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Beta thalassemia: Prevalence, risk and challenges

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Abstract
Thalassemia is an autosomal recessive common genetic disorder throughout the world. Various mutations in globin genes are major cause of thalassemia and require collective measures including carrier identification, genetic counseling and prenatal diagnosis for preventing β-thalassemia. All patients were diagnosed at 18 years of age or less. Patients with homozygous beta-thalassemia was clinically classified into severe transfusion dependent thalassemia major and mild based on criteria such as age at presentation, average hemoglobin level at the steady state and the most important transfusion frequency history. Different methods can be used to detect mutations in disease causing gene. For this, all of the beta-thalassemia alleles can be characterized by a combination of techniques including M-ARMS, direct DNA sequencing, and gap-PCR for 3.4 kb deletion detection. Hence, it is suggested to have proper screening for β-Thalassemia trait in families of Thalassemia major patients. This will help to overcome beta-globin gene mutations among patients and in next generations as well.

Keywords: Beta thalassemia, blood disorder

1. Introduction

Thalassemia is the most common inherited genetic blood disorder characterized by abnormal and low production of hemoglobin resulting in life threatening anemia [1, 2]. Mutations in globin genes are major cause of thalassemia [3]. β-thalassemia is frequently reported single-gene inherited conditions in the world [4]. Almost 70,000 infants are born with β-thalassemia worldwide each year and 270 million people are carriers of haemoglobinopathies [5-7]. More than 300 different beta-globin gene mutations have been characterized. Most of the beta-thalassemia mutations are caused by point mutations, small deletions or insertions within the coding regions and the exon-intron junctions [8]. In Thailand, the prevalence of beta-thalassemia carriers varies from 3%–9% [9]. To date, more than 30 different mutations have been identified [10-13]. Trends of consanguineous marriages, high fertility rate, high birth rate, low educational level, early marriages with unawareness has led Pakistan towards very high number of children with transfusion dependent Thalassemia in the world. The average life expectancy of Beta Thalassemia patients in Pakistan is 10 years in 2003. It has been estimated that over 4000 cases of transfusion dependant Beta thalassemia patients are born in Pakistan every year. In another study, β-Thalassemia carriers were estimated to be 8 million in Pakistan [14].

Adult haemoglobin is composed of two α and two β chains encoded by two α-globin genes on chromosome 16 and one β-globin gene on chromosome 11. β-Thalassemia is associated with two types of mutation β0 and β+. Person with β-Thalassemia minor have one abnormal allele but if two abnormal alleles are inherited then result is β-Thalassemia major. Sometimes patients may present with milder symptoms in β-Thalassemia intermedia, though have both mutant alleles [15]. About 20 mutations account for 90 percent of β-globin genes in the world and it is noted that each ethnic population has its own unique set of most frequent mutations. Previously, there have been few studies investigating the spectrum of β-thalassemia mutations in various regions and ethnic groups of Pakistan [16, 17].

Like many other developing Asian countries, b-thalassemia poses an increasing burden for healthcare services in Pakistan and it is not possible to provide blood transfusion and iron chelation therapy to all patients with limited available national resources. The best chance of preventing thalassemia major from occurring is to detect the carriers at a pre-marital stage and prevent them from getting married by giving them proper marriage counseling. An alteration in the gene for the beta globin is supposed to be the possible cause of b-thalassaemia. The inability to produce b-globin chains allows the a-globin chains to accumulate and precipitate within erythroid precursors in the bone marrow [18]. Typically, b-thalassaemia is characterised by moderate to severe anaemia, caused by haemolysis and ineffective erythropoiesis. The other signs, frequently observed in thalassaemic patients, include endocrine changes and spleenomegaly, diarrhoea, irritability, fever, feeding problems and gradual bulging of the abdomen due to spleen and liver enlargement [19].

2. Methods Used for mutation detection

A number of different methods can determine beta-thalassemia mutations. ARMS can be used to detect 80% mutation of alleles. But major drawback with ARMS is that it can detect only specific mutations in a given set. An advance technique of direct DNA sequencing can be used to detect and identify point mutations and small rearrangements in the beta globin gene. The disadvantage of DNA sequencing is that large deletions of the gene are undetectable [20].

3. Occurrence of thalassemia

Exact data about the prevalence of hemoglobin disorders is not available in Pakistan but its vertical transmission can be prevented by proper screening and counselling in families of Thalassemia patients. Although spread of Thalassemia is difficult to prevent at this time in Pakistan because of unawareness, lack of education, remote health counselling facilities. But this can overcome with a program of health education, testing for the trait, genetic counselling and easy accesses to prenatal diagnosis can provide families with full medical information to help them have healthy children. Young people need to learn about their carrier status early enough to consider all available options, including marriage and undertaking a pregnancy. Pakistan has a population of approximately 180 million people and b-thalassemia has an overall carrier frequency of more than 5% in Pakistan and there are approximately nine million carriers of b-thalassemia in the country [21]. Approximately 40,000 cases of transfusion-dependent children with thalassemia major are presently registered and each year nearly 5000 affected children are born nationwide.

Thalassemia is particularly prevailing in areas in which malaria is found to be endemic in past and present, but the exact mechanism is still not known. It is thought that in areas where malaria was prevalent, humans underwent a small genetic change in their DNA which gave them an advantage over others making them more resistant to the malaria infection. This is because important changes occurred in the RBC environment following this genetic change that did not allow the parasite to survive and multiply, causing illness and ultimately death. In Pakistan, the number of registered thalassemia children in different thalassemia centers is around 22,000 whereas a similar number of children are living in villages and are not registered with any thalassemia center. The occurrence of thalassemia carriers is 5-8% in various racial groups which translate into 7 to 10 million individuals. The average life expectancy of β-thalassemia patients in Pakistan is 10-12 years. Studies have suggested that poverty, consanguinity and unawareness about the disease are the prominent factors in increasing the prevalence of this particular genetic disorder.

4. Discussion

Thalassemia is recognized as the most prevalent genetic blood disorder in the world. The molecular basis of thalassemia has been studied worldwide. However, β thalassemia is found in about 60 nations with a carrier frequency of about 150 million. More than 300 different beta-globin gene mutations have been characterized. Most of the beta-thalassemia mutations are caused by point mutations, small deletions or insertions within the coding regions and the exon-intron junctions. Genetic risk, such as identification of β-globin gene mutations should be integrated routinely into epidemiological studies followed by genetic counseling and prenatal diagnosis to reduce birth rate of affected infants [22-24]. The highest percentage of Beta thalassemia patients was between 3-5years of age group. It was observed that number of young patients was high as compared with old patients. This was due to increase disease load and shortened life expectancy. In Pakistan, the reported age of Beta thalassemia patients was believed to be 10 years. The proportion of male patients was higher than the female. There were 56.95% male while females were 43.05%. Similar results are reported in other studies by different authors. Male-to-female ratio was 1.8:1.0. This gender-ratio difference in thalassemia patients is significant and deserves further investigation considering thalassemia as a single-gene disease transmitted by a recessive mode of inheritance. The dominance of males over females in the present study is difficult to explain. One possible reason is the fact that the people are more concerned with the health of the male offspring and are more concerned to seek medical care for them.

5. References

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