Detection of β-Thalassaemia Trait: A Study of Fifty Families:

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The objective of the study was to examine siblings of β-thalassaemia (β-thal) major children and identify cases of heterozygous β-thal in them. For this purpose 50 cases of β-thal major were selected and complete investigations were carried out in their siblings. The project was carried out in the Abbotabad district of NWFP. In this district β-thal is quite common. The incidence of β-thalassaemia can be reduced by identification of heterozygous cases and then genetic counseling to them. The offsprings of a heterozygous couple have a 25% chances of having β-thalassaemia major children, 25% chances of heterozygous children and a 50% chance of normal children. In this part of the country consanguinous marriages are very common and it is easy to reduce the cases of β-thalassaemia major in the next generation by mere identification of heterozygous cases and marriage counseling. Another aim was to protect these children from iron overload. As β-thalassaemia minor and iron deficiency anemia have similar clinical and laboratory features and these children are more prone to develop iron overload if iron is given to them after wrongly recognizing the condition as iron deficiency anemia..

Key words: β-Thalassaemia Trait

Thomas Cooley (1925) was the first person to recognize thalassaemia as a clinical entity. Thus the condition was labelled as Cooley's anemia. Later it was found to be an inherited disorder of hemoglobin synthesis. Inherited disorders of human hemoglobin synthesis are extremely diverse but fall into three groups (Clegg & Weatheral 1976). There are structural hemoglobin variants which alter the function and stability of the Hb molecules e.g. HbC, HbS & HbD etc.

The thelassaemia syndromes which are characterized by a reduced rate of synthesis of one globin chain leading to clinical manifestations due to an imbalance in globin chain production eg. α and β-thal.

Certain genetically determined conditions in which switch from HbF to HbA (adult Hb) does not occur, such as hereditary persistence of fetal hemoglobin (HPFH) in which there is abnormally elevated level of fetal hemoglobin.

The thalassaemias are a heterogeneous group of genetic disorders of human hemoglobin synthesis, characterized by imbalanced globin chain production which leads to ineffective erythropoesis and anaemia (clegg 1972). Thalassaemias may be classified as α and β forms depending on the basis of deficiency of respective chain (Clegg & Weatheral 1976)

β-thalassaemia are also classified on the basis of clinical severity, thus they are divided into three categories namely.

Thalassaemia major.
Thalassaemia intermedia
Thalassaemia minor

β-thalassaemia major:

In the case of β-thalassaemia major which is the classical homozygous β-thalassaemia (also called Cooley's anemia) there is marked reduction in the production of β chain and a relative excess of α chain (Ritchey et al 1981). The disorder is associated with severe anemia, retarded growth, hepatosplenomegaly , marked skeletal changes and skin pigmentation (Schwartz 1968). The introduction of different transfusion regimens (hypertransfusion and supertransfusion) has greatly improved the survival of these patients (Fosburg and Nathan 1990).

In thalassaemia major the patient remains well until 4-5 months of age i.e., the time when the switch from HbF to HbA synthesis occurs. Thereafter the diagnosis is straightforward with a very low hemoglobin. The peripheral film shows severe microcytic hypochromic anemia along with marked anisocytosis, poikilocytosis, target cells and many nucleated red cells. The reticulocyte count is high, as is the serum bilirubin level. X-ray of skull is also characteristic with thinning of cortex and increased medullary area. The Hb electrophoresis shows raised HbF which may be 10-98% of the total Hb.

β-thalassaemia Intermedia:

Thalassaemia intermedia comprises of an ill defined group ranging in severity from a disorder similar to transfusion dependent thal major to a symptomless anemia which is slightly more severe than that of heterozygous β-thalassaemia (Weatherall et all 1981). These patients have Hb in the range of 7.0 to 10 gm/dl. They do not need regular blood transfusions.

β-thalassaemia minor:

It is the heterozygous state which may present with chronic anemia along with splenomegaly or an almost sysptomless state .Clinically these subjects may present with features of iron deficiency anemia and if iron is given they develop iron overload (Cazzola et al1983) .The disease usually

manifests itself during stress (eg .pregnancy in females) or they are diagnosed on routine blood examination . It is important to exclude iron deficiency anemia in which HbA2 is reduced (Pearson et al1973). On Hb electrophoresis these patients may present in one of the following three forms:

HbA2 is raised (more than 3.5%).

HbA2 and HbF are raised.

HbA2 is normal while HbF is raised in the range3.5%_36%(Schwartz1969)

In the developed countries much attention has been directed to the prevention of disease by detection of thalassaemia carriers and marriage Counselling (Cao et al1989). By using this prevention programme in Sardinia the incidence of homozygous patients decreased from 1:250 live births to 1:1000 live births (Cao et al 1989). Similarly in Cyprus the incidence of thalassaemia major cases dropped by 96% (Burki et al 1998). The present study was mainly designed to decrease the incidence of β-thalassaemia major cases by marriage counselling.

Materials and Methods

The study was carried out in the Pathology department of Ayub Medical College Abbotabad. One hundred subjects were selected. They were the brothers and sisters of β-thalassaemia major patients. The subjects were selected from the Ayub Medical College and from the thalassaemia major patients registered with Abbotonian Medical association and an NGO working for the welfare of thalassaemic children. Twenty five healthy controls were also selected. In all these cases complete blood counts along with reticulocyte count, RBC morphology and red cell indices were performed. In all these cases Hb-electrophoresis was performed. The level of HbF was also seen by modified Betke's method. The level of serum ferritin was also estimated in these patients and controls

Results

A total of 58 cases were seen with β-thalassaemia trail. Maximum cases (58.63%) were detected in the 0-9 years of age group followed by 10-19 years of age group (31.00%). See table

Age (years)	Male	Female	Total	%age
0-9	17	17	34	58.63
10-19	7	11	18	31.03
20-29	2	4	6	10.34
Total	26	32	58	100

The pattern of family distribution was interesting. A total of 50 families were investigated out of them 23 families had one child affected while 14 families had no effected children other than the one having thalassaemia major. See table

No of children effected	No. of families effected	Total No of children	No. of effected children	% of families
1 child	23	65	23	42%
2 children	06	21	12	24%
3 children	05	23	15	12%
4 children	02	12	8	2%
No child	14	32	0	32%
Total	50	153	58	

The hematological parameters were characteristic in the patients of β-thalassaemia trait (see Table)

	Hb-Gm/dl	RBC $\times 10^{12}$/L	PCV	MCV	MCH	MCHC	Retic	HbA_2	HbF	S. Ferritin
Patient Group	9.78 +-1.50	4.79 +-0.91	43.17 +-8.02	89.05 +-12.37	21.61 +-4.67	23.47 +-5.29	2.33 +-1.5	5.06 +-1.29	1.28 +-0.80	130.82 +-153.3
Control Group	12.38 +-1.75	4.99 +-0.6	45.28 +-9.6	92.12 +-10.10	25.2 +-3.6	27.8 +-4.31	0.98 +-0.64	2.67 +-0.92	0.38 +-0.10	96.68 +-52.0

In most (74.17%) of patients HbA_2 was in the range of 3.6-6%. While 14.55% subjects of β-thalassaemia trial had an HbA_2 level 6.1-7 %. Only 10.93% of these subjects had an HbA_2 level in the range of 7.1-9.0%.

In the control subjects two persons out of 25 had an HbA_2 level of more than 3.6% and they were the β-thalassaemia trial cases.

Table: Serum Ferritin Level

	<100ng/ml	101-250 ng/ml	200-400 ng/ml	> 1000ng/ml
Control group	80%	20%	Nil	Nil
Patient group	49.99%	36.11%	11.1%	2.77%

In most of the cases HbF was below 3% while only 10.34% subjects had HbF of more than 3%. In the control group all subjects had HbF level of less than 1%.

Discussion

In the present study out of 100 siblings of thal major children 58% were detected to have β-thalassaemia trait. As the study was carried out in the siblings of β-thalassaemia children thus both the parents were carriers. The incidence has closely followed the Mandelian pattern of inheritance which states that each offspring of a carrier couple at risk of having a child with thal major has a 25% chance of being normal, a 50% chance of hetrozygosity and a 25% chance of thal major (Modell 1972).

Thalassaemia is an autosomal recessive disorder. A child who inherits the abnormal gene from both the parents (homozygous) suffers from thal major leading to severe intractable anemia and dependence on blood transfusion plus iron chelation therapy for all his life. Such cases can be prevented by identification of the carriers subjects and advising them to avoid marrying another carrier.

Even in the healthy control subject (out of 25 subjects) two had HbA2 more than 3.6% which indictates that thalassaemiaa gene is very common in this part of the country.

As seen in the section of results and observations the detections of β-thal triat cases is easy if the red cell indices and RBC morphology are seen by an experienced person. The diagnosis is ultimately confirmed by hemoglobin electrophoresis.

As a result of present study it is concluded to have a mass screening programme for the detection of β-thalassaemia trait carriers in the general population. Because marriage counseling to these carrier subjects is vital to reduce the incidence of β-thalassaemia major cases as has been carried out in the developed countries.

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