*Rom J Leg Med [28] 212-217 [2020]*
*DOI: 10.4323/rjlm.2020.212*



# EXTRAMEDULLARY HEMATOPOIESIS IN BETA THALASSEMIA MAJOR - CASE PRESENTATION

Adriana Diaconu[1,2], Bogdan-Ioan Coculescu[3,4,*], Oana Rizea[1,2], Vlad Herlea[2], Horatiu Vultur[1]

*[1]"Carol Davila" University of Medicine and Pharmacy, [2]Fundeni Clinical Institute, [3]Center for Military Medical Scientific Research, [4]"Titu Maiorescu" University, Faculty of Medicine, Bucharest, Romania*

**Abstract:** *Background.* In beta thalassemia major, extramedullary erythropoiesis, defined by the occurrence of hematopoietic tissue sites outside of the hematogenic bone marrow, appears as a compensatory mechanism for ineffective erythropoiesis, suggesting an inadequate transfusion regimen (increased transfusion necessary or inadequate transfusion program).

*Methods.* We present the case of a 19-year-old teenager who reflects severe complications due to an inappropriate transfusion and iron chelation regimen, with physical development retard, extramedullary hematopoiesis and global hemochromatosis (hepatic, cardiac and endocrinological). The diagnosis of hepatic extramedullary hematopoiesis was confirmed histopathological by ultrasound guided biopsy.

*Results.* Under classical/conservative treatment, evolution was favorable, with satisfactory physical development, endocrine acquisitions and significant reductions from severe to mild global iron overload.

*Conclusions.* In beta thalassemia major, both transfusion treatment for periodic correction of anemia and continuous iron chelation therapy to minimize post-transfusion secondary hemochromatosis are equally essential for the survival of these patients.

**Key words:** beta thalassemia major, hepatic extramedullary hematopoiesis, severe secondary hemochromatosis.

## INTRODUCTION

Beta thalassemia major (Cooley anemia) is a severe recessive autosomal hereditary anemia characterized by a much reduced human haemoglobin A (α2β2) synthesis. This is due to the existence of varied defects at both β-globin genes of an individual, resulting in low production, to the absence of both β-globin chains [1-3].

In order to survive, these patients require periodic transfusion therapy every 2 to 5 weeks at pre-transfusion haemoglobin (Hb) levels of 9-10.5 g/dL, correcting the anemia, avoiding excessive erythropoiesis and reducing hemochromatosis by decreasing the transfusion input and intestinal absorption of iron [3-6]. Because the human body does not have elimination mechanisms of excessive iron accumulation, it is necessary to associate iron chelation therapy in children over 2 years of age when the serum ferritin value exceeds 1000 ng/mL [7].

Thus, correct treatment (both transfusion and chelation) will ensure harmonious growth and development, reduce hemochromatosis and increase long-term survival and quality of life of these patients [2, 3, 8-10].

## MATERIAL AND METHODS

We present the case of a 19-year-old patient diagnosed with beta thalassemia major, splenectomized patient at age 6, in the evidence of another hospital, presenting to our Clinic by transferring from a territorial hospital for significant hepatomegaly with the presence of hepatic nodules.

From the therapeutic history we note that the transfusion regimen was constantly performed at pre-

*Correspondence to: Bogdan-Ioan Coculescu, "Titu Maiorescu" University, Faculty of Medicine, 67A Gheorghe Petraşcu Bucharest, Romania, Tel.: +40722600890, E-mail: bogdancoculescu@yahoo.fr

transfusion hemoglobin values below 6-7 g/dL, and the iron chelation treatment with Deferoxamine was administered at doses of 25 mg/kg/day - 5 days per week, irrespective of the value of serum ferritin.

The clinical examination at admission revealed an non-febrile patient with good general condition, pale skin, sclera-tegument jaundice, thalassemic facies (mongoloid), weight state hypotrophy - weight (W) = 41.7kg, height (H) = 146 cm -, thorax with flared base, normal pulmonary stethacoustic, ventricular rate = 110 beats/min, left parasternal space II systolic murmur grade VI/VI, anamnestic with episodes of spontaneously submitted palpitations, important hepatomegaly that occupies all right hemiabdomen up to the right iliac fossa, delayed puberty (absent thelarche, amenorrhea, absence of pubarche).

## RESULTS

Hematological investigations were suggestive in the context of transfused major thalassemia with anemia (Hb = 8.4 g/dL, HCT = 27.1%, MCV = 85.2 fL, MCH = 26.4 pg, RBC = 3.18 x 106/mm$^3$, RDW = 19.9%, RT = 1%), post-splenectomy thrombocytosis (PLT = 910000/mm$^3$), WBC = 12300/mm$^3$, peripheral blood smear: hypochromia, target red blood cells, erythroblasts = 25%, leucocyte formula: S = 63%, E = 5%, B = 1%, L = 22%, M = 9%. Positive inflammatory biological syndrome (ESR = 100 mm/1h, CRP = 9.75 mg/L, fibrinogen = 445 mg/dL), important hepatic cytolysis syndrome (ALT = 159 U/L, AST = 142 U/L) with normal coagulation samples (PT = 13.8 sec, AP = 74.8%, INR = 1.24, APTT = 34 sec), mildly elevated bilirubin and sideremia within the chronic hemolysis (total BRB = 1.6 mg/L, sideremia = 208 μg/dL), extremely high serum ferritin (7513 ng/mL) - expressing either severe haemochromatosis or marked inflammatory status associated with post-transfusion secondary hemochromatosis, or both.

In order to identify the hepatomegaly etiology, a series of tests were performed: viral serology for hepatitis B and C virus and HIV were negative, tumor markers were also negative (AFP = 4.1 ng/mL, CEA = 0.11 ng/mL). All of the abdominal imaging exams (ultrasound, computer tomography – Figs 1-4, angio-NMR – Fig. 5) reveal important hepatomegaly, the inferior hepatic pole exceeding the lower iliac right crest with a non-homogeneous aspect with multiple nodular lesions in both lobes, round-ovate or polycyclic contours with a maximum diameter of 3.2 cm, which does not show arterial flash and is minimally loaded with the contrast substance; multiple centimeter and smaller adenopathies in the mesentery and upper and middle lombo-aortic groups. The described aspects were not pathognomonic for a particular pathology, which is why liver-biopsy puncture was performed under ultrasound guidance. Histopathological examination reveals outbreaks of extramedullary hematopoiesis, groups of hepatocytes

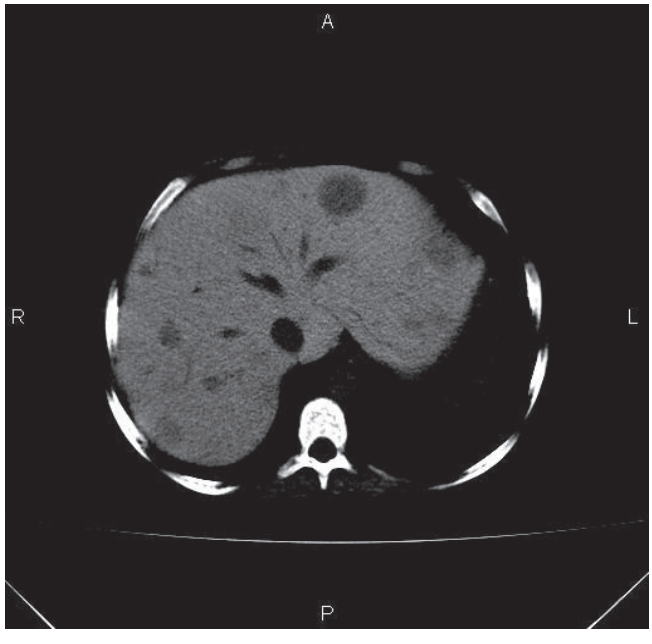



**Figure 1.** Native abdominal CT with the presence of multiple intraparenchymal hepatic nodular lesions spontaneous hypodense, some with native hyperdense inclusions (calcifications *vs*. hematic inclusions).

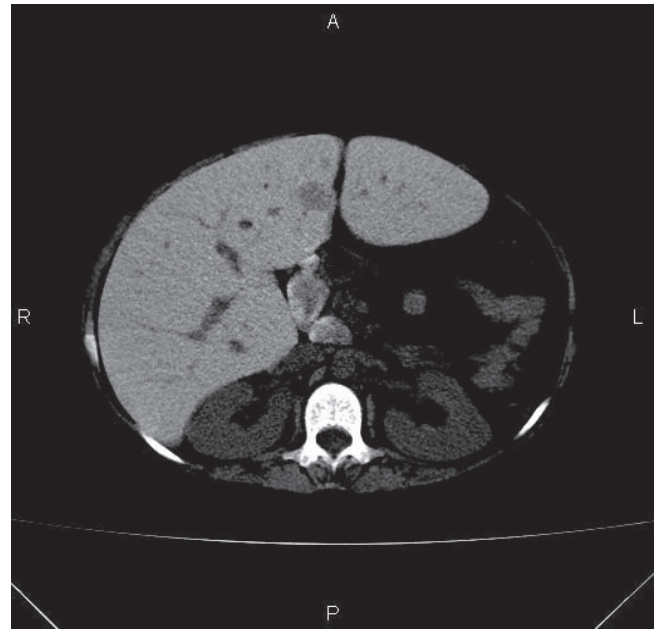
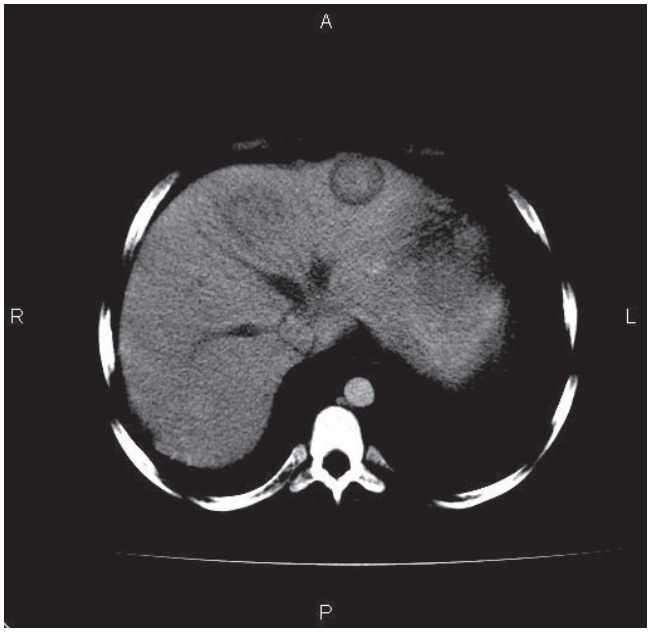



**Figure 2.** Native abdominal CT reveals multiple hilar liver adenopathy with spontaneous peripheral hyperdensity (probably calcifications) and spontaneous hypodens centre.



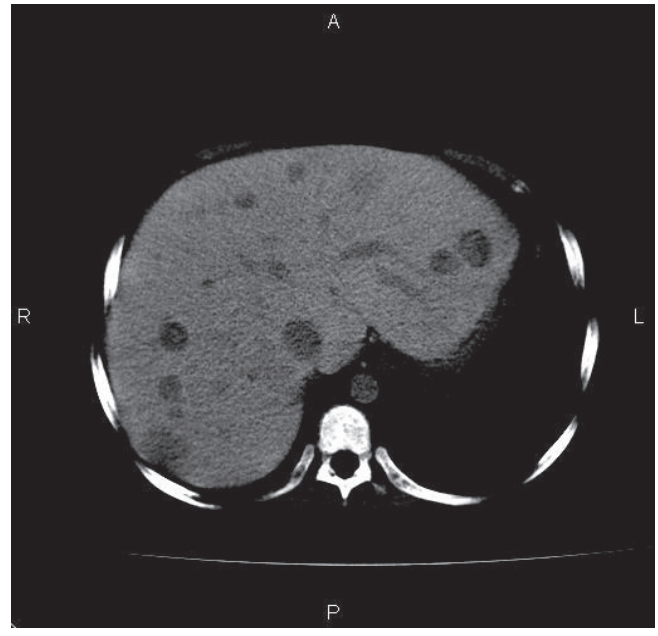




**Figure 3, 4.** Abdominal CT with contrast reveals multiple intraparenchymal hepatic nodular lesions, global cold *versus* hepatic parenchima.

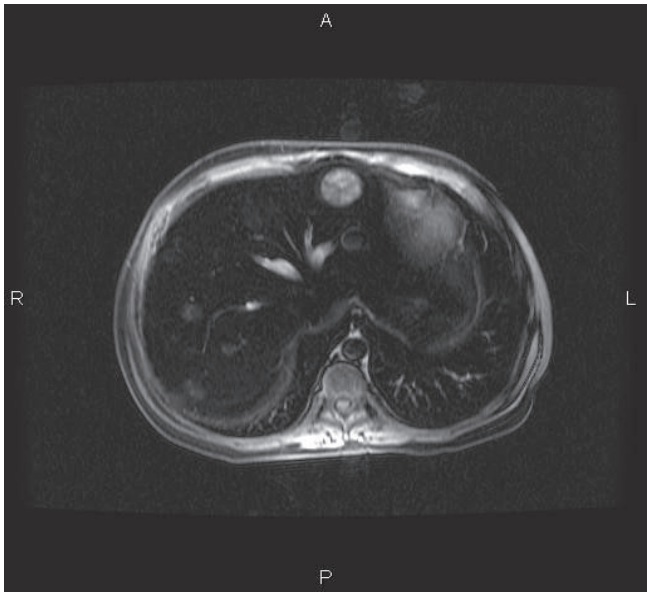



**Figure 5.** Abdominal MRI Axis T1 fspgr - multiple intrahepatic gadophile lesions due to the diffuse decrease of the hepatic signal (T1 hyposemnal accentuated) suggesting hemochromatous infiltration.

loaded with lipofuscin and rare collagen fibrosis strips with pseudonodules delimitation (Figs 6-8).

Thus, taking into account the transfusion and iron chelating incorrect treatment (constant pre-transfusion hemoglobin up to this age of < 6-7 g/dL, deferoxamine administered insufficient (only 25 mg/kg/day - 5 days a week), hepatomegaly is considered in the context of severe hemochromatosis (serum ferritin = 7513 ng/mL) and liver nodules as outbreaks of erythropoiesis (confirmed histopathologically).

The patient was investigated both cardiac and endocrinological. Cardiac ultrasound indicates FE = 70% without left ventricular hypertrophy, normal valves. Fist x-ray: 19-year-old patient, presenting a 13-years and 6-months old bone age (Fig. 9). Phalanges, radial and cubital distal epiphysis growth cartilage are visualized. Endocrinological consultation: breast tissue BII, PI (delayed puberty), normal thyroid on palpation, FrT3 = 2.84 pg/mL, FrT4 = 0.90 ng/dL, TSH = 2.54 μU/mL, atrophic uterine appearance. Cerebral angio-

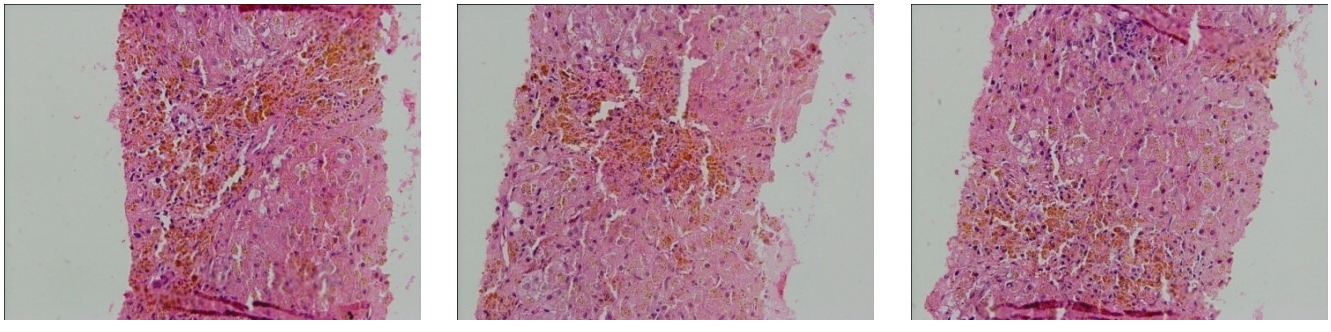


**Figure 6, 7, 8.** Extramedullary hematopoietic outbreaks, lipofuscin loaded hepatocyte groups, and rare collagen fibrosis strips with pseudonodules delineation.

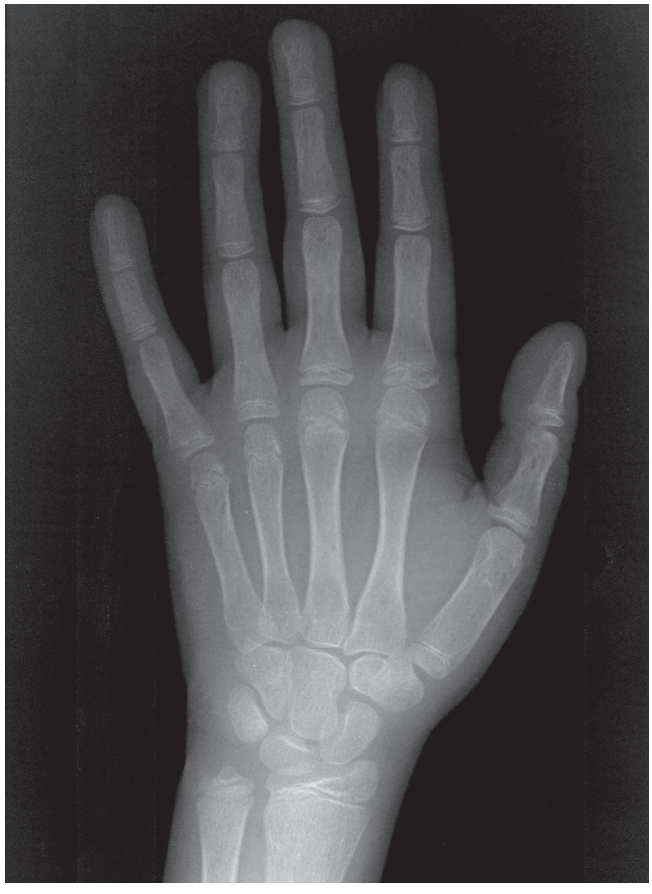


**Figure 9.** Right-hand X-ray highlights the long-delayed bone age (secondary bone ossification nuclei of carpal bones corresponding to an age of 13 years and 6 months).

IRM: pituitary gland with normal size and morphology. Treatment with very low doses of Estrofen ¼ tb of 1 mg per day and Euthyrox ½ tb of 0.25 μg per day is initiated. In 2 months, a staggered gain of 0.8 cm and an evolution from BII to BIII is achieved.

The patient started to receive transfusions every 3-4 weeks with a pre-transfusion hemoglobin of > 9 g/dL. Iron chelation treatment with Deferoxamine was instituted at a dose of 50 mg/kg/day, daily, s.c. on the pump in 10-12 hours, after 1 year and 7 months continuing with Deferasirox 20mg/kg/day p.o. with a favourable clinical evolution (the reduction of hepatomegaly with the lower margin at the umbilical horizontal line confirmed by ultrasound, increased physical growth with weight gain + 5 kg (W = 46 kg) and statural gain + 10 cm (H = 156 cm), onset of the menstruation, of the thelarche and of the pubarche, decreased intensity of the systolic murmur to II/VI grade) and also with a good laboratory response (normal liver enzymes levels AST = 36 U/L, ALT = 54 U/L, reduction of hemochromatosis degree from severe to mild, with serum ferritin = 784.7 ng/mL).

## DISCUSSIONS

Diagnosis of beta thalassemia major is premature, usually in the first year of life, when switching from fetal hemoglobin F (specific to intrauterine life) to adult type A (specific to extra uterine life) [1-2]. To survive, these patients require transfusions every 2-5 weeks intervals for the entire life, with leucodepleted and phenotypic erythrocyte concentrates (compatible with ABO, Rh, C, E, Kell) [11-13]. In the absence of these transfusions, death occurs during the first decade of life (up to 10 years of age) due to chronic hypoxia, with significant retardation of staturo-ponderal growth, severe infections and irreversible heart failure [2, 3, 8]. International protocols recommend a pre-transfusion hemoglobin level between 9-10.5 g/dL and post-transfusion maximum 14-15 g/dL [4-6]. For our patient, the transfusion regimen throughout childhood and puberty was performed at low pre-transfusion Hb values of < 6-7 g/dL, which allowed to maintain a marked degree of chronic hypoxemia, which led compensatory to medullar erythroid hyperplasia (reflected by the characteristic mongoloid facies) and extramedullary (histopathologically demonstrated by the presence of extramedullary hepatic erythropoiesis), as well as physical growth retardation (height and weight under percentile 5 corresponding to age) [1,3,14,15].

But with each transfusion, an iron quantity of about 100 to 200 times the normal daily requirement, corresponding to an amount of 0.32 - 0.64 mg/kg/day, is introduced into the body, without any mechanisms of eliminating this excess iron, resulting in secondary hemochromatosis (iron overload). Accumulated iron will be deposited in all tissues and organs, causing functional impairment, particularly of the heart, liver and endocrine glands, severe cardiac dysfunction being the leading cause of death [3, 7, 16-18]. To prevent and minimize this severe complication, iron chelation treatment is initiated for the entire lifetime, both in the hospital and at home, without which these patients die in the second or third decade of life (up to the age of 20-30 years) [19]. This main post-transfusion complication and its negative effects are also found in this case: iron chelation therapy before taking over the patient was summed up with a minimum dose of 25 mg/kg/day of Deferasirox, 5 days a week, regardless of the serum ferritin level, which determined a severe hemochromatosis (admission in our department: serum ferritin = 7513 ng/mL).

The multi-organ iron overloading was highly suggestive. Impressive clinical and imagistical confirmed hepatomegaly with a non-homogeneous aspect and

multiple nodules in both hepatic lobes, without any pathognomonic pathology, associated with hepatic cytolysis, required numerous investigations to exclude other viral (post-transfusion), chronic inflammatory or malignant etiology, secondary to severe prolonged/ long hemochromatosis [17, 20-26]. Cardiac involvement objectively demonstrated by systolic murmur grade IV/ VI parasternal sp. II i.c. left, and anamnestic with episodes of palpitations spontaneously submitted, was most likely the combined result of chronic hypoxia and iron overload. At that time, the only possible imaging examination was cardiac ultrasound, indicating FEVS = 70% without left ventricular hypertrophy, and normal valves. Without T2 - MRI examination available, intracardiac iron could not be quantified. Last but not least, the endocrinological dysfunction secondary to severe hemochromatosis was significant, noting the failure of physical development (significant staturo-ponderal delay of about 5 years and 6 months of bone age versus the civil one) and puberty (Tanner pre-puberty stage at 19 years old, menses not installed, atrophic uterus appearance at ultrasound examination). We also note the presence of inflammatory status due to excessive general iron overload (ESR = 100 mm/1h, CRP = 9.75 mg/L, fibrinogen = 445 mg/dL).

In addition to the regular clinical examination, monitoring patients with major thalassemia involves a series of biochemical and imaging investigations that allow a more accurate assessment of global evolution and the identification of suggestive preclinical changes in order to prevent symptomatic clinical complications. Thus, the presence and degree of intracardiac and hepatic hemochromatosis through quantitative estimation of iron in these organs are confirmed by the appearance and values of the T2 parameter obtained by magnetic resonance imaging, considered at this time the most non-invasive technique for these determinations [7, 27-33]. Because at the date of taking over the patient, there was no possibility of imaging examination by MRI –in the country, it was not possible to evaluate and compare the quantitative overload with intracardiac and hepatic iron. In our case, the severity of global iron overload and iron chelating efficiency were estimated paraclinically by serum ferritin and transaminases levels [34, 35].

An optimal approach to major thalassemia necessarily involves observing the two therapeutic principles: substitution by blood transfusion and secondary, excess iron chelation. Iron chelation medication has the role of preserving a negative balance inclined to the amount of iron removed from the body versus that introduced by transfusion [4,7]. After admission to our Clinic, the adopted treatment plan was following the international recommendations, with the patient receiving transfusions at a 3-4 week interval with a pre-transfusion hemoglobin of > 9 g/dL and iron chelating treatment with Deferoxamine as intensified dose regimen of 50 mg/kg/day, daily, sc on the pump in 10-12 hours, after 1 year and 7 months continuing with Deferasirox 20 mg/kg/day p.o. daily, with a favourable evolution as described earlier.

**In conclusion,** beta thalassemia major is a rare haematological chronic disease that requires early diagnosis, complex treatment and permanent monitoring throughout life. The survival of these patients depends both on regular transfusions and on the efficient chelation of over-accumulated iron, customized in an individual scheme, both of which are essential for providing a favourable prognosis.

Thus, adequate care of children with such pathology ensures an evolution without severe long-term complications, similar to a normal adult, with a harmonious physical and emotional development, allowing them to build a personal and professional future with normal or near normal integration in society.

*What's known:*

In beta thalassemia major, both transfusion treatment and continuous iron chelation therapy are equally essential for the long-term survival without complications

*What's relevant – clinical and educational practice:*

The personalized iron chelation therapy associated with a patient's good compliance to treatment, reduces significantly the secondary hemochromatosis and the complex multiorgan dysfunction.

It is worth highlighting the long term reversibility up to a point of the changes secondary to chronic anemia and hemochromatosis, with the significant improvement of the general status of the patient.

**Conflict of interest**

The authors declare that they have no conflict of interest.

## References

1. Viprakasit V, Origga R, Fucharoen S. Genetic basis, pathophysiology and diagnosis. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V. Guidelines for the management of transfusion dependent thalassaemia (TDT). 3rd ed. Nicosia, Cyprus: Thalassaemia International Federation; 2014: 14-26.
2. Galanello R, Origa R. Beta-thalassaemia. Orphanet J Rare Dis. 2010; 5:11.

3. Cappellini MD, Porter JB, Viprakasit V, Taher AT. A paradigm shift on beta-thalassaemia treatment: How will we manage this old disease with new therapies? Blood Rev. 2018; 32(4):300-311.
4. Trompeter S, Cohen A, Porter J. Blood transfusion. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V. Guidelines for the management of transfusion dependent thalassaemia (TDT). 3rd ed. Nicosia, Cyprus: Thalassaemia International Federation; 2014. p. 28-40.
5. Cazzola M, De Stefano P, Ponchio L, Locatelli F, Beguin Y, Dessi C, Barella S, Cao A, Galanello R. Relationship between transfusion regimen and suppression of erythropoiesis in beta-thalassaemia major. Br J Haematol. 1995 Mar; 89(3):473-478.
6. Cazzola M, Borgna-Pignatti C, Locatelli F, Ponchio L, Beguin Y, De Stefano P. A moderate transfusion regimen may reduce iron loading in beta-thalassemia major without producing excessive expansion of erythropoiesis. Transfusion. 1997; 37(2):135-140.
7. Porter J, Viprakasit V, Kattamis A. Iron overload and chelation. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V. Guidelines for the management of transfusion dependent thalassaemia (TDT). 3rd ed. Nicosia, Cyprus: Thalassaemia International Federation; 2014. p. 42-96.
8. Amid A, Saliba AN, Taher AT, Klaassen RJ. Thalassaemia in children: from quality of care to quality of life. Arch Dis Child. 2015 Nov; 100(11):1051-7.
9. Angastiniotis M, Taher A, Cappellini MD. Lifestyle and quality of life. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V. Guidelines for the management of transfusion dependent thalassaemia (TDT). 3rd ed. Nicosia, Cyprus: Thalassaemia International Federation; 2014: 224-235.
10. Caocci G, Efficace F, Ciotti F, Roncarolo MG, Vacca A, Piras E, Littera R, Markous RSD, Collins GS, Ciceri F, Mandelli F, Marktel S, La Nasa G. Health related quality of life in Middle East children with beta-thalassaemia. BMC Blood Disord. 2012; 12:6.
11. Spanos T, Karageorga M, Ladis V, Peristeri J, Hatziliami A, Kattamis C. Red cell alloantibodies in patients with thalassemia. Vox Sang. 1990; 58(1):50-55.
12. Singer ST, Wu V, Mignacca R, Kuypers FA, Morel P, Vichinsky EP. Alloimmunization and erythrocyte autoimmunization in transfusiondependent thalassemia patients of predominantly Asian descent. Blood. 2000; 96(10):3369-3373.
13. Thompson AA, Cunningham MJ, Singer ST, Neufeld EJ, Vichinsky E, Yamashita R, Giardina P, Kim HY, Trachtenberg F, Kwiatkowski JL; Thalassemia Clinical Research Network Investigators. Red cell alloimmunization in a diverse population of patients with thalassaemia. Br J Haematol. 2011; 153(1):121-128.
14. Rivella S. The role of ineffective erythropoiesis in non-transfusion-dependent thalassemia. Blood Rev 2012; 26(Suppl. 1):S12-5.
15. Nienhuis AW, Nathan DG. Pathophysiology and clinical manifestations of the β-thalassemias. Cold Spring Harb Perspect Med. 2012; 2(12):a011726.
16. Walker M, Wood J, Taher A. Cardiac complications in thalassaemia major. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V. Guidelines for the management of transfusion dependent thalassaemia (TDT). 3rd ed. Nicosia, Cyprus: Thalassaemia International Federation; 2014: 98-111.
17. Brissot P, Cappellini MD. Liver disease. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V. Guidelines for the management of transfusion dependent thalassaemia (TDT). 3rd ed. Nicosia, Cyprus: Thalassaemia International Federation; 2014: 114-122.
18. De Sanctis V, Skordis N, Soliman AT, Cohen A. Endocrine disease. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V. Guidelines for the management of transfusion dependent thalassaemia (TDT). 3rd ed. Nicosia, Cyprus: Thalassaemia International Federation; 2014: 146-157.
19. Tubman VN, Fung EB, Vogiatzi M, Thompson AA, Rogers ZR, Neufeld EJ, Kwiatkowski JL, and the Thalassemia Clinical Research Network. Guidelines for the Standard Monitoring of Patients with Thalassemia: Report of the Thalassemia Longitudinal Cohort. J Pediatr Hematol Oncol. 2015; 37(3): e162-e169.
20. Deugnier Y, Turlin B. Pathology of hepatic iron overload. Semin Liver Dis. 2011; 31(3):260-271.
21. Deugnier Y, Turlin B. Pathology of hepatic iron overload. World J Gastroenterol. 2007; 13(35): 4755-4760.
22. Aydinok Y, Fucharoen S, Cappellini MD. Infections. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V. Guidelines for the management of transfusion dependent thalassaemia (TDT). 3rd ed. Nicosia, Cyprus: Thalassaemia International Federation; 2014. p. 134-145.
23. Allain JP, Stramer SL, Carneiro-Proietti AB, Martins ML, Lopes da Silva SN, Ribeiro M, Proietti FA, Reesink HW. Transfusion-transmitted infectious diseases. Biologicals. 2009; 37(2):71-77.
24. Singh H, Pradhan M, Singh RL, Phadke S, Naik SR, Aggarwal R, Naik S. High frequency of hepatitis B virus infection in patients with beta-thalassemia receiving multiple transfusions. Vox Sang. 2003; 84(4):292-299.
25. Salama KM, Ibrahim OM, Kaddah AM, Boseila S, Ismail LA, Abdel Hamid MM. Liver enzymes in children with beta-thalassemia major: correlation with iron overload and viral hepatitis. Open Access Maced J Med Sci. 2015; 3(2): 287-292.
26. Di Marco V, Capra M, Gagliardotto F, Borsellino Z, Cabibi D, Barbaria F, Ferraro D, Cuccia L, Ruffo GB, Bronte F, Di Stefano R, Almasio PL, Craxì A. Liver disease in chelated transfusion-dependent thalassemics:the role of iron overload and chronic hepatitis C. Haematologica. 2008; 93(8):1243-1246.
27. Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel J, Wu D, Taylor J, Westwood MA, Anderson LJ, Pennell DJ. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. Circulation. 2009; 120(20):1961-1968.
28. Taigang He T, Gatehouse PD, Smith GC, Mohiaddin RH, Pennell DJ, Firmin DN. Myocardial T2* measurements in iron overloaded thalassemia. An in vivo study to investigate the optimal methods of quantification. Magn Reson Med. 2008; 60(5):1082-1089.
29. Fragasso A, Ciancio A, Mannarella C, Gaudiano C, Scarciolla O, Ottonello C, Francone M, Nardella M, Peluso A, Melpignano A, Veglio MR, Quarta G, Turchetti C. Myocardial iron overload assessed by magnetic resonance imaging (MRI)T2* in multi-transfused patients with thalassemia and acquired anemias. Eur J Intern Med. 2011; 22(1):62-65.
30. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, Firmin DN, Wonke B, Porter J, Walker JM, Pennell DJ. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J. 2001; 22(23):2171-2179.
31. Carpenter JP, He T, Kirk P, Roughton M, Anderson LJ, de Noronha SV, Sheppard MN, Porter JB, Walker JM, Wood JC, Galanello R, Forni G, Catani G, Matta G, Fucharoen S, Fleming A, House MJ, Black G, Firmin DN, St Pierre TG, Pennell DJ. On T2* magnetic resonance and cardiac iron. Circulation. 2011; 123(14):1519-1528.
32. Au WY, Lam WW, Chu WW, Yuen HL, Ling AS, Li RC, Chan HM, Lee HK, Law MF, Liu HS, Liang R, Ha SY. A cross-sectional magnetic resonance imaging assessment of organ specific hemosiderosis in 180 thalassemia major patients in Hong Kong. Haematologica. 2008; 93(5):784-786.
33. Wood JC, Ghugre N. Magnetic resonance imaging assessment of excess iron in thalassemia, sickle cell disease and other iron overload diseases. Hemoglobin. 2008; 32(1-2):85-96.
34. Brittenham GM, Cohen AR, McLaren CE, Martin MB, Griffith PM, Nienhuis AW, Young NS, Allen CJ, Farrell DE, Harris JW. Hepatic iron stores and plasma ferritin concentration in patients with sickle cell anemia and thalassemia major. Am J Hematol. 1993; 42(1):81-85.
35. Angelucci E, Brittenham GM, McLaren CE, Ripalti M, Baronciani D, Giardini C, Galimberti M, Polchi P, Lucarelli G. Hepatic iron concentration and total body iron stores in thalassemia major. N Engl J Med. 2000; 343(5):327-331.