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# Beta Thalassemia Minor as a Risk Factor for Suicide and Violence: A Failure to Replicate

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## ABSTRACT

*The aim of present study was to evaluate the association of thalassemia minor with suicide, impulsivity and aggression. The study group consisted of* 293 *suicidal subjects,* 300 *violent criminals and* 300 *control subjects. Thalassemia trait was slightly more common in criminals* (7.3%) *than in controls* (6.67%)*, this difference was not statistically significant* ($p$ = 0.75)*. Similarly, carrier trait was observed more in suicidal subjects* (8.87%) *though this difference was not statistically significant* ($p$ = 0.3)*. Despite a plausible biological hypothesis, our study results do not support that thalassemia minor could be a risk factor for suicidal, impulsivity and aggressive behaviors.*

***Keywords*:** *Thalassemia Minor, Aggression, Suicide*

## 1. Introduction

Beta-thalassemia is among the most common genetic disorders worldwide. The clinical spectrum of β-thalassemia ranges from the severe transfusion-dependent β-thalassemia major to the asymptomatic β-thalassemia carriers [1].

Showing geographical differences in prevalence, heterozygote β-thalassemia minor is frequent particularly in Mediterranean area and amongst people of Greek, Italian, Middle Eastern, Southeast Asian, Southern Chinese and African descent [2]. The significant clinical manifestations and complications commonly associated with β-thalassemia major are not seen in β-thalassemia minor. That is, most affected individuals are asymptomatic or characterized clinically by mild anemia with persistent microcytosis that usually goes unnoticed [1,3]. Considering the high prevalence of β-thalassemia minor in Iran (7-10 %), the National Thalassamia Program has been launched since 1997 for screening and genetic counseling in attempt to reduce the birth rate of β-thalassemia major [4-6].

Abnormal lipid profile has been repeatedly reported in all clinical phenotypes of β-thalassemia including thalassemia major, thalassemia intermedia and thalassemia minor [7-11]. Patients with β-thalassemia trait have been found to have lower plasma concentrations of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), but unmodified plasma levels of high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) [12,13]. The most suggested underlying mechanism for hypocholesterolemia observed in heterozygous β-thalassemia is the higher erythroid bone marrow activity with the enhanced cholesterol requirement [14]. To date, the clinical implications of this associated hypocholestrolemia are still unknown.

Over the past years, many epidemical and clinical studies have shown the substantial evidences for low serum cholesterol concentrations in people with suicidal, aggressive and violent behaviors meaning that low cholesterol level is significantly related to physical aggression and violence towards self or others [15-23]. The severity of a suicide attempt as well as the degree of suicidal ideation was found to be inversely correlated with serum cholesterol levels. Low levels of cholesterol are associated with a more violent pattern of suicidal behavior [24,25]. There is also a report of low cholesterol levels in parasuicidal patients [24]. Impulsivity is closely associated with suicide and aggression or hostility [26].

The replication of these findings with different study designs across diverse populations has validated such associations. A reduced central serotonergic neurotransmission through decreased serotonergic (5HT) receptor function is a biochemical mechanism responsible for association between low cholesterol level and psychopathological processes involved in suicidal, aggressive

 

and violent behaviors [27-31].

Taking these separate associations together, one may expect that suicidal, aggressive and violent behaviors would be more observed in thalassemia minor, at a population level. Therefore, the attention is called to the psychosocial problems that this thought could emerge in a society where thalassemia trait is common. Without appropriate validation, over the years, this premise could bring the false impression of facing unstable relationships and interpersonal difficulties with β-thalassemia carriers and thus put them in considerable distress. To the best of our knowledge, no study exists that clinically challenges the correlation of β-thalassemia minor phenotype with suicide, aggression and violence. This study was conducted to test this hypothesis.

## 2. Method

### 2.1 Subjects

This cross-sectional, case-controlled study was conducted in Shiraz, south of Iran, from April 2007 to June 2008. The study sample included three separate groups of subjects: Group (A): subjects with attempted suicide (n = 293, mean age = 25.15 ± 10.94 y/o) who had been admitted to Nemazee University Hospital following a suicide attempt. Group (B): violent criminals were the prisoners sentenced to Adelabad jail (main jail of Fars province, southern of Iran) by court because of proven crimes linked to violence against life or health of others (n = 300, mean age = 33.29 ± 11.47 y/o). Violent crimes comprised of murder and/or attempted murder, infanticide, stabbing or wounding or other act endangering life, rape, sexual assault, child abuse, vandalism, arson, criminal damage to a dwelling or vehicle, burglary equipped by weapons, possession of and trafficking in drugs and/or firearms. None of the individuals were the subject of false arrest or self-defense. Only male subjects were investigated because we were not able to identify enough females with the same criteria of recruitment. Group (C): control subjects (n = 300, mean age = 28.15 ± 10.3 y/o) normal healthy volunteers and recruited from couples screened by Iranian National Thalassemia Screening Program as part of mandatory premarital blood tests [5-31]. A detailed medical history was taken from and a complete physical examination was performed on all subjects. Any subject with a history of or current definite physical diseases that could possibly influence the findings was excluded from the study. They were screened not to have personal and familial psychiatric histories as well. None used psychotropic medications or abused substances. Before recruitment, the purpose of the study was explained to each participant. Participants signed an informed consent form, which in case of group B was countersigned by a member of the prison staff. The study was preapproved by medical ethical committee of Shiraz University of Medical Sciences.

### 2.2 Methods

Blood samples were taken from all studied subjects. The diagnosis of β-thalassemia trait was established based on basic hematological criteria: anisocytosis, poikilocytosis, hypochromia and microcytosis (mean corpuscular hemoglobin (MCH) < 27 pg, mean corpuscular volume (MCV) < 80 fL), and the quantity of HbA2 ≥ 3.5% and 2% < Hb F < 10%, performed by high performance liquid chromatography (HPLC)) [31]. Complete blood count was performed by Coulter counter machine, and hemoglobin electrophoresis by Citrate Agar. Suspected results were then confirmed by direct DNA sequencing using polymerase chain reaction (PCR)-based techniques. Subjects with normal hemoglobin, normal MCV, normal MCH, normal morphology, HbA2 < 3.5%, HbF < 2% and normal hemoglobin electrophoresis were regarded as non-β-thalassemia trait. To rule out iron deficiency anemia, individuals with HbA2 < 3.5% and anemia were treated with oral iron (one ferrous sulfate tablet equivalent with 50 mg elemental iron, three times daily) for 2 months. The tests were repeated after this period and a decision was reached using the same laboratory values as above. Alpha and beta-thalassemia trait was differentiated by fresh blood incubated with Leucin H3 method.

### 2.3 Statistical Analysis

The data were analyzed using SPSS software (version 13.0.0; SPSS, Chicago, IL, USA).

Pearson's $\chi^2$-test and Fisher's exact probability test were used, when appropriate. Findings were deemed to be statistically significant at a p-value of less than < 0.05.

## 3. Results

The prevalence of thalassemia trait in all of three groups is shown in Table 1. Thalassemia trait was slightly more common in prisoners (22 (7.3%)) than in controls (20 (6.7%)), but this higher frequency was not statistically significant ($p$ = 0.75). Similarly, carrier trait was observed more in suicidal subjects (26 (8.9%)), but this difference was not statistically significant ($p$ = 0.3). More significantly, the prevalence of Thalassemia minor, in all three groups of studied subjects, was consistent with previous studies reporting the prevalence of β-thalassemia trait to be as 7-10% of Iranian population [5].

## 4. Discussion

Thalassemia is in one of the most prevalent genetic diseases and approximately 7-10% of Iranian population are carriers for this disease [4,5].

Previous studies have consistently shown a higher rate of aggression, violence and impulsivity as well as suicidal behaviors in individuals with low cholesterol level

 

**Table 1. Prevalence of thalassemia-minor in patients with suicidal attempts and violence criminals**

| Patients | Healthy (n)(%) | Thalassemia trait (n)(%) | Total (n)(%) | p-Value |
|---|---|---|---|---|
| Patients with suicidal attempt (Group A) | 267 (91.1%) | 26 (8.9%) | 293 (100%) | 0.3* |
| Prisoners with violence crime (Group B) | 278 (92.7%) | 22 (7.3%) | 300 (100%) | 0.75* |
| Controls (Group C) | 280 (93.3%) | 20 (6.7%) | 300 (100%) | |

n = number, NS = Non-significant

[15-23], due to reduction of serotonergic activity in the brain [27-30]. Given that thalassemia patients (major, minor and intermedia) have lower cholesterol levels [7-13,32-36] one may assume that carrier state may represent a risk factor for these behaviors [37]. Considering the high prevalence of carrier individuals in our population, we were concerned about the emerging problem of the increase of emotional distress, unstable interpersonal relationships and marriage difficulties. These psychosocial concerns brought us to conduct the present study and assess the accuracy of this hypothesis for the first time in literature. We studied a large sample size and designed a reverse approach to evaluate the prevalence of thalassemia trait in individuals with suicidal attempts and in those with extreme aggressive behaviors as violent criminals.

Our findings failed to show significant correlation between being a thalassemia carrier and an increased rate of violence and suicide, that is to say thalassemia trait is unlikely to serve as a risk factor for future suicide and/or violence when considered in isolation. Although, a relation of low cholesterol to suicide and violence is confirmed to be causal, other factors could manipulate the behavioral impact of low cholesterol in thalassemia carriers. Suicide and violence are complex behaviors with multiple causes in nature and any single factor is likely to account for only a relatively small effect [38].

There were limitations in the present study. We used convenience samples consisting of accessible couples screened by National Thalassemia Screening Program, patients admitted to our university hospital and prisoners sentenced to local jail. Also, we only recruited male subjects with proven crimes linked to violence. Due to its selective nature, the sample may not entirely represent the general population. Nevertheless, the findings generated from this large sample may provide valuable information about the psychopathologies; suicide, aggression and violence, that were studied in thalassemia trait. We used a one-time blood sampling, potentially remote from the time of the violent crime. However, the measurement of HbA2 and HbF by HPLC is reproducible and precise. It is a reliable method for rapid screening in population surveys for beta thalassaemia. Moreover, the suspected results were confirmed by direct DNA sequencing techniques.

The importance of these findings is that the individuals with thalassemia trait would not be rejected by the rest of society due to fear of impulsive behaviors. The extent and significance of these findings should be evaluated through further epidemiological studies on greater samples with follow-up periods, after controlling for potential confounding variables.

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