

## PREVALENCE AND PREVENTIVE MEASURES FOR THALASSAEMIA IN HAZARA REGION OF N.W.F.P., PAKISTAN

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65 cases of thalassaemia major were selected out of 300 cases of anaemia (21.667c) admitted to Paediatric Unit A in Women and Children Hospital, Abbottabad since June 1995, based on their family history clinical data, laboratory investigations and X-ray analyses. Most of them were between 1-5 years of age. No difference was noted between the two sexes. Parental consanguinity was present in 49.237c of cases and non-consanguinity in 24.617c, whereas data was not available in 26.157c. of cases.

All the patients had moderate to severe anaemia and failure to thrive as their presenting symptoms. Other predominant associated features were splenomegaly (907c), typical facies (607c), skull changes on X-rays (607c), hepatomegaly (45%), jaundice (107c) and repeated infections such as gastroenteritis, pneumonia, etc. Some of them, particularly older children having received multiple blood transfusions, presented with complications such as viral hepatitis, congestive cardiac failure (4.617c) and diabetic ketoacidosis (1.537c). A variety of problems were encountered in diagnosis and management of these cases and are listed with suggested improvements in patient care.

### INTRODUCTION

The term thalassaemia is derived from the Greek word 'thalassa' meaning great sea<sup>1</sup> referring to the Mediterranean region, where the disease is common. Thalassaemia is a group of genetic disorders of haemoglobin synthesis characterised by total, partial or minimal depression of synthesis of globin chains. Although there are many forms of this genetic disease<sup>1</sup>, two main types are particularly common:

1. Alpha thalassaemia (affecting Alpha Globin chain synthesis).
2. Beta thalassaemia (affecting Beta Globin Chain synthesis).

More than 3% of the world population (150 million) are affected by disorders of the thalassaemia gene. Beta thalassaemia is the commonest disorder and is clinically classified as follows:

1. Thalassaemia Major with severe anaemia requiring blood transfusion.
2. Thalassaemia Intermedia with moderate anaemia rarely requiring blood transfusion.
3. Thalassaemia Minor, the asymptomatic heterozygous carrier state.

Beta Thalassaemia Major patients present in early age with failure to thrive, severe anaemia, hepato-splenomegaly, repeated infections and the classical thalassaemic facies. Diagnosis of this disease is mainly based on laboratory investigations such as haemoglobin electrophoresis (HbF%).

There have been relatively few studies on the extent of the problem in Pakistan, although these have pointed out the high prevalence of the disease in the North and South of Pakistan, figures for the trait ranging from 1.4% to 9.61% in various anaemic and non-anaemic populations from different provinces of the country<sup>2</sup>.

### AIMS AND OBJECTIVES

Hazara division of NWFP, Pakistan is an area known for a higher incidence of thalassaemia, though there have been no detailed epidemiological studies published so far. Trait incidence of thalassaemia for Pathans in the NWFP, estimated at 7.96%<sup>2</sup> gives some idea of the extent of the problem. Some of the factors important to this problem are increased consanguineous marriages, lack of education and knowledge of carrier status and disease transmission, lack of diagnostic facilities till recently and general backwardness of medical care facilities in this region of the province.

The present study was undertaken to assess the prevalence, incidence, management and outcome of the disease, as it exists among the referral population of a tertiary care hospital with diagnostic and management facilities.

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## MATERIALS AND METHODS

A total of 300 cases of anaemia were admitted to Paediatric Unit 'A' in Women and Children Hospital, Abbottabad. Their family history, clinical data, laboratory investigations and X-rays were analysed. Total number of 65 cases were separated, of ages 1-14 years with severe anaemia admitted in Paediatric Unit 'A' since June 1995. They were diagnosed as Thalassaemia Major according to standard criteria listed in standard texts (Table-2). A detailed history was taken, particularly history of parental consanguinity, drug history and feeding history. Physical and systemic examination including onset of pallor, loss of appetite, appearance of typical facies, hepatosplenomegaly, jaundice and other signs of complications were observed.

Haematological tests and radiographs were performed for establishing diagnosis of thalassaemia, as mentioned below:

1. Blood smears
2. Reticulocyte counts
3. Haemoglobin electrophoresis (HbF)
4. Serum iron, serum ferritin
5. X-rays of skull, long bones and chest
6. LFTs
7. Urine RE
8. G-6-PD deficiency

History of previous blood transfusions and parental consanguinity was important to know for decisions regarding management protocols. Treatment given to these patients was blood transfusion to maintain haemoglobin > 10g%. Very few patients who could afford chelation therapy, were advised Infusion Desferol by special pump to get rid of iron over load. Few older patients who developed complications, were treated accordingly.

Only three parents gave consent for performing HbA<sub>2</sub> studies on them to detect carrier status. In addition, they also consented to antenatal sampling of chorionic villi of subsequent pregnancies (performed at AFIP, Rawalpindi) for detection of homozygously affected foetus; however, they did not consent to therapeutic abortion as a preventive strategy.

## RESULTS

Out of 300 cases of anaemia, a total number of 65 cases were diagnosed as Thalassaemia Major (21.66%), 25 cases were of G6PD deficiency (8.33%) and 210 patients were having nutritional anaemia (70.0%). Out of 65 cases of thalassaemia, 32 patients had positive parental consanguinity belonging to Hazara region (49.23%) while among those having no consanguinity (16 cases, 24.61%), 5 out of 9 patients were Afghan refugees from Khaki Camp, Mansehra (55.55%).

The youngest patient was 5 months old and oldest was 14 years old girl. Ages and HbF levels are presented in Table 1.

**Table-1: Age and HbF in thalassaemia major patients (total = 65 cases)**

Ages of patients	No. of patients	HbF %age
Upto 1 year	40	50 - 70%
2 - 14 years	25	> 70%

All patients presented with severe anaemia as their major complaint, evident as marked pallor of skin and mucous membranes. This was correlated with Hb levels less than 5g/dL on average. On examination, splenomegaly was far more frequent than hepatomegaly (2:1).

Jaundice was observed infrequently. Clinical data regarding presenting features and findings on examination is presented in Table 2.

**Table - 2: Signs and symptoms in thalassaemia major patients (total = 65 cases)**

Signs/Symptoms	No.	% age
Anaemia (Hb <5g/dL)	65	100%
Splenomegaly	58	90%
Typical facies	39	60%
X-ray skull changes	39	60%
Hepatomegaly	29	45%
Jaundice	06	10%

**Table-3: Complications in thalassaemia major patients (total = 65 cases)**

Complications	No.	%age
Congestive cardiac failure, infants (due to severe anaemia, Hb: 1.2g/dL - 2.0g/dL)	03	4.61%
Diabetic ketoacidosis, age 14 years (due to pancreatic siderosis)	01	1.53%

A few patients presented with pre or post transfusion therapy complications as listed in Table3.

Consanguineous marriages (first and second cousin marriages) were found in almost half of the parents of affected children. The actual incidence may be even higher, as data for 17 cases was not available. Data regarding consanguinity as available for 48 patients, is presented in Table 4.

**Table-4: Data regarding consanguinity of parents.**

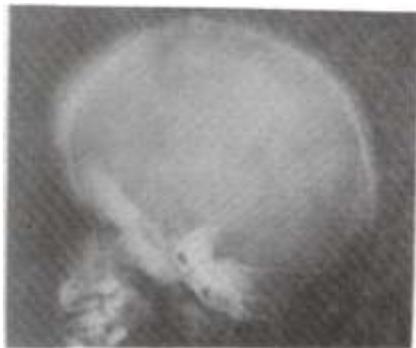
Consanguineous marriages of parents	No. of cases	%ages
First cousin marriages	27	41.53%
Second cousin marriages	05	07.69%
Total	32	49.23%
Non-consanguineous marriages	16	24.61%
Data not available	17	26.15%

Typical facies and typical x-ray changes in skull bones ('hair-on-end' appearance) were found in a majority of patients. (Fig. 1 and Fig. 2).

**Fig. 1: Patient of thalassaemia major with classical facies**



**Fig. 2: Skull X-ray of thalassaemia major patients with "hair-on-end" appearance of cortical bon**



### Treatment and Management

Every patient was given blood transfusion to bring Hb > 10g/dL. Only 10 patients were able to afford chelation therapy by giving injection Desferol 50mg/kg in drip for 7-8 hours overnight 6 days per week. 2 patients were able to receive proper chelation therapy by special pump at their homes. A few patients came with complications such as CCF treated accordingly and one patient of age 14 years' girl came with diabetic ketoacidosis. 2 patients had splenectomy performed for gross splenomegaly.

judged clinically by their growth rates, morbidity-charts and complication rates.

### DISCUSSION

A lot of data and literature has been published on thalassaemia throughout the world. By comparison, data in Pakistan is still in the early stages of clinical and hospital research, based on patient referral for anaemia, and failure to thrive. Much data has been accumulated from blood transfusion services.

The main purpose of our study is to bring awareness about prevalence and prevention of the disease in this particular area of Pakistan. This is only possible in our circumstances by taking following measures aimed at increasing public and physician awareness for diagnosis, management and prevention:

1. Public education
2. Carrier screening
3. Marriage counselling
4. Prenatal diagnosis

In many parts of the world, notably Cyprus, Italy, the USA, and recently the UK and other parts of Europe and Africa, proper implementation of measures listed above has caused a marked reduction in the incidence and prevalence of the disease. A notable example is Cyprus, where the incidence has dropped by 96%, and it is feared that in future the disease will be found there only as a result of cases imported from abroad into the country. This emphasizes the need for a global approach to the disease, as it is not only the most common genetic disease of humans, it is also spread by marriages and inter-marriages, which are now quite common on a global level, because of easier migration and settlement policies of many developed and developing countries.

The notable advent of simpler and less costly carrier detection methodologies has reinforced the impetus directed at total eradication of this carrier-based disease, and strengthened the approach towards other, similar genetic diseases. It is possible to discover upto 70% of hidden carriers by simple screening for HbA2 by Hb Electrophoresis or Column Chromatography, techniques which are not unduly expensive or need highly skilled technical equipment or staff<sup>3-6</sup>. Recent introduction of monoclonal and polyclonal antibodies directed against the various abnormal haemoglobin as tests for thalassaemia and related haemoglobinopathies is another step towards simplification of methodologies for carrier screening<sup>7</sup>. If this screening is done in families harbouring thalassaemic children, pedigree

Patients were followed up during management and treatment protocols and their vital indices measured as needed for their therapy.

Patients responded well to their treatment regimen and showed nearly normal responses as trees can be built outlining the transmission patterns; more important however, is the ability to provide pre-marriage

screening for prospective couples in high-risk families, so that chances of heterozygotes intermarrying is nullified and more severely affected homozygous offspring are not born. Such screening is now mandatory by law in Cyprus and is being conducted in other eastern countries as well with similar implementation strategies in mind<sup>8,9</sup>.

Some noteworthy recent advances in management strategy need mention. One is the use of desferrioxamine infusion pumps for subcutaneous supply of chelator<sup>10</sup>, and the other is the use of a newer oral chelator, LI (Deferiprone) which is far more easy to use and cheaper than desferrioxamine n, 12, o Recent innovations in therapy include alpha interferon for patients contracting Hepatitis C infections and Bone Marrow Transplantation and Gene Therapy for selected groups of patients<sup>13</sup>.

In Pakistan, where these measures are still a long way off, there seems little choice but to embark on a research oriented strategy, aimed at persuading and educating parents and other family members to allow screening for carriers as part of subsidised research projects, so that the cost of screening tests is affordable by poor patients as well. This will ultimately bring us to a level of guided marriage counselling that is scientifically backed by authentic screening, later on supplemented by molecular genetic diagnosis (which is far more accurate) and antenatal molecular genetic diagnosis allowing abortions for severely affected fetuses. This is ethically and religiously allowed in Islamic law, as long as it is done before 120 days of gestation<sup>14</sup>, now possible because chorionic villi can be obtained for molecular genetic analysis as early as 8-11 weeks of gestation (or even earlier in selected cases)<sup>15</sup>.

A study in UK regarding acceptability of prenatal diagnosis by Pakistani patients and their families reported increases from 20% for second trimester prenatal counselling to 80% since introduction of first trimester chorionic villus sampling<sup>16</sup>.

It is also obvious from the present study, that affordability of treatment protocols is the major impediment to standardised care of thalassaemic patients in our country, particularly in the backward areas. Only a handful of patients can afford the laboratory tests required for proper maintenance of the patients' indices in the normal ranges. An even smaller number can afford costly chelation therapy and monitoring for complications relating to therapy, such as transfusion related infections, iron overload status, monitoring and treatment for exotic infections, organ failure therapy, and so on. It is truly a bane to have a Thalassaemia Major child in our poor country, a picture much different from the developed world, where most of the severely affected children are also able to live normal or near-normal lives.

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