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First Cohort Study on Iron Chelation Therapy of Patients with Hemoglobinopathies Born from 1980-2014 Treated in the Main Diagnostic and Treatment Center of Hemoglobinopathies in Albania

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Abstract: ***Albania is affected by thalassemia and hemoglobin disorders. Chronic transfusion therapy plays an important role in the management of them but, inevitably leads to iron overload, which requires chelation therapy. The chelation therapy was regularly initiated at our center on 1998. The aim of this paper is to present a data comparison of the mean serum ferritin level of thalassemia major, sickle cell disease and thalaso-sickle cell disease patients born between 1980- 1997 with that of patients born between 1998-2014, as well as, to estimate the mortality rate between these two groups. This is the first study done on this subject in Albania. A cohort of 358 multi blood transfused patients born between 1980 - 2014 was studied. There was a significant reduced number of patients with high serum level of ferritin in the group born after 1998, which got chelation therapy from the beginning. Comparison of 17-year year mortality rate shows that mortality was significantly lower for those born after 1998.***

Keywords: β-thalassemia major, sickle cell disease, β-thalassemia-sickle cell disease, chelation therapy, serum ferritin level, mortality rate

1. Introduction

Thalassemia major and sickle cell disease are the two most widely disseminated hereditary hemoglobinopathies in the world. 1,2. The chronic transfusion therapy has played an important role in the management of hemoglobinopathies such as thalassemia and sickle cell anemia. 2-5. Repeated transfusions result in an excessive accumulation of iron in the body (iron overload), removal of which is achieved through iron chelation therapy. 3,6-8. Chelation therapy of deferoxamine, deferiprone, deferasirox or deferoxamine-deferiprone combination is required to reduce iron accumulation in target organs and the associated morbidity and mortality. 7-8. The goal of iron chelation has shifted from treating iron overload to preventing iron accumulation and iron-induced end-organ complications, in order to achieve a normal pattern of complication-free survival and of quality of life. New chelation options increase the likelihood of achieving these goals. 6. Several serum markers can be used to follow trends in a patient's iron status over time. Ferritin is the most frequently used measure as it is inexpensive, widely available, and reliable, with extensive clinical validation in monitoring iron status. 7,9-11.

Like most other neighboring coun`tries in the region, Albania is affected by thalassemia and hemoglobin (Hb) disorders. It is estimated that the overall carrier frequency of β-thalassemia and sickle cell anemia is about 7–8%. 12. The Haemoglobinopathies Center of the Department of Pediatrics at the University Hospital "Mother Theresa" in Tirana, is the main reference diagnostic and treatment center of Hemoglobinopathies in Albania. The chelation therapy was regularly initiated at our center in 1998.

The aim of this paper is to present a data comparison of the mean serum ferritin levels of thalasemia major, sickle cell disease and thalaso-sickle cell disease patients born between 1980 -1997 with that of the patients born between 1998-2014, as well as, to estimate the mortality rate between these two groups.

2. Patients and Methods

A cohort of 358 patients, born between 1980 and 2014 with β-thalassemia major (TM), sickle cell disease (SCD) and β-thalassemia-sickle cell disease (TSCD) were studied. The diagnosis was based on the clinical, hematological data and in some of them on genetic studies, too. Patients with intermediate thalassemia were excluded. All the patients in our center were followed up, transfused and treated with chelation therapy according to the specific protocols. In the study were included only multiple blood transfused patients of beta TM, TSCD, SCD.

The transfusion therapy with ABO and Rh(D) compatible blood was begun when hemoglobin level was less than 8 g/dL. The frequency of transfusions is usually one every three weeks. Treatment with chelation therapy was started when; serum ferritin level exceeded repeatedly 1000 ng/mL (~after 12 blood transfusions). Deferoxamine treatment was given as a daily subcutaneous injection (over 10 hours) at a dose of 20; 40; 50 mg/kg BW, 5 to 7 days per week. Adjustment of doses was based on testing of serum ferritin

level. The oral tablets (500mg) of deferiprone, were initiated at a daily dose of 75mg/kg, divided into 3 times /day doses. While in cases when the patient's serum ferritin level was greater than 2500 ng/mL, the dose was increased to a total daily dose of 100 mg/kg. While, in cases when the patient's serum ferritin concentration was greater than 3000 ng/mL, the patients were treated with a combination scheme of: Deferipron each day (3times/day) and Desferal subcutanous injections (3-4 times per week). Some of our patients were only treated with Deferasirox (EXJADE), 20-30mg/kg, once per day, too.

After initiation of the treatment, full blood count was assessed weekly in case when the patient was treated with Deferipron. In other treatment`s schemes, complete blood count was assessed when the patient received blood transfusion. Serum ferritin, liver and renal functions were assessed monthly. We collected all the patients` data during the treatment with blood transfusion and chelation therapy with deferoxamine, deferiprone and deferasirox. The Fisher exact or χ^2 tests were used to compare 2 or 3 or more groups, respectively. P values of or less than 0.05 were considered statistically significant.

3. Results

358 poly-transfused patients, born between 1980 and 2014 with β-thalassemia major (TM), sickle cell disease (SCD) and β-thalassemia-sickle cell disease (TSCD) were enrolled in this study. Entry into the cohort was defined as the date of birth. 228 (63.7%) patients were with TM, 77 (21.5 %) patients with SCD followed by 53 (14.8%) patients with TSCD. 197 (55%) patients respectively (137 of TM, 26 of TSCD, 34 of SCD) were born from 1 January 1980 to 31December 1997. 161 (45%) patients respectively (91 of TM, 27 of TSCD, 43 of SCD) were born from 1.1.1998 till 31.12.2014. p=0.03. According to mean serum ferritin level patients were classified into four groups: (1). <1000, (2). 1000-2000, (3). 2000-3000, (4). >3000. According to the diseases and the year of born, the levels of mean of serum ferritin are as it is shown in table1/fig 1. Of 197 patients born before 1 January 1998, 25 died (21 with TM, 1 with TSCD, 3 with SCD), while of 161 patients born after 1 January 1998, 4 (3 with TM, 1 with SCD) died. p = 0.01. Seventeen year death rate for patients born between 1980 and 1997 was 12.7% versus 2.5 % for those born between 1998 and 2014. Table 2 shows the number of dead patients classified according to the mean serum level of ferritin and years of birth. The age at time of death of patients according to the diagnosis and cohort (related to the years of getting chelation therapy) is presented at table 3.

4. Discussion

Hemoglobinopathies are inherited disorders characterized by anomalies of structure, function or production of globin chains. The most significant clinical disorders are β-thalassemia and sickle cell disease. The clinical management of these disorders engages regular blood transfusions. 1-5, 13. Although blood transfusions are important for patients with hemoglobinopathies, chronic transfusions inevitably lead to iron overload as humans cannot actively remove excess iron. The cumulative effects of iron overload lead to significant morbidity and mortality, if untreated. 13-14, 3-4. Chronic transfusions which make iron overload an important issue to be considered in the management of patients with TM and SCD, require chelation therapy to prevent it. 6-8,13. The aim of our study was the presentation of data regarding the benefit of chelation therapy in our patients, in decreasing serum ferritin related to the prevention of iron-induced end-organ failure and in the improved survival in TM, TSCD, SCD patients. 358 patients born from 1980-2014 were enrolled in our study. Date of birth was considered as the time of entry in the study. Regular iron chelation with was initiated at our center on 1998, year of dividing line of the patients in 2 groups. On the basis of year of birth, all the patients were divided in; the first group of 197 patients included those who were born before 1 January 1998 and the second of 161 patients those who were born after 1January 1998. The endpoint was 31 December 2014.

The degree of hemosiderosis was evaluated on the basis of the mean serum ferritin levels. 7, 9-11, 13, 15. Patients were divided into four groups: (1) (ferritin >3000 μg/L), 319 patients; (2) (ferritin: 2000 to 3000 μg/L), 146 patients; (3) (ferritin 2000-1000 μg/L) and (4) (ferritin <1000 μg/L). Treatment with chelation therapy according to the protocols/guidelines was started when serum ferritin level repeatedly crosses 1000 ng/ml. It consists in using alone either Deferoxamine, Deferiprone, Deferasirox or a combined therapy of Deferiprone and Desferrioxamine. 7, 13. The oral administration of iron chelation is welcome by patients who have problems with the discomfort of deferoxamine injections. 16. Both oral and intravenous iron chelators appeared to be associated with a fall in serum ferritin. 7-8, 11, 15-16. As demonstrated in table 1/fig.1, there is a significantly reduced number of patients with higher serum level of ferritin (>3000 μg/L, 2000 to 3000 μg/L) in the group born after 1998, which got chelation therapy from the beginning. There is an increased number of patients with lower serum level of ferritin (2000-1000 μg/L and <1000 μg/L) in the same group (born after 1998). These significant serum ferritin changes were observed in the overall groups of patients (table 1/fig.1) and in 2 disease subgroups (TM and TSCD table 1), except for SCD group (in which the change is not significant, table 1/fig.1). Group of patients with thalassemia which formed the largest cohort included in this study had a significant (p<0.000) reduction in serum ferritin levels. 8. As serum ferritin level is also affected by inflammatory processes in cases of SCD patients, this could be an explanation of a not significant reduction of it in this subgroup of our study. 8.

Based on our experience and data, we also underline that the doses of chelation therapy should be adjusted on the basis of ferritin levels measured monthly and in case of side effects of the chelating agents a close monitoring of the patient should be done. 7, 13,17.

Many of long-term studies of chelation therapy in hemoglobinopathies demonstrate that regular chelation therapy reduces iron-related organ damage and mortality. 14-15, 17. Comparison of 17-year year estimated mortality rate in our patients born between 1980 and 1997 with that of patients born between 1998-2014 shows that mortality was significantly higher for those born between 1980 and 1997

(n=25) than for those born between 1998-2014 (n=4), who had the benefit of chelation since the first years of life (table 2).7.

In the group of patients born before 1998, the most significant decrease in mortality was observed in those who have lower value of mean serum ferritin levels (table 2), underlining the fact that the ferritin levels can be also predictive of prognosis. 7. 18

The correlation of the age at time of death of patients with diagnosis and cohort (related to the years of getting chelation therapy) presented at (table. 3) stresses the fact the iron removal with chelation therapy should be started early in life. 16.

More than 90% of patients born after 1998 currently survive into adulthood. In the last few decades, the life expectancy of hemoglobinopathic patients has progressively increased, as reported by several groups in different countries 19-20.

5. Conclusions

This study provided the first data of the effect of chelation therapy in the mortality rates and survival of the Albanian patients with thalassemia and sickle cell disease. Our data and their comparison prove that the chelation therapy is an effective treatment in significantly reducing serum ferritin levels in multi blood transfused patients. This study confirms that: - serum ferritin levels can be used by clinicians as dose adjustments for treatments to reduce body iron levels as well as predictive of future prognosis; -an early start of iron chelation therapy significantly reduces mortality.

Even that a lot of different factors can be influencing, we conclude that the effectiveness of chelation therapy is a major influencing factor in prolonging and improving the quality of life of our patients.

Authorship contributions

E.N and M.T equally designed and wrote the study. A.M performed statistical analysis.

The Authors declare no conflict of interest.

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Tables/Figures

Table 1: Number of patients by cohort, diagnosis and mean ferritin level

Tb 1	Mean ferritin serum level			
	>3000	2000-3000	1000-2000	<1000
All patients born 1980-1997	44	128	25	0
All patients born 1998-2014	13	56	66	26
p=0.00				
TM patients born 1980-1997	27	93	17	0
TM patients born 1998-2014	2	24	45	20
p = 0.00				
TSCD patients born 1980-1997	6	18	2	0
TSCD patients born 1998-2014	2	13	8	4
p = 0.02				
SCD patients born 1980-1997	11	17	6	0
SCD patients born 1998-2014	9	19	13	2
p=0.27				

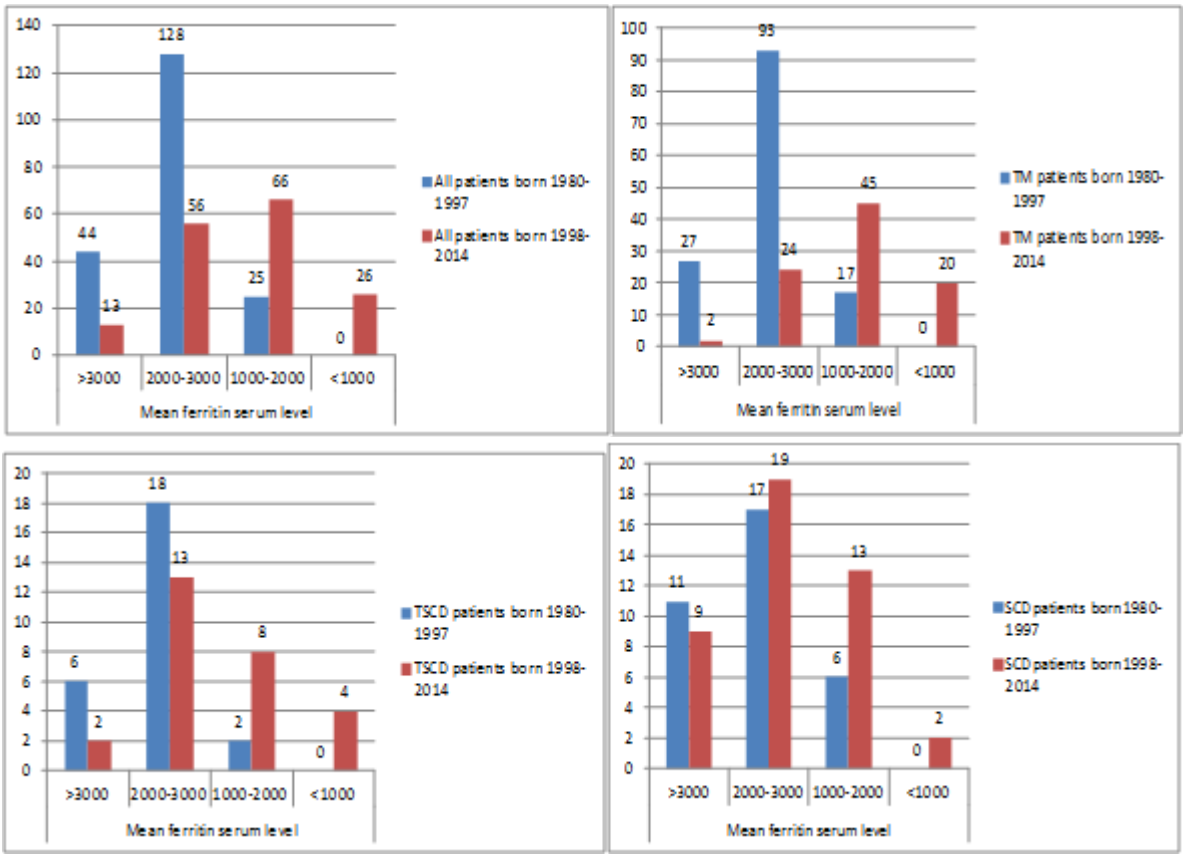

Figure 1: Number of patients by cohort, diagnosis and mean ferritin level.

Table 2: Deaths by cohort and level of ferritin p=0.04

Tab 2	Nr of dead patients according to the mean serum level of ferritin			
	>3000	2000-3000	1000-2000	<1000
1980-1997	16	7	2	0
1998-2014	1	1	1	1

Table 3: Number of deaths by age at time of death, cohort and diagnosis

Tab 3	<10years	10-15years	15-20years	20-25years	25-30years
TM pt born 1980-2014	11	9	4	0	0
TSCD pt born 1980-2014	0	0	0	1	0
CD pt born 1980-2014	0	1	3	0	0
p=0.00					
All pt born 1980-1997	11	9	5	0	0
All pt born 1998-2014	0	1	2	1	0
p=0.02					