Research Paper

Comparison of Immunoglobulins Status in Splenectomized and Non-splenectomized Patients With Major Beta-Thalassemia

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ABSTRACT

Background: Thalassemia is one of the most prevalent genetic disorders globally, and infections are one of the major causes of death in these patients. Various studies have attributed the increased susceptibility to bacterial infections in thalassemia patients to changes in their immunological status.

Objectives: This research aimed to measure serum levels of immunoglobulins (Igs) in Thalassemia Major (TM) patients and in the control group.

Methods: The study included forty TM patients (20 splenectomized and 20 non-splenectomized) and 20 healthy participants (the control group). Three groups were matched for age and gender. Mean serum levels of immunoglobulins (IgG, IgA and IgM) were measured for all individuals by ELISA. P<0.05 was considered the significance level.

Results: Increased serum IgG and IgA levels and significantly reduced serum IgM levels were observed in the splenectomized patients compared to the non-splenectomized ones. A comparison of the study groups revealed that serum IgG and IgA levels in the splenectomized patients and the mean serum IgM and IgG levels in the non-splenectomized patients were higher than those of the healthy participants. The mean serum IgM levels in the splenectomized patients and the mean serum IgG levels in the non-splenectomized patients were lower than those of the control group.

Conclusions: The results showed that splenectomy could change the immunological status of thalassemia patients. Nevertheless, the exact mechanism for this change was not clear. Studying the serum levels of immunoglobulins might be useful in determining the severity of infections in TM patients.

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1. Introduction

Thalassemia is one of the most prevalent genetic disorders globally, with high incidence in tropical and subtropical regions, including the Middle East, the Mediterranean countries, India, Southeast Asia, and North Africa [1]. It is also the most common hereditary anemia in Iran, particularly in Sistan and Baluchestan Province located in the South-East of the country [2]. Thalassemia is an autosomal recessive disease characterized by reductions in the synthesis of globin chains. It is caused by mutations in the genes on chromosome 11 that encode globin chains. Beta-thalassemia major (β-TM) is a disease that results from mutations in the β-globin gene. Reduction in or lack of β-globin gene expression leads to an imbalance of α-globin, and the free insoluble α-globin molecules precipitate, damage, and destroy erythroid precursors. This is referred to as ineffective erythropoiesis [3, 4]. Paleness, insufficient weight gain, and inadequate growth and development are the most common signs and symptoms of thalassemia. The main reasons for anemia are the destruction of red blood cells and ineffective erythropoiesis. Inadequate erythropoiesis and severe anemia in TM patients cause enlarged liver and spleen and skeletal deformities. Thalassemia treatment includes regular blood transfusions and the use of iron-chelating drugs [5].

In addition to severe anemia, TM patients suffer from numerous problems, including susceptibility to bacterial infections, which plays a major role in deaths related to this disease. Factors, such as splenectomy, repeated exposure to foreign antigens during blood transfusions, iron overload, and the use of iron-chelating drugs have profoundly deleterious effects on the immune system. Many studies have evaluated possible changes in the humoral and cellular immune systems of TM patients. Immune deficiency is a common cause of infections in β-TM patients. Immunological abnormalities, such as decreased opsonization and cellular phagocytosis, increased levels of serum immunoglobulins, and iron overload have severely harmful effects on the immune system [6, 7].

The spleen is one of the organs affected in TM patients, in which the degree of splenomegaly is related to the severity of thalassemia and regular blood transfusion. Therefore, splenectomy is required to prevent excessive increases in spleen activity and to reduce the mechanical pressure induced by an enlarged spleen [8]. Excessive activity of the spleen intensifies the destruction of the transfused red blood cells and hence, increases the need for blood transfusion in β-TM patients. This is one of the most common problems in these patients, especially in developing countries where patient compliance is poor. Splenectomy may be accompanied by the increased risk of thrombotic complications and acute infections following surgery. However, it could be useful in reducing the need for blood transfusion [9].

Splenectomy is recommended when the annual transfusion volume exceeds 250 mL/kg. There is a risk of sepsis and severe immune response to bacterial infections in splenectomized patients. Approximately, 25% of these patients are at risk of developing acute infections. This might be happened due to abnormalities in immunoglobulin production and disruptions in the activity of B and T lymphocytes and the function of macrophages and neutrophils, as well as the components of the complement system [10, 11]. Levels of immunoglobulins have been extensively studied in β-TM patients. However, contradictory findings have been reported. In the research by Dwyer et al., [12] increased IgA and IgM levels were reported, whereas higher IgA levels were observed in another study [13] on splenectomized and non-splenectomized patients. Moreover, other studies have reported an increase in the number of B lymphocytes, but their differentiation was disrupted [14].

Splenectomy significantly affects B cells. Accordingly, among patients who had not undergone splenectomy, the number of circulating B cells was found three times more than the normal state. Moreover, the secretion of immunoglobulins increased 10-fold in these patients [15]. On the other hand, a large number of patients in Sistan and Baluchestan Province receive blood transfusions regularly and may require splenectomy in the future. Therefore, the present research was conducted to identify serum levels of immunoglobulins in splenectomized and non-splenectomized TM patients and compare them with the control group.

2. Methods

This cross-sectional study was carried out on 20 splenectomized and 20 non-splenectomized TM patients (groups 1 and 2, respectively) at the Thalassemia Ward in Ali-Asghar Hospital, Zahedan, and also 20 healthy participants (the control group). All TM patients received a regular blood transfusion. The three groups were similar in age and gender. Patients with malnutrition, a history of immune deficiency, those receiving IVIG, cases suffering from an acute and recurrent infection, those taking immunosuppressive drugs, and patients with congenital disorders were excluded from

Table 1. Demographic characteristics of patients and control group

Parameters	Mean±SD		
	Splenectomized Beta-thalassemia (n=20)	Non-splenectomized Thalassemia (n=20)	Control
Age (y)	27±4.15	22.19±4.40	25.73±3.05
Gender (Male)	12	9	11

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the study. All participants were HIV-negative. After obtaining written consent from all the participants, a 5 mL blood sample was taken from them. The samples were taken from the thalassemia patients before blood transfusion. The blood samples were immediately centrifuged and the extracted serums were kept at -20˚C until measurements for immunoglobulins contents were made. Serum levels of IgG, IgA, and IgM were measured for each participant and the means of these immunoglobulins were calculated for all three groups. The data were analyzed using SPSS software version 16 and the P<0.05 was considered statistically significant.

3. Results

Table 1 presents the demographic characteristics of the three groups, including age and gender, and Table 2 showed the mean serum levels of the immunoglobulins. There were no significant differences between groups 1 and 2 in IgA and IgG levels (P=0.37 and 0.09, respectively). However, the IgM levels differed significantly in these groups (P=0.03). Data showed no significant differences between groups 1 and 3 in IgM and IgG levels (P=0.45 and 0.15, respectively), whereas they varied significantly in IgA levels (P=0.006). There were significant differences between groups 2 and 3 in IgM and IgA levels (P=0.03 and 0.04, respectively), but we found no significant differences between them in IgG levels (P=0.62).

4. Discussion

To survive, most TM patients need regular blood transfusions with iron-chelating drugs to reduce iron overload. The spleen starts extramedullary hematopoiesis when the bone marrow cannot compensate for anemia and hypersplenism occurs in β-thalassemia patients. Consequently, hypersplenism resulting from extramedullary hematopoiesis will require splenectomy. The spleen plays an important role in protecting the body against infections by regulating immune homeostasis by establishing links between the innate and acquired immune systems. The most serious infections in splenectomized patients are caused by Streptococcus pneumonia, Haemophilus influenza, and Neisseria meningitides [16, 17].

β-TM patients may require splenectomy secondary to hypersplenism. It has long been proved that splenectomy can reduce blood transfusion requirements and iron overload in these patients. In addition, a splenectomy can relieve the discomfort secondary to massive splenomegaly.18 Considering the role of the spleen in clearing infections, splenectomy increases the risk of infections. Accordingly, studying the levels of immunoglobulins can play a role in identifying the causes of infection and help in treating these patients.

The present research investigated the levels of immunoglobulins in splenectomized and non-splenectomized TM patients. The findings indicated that the mean serum levels of IgG and IgA in the splenectomized patients were higher than those of the non-splenectomized ones. However, these differences were not statistically significant. The mean serum IgM levels in the splenectomized patients were significantly lower than in the non-splenectomized ones. Various results have been reported in this regard. Darzi et al. reported significant reductions in IgA and IgM levels following splenectomy in β-TM patients

Table 2. Levels of immunoglobins in patients and the control group

Immunoglobin	Mean±SD		
	IgG (mg/dl)	IgM (mg/dl)	Age (y)
Splenectomized beta-thalassemiabeta	16.84±3.51	0.49+0.96	172.26±324.26
Non-splenectomized thalassemia	4.36±13.84	1.01+1.65	116.46±279.53
Control grou	4.11±14.39	0.70+1.09	71.64±195.26

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compared to pre-operative levels. Splenectomy could lower serum levels of immunoglobulins as the spleen has an essential effect on releasing immunoglobulins [10]. Amin et al. also reported that serum IgG and IgA levels increased in splenectomized thalassemia patients compared to the non-splenectomized ones. Conversely, they observed no differences between the two groups in IgM levels [18]. Kiani et al. also observed significant increases in IgA levels in non-splenectomized patients (children under the age of five) but normal IgM and IgG levels in the splenectomized and non-splenectomized groups [19]. Ahluwalia et al. reported that serum IgG and IgA levels in splenectomized children were higher than in non-splenectomized ones, but these differences were not statistically significant [20]. Their results were similar to those of the present study. Increased serum IgG and IgA levels and decreased serum IgM levels were also observed between these two groups of patients in the study by Konstantoulakis et al. [21].

Serum IgG and IgA levels in the splenectomized patients were higher than in the control group. The difference in IgA levels was statistically significant, and the mean serum IgM levels in the splenectomized patients were lower than in the control group. However, this difference was not statistically significant. Ghaffari et al. [22] reported results similar to those of the present study. A substantial reduction was found in IgM levels in splenectomized patients with hematologic disorders in the study by Korn et al. [23] However, no changes were observed in IgG and IgA levels. They suggested that the severe decrease in IgM could be due to opsonization defects and the development of acute infection immediately after splenectomy. Mean serum IgM and IgA levels in the non-splenectomized patients in the present study were significantly higher than in the healthy control group. However, their IgG levels were lower and these differences were not statistically significant. Shani et al. [24] also observed significantly reduced IgG levels in thalassemia patients compared to the healthy control group, but they reported no significant differences between the two groups in other immunoglobulins.

Many factors, such as the number of blood transfusions, serum ferritin level, contents of iron in tissues, age and genetic backgrounds of patients as well as the specific mutation responsible for the development of thalassemia phenotype may cause these discrepancies and contradictory results. . Increased serum levels of immunoglobulins in β-TM patients can be attributed to various factors. For example, repeated blood transfusions in β-TM patients may continuously expose them to various antigens that cause serum levels of immunoglobulins to rise. Thalassemia patients are exposed to many bacterial and viral infections. Consecutive infections can also stimulate the immune system and increase levels of immunoglobulins. Increased infections have been reported in splenectomized patients compared to non-splenectomized ones because the spleen is one of the largest lymphoid organs and filters bacteria and many invasive microorganisms from the blood. It is also involved in eliminating microorganisms opsonized by the complement system. It has been assumed that the splenectomy may stimulate secondary lymphoid organs to compensate for the synthesis of the major immunoglobulin classes.

5. Conclusions

The present study results showed a significant decrease in serum IgM levels in splenectomized patients compared to the non-splenectomized patients. Additionally, there was a significant increase in IgA levels in the splenectomized patients and in serum IgM and IgA levels in the non-splenectomized patients compared to the healthy control group. Although splenectomy plays a role in changing the immune status of thalassemia patients, the exact mechanism for this change is not clear yet and assessment of immunoglobulins can be useful in understanding the severity of infection in β-TM patients. There are many differences among thalassemia patients caused by genetic and environmental factors. These differences influence the results of studies and make it difficult to identify the exact mechanisms involved in the complications resulting from splenectomy. Therefore, more research must be conducted to identify the unknown mechanisms involved in the processes making differences between TM patients prior to and post-splenectomy.

Ethical Considerations

Compliance with ethical guidelines

The study was initially reviewed and approved by the Ethics Committee of Zahedan University of Medical Sciences (Code: IR.ZAUMS.REC.1394.207).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declare no conflict of interest.

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