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To Evaluation of Effectiveness of Chelatory Therapy in Patients with Talassemia

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Summary. The term "thalassemia" refers to a group of autosomal-recessive blood diseases charaeterized by a decrease in the synthesis of one of two types of polypeptide chains of globin (α or β), that form a molecule of adult hemoglobin(HbA, α2β2). This leads to a decrease in the filling of erythrocytes with hemoglobin and anemia. In Uzbekistan, the birth rate with this disease is 10-15 per year. At present in the Republic of Uzbekistan, 184 patients with thalassemia are registered at the Research Institute of Hematology and Blood Transfuzion at the Dispensary.

Key words: anemia, hemoglobinopathy, thalassemia, hemosiderosis

Dolzarblik Hemoglobinopathies are among the most common diseases on earth. According to WHO data, in 2006, approximately 7% of the population was considered a carrier of hemoglobinopathy. Every year, from 300,000 to 500,000 carriers with a severe homozygous form of this pathology are born, and 70% of them are sickle cell hemolytic anemia. Of all the babies born with hemoglobinopathy, 60,000-70,000 are born with thalassemia, and about 50,000 of them die at an early age [4,6].

In the United States, 2 million people with hemoglobin beta-chain mutations are registered, and most of them are patients with a heterogeneous population of clinically high penetrance of the mutant gene [2].

Thalassemia is common in Asian countries (Azerbaijan, Turkey, Greece, Malaysia, Turkmenistan, Tajikistan, Uzbekistan, etc.), Caucasus, Dagestan, Moldavia, Arab and African countries. In these countries, consanguineous marriages multiply the number of children born with the risk of thalassemia [5].

b - thalassemia has the highest rate among the population of Azerbaijan compared to other genetic diseases, and the number of heterozygous carriers is 15-20%. About 200 babies with the homozygous form of β-thalassemia are born every year in the Republic. As a result of a selective study of 30,000 people in all Republics of Central Asia and the Caucasus, the average frequency of β-thalassemia was about 4% (the highest in Azerbaijan 9-10%, the lowest 1-2% in Turkmenistan) [1].

The first report on β-thalassemia in the countries of the former USSR was compiled by K. V. Stepanova in 1956. Later, information on the prevalence of thalassemia in the countries of Azerbaijan, Georgia, Tajikistan, the Caucasus, and Uzbekistan was presented [3].

In Uzbekistan, marriage between blood relatives has been going on for many years. This leads to the accumulation of hereditary pathological genes in a certain area and increases the number of children born with the risk of hemoglobinopathy several times [6,5].

In 1991, according to D. A. Settarova, the highest rate of carriers of the heterozygous form of thalassemia in Uzbekistan was determined in the Fergana region (6%) [3].

Summarizing the results of the analysis of the geographical distribution of thalassemia, it should be noted that this disease is present in all countries of the world and its highest frequency is observed among the population of a wide geographical area covering the Mediterranean basin and the countries of the Middle East [4].

The purpose of the study. A prospective analysis of patients with thalassemia and evaluation of the efficacy of chelator therapy.

Materials and styles. For this study, 50 patients were selected as a result of a prospective analysis of thalassemia patients registered in the "Anemia Center" of the Scientific Research Institute of Hematology and Blood Transfusion of UzRSSV for 2019-2021. (Table 1)

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Table 1
Description of patients by gender

Sex	Number	Nourishment
Son	35	70%
Girl	15	30 %
Total	50	100%

According to the above table, 35 (70%) of patients with thalassemia were boys, 15 (30%) were girls.

Table 2
Distribution of thalassemia patients by age

Age	Number of patients		% (in percent)	
	Son	Girl	Son	Girl
0-5 years old	19	9	38%	18%
6-10 years old	10	2	20%	4%
11-15 years old	5	1	10%	2%
16 years and older	1	3	2%	6%
Total:	35	15	70%	30%
	50		100%	

Accordingly, the number of patients aged 0-5 is 28 (56%), 19 (38%) are boys, 9 (18%) are girls. The number of patients aged 6-10 is 12 (24%) - 10 (20%) are boys, 2 (4%) are girls. The number of patients aged 11-15 is 6 (12%) - 5 (10%) are boys, 1 (2%) are girls. There were 4 (8%) patients over 16 years of age, 1 (2%) boys, 3 (6%) girls.

The anamnesis, clinical symptoms at the time of arrival, laboratory and physical examination results of the patients selected for the study confirm the diagnosis of thalassemia.

Due to insufficient diagnostic capabilities in Uzbekistan, methods of examination and treatment have not been fully studied. There are still shortcomings in the field of diagnosis, laboratory-instrumental tests and treatment of thalassemia. Application of the results of scientific research conducted in Uzbekistan in this direction in practical medicine, i.e. wide application of chelator therapy among thalassemia patients in the primary link of the health care system, prevention and early treatment of hemosiderosis, newly obtained information It is important to publish the data in popular scientific journals and educational programs, to apply chelator therapy not only to thalassemia patients, but also to other patients who constantly need transfusions.

The Scientific Research Institute of Hematology and Blood Transfusion is the primary diagnostic center for diagnosing hemolytic anemias in the Republic of Uzbekistan. After the diagnosis of thalassemia, patients are taken to the "Anemia Center" under the supervision of a dispensary ("D") and treated in hematological departments in their area of residence. Until then, the only way to treat thalassemia and prolong the life of patients in our Republic was to apply washed or frozen erythrocyte mass to the patient and fight against infectious complications. In the last decade, as a result of scientific research in medicine, chelator therapy was developed in order to prevent hemosiderosis. The mechanism of action of this therapy is to remove excess iron while preserving the necessary iron in the body [6].

Examinations were conducted in 2019 - 2021 in 165 of 204 b-thalassemia patients (average age 5.8±2.4) registered at the Scientific Research Institute of Hematology and Blood Transfusion of UzRSSV.

Table 3
Distribution of patients in the Republic of Uzbekistan

№	Cities and regions	*Number of registered patients diagnosed with thalassemia*	*Number of patients treated with chelator therapy*
1	Tashkent city	*15*	*15*
2	Tashkent region	*10*	*9*

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3	Andijan region	*4*	*2*
4	Fergana region	*5*	*5*
5	Namangan region	*6*	*4*
6	Syrdarya region	*4*	*2*
7	Jizzakh region	*9*	*8*
8	Khorezm region	*8*	*7*
9	Republic of QQ	*8*	*7*
10	Navoi region	*13*	*8*
11	Bukhara region	*21*	*21*
12	Samarkand region	*18*	*18*
13	Kashkadarya region	*27*	*27*
14	Surkhandarya region	*56*	*32*
	Total	*204*	*165*

Of the remaining 39 patients, 27 are under 2 years of age, 8 are unable to take the drug due to hypersensitivity to the drug, and 4 are drug-rejecting patients, and we randomly selected 50 thalassemia patients receiving chelator therapy. and conducted research to study the mechanism of action of the drug.

According to distribution in regions, patients taking the drug: 15 in Tashkent city, 9 in Tashkent region, 2 in Andijan region, 5 in Fergana region, 4 in Namangan region, 2 in Syrdarya region, 8 in Jizzakh region, 7 in Khorezm region. , 7 in the Republic of Karakalpak, 8 in the Navoi region, 21 in the Bukhara region, 18 in the Samarkand region, 27 in the Kashkadarya region, 32 in the Surkhandarya region. So, the total number of patients and the number of patients receiving the drug were the highest in Surkhandarya, Kashkadarya, Bukhara, Tashkent regions and Tashkent city.

Research conducted on patients made it possible to determine the prevalence of β-thalassemia patients in our regions, their distribution by age and gender (Table 4).

Table 4

№	Indicators	3-5 years old		3-5 years old		3-5 years old		3-5 years old n/%		Total
		Son	**Girl**	**Son**	**Girl**	**Son**	**Girl**	**Son**	**Girl**	
1.	**Tashkent region and Tashkent city**	3	-	1	3	2	1	-	2	12
		6%		2%	6%	4%	2%		4%	24%
2.	**Fergana region**	-	-	1	-	-	-	-	1	2
				2%					2%	4%
3.	**Namangan region**	1	-	1	-	-	-	-	-	2
		2%		2%						4%
4.	**Andijan region**	-	-	1	-	-	-	-	-	1
				2%						2%
5.	**Jizzakh region**	-	-	-	-	-	-	1	-	1
								2%		2%
6.	**Samarkand region**	-	-	1	2	1	-	1	-	5
				2%	4%	2%		2%		10%
7.	**Surkhandarya region**	2	1	4	1	1	-	1	-	10
		4%	2%	8%	2%	2%		2%		20%

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8.	**Kashkadarya region**	-	-	2	1	2	-	-	-	5
				4%	2%	4%				10%
9.	**Bukhara region**	1	-	-	2	1	-	1	-	5
		2%			4%	2%		2%		10%
10	**Navoi region**	-	-	3	1	-	-	-	-	4
				6%	2%					8%
11	**Khorezm region**	1	-	1	-	-	-	1	-	3
		2%		2%				2%		6%
	Total	8	1	15	10	7	1	5	3	50
		16%	2%	30%	20%	14%	2%	10%	6%	
		9		25		8		8		100%
		18%		50%		16%		16%		

According to the above table, 35 (70%) of the patients with thalassemia were boys and 15 (30%) were girls, i.e. the ratio was 2.33:1.

Accordingly, the number of patients under 3-5 years of age is 9 (18%), 8 (16%) are boys, 1 (2%) are girls. The number of patients aged 6-10 is 25 (50%) - 15 (30%) are boys, 10 (20%) are girls. The number of patients aged 11-15 is 8 (16%) - 7 (14%) are boys, 1 (2%) are girls. 8 (16%) patients over 16 years old - 5 (10%) boys, 3 (6%) girls. The patients were aged from 3 to 33 years (median - 10.58 ± 1.85 years). In the Uzbek population, 25 (50%) patients under 6-10 years old with thalassemia. The age ratio of the patients was 1,125:3,125:1:1.

According to distribution in regions: 12 (24%) in Tashkent region, 10 (20%) in Surkhandarya region, 5 (10%) in Samarkand region, 5 (10%) in Kashkadarya region, 5 (10%) in Bukhara region , 4 (8) in Navoi region, 3 (6) in Khorezm region, 2 (4) in Fergana region, 1 (2) in Andijan region, 2 (4) in Namangan region, Jizzakh region 1 (2%). So, the number of patients was the highest in Tashkent region (24%) and Surkhandarya regions (20%).

Family genetic studies conducted in our observations allowed to identify consanguineous marriages of β-thalassemia carriers (Fig. 1)

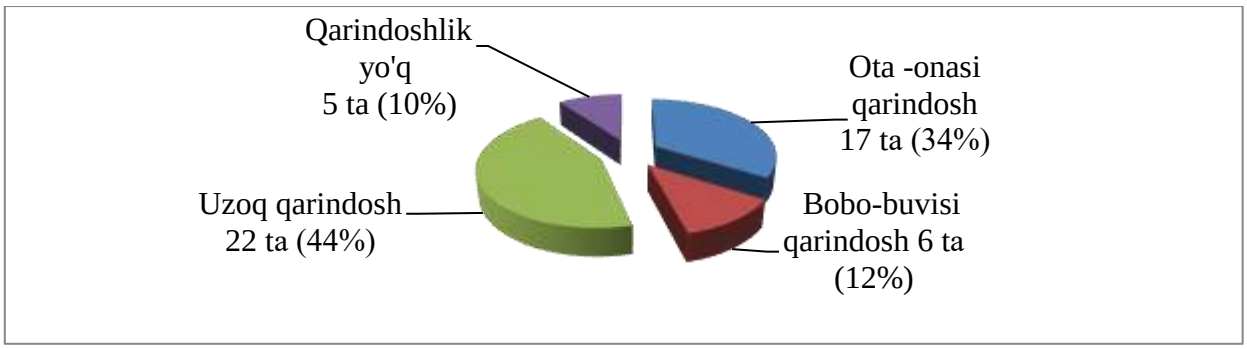

Figure 1. Indicators of consanguineous marriage

Children born from marriages between relatives: parents related - 17 (34), grandparents related - 6 (12), distant relatives - 22 (44), unrelated q – 5 (10%). In a study of consanguineous birth rates, thalassemia was slightly more common among children born to distant consanguineous (44%) and consanguineous (34%) children. Clinical observations of patients with β-thalassemia have shown that homozygous β-thalassemia manifests as a severe form of the disease known as thalassemia major or Cooley's anemia (54, 34, 29, 112, 113).

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Clinical manifestations of homozygous thalassemia are noted in the first year of a child's life (34, 16, 44, 107, 108). A lack of body weight, paleness of the skin and mucous membranes, and an increase in body temperature not related to any infectious diseases are noted. In the second year of the child's life, splenomegaly, yellowing of the skin and mucous membranes, increasing body weight deficiency in all patients, enlargement of the abdominal cavity, a characteristic appearance - mongoloid face (flattened nose, bulging protruding cheek, narrowing of the eye cavity) is evident (29, 14, 15, 18). The skull is deformed: the crown and nape of the skull are slightly larger than the temples and forehead (domed head). Changes in the bones of the face, deepening of the upper palate leads to uneven placement of teeth. A characteristic brown pigmentation of the skin occurs around the eyes, at the roots of the hair, at the base of the nails and in other places. A network of subcutaneous veins is visible on the head. According to X-ray data, the patient's children have a change in the skull or the symptom of a hedgehog - "head with a dragonfly", hyperplasia of the cortical layer in long tubular bones (20, 29, 32, 34).

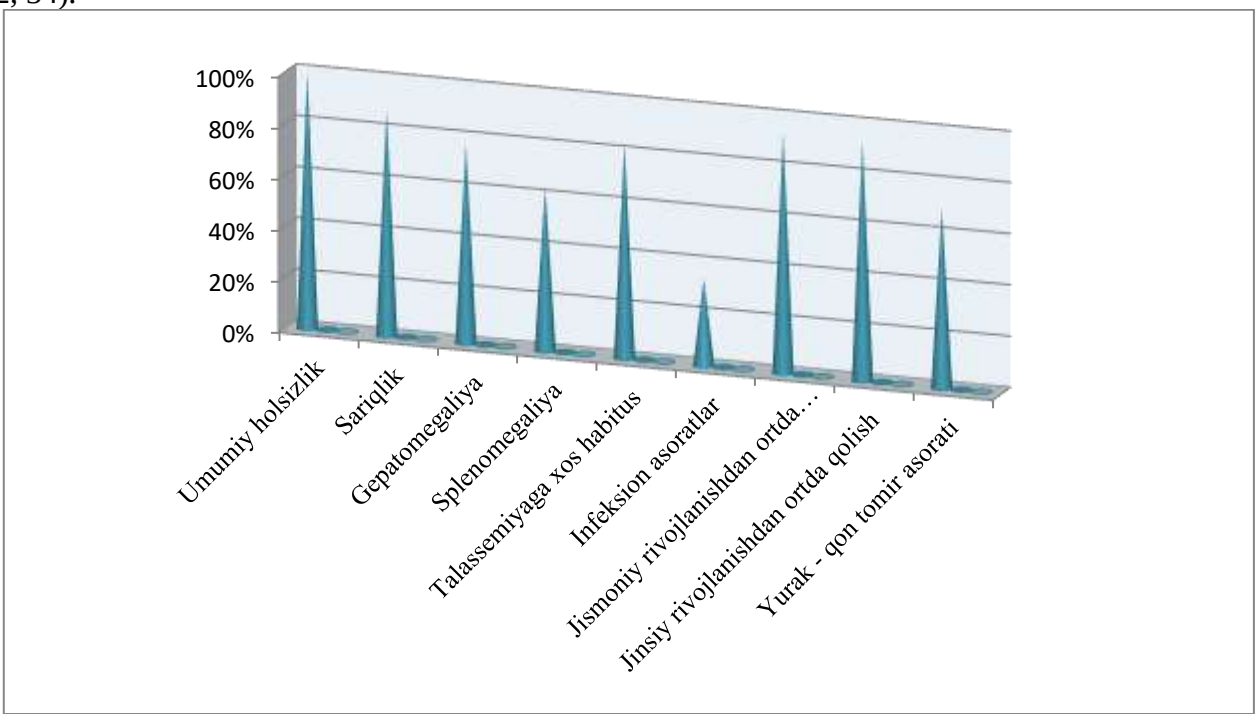

Figure 2. Frequency of clinical symptoms and disease complications before chelation therapy in thalassemia patients (2019y).

General weakness was observed in 50 patients (100%), jaundice - 44 patients (88%), thalassemia-specific habitus - 42 patients (84%), hepatomegaly - 39 patients (78%), splenomegaly (splenoectomy in 18 patients procedure was performed, this symptom was positive in all other patients) - 32 (64%), physical - 47 (94%) and sexual - 47 (94%) delayed development, infectious complications - 17 (34%) and heart - vascular complications - 35 cases (70%) were studied.

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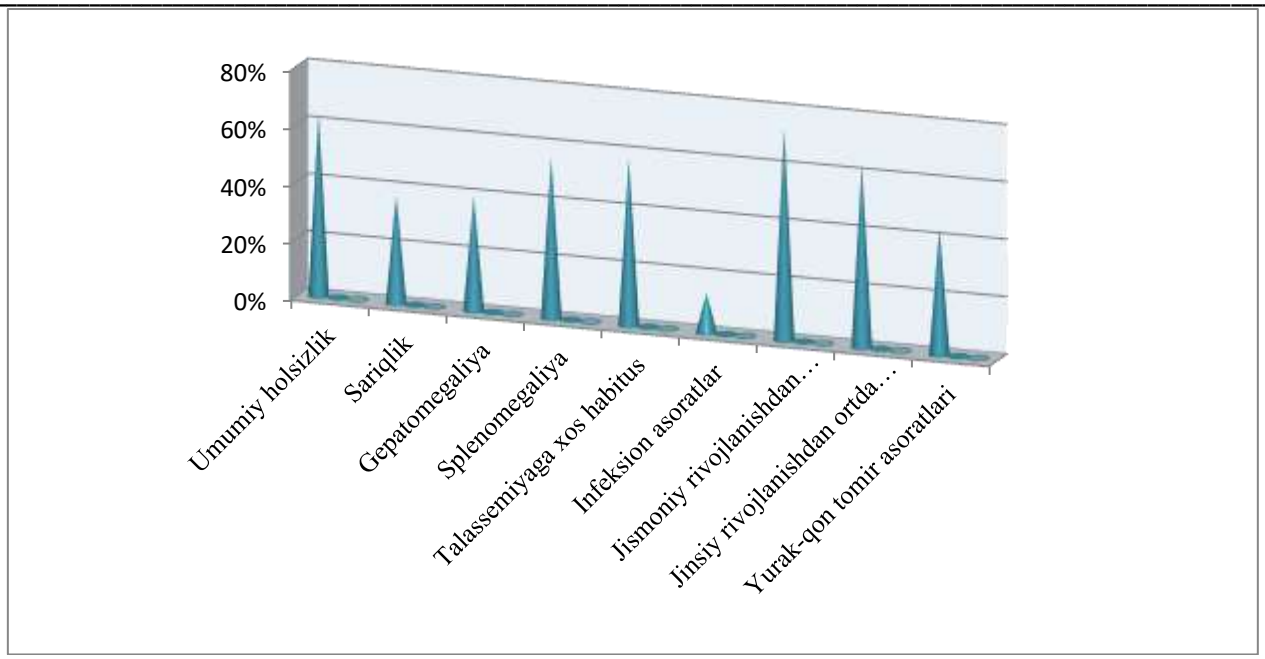

Figure 3. Frequency of clinical signs and complications of the disease after chelation therapy in thalassemia patients (2021y).

General weakness - 27 (54), jaundice - 19 (38), thalassemia specific habitus - 29 (58), hepatomegaly - 20 (40), splenomegaly - 28 (56), physical - 37 (74%) and sexual - 32 (64%) delayed development, infectious complications - 7 (14%) and cardiovascular complications - 22 (44%) were studied. When comparing the frequency of clinical signs and complications before and after chelation therapy in patients, general weakness - 1.85; jaundice - 2.3; thalassemia-specific habitus - 1.45; hepatomegaly – 1.95; splenomegaly – 1.14; lagging behind in physical development - 1.27; lag behind sexual development - 1.47; infectious complications - 2.43 and cardiovascular complications decreased by 1.59 times. This confirms the significant reduction of clinical symptoms that disturb patients under the influence of chelator therapy.

Conclusions.

1. In Uzbekistan, the majority of patients with thalassemia are children from 1 to 5 years old - 56%, thalassemia is diagnosed twice as often among boys than among girls.
2. Most of the thalassemia patients were born from consanguineous marriages: mostly their parents or grandparents are related, distant relatives are less common.
3. Surkhandarya, Kashkadarya, Samarkand and Bukhara regions are the regions where thalassemia is most common, so it is necessary to increase the effectiveness of propaganda work to eliminate marriage between relatives among the population.
4. Thalassemia patients should undergo RT, as this therapy is the only method in the treatment and prevention of hemosiderosis. Clinical and laboratory indicators of patients improve as a result of CT

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