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Review article

A BRIEF REVIEW ON TREATMENT OF BETA-THALASSEMIA

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Abstract

Beta thalassemia is a common inherited blood disease in the world. Individuals with severe thalassemia require blood transfusion, drug therapy , chelation therapy and bone marrow transplant. Remarkable improvements in survival in the severe forms of beta thalassemia have followed the use of blood transfusion and in particular, the ability to manage the iron accumulation resulting from blood transfusion with its severity. Hematopoietic stem cell transplantation is the only available curative approach for beta thalassemia.

Keywords: Fermented, alcoholic beverages, preservation, shelf life, value.

Introduction

Beta Thalassemia is one of the hemoglobinopathies belonging to a class of genetic disorders. It occurs due to mutation of β- gene of autosomal chromosome 11 (1). These mutations are primarily point mutations that affect transcriptional control, translation, and splicing of the HbB gene and gene product (2). Three main forms have been described: thalaseemia major, thalassemia intermediate and thalassemia minor (3). If the synthesis of two β -chains is absent (β/ β), the person has β-thalassemia major (Cooley's anemia). This condition follows severe microcytic and hyochromic anaemia. The person requires lifelong transfusion. β-thalassemia minor is asymptomic and results in microcytosis and mild anaemia and HbA2 level increases , designed as β +/ β or β 0/β. Usually thalassemia intermedia is condition between the major and minor forms depending on the severity of the anaemic condition (β +/ β +or β 0/ β 0) among other cases (4,5) .

Epidemiology

Beta –thalassemia is prevalent in the Mediterranean countries, the Middle-East, Central Asia, India, Southern China, and Far East as well as countries along the north coast of Africa and South America (6). Approximately 68000 children are born with beta-thalassemia. Its prevalence is 80-90 million carriers, around 1.5% of the global population (7). The highest carrier frequency is reported in Cyprus (14%), Sardinia (10.3%) and Southeast Asia. The high gene frequency of beta-thalassemia in these regions is most likely related to the selective pressure from *plasmodium falciparm* malaria (6). Population migration and intermarriage

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between different ethnic group has introduced thalassemia in almost every country of the world, including Northern Europe where thalassemia was previously absent. The total annual incidence of symptomatic individual is estimated 1 in 100,000 throughout the world and 1 in 10,000 people in the European Union. However, accurate data on carrier rates in many populations are lacking, particularly in areas of the world known or expected to be heavily affected (8). The overall prevalence of β thalassemia in India is 3-4% with estimate that around 10,000-12,000 children are born every year with β –thalassemia major. A recent study in India showed that the overall prevalence of β- thalassemia trait was 2.78% and varied from 1.48% to 3.64% in different states, whereas the prevalence of β-thalassemia trait in 59 ethnic groups varied from 0% to 9.3% respectively (9).

Pathophysiology

Haemoglobin is a tetramer of two alpha chains combined with two non –alpha globin chains. Fetal haemoglobin (HbF) is the primary haemoglobin until six months of age and consists of two alpha chains and two gamma chains. Adult haemoglobin is primarily haemoglobin A (HbA), consisting of two alpha chains and two beta chains. A smaller component of adult haemoglobin is haemoglobin A2 (HbA2), consisting of two alpha chains and two delta chains.

The pathogenesis of beta-thalassemia is two-fold. First , there is decreased haemoglobin synthesised causing anemia and an increase in HbF and HbA2 as there are decreased beta chains of HbA formation. Second , and of most pathologic significance in beta- thalassemia major and intermedia, the relative excess alpha chains form insoluble alpha chain inclusions that cause marked intramedullary hemolysis. This ineffective erythropoiesis leads to severe anemia and erythroid hyperplasia with bone marrow expansion and extramedullary haematopoiesis. The bone marrow expansion leads to bony deformities, characteristically of facial bones which cause frontal bossing and maxillary protrusion. Biochemical signalling from bone marrow expansion involving the bone morphogenetic protein (BMP) pathway inhibits hepcidin production causing iron hyper absorption (10).

Treatment of Beta –thalassemia

Although the more severe thalassemia is an extremely heterogenous group of disorders, their general management follows the same principles. At first presentation, it is absolutely essential to obtain an accurate diagnosis of the form of the disease, ideally including its molecular basis. It is also important to perform a detailed family study to assess the pattern of inheritance at the same time. Once this information is available, the family requires well-informed counselling about the likely future course of the illness and, equally important, about the relative risks of having further affected children. It is not uncommon for babies to first present with thalassemia with particularly low haemoglobin levels associated with intercurrent infection. Although they may need to receive transfusions until they recover from the presenting illness, it is important not to establish them on regular transfusion without a reasonable period of observation. Unless this precaution is taken, babies with various forms of thalassemia of intermediate severity may be placed on life unnecessary transfusion. The important features to observation. Unless this precaution is taken, babies with various forms of thalassemia of intermediate severity may be placed on lifelong unnecessary transfusion. The important features to observe before long-term transfusion is considered include the patterns of growth and growth velocity, activity compared with infants of

the same age, the occurrence of progressive splenomegaly and early evidence of any skeletal deformity. Although the haemoglobin level is also important, it should not be the only determinant of whether transfusion is required. In some forms of β-thalassemia intermediate, notably HbE β-thalaseemia in particular, there is increasing evidence that patient may be able to adapt to relatively low haemoglobin levels and not require regular transfusion (11). Recent developments in more radical forms of treatment for the thalassemia notable bone marrow transplantations, gene therapy, and stem cell therapy (12).

Transfusions

The goals of transfusion therapy are correct of anemia, suppression of erythropoiesis and inhibition of gastrointestinal iron absorption, which occurs in non transfused patients as a consequence of increased, although ineffective, erythropoiesis. The decision to start transfusion in patients with confirmed diagnosis of thalassemia should be based on the

presence of severe anemia (Hb<7g/dl for more than two weeks , excluding other contributory causes such infections). However, patients with Hb <7g/dl, other factors should be considered, including facial changes, poor growth , evidence of bony expansion and increasing splenomegaly. When possible, the decision to start regular transfusions should not be delayed until after the second-third year, due to the risk of developing multiple red cell antibodies and subsequently difficulty in finding suitable blood donors. Several different transfusion regimens have been proposed over the years, but the most widely accepted aims at a pre transfusion Hb level of 9 to 10g/dl and a post –transfusion level of 13 to 14 g/dl. This prevents growth impairment, organ damage and bone deformities, allowing normal activity and quality of life (13, 14).

Treatment of individuals with thalassemia intermedia is symptomatic and based on splenectomy and folic acid supplementation. Treatment of extramedullary erythropoietic masses is based on radiotherapy, transfusions, or in selected cases, hydroxyurea (with a similar to that used for sickle cell disease). Hydroxyurea also increases globin gamma chains and may have other undefined mechanisms. Because individuals with thalassemia intermedia may develop iron overload from increased gastrointestinal absorption of iron or from occasional transfusions, chelation therapy is started when the serum ferritin concentration exceeds 300g/l (15).

Transfusional iron overload

The most common secondary complications are those related to transfusional iron overload (16). Thalassemia patients who are not transfused may retain up to 75% of orally administrated iron, accumulating between 3 and 9 mg iron per day. (17). Because transfusions suppress erythroid expansion and reduce ineffective erythropoiesis , thereby reducing iron absorption (18) .

Assessment of Iron overload

Patients maintained on a regular transfusion regimen progressively developed clinical manifestation of iron overload, hypogonadism (35-55% of the patients), hypothyroidism (9-11%), hyperparathyroidism (4%) diabetes (6-10%), liver fibrosis, and heart dysfunction (33%) (19, 20). Iron status should be accurately assessed in order to evaluate its clinical relevance, the need for treatment, and the timing and monitoring of chelation therapy. The iron status of multitransfused patients can be assessed by several methods. Serum ferritin has in general been found to

correlate with body iron stores (21).

Chelation Therapy

Iron-chelating therapy should be considered in all patients with thalassemia who require longterm red cell transfusion. Chelators should be avoided in patients who are pregnant or breast–feeding. Ideally, therapy should be initiated prophylactically, before clinically significant iron accumulation has occurred. Patients who have already undergone repeated transfusion without sufficient chelation can also be successfully treated, but they may require intensive regimens (22). Iron chelators (deferasirox, deferoxamine, deferiprone) are given concomitantly to remove extra iron from the body.

Bone Marrow Transplantation

Bone marrow transplantation (BMT) from an HLA –identical sib represent an alternative to traditional transfusion and chelation therapy. The outcome of BMT is related pre-transplantation clinical conditions, specially the presence of hepatomegaly, extent of liver fibrosis, and magnitude of iron accumulation. In children who lack above risk factors , disease free survival is over 90% (23) . A lower survival rate of approximately 60 % is reported in individuals with all three risk factors. Chronic graft-versus –hot disease of variable severity may occur in 5-8% individuals. BMT from unrelated donors has been performed on a limited number of individuals with beta – thalassemia. Provided that selection of the donor is based on stringent criteria of HLA compatibility and that individuals have limited iron overload, results are comparable with those obtained when donor is a compatible sib (24).

Therapies under investigation

New chelation strategies, including the combination or alternate treatment with the available chelators, are under investigation. Induction of HbF synthesis can reduce the severity of beta-thalassemia by improving the imbalance between alpha and non alpha globin chains. Several pharmacologic compounds including 5-azacytidine, decytabine and butyrate derivatives have had disappointing results in clinical trials (25). These agents induce HbF by different mechanisms that are not yet well defined. Their potential in the management of beta-thalassemia syndromes is still under investigation. Therapeutic strategies aimed at improving iron dysregulation such as minihepcidin and TMPRSS6 and ferroportin inhibitors are showing promise, especially in individuals with nontransfusion-dependent thalassemia (26).

REFERENCES

1. Weatherall DJ, Clegg JB. (2001)Inherited haemoglobin disorders: an increasing global health problem. *Bull World Health Organ*. 79(8):704–712.

2. Cao, A., & Galanello, R. (2010). Beta-thalassemia. *Genetics in medicine : official journal of the American College of Medical Genetics*, *12*(2), 61–76. https://doi.org/10.1097/GIM.0b013e3181cd68ed

3. Galanello, R., & Origa, R. (2010). Beta-thalassemia. *Orphanet journal of rare diseases*, *5*, 11. https://doi.org/10.1186/1750-1172-5-11

4. Cooley TB, Lee P. (2017) A series of cases of splenomegaly in children with anemia and peculiar bone changes. *Medico research Chronicles*. 4(03):325-37.

5. Shah, P. S., Shah, N. D., Ray, H., Khatri, N. B., Vaghasia, K. K., Raval, R. J., Shah, S. C., & Rao, M. V. (2017). Mutation analysis of β-thalassemia in East-Western Indian population: a recent molecular approach. *The application of clinical genetics*, *10*, 27–35.

6. Flint J, Harding RM, Boyce AJ, Clegg JB. (1998). The population genetics of the hemoglobinopathies. *Bailliere's Clinical Hematology*.**11**:1–50.

7. Origa R. (2017) β-Thalassemia. *Genetics in medicine : official journal of the American College of Medical Genetics*. 19(6):609-619.

8. Vichinsky EP. (2005)Changing patterns of thalassemia worldwide. *Ann N Y Acad* 1054:18-24.

9. Mohanty, D., Colah, R. B., Gorakshakar, A. C., Patel, R. Z., Master, D. C., Mahanta, J., Sharma, S. K., Chaudhari, U., Ghosh, M., Das, S., Britt, R. P., Singh, S., Ross, C., Jagannathan, L., Kaul, R., Shukla, D. K., & Muthuswamy, V. (2013). Prevalence of β-thalassemia and other haemoglobinopathies in six cities in India: a multicentre study. *Journal of community genetics*, *4*(1), 33–42. https://doi.org/10.1007/s12687-012-0114-0

10. Frazer DM, Wilkins SJ,Darshan D,Badrick AC,McLaren GD,Anderson GJ. (2012). Stimulated erythropoiesis with secondary iron loading leads a decrease in hepcidin despite an increase in bone morphogenetic protein 6 expression. *British journal of haematology*. 157(5) 615-626

11. Allen, A., Fisher, C., Premawardhena, A., Peto, T., Allen, S., Arambepola, M., Thayalsutha, V., Olivieri, N., & Weatherall, D. (2010). Adaptation to anemia in

hemoglobin E-ß thalassemia. *Blood*, *116*(24), 5368–5370. https://doi.org/10.1182/blood-2010-06-289488

12. Arora, N., & Daley, G. Q. (2012). Pluripotent stem cells in research and treatment of hemoglobinopathies. *Cold Spring Harbor perspectives in medicine*, *2*(4), a011841. https://doi.org/10.1101/cshperspect.a011841

13. Cappellini, M. D., Cohen, A., Eleftheriou, A., Piga, A., Porter, J., & Taher, A. (2008). *Guidelines for the Clinical Management of Thalassaemia*. (2nd Revised ed.). Thalassaemia International Federation.

14. Lippincott Williams & Wilkins. (2004). Thalassemia and related disorders: quantitative disorders of hemoglobin synthesis; 1319– 1365.

15. Borgna-Pignatti, C., Rugolotto, S., De Stefano, P., Zhao, H., Cappellini, M. D., Del Vecchio, G. C., Romeo, M. A., Forni, G. L., Gamberini, M. R., Ghilardi, R., Piga, A., & Cnaan, A. (2004). Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica*, *89*(10), 1187–1193.

16. Pippard, M. J., Callender, S. T., Warner, G. T., & Weatherall, D. J. (1979). Iron absorption and loading in beta-thalassaemia intermedia. *Lancet (London, England)*, *2*(8147), 819–821. https://doi.org/10.1016/s0140-6736(79)92175-5

17. Pippard, M. J., & Weatherall, D. J. (1984). Iron absorption in non-transfused iron loading anaemias: prediction of risk for iron loading, and response to iron chelation treatment, in beta thalassaemia intermedia and congenital sideroblastic anaemias. *Haematologia*, *17*(1), 17–24.

18. Cunningham, M. J., Macklin, E. A., Neufeld, E. J., Cohen, A. R., & Thalassemia Clinical Research Network (2004). Complications of beta-thalassemia major in North America. *Blood*, *104*(1), 34–39. https://doi.org/10.1182/blood-2003-09-3167

19. Borgna-Pignatti, C., Rugolotto, S., De Stefano, P., Zhao, H., Cappellini, M. D., Del Vecchio, G. C., Romeo, M. A., Forni, G. L., Gamberini, M. R., Ghilardi, R., Piga, A., & Cnaan, A. (2004). Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica*, *89*(10), 1187–1193.

20. Brittenham, G. M., Cohen, A. R., McLaren, C. E., Martin, M. B., Griffith, P. M., Nienhuis, A. W., Young, N. S., Allen, C. J., Farrell, D. E., & Harris, J. W. (1993). Hepatic iron stores and plasma ferritin concentration in patients with sickle cell anemia and thalassemia major. *American journal of*

hematology, *42*(1), 81–85. https://doi.org/10.1002/ajh.2830420116

21. Brittenham G. M. (2011). Iron-chelating therapy for transfusional iron overload. *The New England journal of medicine*, *364*(2), 146–156. https://doi.org/10.1056/NEJMct1004810

22. Gaziev, J., & Lucarelli, G. (2003). Stem cell transplantation for hemoglobinopathies. *Current opinion in pediatrics*, *15*(1), 24–31. https://doi.org/10.1097/00008480-200302000-00005

23. La Nasa, G., Argiolu, F., Giardini, C., Pession, A., Fagioli, F., Caocci, G., Vacca, A., De Stefano, P., Piras, E., Ledda, A., Piroddi, A., Littera, R., Nesci, S., & Locatelli, F. (2005). Unrelated bone marrow transplantation for beta-thalassemia patients: The experience of the Italian Bone Marrow Transplant Group. *Annals of the New York Academy of Sciences*, *1054*, 186–195. https://doi.org/10.1196/annals.1345.023

24. Pace, B. S., & Zein, S. (2006). Understanding mechanisms of gamma-globin gene regulation to develop strategies for pharmacological fetal hemoglobin induction. *Developmental dynamics : an official publication of the American Association of Anatomists*, *235*(7), 1727–1737. https://doi.org/10.1002/dvdy.20802

25. Richard, F., van Lier, J. J., Roubert, B., Haboubi, T., Göhring, U. M., & Dürrenberger,
F. (2020). Oral ferroportin inhibitor VIT-2763: First-in-human, phase 1 study in healthy volunteers. *American journal of hematology*, *95*(1), 68–77. https://doi.org/10.1002/ajh.25670

26. Madan, N., Sharma, S., Sood, S. K., Colah, R., & Bhatia, L. H. (2010). Frequency of β-thalassemia trait and other hemoglobinopathies in northern and western India. *Indian journal of human genetics*, *16*(1), 16–25. https://doi.org/10.4103/0971-6866.64941

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