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Research Article

Distribution of thalassemia trait in Balikesir Province according to trait type and age group

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Abstract

Objectives: The aim of this study was to determine the prevalence of the thalassemia disease group in Balikesir Province, Turkey.

Methods: Blood samples provided by 11,558 individuals (5675 males and 5883 females) aged 3-90 years between May 15, 2018 and September 30, 2019 for laboratory analysis at the Balikesir Provincial Public Health Laboratory were included in the study. Hemoglobin chain analyses were carried out using the high-performance liquid chromatography (HPLC) method. The data obtained were analyzed retrospectively.

Results: The level of hemoglobin (Hb) A2 was >3.5% in 591 (5.11%) of the total study group and these individuals were identified as β-thalassemia carriers. The prevalence of the β-thalassemia trait was 5.76% in females and 4.44% in males. A total of 792 cases (446 female and 346 male) had a result outside the normal range: 74.6% were identified as thalassemia carriers, 9.4% had isolated low Hb A2, 12.3% had isolated Hb F elevation, and 3.8% had total abnormal hemoglobin values.

Conclusion: The prevalence of β-thalassemia trait (5.11%) in the study group was extrapolated for the general population of Balikesir (2019 population: 1,228.620) and it was estimated that there were 62,782 potential carriers in the province.

Keywords: Balikesir, hemoglobinopathies, prevalence, thalassemia carrier

Inherited hemoglobin (Hb) disorders can be divided into 2 principal groups: thalassemia syndromes and structural Hb variants (abnormal Hb). Alpha (α), beta (β) and delta beta (δβ) thalassemia are the primary types of clinical significance. The most common and clinically significant structural hemoglobin variants are Hb S, Hb E, Hb C, and Hb D. The inheritance of such disorders follows a typical Mendelian-recessive pattern; asymptomatic heterozygous parents or carriers pass on a copy of a defective gene to their children [1, 2]. Patients with thalassemia syndrome can have a wide variety of clinical manifestations, ranging from asymptomatic presentation to severe anemia and complications in many organ systems requiring lifelong blood transfusions [3].

Thalassemia is one of the most common monogenic diseases in the world. It is estimated that about 70,000 children with various types of thalassemia are born each year [4]. More than 90% of patients with these disorders live in low- and middle-income countries [5]. Approximately 79% of affected infants are born in Asian countries [6]. The prevalence of β-thalassemia is high in Mediterranean countries, Southeast China, Asia, the Middle East, and the Far East, as well as in northern Africa and South America [7]. However, continued worldwide migration has led to spread of these diseases to large, multiethnic Western cities as well, and the incidence of thalassemia in Europe has been estimated at 1.5% [8, 9].

Some 5.2% of the world population (more than 360 million individuals) carry a Hb variant, with a β-thalassemia trait frequency of 1.5%. There are approximately 1.5 million thalassemia carriers and approximately 5500 patients with thalassemia and other hemoglobinopathies in Turkey. Although the rate of car-

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riers in Turkey is 2.1%, the rate rises to 10% in some regions of the country. The rate of thalassemia carriers in some of the 81 provinces of Turkey is provided in Table 1 [7, 10].

Screening studies for sickle cell anemia (SCA) in Turkey have shown that the prevalence of this genetic disease is high in some regions. The total number of patients with SCA in the country has been reported to be approximately 1200 and the prevalence of Hb S has been estimated to be 0.03%. According to data provided by the Ministry of Health and the National Hemoglobinopathy Council, the frequency of Hb S carriers is 10% in Adana, 10.5% in Antakya, 13.6% in Mersin, 2.5% in Antalya, 0.5% in Diyarbakir, and 0.5% in Mugla [11].

Despite the accumulation of substantial knowledge, there are still some difficulties identifying carriers [12]. The most reliable methods to diagnose thalassemia are the quantitative determination of Hb A2, Hb F, and globin chain ratios, and DNA studies for specific mutations. The use of high-performance liquid chromatography (HPLC) and DNA studies in recent years has helped to identify abnormal hemoglobin easily and efficiently [13, 14].

Thalassemia major, which has a high mortality rate and no effective treatment method other than bone marrow transplantation, has a heavy financial burden for society and families, and seriously affects the quality of life of patient families and the general population [15, 16]. Two strategic plans should be considered for the prevention and control of thalassemias. The first is to offer the optimal treatment to improve patient quality of life. The second is to prevent new cases of thalassemia diseases, which includes carrier screening, genetic counseling, and prenatal diagnosis for couples at risk. This approach is very cost-effective and has proven remarkably successful in reducing the frequency of thalassemia in many countries [17].

Thalassemia is considered an important health issue in Turkey. The Ministry of Health recognized the problem with the "Fight against Hereditary Blood Diseases Law" in 1993, and a national hemoglobinopathy control program was enacted in 2002 and came into force 2003 in 33 high-risk provinces [18].

The aim of this study was to contribute to the literature by determining the prevalence of carriers and the risk of disease in Balikesir province in an effort to help address the significant burden of treatment costs for both families and the state, since this disease group is an important cause of morbidity and mortality.

Materials and Methods

The Ufuk University Non-Invasive Clinical Research Evaluation Committee granted ethics approval for this retrospective study on July 8, 2020 (no: 10). In addition, approval for the use of the patient analysis results was granted by the Scientific Research Requests Commission of Balikesir Provincial Health Directorate on December 25, 2020 (no: E.2993). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Hb variant analysis tests were performed by the Balikesir Provincial Public Health Laboratory between May 15, 2018 and September 30, 2019 for premarital screening at family health centers in Balikesir (9280 samples), and upon the request of clinicians at Balikesir Ataturk City Hospital (1585 samples), and Balikesir State Hospital (693 samples) for a differential diagnosis between iron deficiency anemia and the presence of abnormal Hb.

The data of 11.558 individuals (5675 men and 5883 women) aged 3-90 years were included in the study, and the Hb chain analysis results were evaluated. Foreign nationals were excluded.

The blood samples were collected from each individual in a tube with 2 mL K2-ethylenediaminetetraacetic acid at any time of the day and without fasting. They were transferred to the Balikesir Provincial Public Health Laboratory using a sample transport container under the appropriate conditions.

The Hb variant analysis was conducted using the β-thalassemia short mode of the Bio-Rad Variant II system (Bio-Rad Laboratories, Inc., Hercules, CA, USA) and the HPLC method using the instrument manufacturer's solutions to obtain a positive identification of Hb and Hb variants. The reference

Table 1. β-thalassemia trait rates in some provinces of Turkey

Province	β-Thalassemia carrier rate %	Province	β-Thalassemia carrier rate %
Adana	3.0-13	Kahramanmaras	2.35
Adiyaman	1.91	Kayseri	1.71
Antalya	5.7-10.7	Kirklareli	3.06
Bursa	2.6	Kocaeli	0.89
Edirne	6.44	Konya	2.0
Elazig	0.5	Kutahya	5,02
Erzurum	0.68	Mersin	2.04
Gaziantep	1.84	Mugla	4.8
Hatay	7.9	Van	2.6
Izmir	2.1-3.0		

range for Hb A2 is usually 2.0% to 3.3% in normal subjects, and the Hb A2 levels of β-thalassemia carriers are generally >3.5% [19]. In this study, we considered a value of 2%-3.5% as the limit value for Hb A2 and defined patients with a Hb A2 value of >3.5% as carriers of β-thalassemia. Values of <2% were used as the limit for Hb F and >80% was the limit value for Hb 0 in this study. In addition, Hb S, C, D, E, and other Hb variants were also evaluated. The red blood cell indices used for the assessment were analyzed using a Sysmex XN1000 device (Sysmex Corp., Kobe, Japan). A lower limit of 13.5 g/dL for males and 12 g/dL for females was used for the complete blood count results, values of <80 fL were used as the limit value for mean corpuscular volume (MCV) in both genders, and a value of 27 pg was considered the limit value for mean corpuscular hemoglobin (MCH). Two levels of control were used for analysis on all of the devices in order to provide optimal conditions.

Thalassemia and suspected thalassemia samples were examined and the prevalence of hereditary Hb disorders by age, gender, and region was identified and analyzed.

Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) and Microsoft Office Excel 2019 (Microsoft Corp., Redmond, WA, USA) software. First, distribution was examined in order to assess correlations. An independent samples t-test was used to determine correlations between the data of the normally distributed groups, and the Mann-Whitney U test was used to determine correlations between the data of non-normally distributed groups. A p value of <0.05 was considered statistically significant.

Results

Of the 11,558 individuals included in the study (5883 [50.9%] female and 5675 [49.1%] male), 591 (5.11%) had an Hb A2 level >3.5% and were identified as β-thalassemia carriers. Of the 591 β-thalassemia carriers, 339 (57.36%) were female and 252 (42.64%) were male. Based on these data, the prevalence of the β-thalassemia trait in this study was 5.76% in females and 4.44% in males.

When the prevalence value (5.11%) of the β-thalassemia trait was extrapolated to the general population of Balikesir (2019 population: 1,228,620), the number of potential carriers in the province was estimated to be 62.782.

The MCV and/or MCH value was below the limit value in 28 (21 female, 7 male) of 74 patients with a low isolated Hb A2 level (<2%), and the MCV and MCH values of 48 (21 female, 25 male) individuals were normal, according to the defined limit values.

The numerical distribution of the patients by gender and age group and the prevalence throughout the province is shown in detail in Table 2.

Table 2. Distribution of the study patients by gender and age group

Cases	Age group (years) 3-15	Age group (years) 16-30	Age group (years) 31-45	Age group (years) 46-60	Age group (years) 61-75	Age group (years) 76-90	Total
Total	397 (M:192-F:205)	7543 (M:3573-F:3970)	2647 (M:1423-F:1224)	669 (M:333-F:336)	241 (M:125-F:116)	61 (M:29-F:32)	11558 (M:5675-F:5883)
Abnormal case	108 (M:53-F:55)	330 (M:137-F:193)	173 (M:76-F:97)	105 (M:49-F:56)	58 (M:23-F:35)	18 (M:8-F:10)	792 (%6.85) (M:346-F:446)
Normal case	289 (M:139-F:150)	7213 (M:3436-F:3777)	2474 (M:1347-F:1127)	564 (M:284-F:280)	183 (M:102-F:81)	43 (M:21-F:22)	10766 (93.15) (M:5329-F:5437)
β-thalassemia carrier	93 (M:45-F:48)	210 (M:91-F:119)	132 (M:53-F:79)	85 (M:35-F:50)	54 (M:21-F:33)	17 (M:7-F:10)	591 (%5.11) (M:252-F:339)
Isolated Hb A2 low	3 (M:2-F:1)	42 (M:15-F:27)	18 (M:10-F:8)	7 (M:3-F:4)	4 (M:3-F:1)	0	74 (% 0.64) (M:32-F:42)
Abnormal presence of Hb (total)	0	20 (M:9-F:11)	8 (M:5-F:3)	1 (F:1)	0	1 (M:1)	30 (% 0.26) (M:15-F:15)
Isolated Hb F height	12 (M:6-F:6)	58 (M:22-F:36)	15 (M:8-F:7)	12 (M:11-F:1)	0	0	97 (% 0.84) (M:47-F:50)
Hb Shelby	0	3 (M:2-F:1)	2 (M:1-F:1)	0	0	0	5 (% 0.04) (M:3-F:2)
Hb S	0	7 (M:2-F:5)	2 (M:1-F:1)	1 (F:1)	0	0	10 (% 0.09) (M:3-F:7)
Hb C	0	3 (M:2-F:1)	1 (M:1)	0	0	0	4 (% 0.03) (M:3-F:1)
Hb D	0	5 (M:2-F:3)	2 (M:1-F:1)	0	0	1 (M:1)	8 (% 0.07) (M:5-F:3)
Hb C+O Arab	0	0	1 (M:1)	0	0	0	1 (% 0.009) (M:1)
Hb Hasharon	0	1 (K:1)	0	0	0	0	1 (% 0.009) (K:1)
Hb Setif	0	1 (F:1)	0	0	0	0	1 (% 0.009) (F:1)

F: Female; Hb: Hemoglobin; M: Male.

A total of 792 patients (446 females, 346 males) with test values outside the limit range for the analyzed parameters were classified as abnormal cases. Of these 792 patients, 74.6% (n=591) had a β-thalassemia trait, 9.4% (n=75) had a low isolated Hb A2 value, 12.3% (n=97) had an elevated isolated Hb F value, and 3.8% (n=30) had a total abnormal Hb result. Of the 30 total abnormal cases, 16.7% were determined to be Hb Shelby, 33.3% as Hb S, 13.3% as Hb C, 26.7% as Hb D, 3.3% as Hb C+O Arab, 3.3% as Hb Hasharon, and 3.3% as Hb Setif. The distribution of the abnormal hemoglobin types among the total abnormal cases was Hb Shelby: 0.63%, Hb S: 1.27%, Hb C: 0.51%, Hb D: 1.01%, Hb C+O Arab: 0.13%, Hb Hasharon: 0.13%, and Hb Setif: 0.13%.

Examination of the distribution of the abnormal hemoglobin rate by age group revealed an abnormal Hb rate of 28%, and particularly among those between the ages of 3-15 years (total number of participants aged 3-15: 308; number of participants aged 3-15 with abnormal Hb:108). β-thalassemia carrier status was detected in 93 of 108 participants aged 3-15 years with abnormal Hb findings. The high rate of abnormal Hb and β-thalassemia carriage detected in the 3-15 age group may be due to the fact that the samples of the patients in this group were not sent randomly for screening purposes, but by clinicians in hospitals with a suspicion of abnormal Hb.

Examination of the differences between genders of the parameters in groups with a normal distribution of β-thalassemia carriers revealed statistically significant differences in the Hb, hematocrit and red blood cell count tests ($p<0.001$ for all). Examination of the gender differences of non-normally distributed parameters yielded a statistically significant difference in the HbA2, red cell distribution width, and ferritin levels (respectively, $p=0.019$, $p<0.001$, p0.001). When evaluating the differences in parameters between the sexes, it should be taken into account that there are normal significant differences in the reference intervals between males and females, especially in blood count parameters. In addition, a statistically significant difference was also observed between the mean rank of the HbA2 parameter, which had the same cut-off value (>3.5%) for both genders.

The correlations of some laboratory parameters of β-thalassemia carriers between genders and their p values are illustrated in detail with normally distributed parameters in Table 3 and non-normally distributed parameters in Table 4.

Table 3. Correlation of normally distributed tests of β-thalassemia carriers by gender

Tests	Mean±SD	Male (Mean±SD)	Female (Mean±SD)	p
Hb (n=281)	12.06±1.54	13.2±1.35	11.24±1.09	<0.001
Hct (n=281)	39.64±4.59	43.12±3.86	37.17±3.27	<0.001
RBC (n=281)	6.04±0.72	6.52±0.62	5.69±0.57	<0.001
Iron (n=60)	77.5±35.47	88.35±36.23	72.08±34.25	0.094

Hb: Hemoglobin; Hct: Hematocrit; RBC: Red blood cell.

Table 4. Correlation of non-normally distributed tests of β-thalassemia carriers by gender

Tests	Gender	n	Mean rank	Sum of ranks	U	Z	p
Hb F (n=591)	Male	252	291.74	73519	41641	-0.542	0.588
	Female	339	299.17	101417			
Hb A2 (n=591)	Male	252	315.03	79388.5	37917.5	-2.34	0.019
	Female	339	281.85	95547.5			
Hb A0 (n=591)	Male	252	280.95	70798.5	38920.5	-1.848	0.065
	Female	339	307.19	104137.5			
MCV (n=281)	Male	117	146.95	17193	8898	-1.037	0.3
	Female	164	136.76	22428			
MCH (n=281)	Male	117	147.69	17280	8811	-1.166	0.243
	Female	164	136.23	22341			
RDW (n=281)	Male	117	161.72	18921.5	7169.5	-3.612	<0.001
	Female	164	126,22	20699.5			
Iron binding capacity (n=55)	Male	17	22.38	380.5	227.5	-1.74	0.082
	Female	38	30.51	1159.5			
Ferritin (n=66)	Male	19	47	893	190	-3.633	<0.001
	Female	47	28.04	1318			

Hb: Hemoglobin; Hct: Hematocrit; MCH: Mean corpuscular hemoglobin; MCV: Mean corpuscular volume; RBC: Red blood cell; RDW: Red cell distribution width.

Discussion

This retrospective study of 11,558 participants in Balikesir revealed abnormal Hb results of β-thalassemia carrier: 5.11%, isolated Hb A2 low: 0.64%, isolated HbF high: 0.84%, presence of Hb Shelby: 0.04%, presence of Hb S: 0.09%, presence of Hb C: 0.03%, presence of Hb: D 0.07%, presence of Hb C+O Arab: 0.009%, presence of Hb Hasharon: 0.009%, and presence of Hb Setif: 0.009%.

Guler et al. [20] reported a thalassemia trait in 261 (130 male, 131 female) and Hb S in 59 (31 male, 28 female) in a group of 11.040 (5520 male, 5520 female) individuals screened before marriage in Kahramanmaras Province between March 2006 and February 2007; a rate of 2.35% for thalassemia and 0.54% for Hb S (SCA carrier).

In 2001, Bolaman et al. [21] reported on a study of 14,200 participants (aged 14-54 years; 50% female and 50% male) in Denizli Province and found a β-thalassemia trait prevalence of 2.2%. The authors noted that some 22,000 people in Denizli were potential carriers. A comparison of the prevalence of a thalassemia trait in Balikesir Province in our study (5.11%) with that seen in Kahramanmaras and Denizli suggests that the rate is higher in Balikesir.

In a 2010 study in Adana, Guvenc et al. [22] detected an abnormal hemoglobin level in 205 (6.83%) individuals in a group of 3000. They found heterozygous Hb S in 122 (93.65%), Hb D in 7 (3.42%), and Hb E in 6 (2.93%). Among the 3000 individuals in the study, the prevalence of heterozygous Hb S was 6.4%, the prevalence of Hb D was 0.23%, and the prevalence of Hb E was 0.2%. A comparison of abnormal hemoglobin types seen in our study with the results of the research conducted by Guvenc et al. [22] indicates that the prevalence value of both Hb S (6.4% and 0.09%, respectively) and Hb D (0.23% and 0.07%, respectively) was greater in Adana than in Balikesir.

Research conducted by Etem et al. [23] in Usak in 2019, which included 3324 individuals (1672 [0.3%] female and 1652 [49.6%] male], revealed an Hb A2 level of >3.5% in 100 (3%) patients, 41 (41%) of whom were female and 59 (59%) were male, and were classified as β-thalassemia carriers. The authors reported a prevalence of the thalassemia trait of 2.45% in females and 3.57% in males. They detected Hb D in 6 patients (general population prevalence: 0.18%) but no Hb C and Hb S. Based on the prevalence value of the β-thalassemia trait they found (3%), they estimated that the potential number of carriers in Usak was 10,268 (2012 population: 342,269) [23]. A comparison of the prevalence of the β-thalassemia trait in Balikesir province observed in our study (5.11%) with the prevalence found in Usak province shows that the prevalence of β-thalassemia trait was higher in Balikesir, while the prevalence of Hb D was higher in Usak.

A 2014 study conducted by Oktay et al. [24] in the province of Hatay with a total of 70,226 participants (52% female and 48% male) (73% for premarital screening) found the β-thalassemia trait in 6%, SCA trait in 6.3%, α-thalassemia trait in 12.9%, Hb C trait in 0.15%, Hb D trait in 0.16%, Hb E trait in 0.21%, and other rare variants (Hb O-Arab, Hb Hasharon) in 0.04% of patients. A comparison of the results of their research and our study showed that the frequency of the β-thalassemia trait (5.11% and 6%, respectively), SCA trait (0.09% and 6.3%, respectively), Hb D trait (0.07% and 0.16%, respectively), Hb C trait (0.03% and 0.15%, respectively), and other rare variants (Hb O-Arab, Hb Hasharon) (0.018% and 0.04%, respectively) were higher in Hatay Province.

Conclusion

Our analysis of the data yielded a prevalence of the β-thalassemia trait in Balikesir province of 5.11%, which is above the average for Turkey, and given the population of the province (2019 population: 1,228.620), the number of potential carriers in the province is estimated to be 62.782. In terms of the presence of abnormal hemoglobin, the rate of abnormal Hb detected in our study was lower in Balikesir province than in other provinces we evaluated.

This study was conducted retrospectively with data obtained in the Provincial Public Health Laboratory, and interpretation of the results is limited by the fact that clinicians such as a hematology or internal medicine specialist could not be included, and a detailed clinical evaluation of the data could not be made. The addition of a clinical investigator would increase the scientific value of the research.

Confirmation of the HPLC results with a sickle cell test (Sickling test) for the diagnosis of patients with SCA would also be beneficial. Finally, DNA analysis and determination of abnormal Hb prevalence rates would provide useful information to support our data and hypotheses.

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Conflict of Interest: There is no conflict of interest between the authors.

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