis\textsuperscript{6}.

Thalassemia major typically develop enlargement of the centers of ossification of the frontal bones leading to thickening of the skull (caput quadratum), and earlier ossification and premature fusion of the epiphyses, affecting longitudinal growth; the humerus is typically more affected than the femur\textsuperscript{9}. The spine is also commonly affected by scoliosis, kyphosis, and osteoporosis. Despite supportive treatment fractures are common affecting around 30\% of patients (with 20\% suffering multiple fractures)\textsuperscript{2}. The femur and tibia are the most affected bones, with two peaks in the incidence of femoral fractures (at 5-12 years and 14-17 years)\textsuperscript{8}.

Thalassemia patients with bone pain should undergo radiography. Our patients were found to have typical decreases in the cortical bone thickness, and dilated metaphyses. Patients may also have "punched-out" osteolysis, Erlenmeyer bone deformities, Schmörl nodes and bony deformity angulations and bone shortening (our X-ray of humerus). Fracture lines are generally transverse, and bone scintigraphy and MRI can reveal microfractures, especially around the ankles\textsuperscript{9,10}. Differential diagnoses should also be borne in mind, such as vitamin D resistant rickets, osteomyelitis, leukemia, lymphoma, and metastases.

Fractures in thalassemia major patients are preferably managed non-operatively as the bone is often not strong enough to accommodate the implants\textsuperscript{11}; obvious exceptions include femoral neck fractures where internal fixation is more appropriate. Though callus formation is unusual, the bone healing time is generally normal or slightly prolonged. This is not the case in patients with severe anemia where delayed union may develop (as was seen in our two patients). Refractures are common, though bone remodeling can be good, and osteotomies can be performed for residual limb deformity.
Our patients’ long-bone fractures coincided with their general clinical deterioration, and both died of hepatic failure within a year despite intensive supportive care. It thus appears that these fractures may both herald and contribute to a terminal phase in beta thalassemia. It is hoped that the significant morbidity and mortality associated with severe form of this disease will be resolved through advances in stem cell grafting and better other supportive and chelating treatment with new oral agents.

**SUMMARY**

**BETA TALASEMIIJA. PRIKAZ DVA SLUČAJA SA FRAKTURAMA DUGIH KOSTIJA**


Ključne reči: beta talasemija maior, osteopenia, frakture dugih kostiju.

**BIBLIOGRAPHY**


**NAPOMENA**: Izrada rada je potpomognuta projektom Ministarstva za nauku i tehnološki razvoj Srbije.