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Thalassemia: Impact of consanguineous marriages on most prevalent monogenic disorders of humans

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ABSTRACT

Thalassaemia is an inherited autosomal recessive disorder closely associated with consanguineous marriages. A literature search was conducted with an aim to investigate thalassemia and consanguineous marriages. Articles were searched from Google Scholar and Pubmed information regarding thalassemia associated complications, epidemiology of thalassemia and association between consanguineous marriages and thalassemia, which was subjected to contemplation. Thalassemia carrier rate varies differently in different regions of the world. In Indian subcontinent and China, Central Asia, South Europe (also known as North Mediterranean) and Arab Region, the thalassemia carrier rates were approximately 1%–40%, 4%–10%, 1%–19% and 3%, respectively. In Pakistan, the annual number of infants born with beta thalassemia is the highest as compared to other countries from Eastern Mediterranean Region. Although the management and control of thalassemia is a difficult task, it can easily be achieved via the assistance of prenatal diagnosis and prevention programs. Consanguineous marriages should be avoided to further limit the future burden of thalassaemia disease.

1. Introduction

Thalassemia disorder was initially described by Cooley and Lee in 1925[1]. Italian children with characteristic severe anemia and splenomegaly were among the early reported cases from Mediterranean Region. Because of the close link towards the prevalence of this disease with Mediterranean Region, the disease attained the name of thalassemia. The word thalassemia has been derived from two Greek word, thalassa (sea) and haema (blood)[2,3]. Later on, various studies confirmed the prevalence of thalassemia in different parts of the world especially throughout tropical regions. Thalassemia disease can be described as disorder associated with defective synthesis of α - or β -globin subunit chains of hemoglobin. Thalassemia has been majorly recognized as the most prevalent monogenic disorder of humans[4]. The gene responsible for encoding β -globin subunit chain of hemoglobin is located on chromosome 11, whereas the gene responsible for α -globin subunit

chain is present at chromosome 16[5,6]. It has been reported that severe beta thalassemia accounts for approximately 50000–100000 deaths annually, which represents 0.5%–0.9% of all children deaths from developing countries[7]. Clinical data suggest that this disease ranges from asymptomatic phase to severe anemic disorder. It has been reported that the annual incidence of this disease among the majority of symptomatic individuals worldwide is approximately 1 among 100000.

2. Literature search

A literature search was conducted with an aim to investigate thalassemia and consanguineous marriages. Articles were searched from Pubmed and Google Scholar to find out research findings related to thalassemia, thalassemia associated complications, epidemiology of thalassemia and association between consanguineous marriages and thalassemia.

3. Thalassemia

Almost 60–80 million people in the world are carriers of beta thalassemia trait[8]. The major forms of thalassemia include thalassemia minor and thalassemia major. Individuals who have a defect in only one of their β -globin genes usually develop non-

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life threatening thalassemia minor. This disease only causes mild anemia which usually does not require any treatment. But both parents who are positive for thalassemia minor trait usually give birth to offsprings with thalassemia major. An individual having both genes (encoding for β -subunit) affected, usually develops beta thalassemia major. In such patients, severe anemic condition arises at few months of age, and bone marrow cavities get increased due to the overburden of hemoglobin production. This situation leads to abnormalities in bones especially in facial bones. In such individuals, abnormal hemoglobins are formed, which are unable to transport oxygen efficiently. These are termed as unstable hemoglobins which are dangerous for body because bone marrow, liver and spleen undergo stress. Due to extra pressure exerted on spleen for the eradication of abnormal blood cells from human blood circulation, splenomegaly usually takes place. The only available hope for the continuation of patients' life is frequent blood supply. Unfortunately, due to continuous blood supply, breakdown of unhealthy blood cells and unstable hemoglobin, the level of iron increases in thalassemia patients. This iron overload leads towards therapeutic option via chelation therapy.

4. Thalassemia associated complications

Among patients who do not receive regular blood transfusions, the average increase in iron is approximately from 2 g to 5 g each year probably due to the severity of erythroid expansion. And among patients who receive multiple blood transfusions, the accumulation level of iron gets doubled[9]. It has been reported that approximately after 1 year of blood transfusions, the iron level tends to accumulate more in parenchymal tissues which ultimately results into substantial toxicity as compared to reticuloendothelial cells[10,11]. In such circumstances, if patients are unable to receive chelation therapy, then the increased accumulation of iron would ultimately cause dysfunction of their heart, kidney, liver and endocrine gland[12]. It has been reported that among the most common causes of deaths in old aged thalassemia patients, the major cause is iron-induced liver dysfunction which is further aggravated by viral hepatitis[13]. Various studies have reported that in absence of chelation therapy, after two years of blood transfusion in thalassemia patients, liver cirrhosis, portal fibrosis and collagen formation may take place. Risk of liver fibrosis is further aggravated when the concentration of iron increases more than 7 mg/g of the liver dry weight[14-17]. The management and control of thalassemia is a difficult task, but it can easily be achieved by the help of various prenatal diagnoses and prevention programs. Some of the other treatment options against thalassemia patients include bone marrow transplantation, use of chelators other than desferoxamine, the augmentation of fetal hemoglobin synthesis and gene therapy[3].

It is a well-known fact that when there is an increased accumulation of iron in the heart, it becomes much larger and beating becomes irregular. Later on, if the iron keeps on accumulating, it becomes unable to pump the blood. This is the main reason of death in iron-overloaded thalassemia patients. The main advantage of using desferal is that it protects heart from iron. Intensive use of desferal treatment can prevent serious heart problems in thalassemia patients.

In thalassemia patients, liver problems are generally caused due to iron overload and/or viral infection. The best preventive measure would be accurate use of desferal and appropriate screening of blood prior to blood donation. Sometimes endocrinological complications are also associated with iron overload. When iron gets incorporated into vital endocrine glands, it can get accumulated in thyroid gland and parathyroid gland. In some cases, iron can even lower calcium level in blood and also accumulate in pancreas but rarely cause trouble here. But if it disturbs the function of islets of Langerhans then thalassemia patients may develop diabetes. Although treatment of such diabetes is available, there would be an increased risk of other complications.

5. Epidemiology of thalassemia

It has been reported that among the populations at risk for beta thalassemia, some similar kinds of mutations and some rare types of mutations exist. Every mutation is thought to be associated with powerful linkage disequilibrium along with definite arrangements of the restriction fragment length polymorphism within cluster of β -globin. It has been further observed that there are approximately 80% of mutations which are in association with twenty different restriction fragment length polymorphisms. This phenomenon leads to the conclusion of independent beta thalassemia originating in various populations[3,18]. The carrier rates of this disease are various depending upon different areas of the world. The carrier rates of thalassemia in Indian subcontinent and China, Central Asia, South Europe (also known as North Mediterranean) and Arab Region is approximately 1%–40%, 4%–10%, 1%–19% and 3%, respectively. But in Australia, North Europe, South Africa and America, the thalassemia carrier rates are very low[19]. In Pakistan, the annual number of infants born with beta thalassemia is the highest in Eastern Mediterranean Region as compared to other parts of the world[20].

6. Consanguineous marriages and thalassemia

In educational institutes such as schools and colleges, sex education is mostly avoided[21]. The proportion of marrying cousins and relatives is higher in Pakistan as compared to the rest of the North African Muslim countries[22]. In most of the Asian countries, marriages of couples are decided by parents. It would be a positive step if teachers would discuss the outcomes of consanguineous marriages with youngsters and their parents in order to prevent genetic abnormalities in families. Informed consent and guarantees of privacy are extremely important for the success of premarital screening programs. Premarital screening is strongly opposed by Pakistani culture and behavior of general public. For premarital screening, cultural, ethnic, religious and social issues must be resolved. Although tribal marriages are encouraged in many parts of Asia and East Mediterranean (occupied mainly by Arabs and Muslims), yet unfortunately due to inadequate knowledge, negative role of culture and poor genetic counseling, premarital screening for haemoglobinopathies, HIV, HBV and HCV for young couples is a very difficult task. It has been reported that 25%–60% of

all marriages from Arab Regions were consanguineous[23]. The Government of Saudi Arabia has implemented this program at national level in 2004. In the beginning of 2008, Saudi Government implemented mandatory premarital screening for HBV, HCV and HIV. Counseling and premarital screening are free of cost and strongly supported by the government. There are more than 100 health reception centers, 70 blood screening departments and 20 genetic counseling clinics in the country[24]. Al-Khaldi *et al.*[25] reported positive attitude towards premarital screening in 86% of female students from King Saud University. Similarly, in another report by El-Hazmi[26], it has been reported that 87% of participants thought testing should be compulsory. And 94% of participants considered that counseling and premarital screening are important steps for the prevention of genetic blood disorders[25,26].

Some of the countries with appropriate premarital screening programs running at national level include Italy, Bahrain, Iran, Jordan, Saudi Arabia, United Arab Emirates, Tunisia, Egypt, Spain, Portugal, Turkey, Cyprus, Canada, Greece, United Kingdom, USA, China, Taiwan, Brazil, Palestine, Malaysia, India, Indonesia, Maldives, Singapore and Thailand. According to the Committee of Islamic Fiqh Academy in Makkah, the termination of pregnancy is permissible only before a fetal age of 120 days. But after 120 days, termination of pregnancy is religiously banned[27,28]. End of pregnancy before birth is a traumatic event for both family and doctors. All of efforts must be employed to avoid reaching this stage by assistance of premarital testing and prenatal diagnosis of genetic disorders. In Pakistan, limited studies have been conducted to interpret the prevalence of thalassemia in different cities. About 62% of population belongs to rural areas with poor level of awareness with increasing threat of viral prevalence in multiple societies[29]. There is an urgent need for epidemiological patterns of HBV and HCV in high risk populations such as thalassemia. It is anticipated that hepatitis viruses would soon emerge as the most dangerous viral pathogen[30]. Such studies will be helpful for the implementation of blood safety laws in various public health sectors. Previous studies depicting the prevalence of HCV in thalassemia population from urban areas have reported the prevalence of HCV in range of 34.8% to 60.0%. It is a well-known fact that thalassaemia patients acquire hepatitis C through administration of unscreened blood collected during donor window period. In thalassaemia patients, seroprevalence of HCV infection varies in different parts of the world. In our previous study, the overall seroprevalence of hepatitis B virus surface antigen, anti-HCV and anti-HIV among 160376 blood donors of capital twin cities of Pakistan were 2.350%, 3.260% and 0.017%, respectively. The prevalence of HBV and HCV co-infection was 0.084%[31]. In Iran and India, the prevalence rates of HCV in thalassaemia patients were reported as 63.8% and 16.7%, respectively[32,33]. According to a study conducted at Rawalpindi Region of Pakistan, the HCV prevalence in thalassaemia patients was 60%[34]. It has been reported from Karachi that the prevalence rate of HCV infection in thalassemia children was 20.5%[35]. There is a strong need to raise awareness among general public about the prevention of viral and genetic diseases[36]. The need of time included efficient use of preventive vaccine for healthy people to prevent them from being infected and therapeutic vaccine for the

treatment of already infected patients[37,38].

It is a well-known fact that nature has many hidden remedies against multiple disorders (cancer, cardiovascular diseases, metabolic disorders, chronic inflammation and many others). There is a strong need to discover therapeutic potentials of those natural products. It has been reported that elevated activation of various cellular proteins may cause cancer proliferation, which can be further inhibited by potential inhibitors[39-49]. But the genetic diseases such as thalassaemia are not easily treatable. The most important way to prevent such genetic disorders among families is to discourage consanguineous marriages in society. There is a strong correlation between thalassemia and consanguineous marriages. In Pakistan, consanguineous marriages are quite often. This is the major reason of increased sustainability of hereditary disorders in many families. The thalassemia patients regularly require blood for continuation of their lives. On average, thalassemia patients require 25 blood transfusions per year, which increases the risk of transfusion-transmitted infections such as HBV, HCV and HIV. Consanguineous marriages should be avoided to limit the future burden of deadly diseases in Pakistan.

Conflict of interest statement

We declare that we have no conflict of interest.

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