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Chapter 1

Hemoglobinopathy Approach Diagnosis and Treatment Policy

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Abstract

Hemoglobinopathies are the most common single gene disorders worldwide with a considerable frequency in certain area particularly Mediterranean and Middle Eastern countries. Hemoglobinopathies include structural variants of hemoglobin (Hb S, Hb C, HbE,...) and thalassaemias which are inherited defects in the globin chains synthesis. The present study was conducted to determine the prevalence of hemoglobinopathies in western Iranian patients. A total of 344 patients (151 males and 193 females) with abnormal CBC and/or hemoglobin electrophoresis were enrolled in the present study. Cellulose acetate gel electrophoresis was performed for all patients and abnormal bands were identified by citrate agar gel electrophoresis and PCR based methods. Iron deficiency anemia (IDA) was present in 156 (45.3%) individuals. Thirty four (9.8%) patients had both iron deficiency anemia and α-thalassemia trait trait, 41(11.9%) patients were with both iron deficiency anemia and minor β-thalassemia. There were 31(9%) patients with α-thalassemia trait and 5 (2.2%) patients with Hb H disease. Fifty six (16.2%) patients had minor β-thalassemia. Also, there were 10 (2.9%) individuals homozygous for hemoglobin D-Punjab and one patient with hemoglobin G (0.3%). There was one sample with hemoglobin C. Further, we found 3 patients (0.9%) with sickle cell trait and more 3 patients (0.8%) with S/ β +-thalassemia. Our results indicated that the most frequent cause of hypochromic and/or microcytic anemia in our population was IDA and the minor β-thalassemia was the second cause that needs to more attention in screening programs.

Keywords: Hemoglobinopathies, alpha- thalassemia, beta- thalassemia, anemia

1. Introduction

These two major groups, α- and β-thalassemia, are subclassified according to absent ($\alpha 0$ and $\beta 0$) or reduced ($\alpha+$ and $\beta+$) globin chain synthesis. The difference in the amount of fetal

hemoglobin (HbF) that persists into adulthood affects the severity of β-thalassemia syndromes [4]. Hemoglobinopathies are the most common single gene disorders in man. There are several hundred of these disorders, but the thalassemias—alpha and beta—and the sickling disorders make up the vast majority [1]. The wide variation in the clinical manifestation of hemoglobin disorders could be attributed to the influence of various genetic modifiers and environmental factors. The heterogenous distribution of the disease and the presence of high variation in the phenotypic manifestation of a specific mutation are major problems with the development of programs for the control of the hemoglobinopathies [2] Thalassemia is one of the most common genetic diseases worldwide, with at least 60, 000 severely affected individuals born every year [3].

2. Pathophysiology

At the molecular level, the underlying cause of thalassemia is any of a number of genetic lesions that reduce or abolish the production of the globin chains of hemoglobin. The resulting chain imbalance is the key factor initiating the damage to RBC, and it is the major pathophysiological event in all forms of the thalassemia syndromes [4]. Severe IE, chronic anemia, and hypoxia also cause increased gastrointestinal (GI) tract iron absorption [5]. Repeated blood transfusions are one of the major causes of iron overload in several of these disorders, including β-thalassemia major, which is characterized by a defective β-globin gene. In addition to repeated blood transfusions and increased iron absorption, chronic hemolysis is the major cause of tissue-iron accumulation in anemic iron-overload disorders caused by hemolytic anemia [6]. Molecular studies using nucleic acid hybridization techniques and endonuclease analysis have identified loss of alpha-gene function related to gene deletion or nondeletional mutations causing hypofunctional genes and terminator codon mutations as responsible for the various alpha-thalassemia syndromes [7]. A number of reports of heterozygous *KLF1* mutations in humans either show concomitant disruption of erythropoiesis or show little effect on HbF expression, and recent studies suggest that rare variants in *KLF1* are indeed associated with elevations in HbF, but this does not appear to occur consistently or to the same extent even with similar mutations. The basis of this variation remains to be determined and will be important to better understand the mechanisms by which KLF1 acts both directly and indirectly to affect HbF expression [6]. Also, β-thalassemia major is suspected in an infant or child younger than age 2 years with the following clinical or newborn screening findings: severe microcytic anemia, mild jaundice and hepatosplenomegaly [8].

Couples and their close relatives should be evaluated for silent or atypical alpha- and beta-mutations, and if they are detected, prenatal genetic counseling for diagnostic purposes should be provided [7].

3. Clinical manifestations

Nearly 10% beta-thalassemia patients have beta-thalassemia intermedia (TI) [10]. TI is associated with a variety of serious clinical complications that require proactive and compre-

hensive management such as skeletal deformities and osteopenia, compensatory extramedullary hematopoiesis and tumor formation, progressive splenomegaly, a hypercoagulable state resulting in thromboembolic events and pulmonary hypertension, and increased gastrointestinal iron absorption that often results in nontransfusional iron overload and liver damage [9]. TI patients who develop progressive anemia, fatigue, and cardiopulmonary complications also require regular transfusions to maintain Hb levels <9–10 g/dL [10, 11]. Beta-thalassemia major (also called Cooley anemia, Mediterranean anemia, and von Jaksch anemia) denotes the homozygous or compound heterozygous forms of the disease, which are characterized by severe anemia (range, 1–7 g/dL of Hb), hemolysis, and massive IE [12]. Affected infants with thalassemia major fail to thrive and become progressively pale. Feeding problems, diarrhea, irritability, recurrent bouts of fever, and enlargement of the abdomen may also occur due to splenomegaly [13].

4. Strategies for TM treatment

4.1. Transfusion therapy

Early and regular blood transfusion therapy in patients with homozygous beta-thalassemia decreases the complications of severe anemia and prolongs survival that in the long term. The beneficial effects of transfusions are limited by the organ damage resulting from iron overload, a consequence of the body's limited capacity to excrete iron, and by the complications of infection with blood-borne agents [14]. Current therapeutic approaches for homozygous beta-thalassemia entail blood transfusions and iron chelation therapy with deferoxamine or deferiprone for preventing tissue hemosiderosis. Nowadays, much effort has focused on various inducers of HbF, such as recombinant human erythropoietin, especially in beta-thalassemia intermedia [15]. Cytomegalovirus-negative blood products are recommended for potential candidates for curative stem cell transplantation (SCT). Parents and first-degree relatives should not be blood donors for these candidates. Hepatitis B vaccination is given before transfusion therapy [16]. Transfusions of washed, leukocyte-depleted RBCs are recommended for all the patients to reduce the incidence of febrile and urticarial reactions as well as infectious cytomegalovirus contamination. If they are not available, frozen–thawed RBCs should be administered [17, 18]. Current transfusion regimen guidelines state that the pretransfusion hemoglobin (Hb) should ideally be in the 9- to 10-g/dL range. This recommended transfusion scheme generally leads to the transfusion of 100–200 mL/kg/year of packed red blood cells, which is equivalent to 0.3–0.6 mg of iron per kg body weight per day [19].

4.2. Managing of the complications

Cardiac failure and serious arrhythmias are the major causes of life-threatening morbidity and mortality in iron-overload patients [20]. In the modern era, with iron chelation treatment, the clinical manifestation of cardiac disease has changed, and pericarditis and myocarditis are now rare. Historical postmortem studies showed severe replacement cardiac fibrosis [21], but this

is now rare in more modern cohorts of patients dying of HF [22]. Patients receiving regular transfusion and iron chelation should be assessed formally for their cardiac status (history, physical examination, and auscultation) beginning at the age of 10 years and annually thereafter [23]. There are ongoing clinical trials that are relevant to the treatment of cardiac iron overload by deferasirox. One that is relevant is the Novartis 2214 trial, with open-label treatment in TM patients with combined deferoxamine with deferasirox. In addition, clinical trials of new chelators are ongoing [24]. Diuretics, including loop diuretics (furosemide) and potassium-sparing agents (spironolactone), as well as angiotensin-converting enzyme (ACE) inhibitors should be prescribed based on arterial blood pressure. Also, in cases of persistent normal sinus tachycardia, small doses of carvedilol and digoxin may be given and must be prescribed to patients with atrial fibrillation resistant to conversion [25].

4.3. Bone disease

Therefore, the detection of low bone mass in many regularly transfused and well-chelated β TM patients over the last decade was quite unexpected [26]. DiStefano et al. [27] reported that the etiology of bone disease in thalassemia is poorly understood. Therefore, a number of studies have examined the effect of various conditions on the pathogenesis of bone disease, including ineffective erythropoiesis, iron overload, treatment with DFO, vitamin D concentrations, influence of endocrinopathies (such as hypogonadism and growth hormone deficiency), and thalassemia genotype. Beginning in childhood, yearly examination of bone mineral density as well as calcium, vitamin D3 metabolism, and thyroid and parathyroid functions should be performed. Some short-term success has been seen with the administration of pamidronate in patients with Z-/T-score <2.5. It seems that early administration of iron chelation is effective in preventing endocrine complications [28].

4.4. Splenectomy

Splenectomy determines immediate drop in blood consumption and iron intake but slow downtrend of ferritin, which are direct measurements of iron overload [29]. Also, Splenectomy reduces transfusion requirements in the first year after surgery in patients with thalassemia major and hypersplenism [30]. Splenectomy should generally be avoided in NTDT patients <5 years, and it should be reserved for the following cases [31]:

a. When transfusion therapy is not possible or iron chelation therapy is unavailable

b. Worsening anemia leading to poor growth and development

c. Hypersplenism and splenomegaly

d. Leading to worsening anemia, leucopenia, or thrombocytopenia and causing clinical problems such as recurrent bacterial infections or bleeding

e. Accompanied by symptoms such as left upper quadrant pain or early satiety

f. Massive splenomegaly (>20 cm) with concern about possible splenic rupture

The susceptibility to overwhelming infections after splenectomy can be reduced by immunization with pneumococcal and meningococcal vaccines before splenectomy and antimicrobial

prophylaxis with penicillin after splenectomy [32]. In cases of ongoing transfusion therapy, with each RBC unit containing >200 mg of iron, cumulative iron burden is an inevitable consequence [33].

4.5. Prevention: prenatal diagnosis

The prenatal diagnosis of β-thalassemia was accomplished for the first time in the 1970s by globin chain synthesis analysis on fetal blood obtained by placental aspiration at 18–22 weeks gestation [34]. Acceptance of prenatal diagnosis and termination of affected fetuses are dependent on the early identification of couples at risk, culturally sensitive genetic counseling, cost, and religious beliefs even when PCR technologies are available [35]. Preimplantation genetic diagnosis is generally defined as the testing of preimplantation stage embryos or oocytes for genetic defects, and preimplantation embryo diagnosis requires in vitro fertilization, embryo biopsy, and using either fluorescent in situ hybridization or polymerase chain reaction at the single cell level [36]. Current PCR technologies and precise hybridization assays to detect single point mutations with great reliability using very small DNA samples have been developed. New technology using fetal DNA obtained from maternal plasma or maternal peripheral blood has also been developed but is not routinely available [37].

4.6. Cure: HSCT

Hematopoietic SCT (HSCT) is an established procedure for many acquired and congenital disorders of the hematopoietic system [38]. The European Group for Bone Marrow Transplantation analyses in previous years have shown an increase in the annual absolute HSCT numbers and transplant rates (number of HSCT/10 million inhabitants) of about 4–13% (median 8%) for allogeneic and 1.5–9.5% (median 4%) for autologous HSCT [39]. The success of an allogeneic HSCT is dependent on a multitude of factors, including the procurement of an optimal graft source. Further, the quality of this graft depends on a variety of donor and/or host characteristics. Most importantly, HLA compatibility between the recipient and the donor is considered the dominant characteristic in this field [40]. There are other important donor characteristics that these non-HLA characteristics may be broadly considered to be either traditional characteristics, such as ABO compatibility or novel, such as cytokine or KIR polymorphisms [41]. Approximately 10% of SCT patients are transfusion-free for years, although they experience persistent mixed hematopoietic chimerism [42]. This suggests that only a few engrafted donor cells are sufficient for correction of donor phenotype. Approximately 30% subsequently reject their grafts. Another option is to use matched unrelated donor if a matched sibling is not available or when patients are not compliant with conventional therapy [43].

4.7. Cord blood transplantation

Although the clinical application of hematopoietic cell transplantation has relied on marrow collected from related and unrelated donors as the primary source of donor hematopoietic cells, umbilical cord blood (UCB) is an alternative source of hematopoietic cells and represents a suitable allogeneic donor pool in the event that a marrow donor is not available [44]. The small size or small number of stem cells in the UBC collection relative to the number required

for engraftment are probably the main causes of failure of UCB transplantation; therefore, this procedure is being used mainly in pediatric patients [45].

5. Therapies for future

5.1. Fetal hemoglobin inducers

Recently, a novel therapeutic strategy (HbF) has been hypothesized for β-thalassemia, based on the observation that the coexistence of the hereditary persistence of fetal hemoglobin in patients with β-thalassemia reduces the severity of the disease [46]. Several drugs, including erythropoietin, demethylating agents, such as 5-azacytidine, and short chain fatty acids, such as butyrate, have been studied individually and in various combinations [7]. Hydroxyurea (HU), which is very effective in increasing HbF levels, has been used extensively for many years in patients with sickle cell anemia (SCA) [47].

5.2. Gene therapy

Requirements for effective gene transfer for the treatment of β-thalassemia are regulated, erythroid-specific, consistent, and high-level β-globin or γ-globin expression that Gamma retroviral vectors have had great success with immune deficiency disorders, but due to vector-associated limitations, they have limited utility in hemoglobinopathies. Nowadays, lentivirus vectors have been shown in several studies to correct mouse and animal models of thalassemia [48]. In total, concerns regarding gene transfer include the need for improved efficiency of gene delivery and mastery of vector stability, viral titers, nononcogenic insertion, the variable expression of globin genes, and the variable contributions of the beta-thalassemia phenotype and other modifiers to the effectiveness of gene transfer [49].

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