Review Article

COMPLICATIONS IN TRANSFUSION–DEPENDENT PATIENTS OF ß-THALASSEMIA MAJOR: A REVIEW

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SUMMARY

ß- thalassemia is an inherited disorder of hemoglobin synthesis characterized by deficient synthesis of the ß-globin chain that causes severe anemia. Over the years, the combination of hypertransfusion and chelation therapy has significantly increased the survival of patients of ß-thalassemia. At the same time, there has been an increase in the frequency of complications, mainly caused by iron overload. These include cardiac disorders which are the main determinants of survival. Endocrine complications include hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism and hypoadrenalism. Low bone mineral density and trace element deficiencies are among the metabolic complications seen in chronically transfused patients of ß- thalassemia whereas hepatic problems and neuropsychologic disorders are also common.

KEY WORDS: ß- thalassemia, chelation, Cardiac complications, multiendocrine dysfunction

Pak J Med Sci July - September 2009 Vol. 25 No. 4 678-682

How to cite this article:

Malik S, Syed S, Ahmed N. Complications in transfusion–dependent patients of ß-thalassemia major: A review. Pak J Med Sci 2009;25(4):678-682.

INTRODUCTION

ß- thalassemia is a group of recessively inherited disorders of hemoglobin synthesis characterized by reduced synthesis of the ß-globin chain caused by a mutation. The homozygous state results in severe anemia which needs regular blood transfusion.[1]

Thalassemia is the most common monogenic disorder in the world.[2] Thalassemia major (beta-thalassemia) affects a significant segment of the population in certain areas of the world. Alterations in migration patterns have changed the geographic distribution of this disease and made it a worldwide health problem with a high frequency in Africa, India, Southeast Asia and the Mediterranean area.[3]

The combination of transfusion and chelation therapy has dramatically extended the life expectancy of these patients, thus transforming thalassemia from a rapidly fatal disease of childhood to a chronic illness compatible with a prolonged life.[4] On the other hand, frequent blood transfusions leading to iron overload and the chronic nature of the disease have contributed to a whole new spectrum of complications in adolescents and young adults suffering from thalassemia major.[5,6]

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* Received for Publication: May 13, 2009

* Accepted: June 24, 2009

COMPLICATIONS

Cardiac Complications: Cardiac disorders and, most notably, left-sided heart failure are responsible for more than half of the deaths in these patients and are thus the main determinants of survival.[7] Heart disease may manifest as hemosiderrhotic cardiomyopathy, heart failure, pulmonary hypertension, arrythmias, systolic/diastolic dysfunction, pericardial effusion, myocarditis or pericarditis.[8,9] Iron overload is mainly implicated although genetic and immunologic factors, infections and chronic anemia are also important role players. Left ventricular dysfunction attributed to myocarditis in this patient population especially appears to be mediated by immunologic mechanisms rather than viral infection and iron overload. It has been documented that certain major histocompatibility antigens may protect (HLA-DRB1*1401) or predispose (HLA-DQB1*0501) patients to develop cardiac failure[10]. With the advent of chelation therapy, there has been a decline in the severity of these complications but they still remain the leading cause of morbidity and mortality in these patients.

Endocrine Complications: A high incidence of multiendocrine dysfunction has been reported in children, adolescents and young adults suffering from thalassemia major.[11,12] Of these, the commonest is hypogonadotrophic hypogonadism reported in upto 75% of patients.[13,14] The anterior pituitary is particularly sensitive to iron overload which disrupts hormonal secretion, leading to gonadal dysfunction.[15] Thus these patients show decreased gonadotrophin reserves when compared with those of normal controls. This usually presents as delayed or absent puberty, primary or secondary amenorrhea, menstrual irregularities and fertility problems later in life. Many of these complications are reversible once the patients are started on hormone replacement therapy.[16,17] Also, reports have shown that a successful pregnancy is possible in women who are well chelated with or without ovulation induction therapy.

Apart from sexual development, retarded growth velocity is another issue in the long-term follow-up of patients with thalassemia. During childhood, growth may be affected by anemia and other potential endocrine problems, however puberty is the stage of maximum growth insult. There is a reduced or absent pubertal growth spurt in these patients, leading to short adult stature.[18,19] This has been attributed to factors such as multiendocrine dysfunction, chronic anemia, infections, undernutrition , malabsorption of vitamin D, deficiencies of calcium, zinc and copper, and lower serum levels of insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 (IGFBP-3), all of which have been reported in thalassemics.[20,21]

Other endocrine complications include glucose intolerance in adolescence and overt diabetes in later life, mainly due to iron deposition in the pancreas.[22] Rarely patients have also presented with diabetic ketoacidosis. The postulated risk factors for abnormal glucose tolerance tests (GTT) in transfusion-dependent ß-thalassemic patients are serum ferritin as well as hepatitis C infection.[23]

Thyroid dysfunction has been reported in 13-60% of patients but its severity is variable in different series. Most studies report a high prevalence of subclinical primary hypothyroidism (normal FT4, FT3; increased TSH) whereas prevalence of overt hypothyroidism (low FT4 and/or FT3; increased TSH) is relatively low.[1,24] Moreover, as opposed to the gonadal axis, the thyroid gland appears to fail before the central components of the pituitary-thyroid axis.[25] No correlation between ferritin levels and thyroid functional status has been shown although abnormal thyroid function appears to be reversible in early stages with intensive chelation.[26]

Hypoparathyroidism assessed by serum calcium, phosphate and parathyroid hormone levels has also been reported in various studies with a frequency of 4-12% and a higher incidence in males.[1] It is typically seen in the second decade of life. Serum-intact parathyroid hormone, and total and ionized calcium have been shown to be significantly lower, while phosphorus is significantly higher in thalas-

semic patients with hypoparathyroidism.[27] However, severe symptomatic hypocalcemia with signs of tetany or seizures is uncommon. It is thought to be mainly the consequence of iron deposition in the parathyroid glands, individual sensitivity to iron toxicity[28] as well as phosphate content of the diet. Hypoadrenalism, though very rare, has been reported in some series.[29]

Metabolic complications: Cooley's original description of ß-thalassemia major included marked bone deformities as a characteristic feature. There is a high prevalence of low bone mass in these patients.[30,31] BMD is assessed using dual x-ray absorptiometry at three common sites including the lumbar spine, head of femur and forearm. Low bone mass manifesting as osteoporosis (T score <-2.5) or, more commonly osteopenia (T score -1 to -2.5) has been reported in 40-60% of patients.[1,32] Factors contributing to lower bone mineral density (BMD) in these patients include lack of spontaneous puberty, malnutrition, multiendocrine dysfunction and deficiencies of vitamin D, calcium and zinc. Patients with normal gonadal function and those who receive hormone replacement therapy have shown higher BMD values than hypogonadotrophic patients.[33] However according to Ersi Voskaridou et al,[34] it is the increased bone resorption (evidenced by measurement of urinary N-terminal peptides of collagen-1), rather than impaired bone formation (assessed by levels of serum alkaline phosphatase & osteocalcin) that leads to low BMD.

Thalassemic patients show lower levels of serum 25-hydroxy vitamin D than controls. This has been attributed to malabsorption of vitamin D as well as inadequate nutrient intake.[1,35]

Deficiencies of trace elements including zinc and copper have also been reported. Zinc deficiency is considered to be one of the main factors contributing to growth and puberty disorders in thalassemic patients.[1] According to Arcasoy et al it is the hyperzincuria under the influence of chelating agents that is responsible for this deficiency.[36] However other authors attribute it to nutritional deficiencies in the population.

Hepatic complications: During the last years, liver disease has emerged as a major cause of mortality in patients with ß-thalassemia major. In spite of its clinical relevance, thalassemia-associated liver damage has been insufficiently characterized.[37] Liver disease in these patients can manifest as hepatomegaly, decreased albumen concentrations, increased aspartate and alanine transaminase activities, Hepatitis B and C. Hepatitis C virus antibodies have been reported in 85% of multitransfused Italian patients, 23% of patients in the United Kingdom, 35% in the United States, 34% in France, 35% in Pakistan and 21% in India.[5] Hepatocellular carcinoma can complicate the course of hepatitis B and C. Significant fibrosis is frequent and its progression is mostly influenced by iron overload which may be attributable to, hypertransfusion, inadequate chelation, erythrocyte catabolism and iron hyperabsorption.[38]

Neurologic complications: Several reports have demonstrated involvement of the nervous system in ß-thalassemia patients.[39] Neurological complications have been attributed to various factors such as chronic hypoxia, bone marrow expansion, iron overload, and desferrioxamine (DFO) neurotoxicity. In most cases, neurological involvement is initially subclinical and can only be detected during neurophysiological or neuroimaging evaluation. Abnormal findings in the visual, auditory, and somatosensory evoked potential recordings are mainly attributed to DFO neurotoxicity. On the other hand, nerve conduction velocity abnormalities are associated either to chronic hypoxia or to hemosiderosis.

Neuropsychological studies available reveal a considerably high prevalence of abnormal IQ, not correlating, however, to factors such as hypoxia or iron overload. It is proposed that chronicity of the illness, rather than the disease per se, could be responsible for these findings. Also, regular school absence due to transfusions and frequent hospitalizations, physical and social restrictions resulting from the disease and its treatment, abnormal mental state due to the awareness of being chronically

ill, dependence on blood transfusions and the overly protective family attitude leads to restricted initiative and psychosocial development. These psychological problems affect the quality of life of thalassemic patients.[40]

Other Complications: Among other complications are transfusion-related infections especially viral infections like hepatitis B and C as well as HIV. In Pakistan a substantive number of the patients are either Hep C (35%) or Hep B (1.7%) positive.[41]

Massive splenomegaly in these children is a cause of major distress. Hypersplenism can cause thrombocytopenia and abnormal bleeding in thalassemics.[42] On the other hand, patients undergoing therapeutic splenectomy run a very high chance of developing bacteremia and post-splenectomy sepsis.

Bone marrow transplantation is the only definitive cure for thalassemics at present. However this procedure has its own fair share of complications. Chern JP et al investigated complications in patients with ß-thalassemia major in Taiwan and found BMT-related deaths to be among the major causes of death in this patient population.[43]

Chelating agents like desferrioxamine, deferiprone and deferasirox have their own side effects for instance, retinal damage, hearing loss, bone abnormalities, growth retardation, deranged liver function tests, arthropathy, agranulocytosis, neutropenia, gastrointestinal disturbance, zinc deficiency, pruritis and increased serum creatinine levels.[44]

Less significant complications include hyperuricemia caused by increased cell turnover and expansion of medullary cavities leading to problems like distorted facies, poor drainage of sinuses and deafness.

CONCLUSION

Treatment of ß-thalassemia still remains a challenge. Steps need to be taken to develop preventive measures like premarital screening (especially of high risk ethnic groups or "targeted screening" of families with a thalassemic child), genetic counselling and prenatal diagnosis because the cost of treatment depending on the quality of care, is tremendous and associated with major complications. At the same time we must also increase therapeutic facilities like blood transfusions, chelation and bone marrow transplantation for the betterment of these patients.

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