**Middle East Special Report**
Middle East Journal of Cancer 2011; 2(1): 27-31

# The Protective Effect of β-Thalassemia Trait Against Childhood Malignancies in an Unselected Iranian Population

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## Abstract

**Background:** β-thalassemia trait is one of the most common genetic disorders in Mediterranean countries. Previous studies have shown that β-thalassemia trait has a protective effect against malaria, coronary artery disease, hypertension and Alzheimer disease. We hypothesize that due to the shorter life span of red blood cells and increased hematopoiesis, these patients are at increased risk of developing hematological malignancies. Thus, this study investigated the possible effect of β-thalassemia trait on childhood malignancies.

**Methods:** This was a case-control study that included 432 children with malignancies (leukemias and lymphomas as well as solid tumors) as the case group and 432 healthy individuals who referred for premarital β-thalassemia trait screening as the control group. All patients underwent a complete blood count as well as hemoglobin electrophoresis. Hemoglobin $A_2 \geq 3.5\%$ or hemoglobin F between 2% and 10% were considered diagnostic for β-thalassemia trait. The results were compared between groups with the chi-squared test.

**Results:** Mean age of the patients was 7.08 ± 5.1 years and mean age in the control group was 25.46 ± 7.3 years. There were 253 (58.6%) boys and 179 (41.4%) girls among the patients and 308 (71.3%) men and 124 (28.7%) women among the controls. The prevalence of β-thalassemia trait was 5.6% in the case group and 11.3% in the control group ($P$=0.001). The mean hemoglobin level was 9.81 ± 3.1 g/dL in those with malignancies and 15.3 ± 1.7 g/dL in healthy individuals ($P$<0.001).

**Conclusion:** β-thalassemia trait is a protective factor against developing childhood malignancies in an unselected Iranian population. However, more studies are needed to clarify this issue.

***Keywords:*** β-thalassemia trait, Childhood malignancy, Protective effect, Iran

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Middle East Journal of Cancer

Received: October 6, 2010; Accepted: November 1, 2010

## Introduction

Thalassemia, as the most frequent single gene mutation in humans, is caused by defects in the synthesis of globin chains.A defect in synthesis of the α globin chain leads to α-thalassemia, whereas β-thalassemia arises from a defect in the synthesis of the β globin chain. Approximately 7% of the world's population carries the thalassemia gene. Annually, 300 000 to 500 000 children with severe forms of thalassemia are born.[1] In the Mediterranean region, β-thalassemia trait (BTT) is the most prevalent genetic disorder. Depending on the place of residence, and especially in the northern and southern provinces of Iran, between 6% and 10% of the Iranian population has BTT. [2-4]

Crowley et al.[3] demonstrated that Italian men with acute myocardial infarction (MI) had a significantly lower prevalence of thalassemia trait, suggestive of its protective effect for this event. Later, Gallerani et al.[4] confirmed these results in a prospective study that included 4401 participants over 7 years. The study documented the protective effect of BTT on the occurrence of acute MI in men, and these findings were later confirmed by Shahriari et al.[5] Considering the risk factors for this event, the decline in the prevalence of acute MI may be due to lower levels of cholesterol, hematocrit or blood pressure in people with BTT. Because anemia is clearly associated with hypocholesterolemia,[6,7] it has been suggested that accelerated erythropoiesis and increased uptake of low-density lipoproteins by histiocytes and macrophages of the reticuloendothelial system result in lower cholesterol levels in people with anemia, especially those with β-thalassemia.[8]

In people with BTT, anemia and hypocholesterolemia are two major protective factors against atherosclerosis. In addition, there is some evidence that arterial blood pressure in subjects with thalassemia trait is lower than in people without β-thalassemia (non-BTT).[4] In this regard, Karimi et al.[9] have shown that BTT may have a protective effect against ischemic cerebrovascular accident (CVA), which may be related with the lower arterial blood pressure in persons with this trait. In another study, Karimi et al.[10] demonstrated that BTT also has a protective effect on the development of hypertension in young men. Namazi[11] has postulated that patients with BTT are at increased risk of developing impulsiveness secondary to low levels of cholesterol.

Other studies have investigated the role of BTT in the development of depression in young adults,[12] and have shown that patients with BTT are at increased risk of developing major depressive disorder. Several studies have postulated a protective effect of BTT against developing Alzheimer disease.[13,14] This association has been explained as a result of the lower serum cholesterol concentration, blood pressure and blood viscosity in patients with BTT.

To date, no study has investigated the prevalence of BTT in children with malignancies including leukemia, lymphomas or solid tumors. We hypothesized that due to the shorter life span of red blood cells and increased hematopoiesis, these patients may be at increased risk of developing hematological malignancies. Thus, we designed this study in order to investigate the prevalence of BTT in children with malignancies and its possible effect on these malignancies.

## Materials and Methods

### *Patients*

This case-control study was done from March 2009 to March 2010 at the Pediatric Hematology and Oncology Department of Shahid Faghihi and Namazee Hospitals (tertiary health care centers) affiliated with Shiraz University of Medical Sciences in Shiraz, Iran. Because thalassemia is not age- or sex-dependent, the control group consisted of individuals referred to Nader Kazemi Clinic of Shiraz University of Medical Sciences for premarital screening tests. Based on 95% confident intervals and an 80% power to detect a significant difference at a 5% level, 432 participants were needed for each group. Thus, we included 432 children with malignancies as the case group and 432 normal individuals as the control group. The Institutional Review Board and Ethics Committee of Shiraz University of Medical Sciences approved the study protocol.

**Table 1.** Frequency of different malignancies in the case group.

| Type of malignancy | Frequency (%) |
|---|---|
| Acute lymphoid leukemia | 254 (58.8) |
| Acute myeloid leukemia | 31 (7.2) |
| Neuroblastoma | 31 (7.2) |
| Hodgkin lymphoma | 25 (5.8) |
| Rabdomyosarcoma | 23 (5.4) |
| Ewing sarcoma | 12 (2.8) |
| Wilm's tumor | 12 (2.8) |
| Osteosarcoma | 10 (2.3) |
| Giant cell tumor | 9 (2.1) |
| Non-Hodgkin lymphoma | 7 (1.7) |
| Meduloblastoma | 6 (1.4) |
| Retinoblastoma | 5 (1.2) |
| Histiocytosis | 3 (0.7) |
| Epandymoma | 2 (0.5) |
| Hepatoblastoma | 1 (0.2) |
| Primary neuro-ectodermal tumor | 1 (0.2) |

Written informed consent was obtained from each patient or their parents, as well as all individuals recruited to participate in the control group.

In the case group, children presented with biopsy-proven malignancies that included leukemia, lymphoma and solid tumors. All patients were referred to our centers for chemotherapy or follow-up visits. The control group included 432 normal individuals referred to Nader Kazemi Clinic for premarital BTT screening. A brief medical history was taken from all participants. Excluded from the study were those who had a history of cardiovascular diseases, diabetes mellitus, hyperlipidemia or secondary hypertension.

The diagnosis of BTT was established based on the following criteria: hypochromia {mean corpuscular hemoglobin (MCH) <27 pg}, microcytosis {mean corpuscular volume (MCV) <80 fL} and hemoglobin $A_2$ ≥3.5% or fetal hemoglobin between 2% and 10%. Complete blood count was done with a Coulter counter, hemoglobin A2 by column chromatography, fetal hemoglobin by alkaline denaturation and hemoglobin electrophoresis by citrate agar.[15] Patients were compared to controls regarding the prevalence of BTT as well as mean hemoglobin, hematocrit, MCV, MCH and mean corpuscular hemoglobin concentration.

### *Statistical analysis*

All statistical analyses were done with the Statistical Package for Social Sciences v. 17.0 (SPSS Inc., Chicago, IL, USA). The chi-squared test was used to compare the prevalence of BTT between groups and the proportions between groups. We used Student's t-test to compare parametric data sets. *P* values <0.05 were considered statistically significant.

## Results

Overall, we included 432 patients and 432 controls in this study. There were 253 (58.6%) boys and 179 (41.4%) girls among the patients. Controls consisted of 308 (71.3%) men and 124 (28.7%) women. According to the chi-squared test, the difference between the two groups in sex ratio was statistically significant (*P*<0.001). Mean age was 7.08 ± 5.1 years for patients and 25.46 ± 7.3 years for controls. The most common malignancy in the case group was acute lymphoid leukemia, detected in 254 (58.8%) patients, followed by acute myeloid leukemia in 31 (7.2%), neuroblastoma in 31 (7.2%), lymphoma in 25 (5.8%) and rhabdomyosarcoma in 23 (5.3%) patients (Table 1).

Out of 432 patients with malignancies, 24 (5.6%) tested positive for BTT. In the control group, out of 432 normal individuals, 49 (11.3%) tested positive for BTT. The chi-squared test showed a significant difference between the two groups regarding the prevalence of BTT (*P*=0.001). The mean hemoglobin level was 9.81 ±3.1 g/dL in patients with malignancies and 15.3 ±1.7 in normal individuals, which shows significant difference by the independent t-test (*P*<0.001). In the case group the mean MCV was 81.9±8.5 fL, whereas it was 82.6±7.3 fL in the control group (*P*=0.286). Patients with malignancies had significantly higher white blood cell counts (*P*<0.001) and platelet counts (*P*<0.001), and lower hematocrit (*P*<0.001), mean corpuscular hemoglobin concentration (*P*<0.001) and red blood cell count (*P*<0.001) compared to normal individuals.

**Table 2.** Comparison in hematological indices.

| *P* value | Controls (n=432) | Cases (n=432) | Index |
|---|---|---|---|
| <0.001 | 15.3 ± 1.7 | 9.81 ± 3.1 | Hemoglobin (g/dL) |
| <0.001 | 44.2 ± 4.3 | 30.8 ± 14.6 | Hematocrit (%) |
| 0.286 | 82.6 ± 7.3 | 81.9 ± 28.5 | MCV (fL) |
| 0.346 | 28.4 ± 3.9 | 27.1 ± 29.3 | MCH (pg) |
| <0.001 | 34.3 ± 2.7 | 31.8 ± 2.5 | MCHC (g/dL) |
| <0.001 | 6592 ± 1649 | 11913 ± 27790 | WBC count |
| <0.001 | 5.47 ± 0.68 | 3.84 ± 0.9 | RBC count |
| <0.001 | 236319.4 ± 52903.6 | 165961.8 ± 144578.2 | Platelets |

Abbreviations: MCH, mean corpuscular hemoglobin; MCHC,mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cells; WBC, white blood cells

## Discussion

β-thalassemia minor or BTT is one of the most common genetic disorders in Mediterranean countries, including Iran. Previous studies have shown that BTT is protective against some diseases such as malaria,[15] coronary artery syndrome,[5] CVA,[9] hypertension[10] and Alzheimer disease.[13,14] In our study, the prevalence of BTT was 5.6% in patients with malignancies and 11.3% in healthy individuals. This suggests that BTT is a protective factor against childhood malignancies, because normal individuals had a higher prevalence of BTT.

Karimi et al.[9] performed a case-control study in which 148 patients with thromboembolic cerebrovascular events were evaluated for the presence of hypertension, diabetes mellitus, hyperlipidemia and BTT. The control group consisted of 156 age- and sex-matched patients with no cardiac or cerebrovascular diseases. They found that 6.1% of patients with ischemic CVA and 12.2% of the control group had BTT. In male patients, the negative association between ischemic CVA and the presence of BTT was significant. In all patients, the prevalence of hypertension was significantly lower in those with BTT. The authors concluded that BTT may have a protective effect against ischemic CVA, which might be caused by the lower arterial blood pressure in those with this trait.

In another study by Karimi et al.,[10] the authors analyzed the effect of BTT on arterial blood pressure in young adults. A total of 408 participants referred for premarital screening for BTT (208 BTT patients as the case group and 200 healthy individuals as the control group) were recruited. Mean systolic blood pressure in the control group was 122.8 mmHg, compared to 117.0 mmHg in the case group. However, mean diastolic pressure was the same in both groups. Analysis of blood pressure by sex showed that in men with BTT, systolic blood pressure was 10 mmHg lower than in healthy individuals. The authors concluded that BTT had a protective effect on the development of hypertension in young men.

Crowley et al.[3] studied the prevalence of thalassemia trait in a group of Italian men with MI and an ethnically similar group of men admitted for other conditions. Italian men constituted approximately 13% of each group. Of 359 Italian men with MI, only 2 had the thalassemia trait. In contrast, of 330 Italian men in the non-MI group (mean age 59.6 years),[11] had the thalassemia trait. Because the frequency of the thalassemia trait was significantly lower in the MI group, they concluded that this trait may be protective against MI. Later, Gallerani et al.[4] investigated this issue in a total of 4401 men in Italy over a period of 7 years. They attempted to determine whether heterozygous BTT could be considered a protective factor against acute MI. Of the total patient sample, 3954 men were non-BTT, and 447 were heterozygous for BTT. Acute MI was diagnosed in 384 patients, of whom 17 had BTT and 367 did not. The prevalence of BTT in this group was significantly lower than expected. Furthermore, an analysis by sex showed that this lower prevalence could be attributed to male sex. Moreover, a significant negative correlation between acute MI and BTT was found only in

men. Mean age at which acute MI occurred in men with BTT was significantly higher than in non-BTT men, whereas no differences were found in the mean age at which acute MI occurred between women with and without BTT. This study showed that thalassemia trait may afford some protection against acute MI in men. Shahriari et al.[5] subsequently confirmed these results. Other authors have suggested that BTT may be protective against Alzheimer disease.[13,14]

Some studies have hypothesized that BTT may be a risk factor for certain diseases because of its correlation with hypocholesterolemia. In this regard, Marvasti et al.[12] showed that patients with BTT are at increased risk of developing major depression. They studied 208 individuals with BTT and 200 control participants without BTT. Beck's Depression Inventory was used to detect depression in both groups. The results showed that the risk of developing depression in men with BTT was slightly higher than in non-BTT participants. It was also postulated that BTT increased the risk for developing impulsiveness secondary to low levels of cholesterol.[11]

In the present study, of 24 patients with BTT who had malignancies, 5 (1.2%) had normal MCV, which can be explained by folate or vitamin B12 deficiency (a factor that may increase MCV and compensate for genetic microcytosis). In our control group, 6 (1.4%) participants out of 49 with BTT had normal MCV. This suggests that patients with normal MCV might have BTT; hemoglobin electrophoresis is recommended in all individuals referred for screening.

In conclusion, BTT was a protective factor against developing childhood malignancies in an unselected Iranian population. However, more national and international studies are needed to clarify this issue.

## Acknowledgment

This study was supported by grant number 88-4636 from Shiraz University of Medical Sciences.

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