

Review on Thalassemia Epidemiology and Management in Children

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Abstract

Background: Thalassemia is a genetic disorder which involves the formation of abnormal hemoglobin. Thalassemia is autosomal recessive, meaning both parents must be affected with the disease or carriers for it to be passed to the next generation.

A patient with thalassemia not only has low levels of hemoglobin present in his or her bloodstream but also lacks good quality hemoglobin. Although some mild forms of thalassemia can even go unnoticed and cause only mild anemia and patients with iron deficiency problems, some more serious types of thalassemia can also lead to death.

Aim of the Study: This review aims to highlight epidemiology and management of thalassemia in Children.

Conclusion: Thalassemia has adverse effects for many organs and it has high morbidity without a cure. An interprofessional team that involves a thalassemia treatment manager, cardiologist, hepatologist, endocrinologist and psychologist may better treat the condition. Community treatment, health assistance and social service are also an important part of the management. Education of patients is crucial and participation of social workers, including a geneticist, is important. Preventive approaches in some parts of the world include prenatal screening, prohibitions on issuing marriage licenses to two individuals with the same disease. Screening of children and pregnant women visiting clinics is an important method to reduce morbidity of the disease. Finally, successful high school screening should be considered instead of premarital testing, as high school screening has been shown to be more effective in reducing the incidence of β -thalassemia.

Keywords: *Thalassemia; Management of Thalassemia; Epidemiology of Thalassemia*

Introduction

Thalassemia is a genetic disorder which involves the formation of abnormal hemoglobin. Hemoglobin consists of alpha and beta 'chains' which are defective in a patient with thalassemia, as a result of which the hemoglobin produced, is defective [1]. Alpha thalassemia is caused by deletion of the alpha-globin gene which results in the production of alpha-globin chains being reduced or not present. The product of point mutations in the beta-globin gene is beta thalassemia. This is classified into three groups, depending on the beta-gene mutation zygosity [2]. A heterozygous mutation (beta-plus thalassemia) results in a minor beta-thalassemia which under produces beta chains which is mild and asymptomatic in common. A homozygous mutation (beta-zero thalassemia) of the beta-globin gene causes beta thalassemia major, resulting in complete absence of beta chains. It clinically presents as jaundice, growth retardation, hepatosplenomegaly, endocrine defects and serious anemia requiring lifelong transfusions of blood. A beta-thalassemia intermedium is the disorder in between these two forms, with mild to moderate clinical symptoms [3].

Thalassemia is autosomal recessive, meaning both parents must be affected with the disease or carriers for it to be passed to the next generation [4]. A thalassemia family history increases an individual's chances of being affected by the disease. The severity of the disease however depends on the type of gene mutation has occurred, as certain gene mutations result in more serious types of thalassemia than others [5]. A patient with thalassemia not only has low levels of hemoglobin present in his or her bloodstream but also lacks good quality

hemoglobin [6]. Although some mild forms of thalassemia can even go unnoticed and cause only mild anemia and patients with iron deficiency problems, some more serious types of thalassemia can also lead to death [7].

Routine blood transfusions are most widely used to treat patients with thalassemia because blood transfusions allow sufficient amounts of hemoglobin to flood the bloodstreams of these individuals. This allows excess iron to build up in the blood stream, this excessive iron can then cause numerous heart problems for the patient including irregular heartbeats, heart attacks, and even heart failure death. The incidence of complications is decreasing in younger cohorts of patients who have been transfused with blood that has been screened for viruses and thanks to the introduction of new oral iron chelators and imaging methods [8,9].

The high complication and mortality rates are attributed to lack of knowledge of thalassemia and its genetic aspects, the late diagnosis of the disease, the unavailability of some of the chelator agents attributed to the unstable current situation, low incomes of the population concerned and the lack of a national insurance scheme, all of which contribute to difficulties in following up the patients, buying the costly chelating agents and affording proper treatment [6].

A primary preventive program is focused on the detection and counseling of carriers (heterozygous), to discourage marriage between carriers. Overall, premarital screening (PMS) is commonly used in many parts of the world for thalassemia and other preventable genetic diseases [10]. PMS has yet to be established in the countries where consanguineous marriage rate is high (40%); more than 85% of which are between first cousins and traditional marriages, which may make its acceptance difficult [11].

This review aims to highlight epidemiology and management of thalassemia in Children.

Epidemiology

Worldwide, about 60000 new patients are born with thalassemia annually [12]. Thalassemia is expanding to non-endemic areas of the world because of the high rate of foreign migration. According to the International Federation of Thalassemia, only about 200000 patients with severe thalassemia are alive and reported as receiving routine care around the world [13]. β -Thalassemia carriers comprise 1.5% of the worldwide population, with an estimated 60,000 infants with a serious defect being born every year [14]. In the United States, approximately 1,000 individuals have β -thalassemia major, the most severe form of thalassemia [15]. It occurs at high frequency in a broad belt extending from the Mediterranean basin to the Middle East, Indian subcontinent and Southeast Asia About 3% of the world's population (about 200 million people) carries the β -thalassemia gene [16,17]. The prevalence rates of β -thalassemia (β -thal) in Saudi Arabia are considered one of the highest compared to surrounding countries in the Middle East (0.05% and 4.50%, respectively) [18].

In Egypt, El-Beshlawy and Youssry [19] reported in 2009 that β -thalassemia is the most common form, with a carrier rate ranging from 5.3% to 9% or more in various Egyptian governorates. Many studies show thalassemia is widespread in the Gulf region, such as Bahrain (18% α -thalassemia and 11% β -thalassemia) [20], Oman (6% α -thalassemia and 5.3% β -thalassemia) [21] and UAE (3% α -thalassemia and 2.40% β -thalassemia) [22].

Thalassemia is also common in other Arab countries such as Libya (5% α -thalassemia and 4% β -thalassemia) [23], Tunisia (4.8% α -thalassemia and 4.4% β -thalassemia) [24], Algeria (9% α -thalassemia and 3% β -thalassemia) [25], Qatar (28% α -thalassemia and 17% β -thalassemia) [26], and Jordan (3.3% α -thalassemia and 3.5% β -thalassemia) [27].

In response to the high prevalence of inherited blood disorders in Saudi Arabia, a national mandatory premarital testing detection program for thalassemia and sickle cell anemia was initiated in 2004 in all regions of the country and is free of charge [28]. The premarital testing program in Saudi Arabia has not significantly decreased the occurrence of high-risk couple marriages; 90% of the high-risk couples in 2007 and 98% in 2010 were later married despite receiving genetic counseling [29,30].

Management and treatment

As the more serious thalassemia are an exceedingly heterogeneous group of disorders, they follow the same rules for their general management. At first appearance, an objective diagnosis of the disease type, preferably including its molecular base, is absolutely necessary. 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 counseling about the likely future course of the illness and equally important, about the relative risks of having further affected children [31].

There are studies that drinking tea helps reduce the absorption of iron from the gut tract. So, tea can be a safe drink to use regularly in thalassemia patients. Vitamin C assists in the excretion of iron from the gut, especially when used with deferoxamine [32].

Patients with severe thalassemia require medical treatment. Regular blood transfusion combined with well-monitored chelation therapy is the standard therapy. The goal is to keep Hb at about 9 to 10 mg/dl in order to give patients a sense of well-being and also to monitor erythropoiesis and to suppress extramedullary hematopoiesis. To restrict transfusion-related complications, washed, packaged red blood cells (RBCs) at about 8 to 15 mL per kilogram of body weight over 1 to 2 hours are recommended [32]. Because of repeated transfusions, iron starts to get stored in various body organs. Iron chelators (deferasirox, deferoxamine, deferiprone) are given simultaneously for extra iron removal from the body. Effective chelation therapy in chronically transfused patients is achieved when iron chelators remove sufficient amounts of iron, equivalent to that accumulated in the body from transfusion, to be able to maintain the body iron load at a non-toxic level [33].

In the early 1960s, Desferrioxamine Mesylate was first used in short-term trials of patients carrying iron. It has gained acceptance in those countries as standard therapy capable of supporting the high costs involved and has been a life-saving drug for thousands of patients in the last 40 years. Desferrioxamine is typically supplied via subcutaneous infusion (40 - 60 mg/kg, over 8 - 12h, 5 days per week) [34]. In 2010, on the basis of post-marketing studies, the Food and Drug Administration required a change in the prescribing information for deferasirox, stating that the drug could cause potentially fatal renal and hepatic impairment or failure as well as gastrointestinal hemorrhage [34]. The most common complication of iron loading in thalassemia, hypogonadism, is also prevented by effective use of deferoxamine, although secondary amenorrhea in women, and secondary hypogonadism in men, may develop after age 21, even in those who have attained normal puberty [35].

Another orally active iron-chelating agent, Deferiprone (1, 2 dimethyl-3-hydroxypyrid-4-one, L1) has emerged in the last 10 years that has been reported to have the ability to alter the prognosis of all patients with transfusional iron load. This has been widely studied in clinical trials [36]. Nausea, vomiting, and arthropathy, including arthritis associated with a clinically relevant impairment, are common adverse effects. The most significant adverse effects are agranulocytosis and neutropenia, elevated liver enzymes and hepatic fibrosis progression associated with rise in iron overstatement or hepatitis C [37].

Transplantation of haemopoietic stem cells is the conventional curative option for patients with thalassemia. This therapy infuses stem cells obtained from a compatible donor to the thalassemia patients. The sources of stem cells include bone marrow (compatible sibling or matched unrelated donor), cord blood (sibling or cord blood registry) and peripheral blood (sibling or unrelated donor) [38]. This procedure has its own risks, though, and the clinician needs to balance these against the benefits. Risks include infection vs. host disease, persistent immunosuppressive treatment, graft failure and mortality associated with transplantation [39]. Since thalassemia families tend to have fewer children, the chances of obtaining a natural and healthy sibling donor are about 15 - 25%. For patients with appropriate sibling donors, stem cell transplantation is therefore recommended [40]. Unmatched hematopoietic cord blood stem cell transplantation and hematopoietic bone marrow stem cell transplantation offer the advantages of: lower incidence and frequency of graft versus host disease; lower risk of infection and spread of latent viruses such as cytomegalovirus, Epstein-Barr virus, hepatitis B virus, and HIV; faster immune post-transplantation immune reconstruction of recipients; and no risk of damage to donor hematopoietic stem cells [41].

Gene therapy is the current advance in the treatment of severe thalassemia. This includes collecting the patient's autologous hematopoietic stem cells (HSCs) and genetically manipulating them, using vectors that transmit the normal genes. These are then reinfused to the patients after having undergone the training needed to kill the current HSCs. The genetically engineered HSCs produce normal hemoglobin chains, and normal erythropoiesis ensues [42].

Thalassemia-major patients frequently undergo splenectomy to reduce the amount of transfusions needed. Splenectomy is the standard procedure if the annual demand for transfusion raises to or above 200 to 220 mL RBCs/kg/year with a 70% hematocrit value. Splenectomy not only reduces the amount of transfusions needed but also controls the occurrence of extramedullary hematopoiesis [43].

Since all thalassaemic children have a normal immune response system, they are subject to the usual schedule of immunization. For thalassaemic children who need splenectomy, additional vaccinations with *Haemophilus influenza* B, pneumococcal and meningococcal vaccines are typically performed [44].

Conclusion

Thalassemia has adverse effects for many organs and it has high morbidity without a cure. An interprofessional team that involves a thalassemia treatment manager, cardiologist, hepatologist, endocrinologist and psychologist may better treat the condition. Community treatment, health assistance, and social service are also an important part of the management. Education of patients is crucial and participation of social workers, including a geneticist, is important. Preventive approaches in some parts of the world include prenatal screening, prohibitions on issuing marriage licenses to two individuals with the same disease. Screening of children and pregnant women visiting clinics is an important method to reduce morbidity of the disease. Finally, successful high school screening should be considered instead of premarital testing, as high school screening has been shown to be more effective in reducing the incidence of β -thalassemia.

Bibliography

1. Joly P, *et al.* "[Beta-thalassemsias: molecular, epidemiological, diagnostical and clinical aspects]". *Advances in Clinical Chemistry* 72.6 (2014): 639-668.
2. Ahmadpanah M., *et al.* "In Patients with Minor Beta-Thalassemia, Cognitive Performance Is Related to Length of Education, But Not to Minor Beta-Thalassemia or Hemoglobin Levels". *Iranian Journal of Psychiatry* 14.1 (2019): 47-53.
3. Vichinsky E., *et al.* "Epidemiologic and clinical characteristics of nontransfusion-dependent thalassemia in the United States". *Pediatr Blood Cancer* 65.7 (2018): e27067.
4. Beck WS. "Hematology". USA: The Massachusetts Institute of Technology (1998).
5. Verma IC., *et al.* "Past, present and future scenario of thalassaemic care and control in India". *Indian Journal of Medical Research* 134 (2011): 507-521.
6. Bernaudin F., *et al.* "G6PD deficiency, absence of alpha-thalassemia, and hemolytic rate at baseline are significant independent risk factors for abnormally high cerebral velocities in patients with sickle cell anemia". *Blood* 112.10 (2008): 4314-4317.
7. Jalil T., *et al.* "Mutational Analysis of Beta Thalassaemia By Multiplex Arms-Pcr In Khyber Pakhtunkhwa, Pakistan". *Journal of Ayub Medical College Abbottabad* 31.1 (2019): 98-103.
8. Habibian N., *et al.* "Association between Iron Deficiency Anemia and Febrile Convulsion in 3- to 60-Month-Old Children: A Systematic Review and Meta-Analysis". *Iranian Journal of Medical Sciences* 39.6 (2014): 496-505.
9. Hartevelde CL and Higgs DR. " α -thalassaemia". *Orphanet Journal of Rare Diseases* 5 (2010): 13.

10. Koren A., et al. "Prevention of beta thalassemia in Northern Israel: a cost-benefit analysis". *Mediterranean Journal of Hematology and Infectious Diseases* 6 (2014): e2014012.
11. Alswaidi FM and O'Brien SJ. "Premarital screening programmes for haemoglobinopathies, HIV and hepatitis viruses: review and factors affecting their success". *Journal of Medical Screening* 16 (2009): 22-28.
12. Olivieri NF., et al. "Hb E/beta-thalassaemia: a common and clinically diverse disorder". *Indian Journal of Medical Research* 134 (2011): 522-531.
13. Vichinsky EP. "Changing patterns of thalassemia worldwide". *Annals of the New York Academy of Sciences* 1054 (2005): 18-24.
14. Higgs DR., et al. "Thalassaemia". *Lancet* 379 (2012): 373-383.
15. Thalassemia.
16. Verma IC., et al. "Multicenter study of the molecular basis of thalassemia intermedia in different ethnic populations". *Hemoglobin* 31 (2007): 439-452.
17. Alamiry AAN., et al. "Detection of Hemoglobinopathies in Hypochromic, Microcytic and Sickled Cell Blood Films by Hemoglobin Electrophoresis". *Thi-Qar Medical Journal* 5 (2011): 139-148.
18. ZA Memish and MY Saeedi. "Six-year outcome of the national premarital screening and genetic counseling program for sickle cell disease and beta-thalassemia in Saudi Arabia". *Annals of Saudi Medicine* 31.3 (2011): 229-235.
19. El-Beshlawy A and Youssry I. "Prevention of hemoglobinopathies in Egypt". *Hemoglobin* 33 (2009): 14-20.
20. Almutawa F and Alqamish J. "Prevalence of hemoglobinopathies among candidates attending premarital counseling in Bahrain". *Journal of the Bahrain Medical Society* 20 (2008): 145-149.
21. Hassan SM., et al. "Extended molecular spectrum of beta- and alpha-thalassemia in Oman". *Hemoglobin* 34 (2010): 127-134.
22. Baysal E. "Molecular basis of beta-thalassemia in the United Arab Emirates". *Hemoglobin* 35 (2011): 581-588.
23. Jain RC. "Sickle cell and thalassaemic genes in Libya". *Transactions of the Royal Society of Tropical Medicine and Hygiene* 79 (1985): 132-133.
24. Chouk I., et al. "Contribution to the description of the beta-thalassemia spectrum in Tunisia and the origin of mutation diversity". *Hemoglobin* 28 (2004): 189-195.
25. Boudrahem-Addour N., et al. "Molecular heterogeneity of beta-thalassemia in Algeria: how to face up to a major health problem". *Hemoglobin* 33 (2009): 24-36.
26. Tremblay C., et al. "Prevalence of haemoglobinopathy in sportsmen in Qatar". *British Journal of Sports Medicine* 45 (2011): 317-324.
27. Abu-Ghoush MW. "Subtypes of alpha thalassemia diagnosed at a Medical Center in Jordan". *TAF Preventive Medicine Bulletin* 7 (2008): 373-376.
28. El-Hazmi MAF. "Pre-marital examination as a method of prevention from blood genetic disorders. Community views". *Saudi Medical Journal* 27.9 (2006): 1291-1295.
29. Al Sulaiman A., et al. "Postmarital follow-up survey on high risk patients subjected to premarital screening program in Saudi Arabia". *Prenatal Diagnosis* 30.5 (2010): 478-481.

30. Alhamdan NA, *et al.* "Premarital screening for thalassemia and sickle cell disease in Saudi Arabia". *Genetics Medicine: Official J Am College Medical Genetics* 9.6 (2007): 372-377.
31. Olivieri NF and Brittenham GM. "Management of the thalassemias". *Cold Spring Harbor Perspectives in Medicine* 3.6 (2013): a011767.
32. Darvishi Khezri H., *et al.* "Is Vitamin C Supplementation in Patients with β -Thalassemia Major Beneficial or Detrimental?" *Hemoglobin* 40.4 (2016): 293-294.
33. Paul A., *et al.* "Cardiac involvement in beta-thalassaemia: current treatment strategies". *Postgraduate Medical Journal* 131.4 (2019): 261-267.
34. Waldmeier F, *et al.* "Pharmacokinetics, metabolism, and disposition of deferasirox in β -thalassemic patients with transfusion-dependent iron overload who are at pharmacokinetic steady state". *Drug Metabolism and Disposition* 38 (2010): 808-816.
35. Novartis Pharmaceuticals. Exjade (deferasirox) prescribing information (2010).
36. Porter JB and Shah FT. "Iron overload in thalassemia and related conditions: Therapeutic goals and assessment of response to chelation therapies". *Hematology/Oncology Clinics of North America* 24 (2010): 1109-1130.
37. Cohen AR, *et al.* "Safety and effectiveness of long-term therapy with the oral iron chelator deferiprone". *Blood* 102 (2003): 1583-1587.
38. Gamberini MR, *et al.* "Hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism: Incidence and prevalence related to iron overload and chelation therapy in patients with thalassaemia major followed from 1980 to 2007 in the Ferrara Centre". *Pediatric Endocrinology Reviews* 6 (2008): 158-169.
39. Locatelli F, *et al.* "Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling". *Blood* 122 (2013): 1072-1078.
40. Li C., *et al.* "Related and unrelated donor transplantation for β thalassemia major: Results of an international survey". *Blood* 132 (2018): 308.
41. Locatelli F, *et al.* "Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling". *Blood* 122 (2013): 1072-1078.
42. Darvishi Khezri H., *et al.* "Is Vitamin C Supplementation in Patients with β -Thalassemia Major Beneficial or Detrimental?" *Hemoglobin* 40.4 (2016): 293-294.
43. Weatherall DJ. "The inherited diseases of hemoglobin are an emerging global health burden". *Blood* 115 (2010): 4331-4336.
44. Zurlo MG., *et al.* "Survival and causes of death in thalassaemia major". *Lancet* 2 (1989): 27-30.

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