



Original Article

Seroprevalence of Hepatitis E in with Major Thalassemia Patients

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Abstract

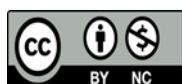
Background: Hepatitis E is primarily transmitted via the fecal-oral route, although transfusion transmission is also possible. Blood transfusion-dependent thalassemia patients represent a high-risk group for transfusion-transmitted viruses.

Methods: This cross-sectional study was conducted on 180 major thalassemia patients referred to the Thalassemia Center of Babol University of Medical Sciences in 2020. Patient information was extracted from medical records and entered into pre-prepared questionnaires. For patients with incomplete records lacking serological results, five mL of blood was collected and analyzed for IgM and IgG antibodies using ELISA. Data were analyzed using SPSS version 24.

Results: Of the 180 patients, 92 (51.1%) were male and 88 (48.9%) were female, with a mean age of 30.5 ± 8.4 years. No samples tested positive for hepatitis E antibodies (0.18%). A family history of thalassemia was reported by 55 (30.6%) patients, 82 (45.6%) had a history of splenectomy, and three (1.7%) had undergone bone marrow transplantation. All patients had a history of blood transfusion; 4 (2.2%) received less than one unit per month, 111 (61.7%) received one unit, and 65 (36.1%) received two units. No patients reported a history of imprisonment or injecting drug use. One patient (0.6%) reported extramarital sex, and four (2.2%) had tattoos. Eighty-two patients (45.6%) had undergone splenectomy, and 51 (28.3%) had a history of other surgeries.

Conclusion: This study found no evidence of hepatitis E infection among patients with major thalassemia. Further research is warranted to determine whether screening for hepatitis E is necessary in this population.

Keywords: Beta-thalassemia, Seroepidemiology, ELISA, Hepatitis Ebullosa; Nasal septum; Sinusitis; Tomography, X-Ray Computed



Introduction

Based on the type of globin chains, three types of hemoglobin are detectable in humans: HbA1, HbA2, and HbF. HbA2 comprises two alpha and two delta chains [1].

Thalassemia is a group of blood disorders in which the ratio of alpha to beta globin production deviates from the normal range due to impaired globin chain synthesis [2]. This imbalance leads to precipitation of unpaired globin chains, resulting in accelerated destruction of red blood cell precursors in the bone marrow (ineffective erythropoiesis) and hemolysis [3, 4]. Patients present with varying degrees of anemia and extramedullary hematopoiesis, which can cause bone changes and stunted growth. Furthermore, frequent blood transfusions increase iron overload [5-7]. The disease was first reported independently in the United States and Italy in 1925 [2]. The disease has been reported in all races but is prevalent primarily in Mediterranean countries, tropics, and regions of Asia and Africa. Parts of Africa, Turkey, Iran, the Netherlands, and Southeast Asia are geographically called the Global Thalassemia Belt [4, 5]. The highest incidence of thalassemia is reported in Cyprus (14%), Sardinia (12%), and Southeast Asia. Thalassemia is common in Iran along the Caspian Sea and the Persian Gulf, Kohkiluyeh and Boyer-Ahmad, Fars, Kerman, Isfahan and Sistan, and Baluchestan. [4-6].

It is estimated that 5% of the world's population has at least one of the thalassemia-related alleles [7]. Mutations related to beta-thalassemia are divided into two groups: one group in which no beta chain is produced and the second group in which is reduced beta chain production. Unlike alpha thalassemia, which is due to deletion in one or more alpha globin genes, in beta-thalassemia, most of these mutations are related to changes in the beta-globin chain gene [8, 9]. Two mechanisms contribute to beta-thalassemia anemia, which includes decreased beta-globin production and unbalanced production of alpha and beta globin chains [10]. These patients receive regular blood transfusions to prevent the complications of chronic anemia and bone changes. Over the past 2-3 decades, blood transfusions have significantly increased life expectancy in patients with major thalassemia. Increased use of this treatment may cause complications, such as iron overload [1, 11, 12].

Hepatitis is a well-known transfusion-transmitted infection. While hepatitis B and C have been extensively studied in patients receiving blood products, few studies have investigated other hepatitis viruses, particularly in patients with thalassemia major. Hepatitis E virus (HEV), a member of the family Hepeviridae, is transmitted

through contaminated water and food and can cause clinical manifestations ranging from asymptomatic infection to fulminant, fatal disease [13-15].

Patients who receive repeated blood transfusions have a higher HEV seroprevalence than the general population. Similarly, dialysis patients requiring continuous blood transfusions show elevated seropositivity. Furthermore, transmission can occur from donors with subclinical infections [16-18]. Hepatitis E is probably one of the causes of elevated liver enzymes in individuals who receive blood products [19]. Studies have shown that HEV infection is endemic in Iran, with significantly higher prevalence in certain regions, particularly among the elderly and individuals with high-risk behaviors [20]. However, research on this hepatotropic virus remains limited in our region compared to other hepatitis viruses. This study aimed to determine the frequency of hepatitis E virus (HEV) infection among patients with thalassemia major receiving care at the Amirkola Thalassemia Center.

Methods

Ethical considerations

This study was approved by the Research Ethics Committee of Babol University of Medical Sciences (approval code: IR.MUBABOL.HRI.REC.1398.197). All patient information was recorded with complete confidentiality and was not disclosed to any natural or legal person. No additional costs were imposed on the patients.

Study Design and Population

This cross-sectional study was performed on patients with thalassemia major who attended the thalassemia center of Babol University of Medical Sciences for follow-up care. Patients were included based on the following inclusion criteria: definitive confirmation of thalassemia major diagnosis and repeated receipt of blood products. After excluding patients who met the exclusion criteria (including those with other causes of hemolytic anemia besides thalassemia and those receiving fewer than ten units of blood per year), 180 patients were enrolled in the study.

Procedure

Data from 180 patients with thalassemia major receiving care at the Amirkola Thalassemia Center in Babol were extracted from their medical files and entered into pre-prepared questionnaires. The collected

information included age, sex, frequency of blood transfusions, history of splenectomy and other surgeries, and history of antibody testing for hepatitis E virus (HEV). For patients with no serological results available in their files (due to incomplete records), 5 cc of blood was collected to determine HEV serology. Samples were transported to the laboratory via a cold chain protective process, centrifuged, and tested using ELISA for anti-HEV IgM and IgG antibodies.

Data analysis

The seroprevalence of HEV infection and possible risk factors for seropositivity were determined by examining the collected data. Data were analyzed using SPSS version 24.0. Student's t-test and Pearson's correlation coefficient were used for statistical analysis. A p-value less than 0.05 was considered statistically significant.

Results

In this study, 92 patients (51.1%) were male, and 88 (48.9%) were female. The minimum age was 12 years, the maximum age was 67 years, and the mean age of the patients was 30.5 ± 8.4 years. Among 180 samples, all cases were negative for total antibodies against HEV. No statistically significant relationship was found between anti-HEV antibodies and gender ($p > 0.05$). Regarding marital status, 84 patients (46.7%) were married; however, due to the zero prevalence of HEV in the study population, the association between marital status and HEV infection could not be evaluated.

Patients were also evaluated for thalassemia-related characteristics. In this study, 55 patients (30.6%) had a family history of thalassemia, 82 patients (45.6%) had a history of splenectomy, and three patients (1.7%) had a history of bone marrow transplantation. All patients had

a history of blood transfusion. Among them, four patients (2.2%) received an average of less than one unit of blood per month, 111 patients (61.7%) received one unit per month, and 65 patients (36.1%) received two units per month. Regarding iron chelation therapy, 26 patients (14.4%) were receiving oral deferoxamine, and 154 patients (85.6%) were receiving injectable deferoxamine (Table 1).

Table 1: Features of patients with thalassemia

Thalassemia Features*		Prevalence, n (%)
Familial history of Thalassemia		55 (30.6)
Splenectomy history		82 (45.6)
Bone marrow transplantation		3 (1.7)
Deferoxamine	Oral	26 (14.4)
	Injection	154 (85.6)
Blood transfusion	Less than one unit per month	4 (2.2)
	One unit per month	111 (61.7)
	Two units per month	65 (36.1)

*Since no person with hepatitis E was found in the study population, the relationship between the below variables and hepatitis E could not be examined

Ferritin levels were measured in 67 patients, with a mean of 1971 ± 176 ng/mL (normal range: 24–336 ng/mL). Although statistical analysis of risk factors was not possible due to zero prevalence (Figure 1), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured in 63 patients. The mean ALT level was 36.7 ± 25 U/L, and the mean AST level was 37.4 ± 21 U/L, both within the normal range.

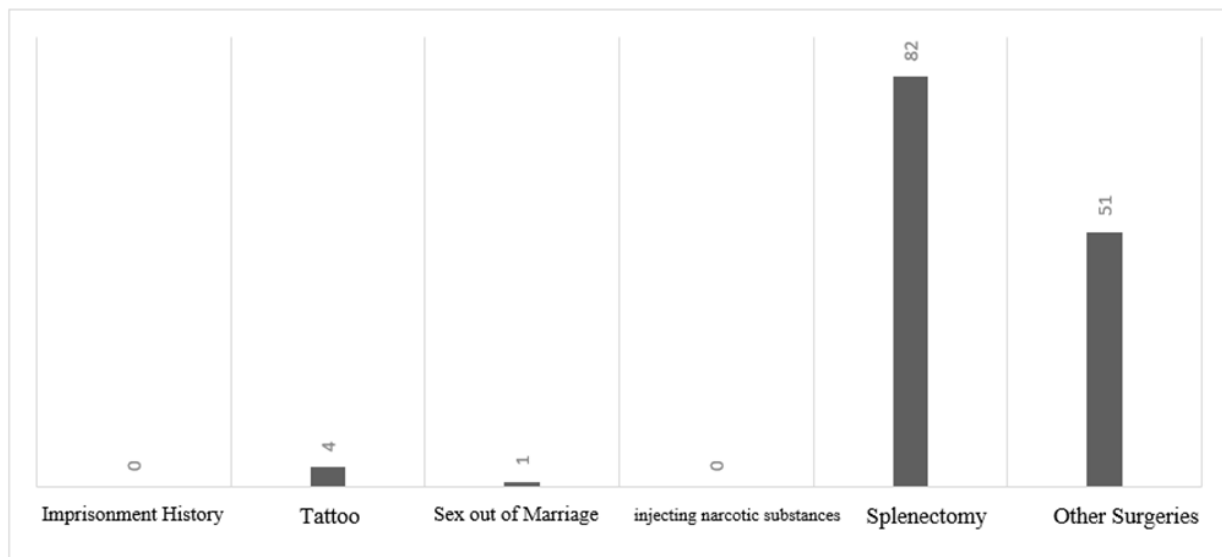


Figure 1. Prevalence of risk factors in patients with thalassemia

Discussion

Hemoglobin abnormalities generally arise from two main mechanisms. First, the production of abnormal globin chains leads to the formation of abnormal hemoglobin variants, resulting in diseases such as hemoglobin S, hemoglobin D, and hemoglobin C [21]. Many of these abnormal hemoglobins have a higher affinity for oxygen and are therefore usually associated with polycythemia in their carriers [21]. Second, decreased production of globin chains comprises a minor disorder in the production of globin chains, with thalassemia being the most prevalent and critical disease in this category [21]. In severe cases of thalassemia, hemolysis occurs. Thalassemia, in severe cases, is a blood-dependent disease, so they do not live more than five years without receiving blood due to severe anemia. However, repeated blood intake causes iron accumulation in various tissues, including the liver and heart, resulting in functional insufficiency and, eventually, the patient's death. However, with iron chelators, iron accumulation in various tissues can be reduced [22-25]. The alpha-thalassemia manifests itself in severe forms of fetal disease due to the presence and expression of alpha chains in fetal hemoglobin [26].

The severity and clinical manifestations of the disease vary depending on the type of thalassemia; The severity of symptoms in homozygous individuals is higher than in heterozygous cases [27, 28]. Thalassemias are classified as hypochromic microcytic anemias, so MCV and MCH are reduced to less than normal. Patients with

hypochromic microcytic anemia are the most important differential diagnosis of iron deficiency anemia [27]. Other tests, such as hemoglobin electrophoresis and gene mutation analysis, should be used to confirm thalassemia [29].

In addition to treating, one of the necessities of our country's health system is to prevent the birth of children with thalassemia. If the parents carry beta-globin gene mutations, the risk of having an infected child for the couple is 25% per pregnancy, based on the autosomal recessive inheritance pattern. In this case, first, the parents' mutation is determined, and then, during pregnancy, genetic methods will be used in the 11th week of pregnancy after CVS to diagnose the fetus with major thalassemia, and abortion will be performed under 12 weeks of pregnancy. A national program to prevent thalassemia was started in 1997 [30]. Today, definitive treatment can be achieved using stem cell transplantation in patients with thalassemia. In this procedure, stem cells are taken from compatible donors' umbilical cord blood or bone marrow and given to transplant patients. These methods may be associated with side effects such as graft versus host disease (GVHD) or graft rejection. Newer methods, such as induced stem cells and gene therapy, are also proposed [31].

Hepatitis E virus is a small single-stranded RNA virus belonging to the Hepeviridae family [13, 32]. According to the World Health Organization, 20 million new cases of hepatitis E occur each year, leading to approximately 3 million cases of acute hepatitis. It causes about 55,000

deaths. The prevalence of serum antibodies against hepatitis E in developing countries is higher than in developed countries (10 to 70% vs. 1 to 21%), and its highest prevalence is in Asia and Africa [16-18, 33]. Hepatitis E transmission can occur through contaminated food and water, blood transfusions, and mother-to-child transmission. However, transmission from person to person is uncommon. Each specific genotype is transmitted through a specific transmission. Genotypes 1 and 2 are transmitted through contaminated water in endemic areas and are found in poor areas and areas with low socioeconomic status. Types 3 and 4 are transmitted through the consumption of contaminated food or blood transfusions.

The incubation period for hepatitis E infection is 15 to 60 days [34]. Most patients with acute infection are asymptomatic or have mild symptoms. In patients with symptoms, jaundice is often accompanied by lethargy, anorexia, nausea and vomiting, abdominal pain, fever, and hepatomegaly. Extrahepatic symptoms may be present in rare cases such as blood disorders and acute thyroiditis [13-15, 35]. Laboratory tests show increased bilirubin, alanine aminotransferase, and aspartate transferase. Elimination of laboratory changes usually occurs one to six weeks after the onset of the disease. Most patients with hepatitis E infection recover independently, although patients may develop complications such as acute liver failure, cholestatic hepatitis, or chronic hepatitis E infection [36]. In addition to the classic manifestations of hepatitis E, this infection leads to extrahepatic manifestations, which include a wide range of neurological complications, kidney damage, pancreatitis, and blood problems. Neurological manifestations in HEV patients can include Guillain-Barré syndrome, Bell's palsy, and acute transverse myelitis. HEV1 and HEV3 infections cause neurological manifestations. Renal damage manifests as glomerulonephritis. Thrombocytopenia and aplastic anemia in HEV patients have also been reported [16-18].

According to previous studies, there is a possibility that receiving blood products is effective in major thalassemia patients being infected with hepatitis E. Using the ELISA method, the serum prevalence of hepatitis E in transfusion-dependent thalassemia patients was evaluated. None of the patients had positive serology against hepatitis E, and this infection's prevalence in thalassemia patients was reported to be zero. In a similar study published by Dalvand et al. in 2019, only 2 cases (1.67%) had positive serology in the ELISA method, which was also performed by RT-PCR, which was negative in all patients [13]. In our study The serum prevalence of hepatitis E in major thalassemia patients was lower than in the general population. A study by Golshan et al. in 2017 showed that the serum

prevalence of hepatitis E in the group with major thalassemia was 2.6%. It is less than the control group and the general population [15]. In the study of Jahromi et al., the serum prevalence of IgG and IgM antibodies was 10% and 1.8%, respectively, which showed a higher prevalence than our study, which could be due to differences in the study location [20]. Some of the studies were conducted in the north and northeast of Iran, but the study by Jahromi et al. was conducted in the south of Iran. [13, 15, 20]. In a study in Greece, Klonizakis et al. reported a low prevalence of hepatitis E virus in patients with major thalassemia [37].

In a study by al-Fawaz et al., the difference in the results of different studies on thalassemia patients is primarily related to the difference in the prevalence of hepatitis E in different areas and the health conditions of the study population. In Klonizakis et al. and al-Fawaz et al., no statistically significant relationship was found between hepatitis E infection and major thalassemia [37, 38]. Based on the results of ELISA in our study, as in the study of Dalvand et al., no significant relationship was found between the demographic data of patients (sex, age, marital status) and risk factors studied (addiction, blood transfusion) [13]. Golshan's study found no significant relationship between demographic characteristics and hepatitis E [15]. In Jahromi et al. Study, no significant relationship was found between age, sex, and history of splenectomy, and the only significant finding was higher levels of liver enzymes in positive serology individuals compared to negative individuals for hepatitis E [20].

In a study by Karimi et al. from 2009 to 2010, 219 thalassemia and hemodialysis patients with hepatitis C were studied. The prevalence of hepatitis A in thalassemia patients was 93.8%, and the prevalence of antibodies against hepatitis E was 1.6%. In the study of Karimi et al., as in our study in thalassemia patients, no significant relationship was found between hepatitis E infection and other variables of patients (demographic and possible risk factors) of thalassemia [39].

In a study of Egyptian children with major thalassemia, a statistically significant relationship was found between hepatitis E infection and age, place of residence, level of liver enzymes, and the number of blood units received. The different epidemiology of the virus in the two communities is due to differences in age and race groups [40]. In our study, the prevalence of hepatitis E in thalassemia major patients was reported, indicating the need for more research to decide on screening for this infection.

Conclusion

Our study assessed the serum prevalence of HEV infection in patients with thalassemia major and detected no positive samples for anti-HEV antibodies. This finding points to the efficacy of current protective protocols and may also reflect the lower prevalence of HEV in the general population due to fewer exposure risk factors, although the sensitivity of the ELISA method, the specific population studied, or regional differences may influence this result. This study examined the variables of age, sex, geographic location, possible risk factors, and clinical symptoms. The serum prevalence of HEV infection was not statistically significantly associated with any of the above factors. The results of this study will help clarify the epidemiological status of HEV infection in patients with thalassemia major and contribute to the understanding of pediatric hematologists and other health professionals.

However, this study had several limitations that should be acknowledged. These include its single-center design, reliance solely on ELISA without molecular confirmation (e.g., PCR), and a relatively small sample size. Future multicenter studies with larger sample sizes and molecular testing are warranted to better estimate the prevalence of this viral infection and to validate our findings.

Acknowledgment

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author's contribution

S.K. and M.V.S. contributed to conceptualization. M.S. and H.G.H. contributed to methodology. M.M. contributed to sampling. H.G.H. and M.S. contributed to statistical

analysis and investigation. M.V.S. contributed to writing – original draft preparation. M.V.S., M.N., and M.M. contributed to writing – review and editing.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Ethical Statement

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