BLOOD GROUP AND B-THALASSEMIA MAJOR IN DISTRICT SWAT, KPK, PAKISTAN

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Abstract—Thalassemia are defined as a group of inherited hematological disorders characterized by early onset of anemia resulting from reduced rate of synthesis of one or more globin chains caused by globin chain mutations. The present study was designed to find out the occurrence and comparison (prevalence) of beta thalassemia major in the population of Urban (Mingora) and Rural (tehsil Kabal) localities of District Swat. Occurrence of thalassemic patients in both the localities were categorized, regarding three aspects i.e. age wise, gender wise and blood group wise. It was also examined to test out if there is any correlation of blood group with the disease or not? Prevalence ratio of both the localities was also determined. Data of patients was collected from Wajeeha thalassemia Center Swat and Alfajr Foundation Swat. In the total population of 440000 persons of Mingora, 35 (0.008%), while in that of 170000 population of tehsil Kabal 42 (0.024%) registered patients were reported. Out of all these 70 patients, 40 (51.94%) were male while 37 (48.05%) were female. 24 (31.16%) were in age group 1-5, 25 (32.46%) in age group 6-10, 17 (22.7%) in 11-15, 08 (10.38%) in 16-20 and 03 (03.89%) were in age group 21-25. There were no patients above the age of 25. In blood group wise distribution, as Rh positive blood group occur 85% in nature, so the individuals having these group in our data were examined to be 74 out of 77 in which A+ were 22 (31.42%), no one in A-, 26 were B+ (33.76%), one was B- (01.29%), 3 were AB+ (03.89%), no one in AB-, 23 were O+ (29.87%) and 2 were O- (02.59%). This shows that there is no correlation of the disease with blood group. The recent study will provide reports and recommendations to the concerned field and will make awareness of beta thalassemia major disease among patients and public for their safety. Moreover, same study should be conducted in large population size to determine the other risk factors.

Index Terms— Thalassemias , Alpha-thalassemia , β thalassaemia , iron-deficiency anemia, Anemiais.

1 INTRODUCTION

IN 1940 Win Trobe described a milder form of thalassemia. In Italy many patients with Mediterranean anemia of intermediate severity have been reported (Marmont and Bianchi 1948).

A mild form of hemolytic jaundice in which red cells showed increased osmotic resistance was reported in 1925 by Fernando Rietti of Ferrara (Rietti, 1925). Many description were published shortly afterwards by other Italian workers including (Greppi, 1928) and (Micheli et al., 1935). This form of anemia was described by Rietti, Greppi and Michli and was reviewed by (Chini and Valeri, 1949).

The earliest reports of milder forms of thalassemia called it thalassemia Intermedia. The term thalassemia intermedia appeared in the literature in the 1950s (Sturgeon et al.,1995).The term thalassemia intermedia is a useful descriptive title for clinical phenotype that can result from the interaction of many different thalassemia alleles, either among themselves or with those for structural hemoglobin variants.

Thalassemia Intermedia entails considerable clinical and genetic heterogeneity. Anemiais variable and many patients have splenomegaly. They are clinically as well as genetically variable. Parents may have mild thalassemia or a single gene may be inherited in the families (Weatherall, 2001).

Thalassemia are defined as a group of inherited hematological disorders characterized by early onset of anemia resulting from reduced rate of synthesis of one or more globin chains caused by globin chain mutations (Low, 2005).

Thalassemias are the commonest monogenic syndromes (Thein, 1992), characterized by decreased synthesis of one or the other polypeptide chains resulting by decreased intracellular heamoglobin content (hypochromia) and small size of red cells (microcytosis). Because of continued normal production of unaffected globin chain the imbalanced globin – chain synthesis leads to the accumulation of unstable aggregates of these unpaired globin chains leading to oxidative membrane damage and premature destruction of erythrocytes in the peripheral circulation and also at earlier stages of maturation in the bone marrow (Forget and Olvieri, 2003). This decreases the heamoglobin level in the blood and oxygen carrying capacity of the red blood cells.

Body makes three types of blood cells: red blood cells, white blood cells, and platelets. Red blood cells contain heamoglobin, an iron-rich protein that carries oxygen from lungs to all parts of the body. Heamoglobin also carries carbon dioxide from body to lungs, where it is exhaled.

Heamoglobin has two kinds of protein chains: alpha globin and beta globin. If body doesn't make enough of these protein chains or they are abnormal, red blood cells won't form correctly or carry enough oxygen. Body won't work well if red blood cells don't make enough healthy hemoglobin. Genes control how the body makes heamoglobin protein chains. When these genes are missing or altered, thalassemias occur.

Thalassemias are inherited disorders that are passed from parents to children through genes. People who inherit faulty heamoglobin genes from one parent but normal genes from the other are called carriers. Carriers often have no signs of illness other than mild anemia. However, they can pass the faulty genes on to their children. People who have moderate to severe forms of thalassemia have inherited faulty genes from both parents (NIH, 2012).

Alpha Thalassemia

Four genes are responsible (two from each parent) to make enough alpha globin protein chains. If one or more of the genes is missing, this will be alpha thalassemia trait or disease. This means that body doesn't make enough alpha globin protein.

- If it is missing one gene, it is a "silent" carrier. This means that there is no sign of illness.
- If it is missing two genes, It will be alpha thalassemia trait (also called alpha thalassemia minor). There will be mild anemia.
- If there is missing three genes, It will be heamoglobin H disease (which a blood test can detect). This form of thalassemia causes moderate to severe anemia.

Very rarely, a baby is missing all four genes. This condition is called alpha thalassemia major or hydropsfetalis. Babies who have hydropsfetalis usually die before or shortly after birth.

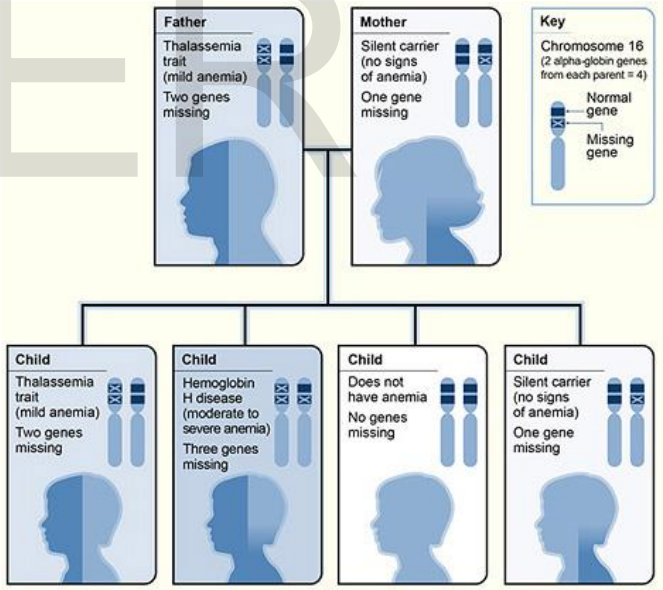


Fig 1.4: Inheritance Pattern for Alpha Thalassemia

The picture shows one example of how alpha thalassemia is inherited. The alpha globin genes are located on chromosome 16. A child inherits four alpha globin genes (two from each parent). In this example, the father is missing two alpha globin genes and the mother is missing one alpha globin gene. Each child has a 25 percent chance of inheriting two missing genes and two normal genes (thalassemia trait), three missing genes and one normal gene (heamoglobin H disease), four normal genes (no anemia), or one missing gene and three normal genes (silent carrier).

Beta Thalassemia

Two genes are responsible (one from each parent) to make enough beta globin protein chains. If one or both of these genes are altered, this will be beta thalassemia. This means that body won't make enough beta globin protein.

- If a person has one altered gene, he will be a carrier. This condition is called beta thalassemia trait or beta thalassemia minor. It causes mild anemia.
- If both genes are altered, he will have beta thalassemia intermedia or beta thalassemia major (also called Cooley's anemia). The intermedia form of the disorder causes moderate anemia. The major form causes severe anemia.

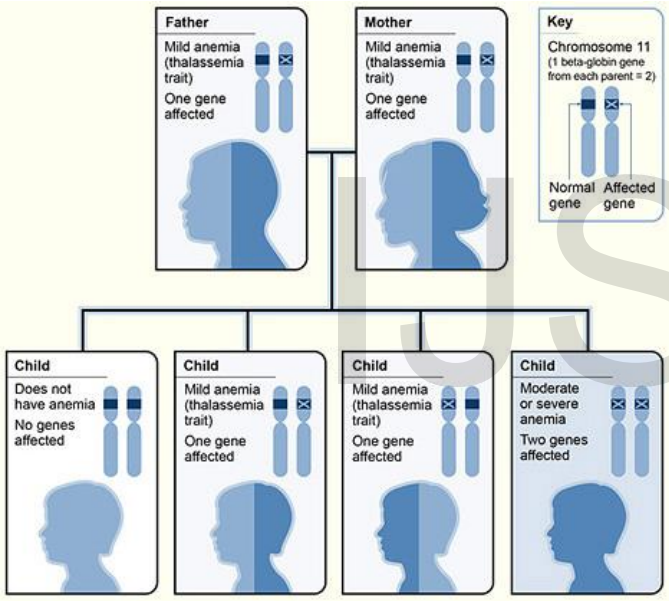


Fig 1.5: Inheritance Pattern for Beta Thalassemia

The picture shows one example of how beta thalassemia is inherited. The beta globin gene is located on chromosome 11. A child inherits two beta globin genes (one from each parent). In this example, each parent has one altered beta globin gene. Each child has a 25 percent chance of inheriting two normal genes (no anemia), a 50 percent chance of inheriting one altered gene and one normal gene (beta thalassemia trait), or a 25 percent chance of inheriting two altered genes (beta thalassemia major) (NIH, 2012).

Thalassemia Intermedia

Thalassemia Intermedia is the term used to describe the clinical and hematological findings in patients with β - Thalassemia. Although not transfusion dependent, these patients manifest a more sever degree of anemia than that found in heterozygous carriers for α - or δ thalassemia (Weatherall., 1996). Beta(0)-thalassaemia intermedia (beta(0)-TI)describes patients who lack beta-globin synthesis yet manifest a non-transfusion dependent form of beta-thalassaemia (Chang et al.,2001).

The proportion of patients with homozygous thalassemia intermedia is strikingly different among different ethnic groups. About 10% of patients of Mediterranean ethnicity who are homozygous can be classified as intermediates. In contrast, more than 70% of African- American patients who are homozygous may be classified as such. This difference reflects the kinds of thalassemia mutations, especially so-called "mild mutations," that are prevalent in these ethnic groups (Pearson et al., 1996).

Incidence and prevalence of Thalassemia

Thalassemias are particularly associated with people of Mediterranean origin, Arabs, and Asians. The Maldives has the highest incidence of Thalassemia in the world with a carrier rate of 18% of the population. The estimated prevalence is 16% in people from Cyprus, 1% in Thailand, and 3-8% in populations from Bangladesh, China, India, Malaysia and Pakistan. There are also prevalence in descendants of people from Latin America and Mediterranean countries (e.g. Greece, Italy, Portugal, Spain, and others). A very low prevalence has been reported from people in Northern Europe (0.1%) and Africa (0.9%), with those in North Africa having the highest prevalence. It is also particularly common in populations of indigenous ethnic minorities of Upper Egypt such as the Beja, Hadendoa, Sa'idi and also peoples of the Nile Delta, Red Sea Hill Region and especially amongst the Siwans.

Beta thalassemia is a condition most prevalent in the North Mediterranean and among people who trace their ancestry from that part of the world. In fact, the name 'Thalassemia' is derived from the Greek word 'thalassa' which means 'the sea'. So, whilst in Britain the carrier rate for beta-thalassemia

is 1 in 1500; in countries like Cyprus it is many times that at almost 1 in 7. In the United States, the carrier rate is highest among Greek and Italian immigrants and their descendants. Beta thalassemia is also common in India and South East Asia. Beta thalassemia also goes by the name 'Cooley's anaemia' after the Paediatrician (Dr Thomas Cooley) who first described the condition among children at the beginning of the 20th century.

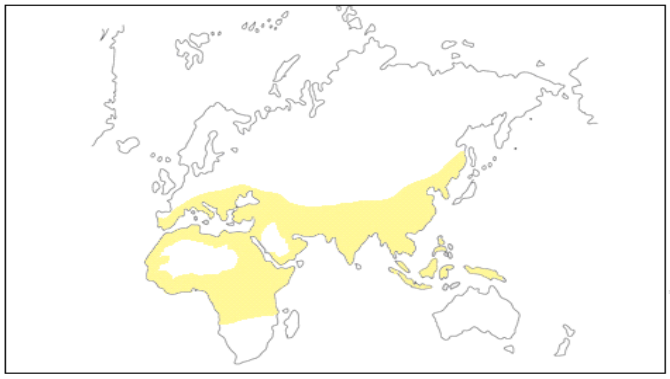


Fig 1.6: People from around the Mediterranean are the ones most affected by Beta-thalassemia. Also affected are people from parts of India and South East Asia

The Thalassemias are widespread with about 5% of the world population affected by it. It is most prevalent around the Mediterranean Sea i.e. countries like Greece, Italy, Turkey and North African countries.3 It is also seen in Saudi Arabia, Iran, Afghanistan, Pakistan, India and south East Asian countries like Thailand and Indonesia. The prevalence is highest in Italy, Greece and Cyprus (Hazza and Jamal, 2006).

Thalassemia in Pakistan

It is most widespread hereditary disease in Pakistan; presently there are an estimated 160,000 cases of Thalassaemia in Pakistan which makes up for almost five percent of the world cases. This number is increasing by about 5,000 new births every year. In a recent report from to the Ministry of Health Govt. of Pakistan, it is reported that 5–7% of our population are carrying genes of Thalassaemia and are known as Thalassaemia carriers (Haider, 2005).

Among the two main types of alpha and beta thalassaemia, the latter is common in Pakistan, and may present clinically as thalassaemia minor, thalassaemia intermedia or thalassaemia major. Although reliable data is lacking for many regions, recent studies indicate that about 7% of the world's population is carrier of some heamoglobin disorder. About 300,000- 500,000 children are born each year with the severe homozygous state of these diseases.

Each year 70,000- 100,000 beta- thalassaemia major (BTM) cases are born with most of them in developing countries with limited resources e.g. in Asia and Africa. (Weatheralland Clegg,2001). Thalassaemia is also one of the commonest inherited disorders in Pakistan. (Khateeb et al., 200).

With a population of 170 million, a birth rate of 3.6%, and carrier rate of 4.5-7%, the total number of thalassaemia traits is estimated to be around 10 million and each year more than 5000 thalassaemia major cases are born resulting in a total burden of around 90,000 thalassaemics. (Khattak and Saleem, 1992).

Thalassemia in Khyber Pakhtunkhwa

The incidence of Thalassemia is highest in Khyber Pakhtunkhwa (KPK) due to strict inter familial marriages in Pathan society. There is very little concept of counseling of individuals with a family history of this disease and in fact most of these individuals are unaware of their carrier status. Test facilities even for the diagnosis of thalassaemia are not available in the major cities of the province. The nearest facility for prenatal diagnosis is at Armed Forces Institute of Pathology (AFIP) Rawalpindi. Moreover, if homozygous state is confirmed, termination of pregnancy in an affected fetus is an ethical and religious issue in a typical Pathan family. (Rahman and Lodhi, 2004).

Thalassemia in Swat

Thalassemia is a widespread disease among the people of Swat where it is prevalent to approximately a population of 6000 persons. Large numbers of patients suffering from beta thalassemia are reported from almost

every part of the region. Estimated count of beta thalassemic patients in Swat is 3500, in which approximately 1150 patients are registered in Wajeeha Thalassemia foundation Saidu Sharif Swat and Alfajr foundation Rahim Abad Mingora Swat. These patients get free blood transfusion once or twice in a month depending upon the condition of the patients. Nonregistered patients receive donated blood from hospital blood banks, from students of schools and colleges or from other people.

Symptoms

Symptoms of Alpha-thalassemia

Alpha thalassemia silent carriers generally have no signs or symptoms of the disorder. This is because the lack of alpha globin protein is so minor that the body's heamoglobin works normally. The most severe form of alpha thalassemia major causes stillbirth (death of the unborn baby during birth or the late stages of pregnancy) (NYTimes, 2012).

Mild Anemia

People who have alpha or beta thalassemia trait can have mild anemia. However, many people who have these types of thalassemia have no signs or symptoms. Mild anemia can make you feel fatigued (tired). Mild anemia caused by alpha or beta thalassemia trait often is mistaken for iron-deficiency anemia (NIH, 2010).

Beta-thalassemia

Children born with thalessemia major (Cooley's anemia) are normal at birth, but develop severe anemia during the first year of life (NYTimes, 2012).

Mild to Moderate Anemia

People who have beta thalassemia intermediate have mild to moderate anemia. They also may have other health problems, such as:

- Slowed growth and delayed puberty. Anemia can slow down a child's growth and development.
- Bone problems. Thalassemia may cause bone marrow to expand. Bone marrow is the spongy substance inside bones that makes blood cells. When bone marrow expands, the bones become wider than normal. They may become brittle and break easily.
- An enlarged spleen. The spleen is an organ that helps body fight infection and remove unwanted material. When a person has thalassemia, the spleen has to work very hard. As a result, the spleen becomes larger than normal. This makes anemia worse. If the spleen becomes too large, it must be removed.

Severe Anemia and Other Signs and Symptoms

People who have heamoglobin H disease or beta thalassemia major (also called Cooley's anemia) have severe thalassemia. Signs and symptoms occur within the first 2 years of life. They may include severe anemia and other health problems, such as:

- A pale and listless appearance
- Poor appetite
- Dark urine (a sign that red blood cells are breaking down)
- Slowed growth and delayed puberty
- Jaundice (a yellowish color of the skin or whites of the eyes)
- An enlarged spleen, liver, and heart
- Bone problems (especially bones in the face)
- Shortness of breath.
- Rapid heartbeat.
- Dark urine

Complications of Thalassemias

Better treatments now allow people who have moderate and severe thalassemias to live much longer. As a result, these people must cope with complications of these disorders that occur over time.

Heart and Liver Diseases

Regular blood transfusions are a standard treatment for thalassemias. As a result, iron can build up in

the blood (iron overload). This can damage organs and tissues, especially the heart and liver.

Heart disease caused by iron overload is the main cause of death in people who have thalassemias. Heart disease includes heart failure, arrhythmias (irregular heartbeats), and heart attack.

Infection

Among people who have thalassemias, infections are a key cause of illness and the second most common cause of death. People who have had their spleens removed are at even higher risk because they no longer have this infection-fighting organ.

Osteoporosis

Many people who have thalassemias have bone problems, including osteoporosis. This is a condition in which bones are weak and brittle and break easily (NIH, 2010).

Diagnosis

The diagnosis of thalassemia trait and thalassemia major is made from microscopic examination of the blood, which shows many small, pale red blood cells, and from other blood tests that show reduced levels of adult hemoglobin in the blood (HCN, 2009).

Thalassemia is usually diagnosed in infancy and is characterized by ineffective erythropoeisis, bone marrow expansion and rapid destruction of erythrocytes. Thecurative treatment available for this disease is either blood transfusion or chelation orbone-marrow transplantation which is too expensive. Therefore, the only option is to prevent the birth of an affected child by Carrier testing and prenatal diagnosis. Carrier screening refers to identification of heterozygotes (carriers). In obstetrics, screening provides the prospective parents with information about whether their children could inherit a genetic disorder so that they could consider reproductive alternatives. It can be made retrospectively, following the birth of an affected child or prospectively. Carrier detection is based on the full blood counts and Hb electrophoresis and estimation of HbA2 and F levels followed by definitive diagnosis (mutation detection) by DNA analysis which is guided by the results of hematological parameters. Prenatal diagnosis is one of the most effective and direct approaches for prevention of thalassemia. The object of prenatal diagnosis is to provide an accurate and rapid result as early in the pregnancy as possible (Richard et al., 1993).

Treatment

Treatment of β -thalassemia depends on the clinical severity and ranges from no treatment, in cases of β-thalassemia traits or some mild thalassemia Intermedia , to frequent transfusions with chelation therapy and augmentation of fetal-heamoglobin synthesis, in cases of thalassemia major or intermedia (Robin et al.,2006). Pleurodesis seems to be an effective and safe therapeutic option for exudative effusions, while transfusion-chelation therapy combined with hydroxyl urea may be helpful in suppressing increased erythropoiesis (Aessopos, 2006).

Recently, novel modes of therapy have been developed for thalassemia based on the pathophysiology and molecular pathology of the disease, both of which have been extensively studied. This includes transfusion, chelation (intravenous and oral), antioxidants and various inducers of fetal heamoglobin (hydroxyurea, erythropoietin, butyrates, hemin). Most of the newer therapies are suitable primarily for thalassemia intermedia patients (Rund, 2000).

Clinical squeal of thalassemia includes; delay and growth and development, deformity of bones due to ectopic marrow expansion, osteopenia and most important iron overload. It is iron overload and tissues that is eventually fetal in patients with or without transfusion dependency if not adequately treated with iron chelating therapy. In absence of chelating therapy, iron accumulates in damages heart, liver, endocrine glands and reproductive organs. Onset of puberty is delayed and growth stunted.

Defroxamine has been the main stay of iron chelation since its introduction in the 1980s (Smier et al., 2009).

Blood transfusion

The primary treatment is regular blood transfusions, usually every four weeks. In addition to the blood transfusions, doctors recommend injections of Desferal to help the body flush out the extra iron created by the new blood. The injections are given under the skin from a small pump 5 to 7 nights a week (HCN, 2009).

Children born with thalassemia, a type of blood disorder, must receive blood transfusion about once or twice a month. This child is receiving Desferal treatment for the removal of excess of iron from the blood. Desferal pumps usually are worn 8-10 hours each day, 4-7 days a week for life. Too much iron in the blood can lead to severe complications and death. Research is underway to find a way to administer iron chelation orally instead of by needle.

Iron chelation therapy

Cardiac complications caused by iron depositions are major causes of death in patients with beta thalassemia major. Deferiprone (LI) was found to have greater efficacy at depleting myocardial iron than Desferrioxamine (DFX). Furthermore, combined therapy with LI and DFX produced an additive or synergistic iron chelating effect. We report the successful treatment of severe heart failure in two patients with beta thalassemia major with the combined therapy. Magnetic resonance images showed a marked recovery of signal intensity in the heart, indicating a significant reduction of iron load in the heart. No significant adverse effects were noted. Therefore, combined therapy with LI and DFX should be considered in patients with beta thalassemia major and cardiac complications (Wu, et al., 2003).

Stem cell transplantation

Stem cell transplantation facility became available in Pakistan in 1999. Since then bothallogeneic and autologous procedures have been carried out for severe aplastic anaemia, β thalassaemia major and certain haematological malignancies. Allogeneic peripheral blood stem cell transplantation is also feasible and lifesaving in otherwise fatal disorders.This could be carried out effectively in Pakistan (Farzana et al., 2003). Allogeneic BMT is the only curative therapy for beta-Thalassaemia patients. Success rate can be increased if patients are selected carefully and transplanted at an early age (Hashmi et al., 2004).

Prevention of Beta thalassemia

Preventive programs for beta thalassemia comprising of genetic counseling, carrier detection and prenatal diagnosis are the most effective approaches. Since the implementation of these programs in several countries the birth rate of transfusion dependent beta thalassemia children has reduced dramatically (Cao, 1997).

Carrier screening

The thalassemias were the first recessive disorders to be targets of large scale population carrier screening, resulting in marked reduction in birth rate of affected children in Italy, Cyprus, Greece, Sardinia, China, Taiwan, and Southeast Asia, and even such sophisticated interventions as pre implantation genetic diagnosis. Molecular diagnosis of alpha thalassemia entails dosage and sometimes phase analysis of the four alpha genes, while diagnosis of beta thalassemia is more complicated because of the wide variety of promoter, termination, deletion, insertion, substitution, splice site and frameshift mutations that are documented. However, within a given target population, the spectrum of mutations may be much more limited, making screening with a select panel of mutation probes, often in a reverse dot blot format, more feasible. In fact, less than 10 mutations usually account for the majority of mutations in a given population, and about 20 mutations account for 80% of all beta thalassemia alleles worldwide (Yong et al., 1990).

Genetic counseling

Genetic counselors are trained professionals who work as a part of a health care team. They provide genetic and medical information, along with support, to families affected by genetic disorders or the possibility of one. A genetic counselor's role is unique because the counselor does not provide medical care. Instead, genetic counselors, working with a team of medical professionals, help by providing patients the information they need to make important decisions about genetic testing and future care.

Prenatal diagnosis of Beta Thalassemia

Thalassemia and abnormal heamoglobins are common genetic disorders in Asia. Thalassemia is not only an important public health problem but also a socio-economic problem of many countries in the region. The approach to deal with the thalassemic problem as to prevent and control birth of new cases. This requires an accurate identifications of the couple at high risk for thalassemia. However, the diagnosis of thalassemia carrier states needs several tests that are not practical for screening the population at large (Suthat et al., 2002).

A complete prenatal evaluation begins with a careful medical and family history. When used in conjunction with a thorough physical examination (Ultrasound evaluation) and laboratory testing, the practitioners is better able to individualize the patients risks and recommend the appropriate diagnostic (Greigh et al., 2002).

The introduction of first trimester Chorionic Villus Sampling (CVS) in combination with polymerase chain reaction (PCR) based molecular techniques has made the prenatal diagnosis rapid, reliable and possible at an early stage of pregnancy (Cao et al., 1996).

Aims and objectives of the study

1. To study the occurrence of Thalassemia in term of blood group, gender, age, and residence.
2. To evaluate the institutional based occurrence of thalassemia in Swat.
3. To compare the occurrence of thalassemia in the Swat with other regions.

2 MATERIALS AND METHODS

Geography of Pakistan

Pakistan lies between 23 degrees 35 minutes to 37 degrees 05 minutes to north latitude and 60 degrees 50 minutes to 77 degrees 50 minutes to east longitude. To its north it touches the Hindukush Mountains and extends from the Pamirs to the Arabian Sea. Its total area is 796,095 sq km and is four times the size of the United Kingdom. From Gwadar Bay in its south-eastern corner, the country extends more than 1,800 km to the Khunjerab Pass on China border. It consists of such physical regions as the western offshoots of Himalayas which cover its northern and north western parts of which the highest peak K-2 rises to 8611 meters above sea level, the Baluchistan plateau, the Potohar Plateau and salt range and the Indus plain, the most fertile and densely populated area of the country (AIPS, 2011). The estimated population of Pakistan in 2011 is over 187000000 due to which it is the world's sixth most populous country, after Brazil and ahead of Bangladesh (Pakistan Govt, 2011).

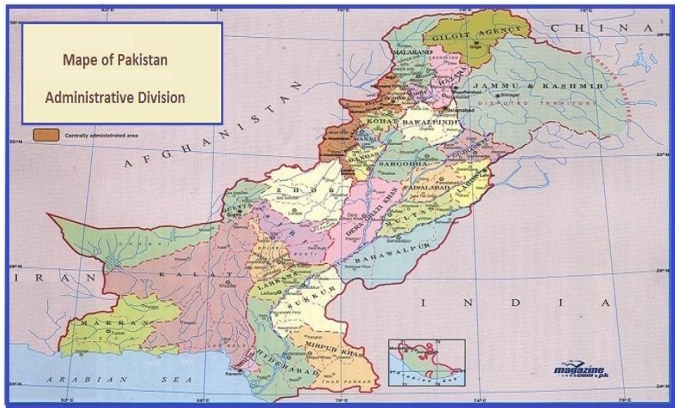


Fig 1.1: Map of Pakistan

Geography of Khyber Pakhtunkhwa

Khyber Pakhtunkhwa is mainly located on the Iranian plateau and Eurasian land plate, while peripheral eastern regions are located near the Indian subcontinent. It has an area of 74,521 km². According to the 1998 census, the total population of Khyber Pakhtunkhwa was approximately 17 million out of whom 52% were males and

48% females. Geographically the province could be divided into two zones, the northern one extending from the ranges of the Hindu Kush to the borders of Peshawar basin and the southern one extending from Peshawar to the Derajat basin.

The northern zone is cold and snowy in winters with heavy rainfall and pleasant summers with the exception of Peshawar basin, which is hot in summer and cold in winter. The southern zone is dry with hot summers and relatively cold winters and scarce rainfall. Its climate varies from very cold to very hot in places like D.I. Khan. The major rivers that cross the province are Kabul River, Swat River, Chitral River, Panjkora River, Bara River, Karam River, Gomal River and Zob River (Khyber Pakhtunkhwa Govt, 2011).

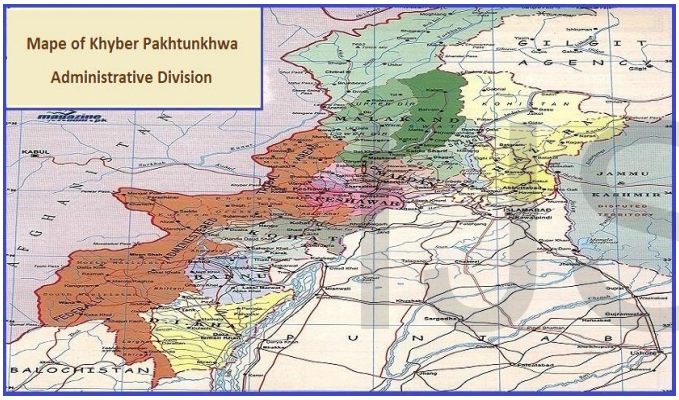


Fig 1.2: Map of Khyber Pakhtunkhwa

valley is Pashto/Pakhto. With high mountains, green meadows, and clear lakes, it is a place of great natural beauty and is popular with tourists as "the Switzerland of the region". The population at the 1981 Census was 715,938, which had risen to 1,257,602 at the next Census in 1998. The main language of the area is Pakhto. The people of Swat are mainly Pakhtuns, Yusufzais, AkhundKhel Miangan (Syed), Chitralis, Kohistani Akhundkhel Yousafzai, Nooristani, and Awans. Most probably they are originated from the same tribe that roamed around the great trans-Himalayan mountain ranges thousands of years before and now remained in some isolated pockets of the Himalayan mountain ranges (www.ZamaSwat.com).

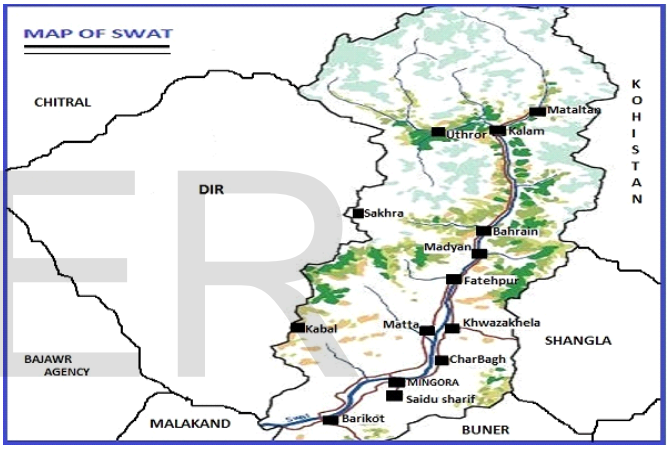


Figure 1.3: Map of Swat

Geography of Swat

The valley of Swat is situated in the north of KPK, 35° North Latitude and 72° and 30° East Longitude, and is enclosed by the sky-high mountains. Chitral and Gilgit are situated in the north, Dir in the west, and Mardan in the south, while Indus separates it from Hazara in the east.

Swat is a valley and an administrative district in the Khyber Pakhtunkhwa Province, located close to the Afghan-Pakistan border. It is the upper valley of the Swat River, which rises in the Hindu Kush range. The capital of Swat is Saidu Sharif, but the main town in the Swat valley is Mingora. It was a princely state in Khyber Pakhtunkhwa until it was dissolved in 1969. The valley is almost entirely populated by ethnic Pashtuns. The language spoken in the

Area selection

For the present study Mingora was selected. Mingora is the largest city in Swat district Khyber Pakhtunkhwa province of Pakistan. It is located at an altitude of 984 meters (3228 ft) and lies on the bank of river Swat about 2 kilometers away from Saidu Sharif, the present capital of Swat. As of 1998 census, the population of Mingora was about 175000.

Data collection procedure

The data was collected from the following institutes of district Swat.

Wajeeha Thalassemia Centre

This center is located in children ward Central hospital Saidu Sharif located on main road to Marghazar. This center

was established in October 2011 where there is registered about 400 thalassemic patients. Blood transfusion is provided free for these patients.

Alfajr Foundation

Alfajr foundation was established by the administration of Swat Public Schools (SPS) in 2004. The building is located outside of the SPS College on GT road Rahim Abad 1 kilometer away from Mingora city. About 1000 patients of thalassemia are registered in the institute where they get free regular blood transfusion once or twice in a month depending upon the condition of the patient.

Data analysis

The data of all patients were collected from the above mentioned institutes during six months study i.e. from from January, 2020 to June, 2020. The data was analyzed for the following parameters.

Age wise occurrence of β-thalassemia major

The patients of β-thalassemia were divided into different age groups years.

Gender wise occurrence of β-thalassemia major

The occurrence rate of β-thalassemia disease was determined in males and females and the ratio was compared with respect to age groups.

Blood group wise occurrence of β-thalassemia major

The patients were grouped in different blood groups and Rh factors and their occurrence ratio was determined.

Comparison of urban with rural locality

The occurrence of β-thalassemia in urban (Mingora) is compared with rural (tehsil Kabal) locality and the fluctuation in its rate have been also determined.

3 RESULTS

Occurrence of β-Thalassemia major (BTM) in Mingora district Swat

35 thalassemic patients of Mingora are registered in Wajeeha thalassemia center Swat and Alfajr foundation Swat. According to Election Commission of Pakistan (2012), the total population of Mingora is about 440000 in which the percentage of these registered patients is 0.008%.

TABLE 3.1
BTM PATIENTS IN MINGORA

Patient No	Gender	Blood Group	Age (Year)
01	♂	O+	23
02	♀	A+	01
03	♂	O+	03
04	♂	A+	05
05	♀	A+	14
06	♂	A+	16
07	♂	A+	13
08	♂	O+	05
09	♀	B+	03
10	♀	B+	08
11	♀	B+	13
12	♂	O+	06
13	♂	O+	03
14	♀	O+	03
15	♂	B+	04
16	♀	A+	06
17	♀	B+	10

Patient No	Gender	B.group	Age (years)
01	♂	O+	15
02	♀	B-	07
03	♂	B+	07
04	♂	AB+	14
05	♀	A+	11
06	♂	O+	09
07	♂	AB+	17
08	♂	B+	12
09	♂	B+	19
10	♂	B+	15
11	♀	O+	10
18	♀	O+	07
19	♀	A+	18
20	♀	O+	03
21	♂	A+	10
22	♂	O+	06
23	♀	A+	08
24	♂	A+	03
25	♂	O-	04
26	♂	O+	01
27	♂	A+	09
28	♀	B+	05
29	♀	B+	06
30	♀	O-	10
31	♂	O+	08
32	♂	B+	08
33	♂	B+	04
34	♂	O+	05
35	♂	B+	05

Occurrence of BTM in tehsil Kabal

The total population of Tehsil Kabal is estimated to be composed of 170000 persons in which there is reported 42 cases of thalassemia major. It becomes 0.024% of the disease in the total population.

TABLE 3.2

BTM PATIENTS IN TEHSIL KABAL

Age groups and residence wise occurrence of BTM in district Swat

All the registered patients in Mingora and tehsil Kabal were grouped in different age groups. Total patients were 77 in which 24 (31.16%) were in age group 1-5 years, 25 (32.46%) were in age group 6-10 years, 17 (22.7%) were in age group 11-15 years, 08 (10.38%) were in age group 16-20 years and 03 (03.89%) patients were in 21-25 years. There were no patients above than 25 years of age.

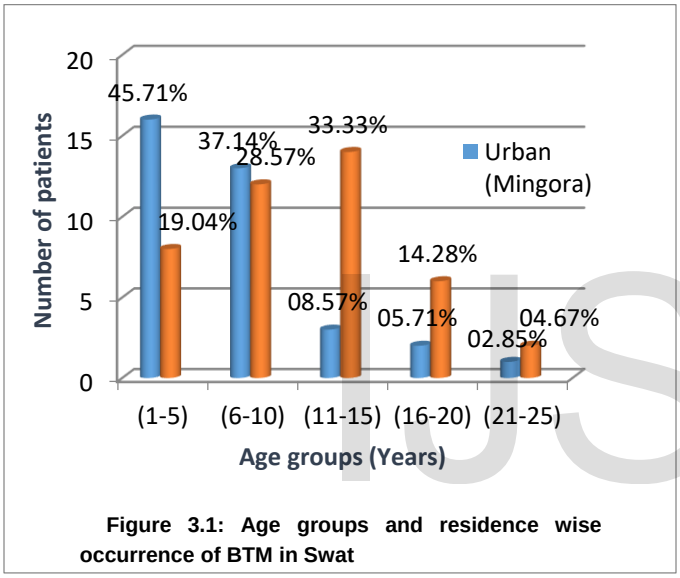
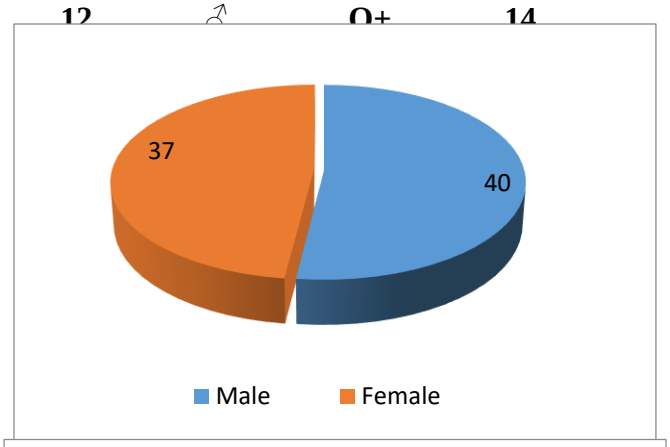


Figure 3.1: Age groups and residence wise occurrence of BTM in Swat

Gender wise occurrence of BTM in Swat

Male and female ratio was observed in both these regions to be 40 (51.94%) patients were male while 37 (48.05%) were female out of the total 77 patients.



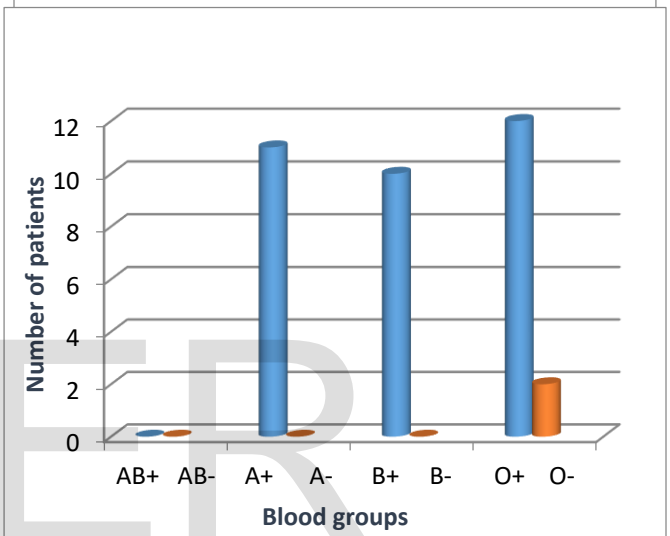


Figure 3.3: Blood group wise occurrence of BTM in Mingora

31	♂	O+	08
32	♀	O+	19
33	♀	A+	05
34	♂	A+	06
35	♂	B+	04
36	♀	O+	03
37	♀	B+	05
38	♀	B+	06
39	♀	O+	03
40	♂	B+	02
41	♀	B+	05
42	♀	B+	02

Blood group wise occurrence of BTM in Swat

As Rh positive blood group occur 85% in nature, so the individuals having these group in our data were examined to be 74 out of 77 in which A+ were 22 (31.42%), no one in A-, 26 were B+ (33.76%), one was B- (01.29%), 3 were AB+ (03.89%), no one in AB-, 23 were O+ (29.87%) and 2 were O- (02.59%).

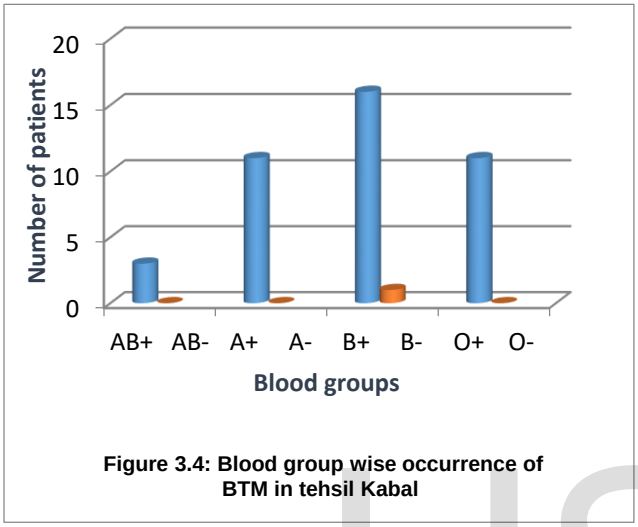


Figure 3.4: Blood group wise occurrence of BTM in tehsil Kabal

4 DISCUSSION & CONCLUSION

Thalassemia is a widespread disease with about 5% of the world population affected by it. It is most prevalent around the Mediterranean Sea i.e. countries like Greece, Italy, Turkey and North African countries. It is also seen in Saudi Arabia, Iran, Afghanistan, Pakistan, India and south East Asian countries like Thailand and Indonesia. The prevalence is highest in Italy, Greece and Cyprus (Hazza and Jamal, 2006).

High disease gene frequency, consanguineous marriages, large pedigree size and high birth rate mark Pakistani population at a high risk of many genetic disorders including Beta thalassemia. The average allele frequency in Pakistan is more than 5% and the carrier couples have 25% risk to have an affected child in each pregnancy (WHO, 2001).

Occurrence of BTM in District Swat

The current study was designed to perform analysis of thalassemia in district Swat, so the comparison of both the Mingora (urban) and Tehsil Kabal (rural) showed that the age, sex and blood group was distributed equally in both of these regions and the ratio was the same but according to the study of (Khateeb et al., 2000), the difference was observed in prevalence of patients to locality. The ratio indicated the higher percentage of thalassemic cases in tehsil Kabal than Mingora although the total population of Mingora is greater than tehsil Kabal, but the fact is that incidence is high in tehsil Kabal due to the strict interfamilial marriages in the rural society of tehsil Kabal and it was noticed that most of the affected children were born by the parents which were cousins in relation (first cousin or second cousin). (Ghosh et al., 2008) also described the same reason and concluded that the prevalence of beta thalassemia major is especially high in regions where there are close family marriages.

The results showed that there were no patients more than the age of 25 years. Most of the patients loss their intellectual capacity during 20-25 years of age and at last death occurs. (Agouzal et al., 2009), also mentioned that the limit age of BTM patients is 20-25 years. The fact that the number of patients with thalassemia decreases beyond 15 years could be explained by death mostly among children older than 15 years. This can be explained by the fact that if children are not transfused, they die before the age of 6 years and if they are transfused and non-chelated, they die before the age of 20.

The male and female ratio in the total 77 patients was determined to be 40 (51.94%) were male and 37 (48.16%) were female. This ratio is equal because according to Government of KPK 2011, during 1998 census 52% population of KPK was male population and 48% was female population. This means that the incidence of thalassemia is distributed equally both in male and female population.

According to the investigation of (Rund et al., 2000), there is no any correlation of blood group or Rh factor with thalassemia. All the patients were distributed equally with respect to the natural occurrence of blood groups and Rh factors.

The present study is much informative for the occurrence of thalassemia in district Swat. From the current study it is concluded that the occurrence of thalassemia is more common in patients born through interfamilial marriages and indigenous ethnic groups. That's the reason that its incidence is higher in rural areas as compared to urban.

Recommendations

The present study extends the observations of previous workers and provides information on the distribution of the β-thalassemia mutations among the carriers. This suggests the need to establish a program for genetic counseling and prenatal diagnosis of beta thalassemia for affected families and for initiating a control program by prospective screening of pregnant women as a multicentric study in our society. Such activities would eventually reduce the burden of this dreaded yet a common disease and lead to its control. The application of the knowledge about mutation pattern was found to be beneficial since the mutations could be screened in the order in which they are present in our population. Hence it will not only help to reduce the screening cost but also to promote early genetic counseling and prevention of an affected child.

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