Thalassemia Major and Intermedia in Patients Older than 35 Years: A Single Center Experience

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ABSTRACT: **Background:** During the past decades, beta thalassemia major (TM) and beta thalassemia intermedia (TI) have transformed from a universally fatal disease at a young age into a chronic disease. This advancement is attributed to improved chelation therapy as well as enhanced management strategies, with focused attention on disease and treatment-related complications.

Objectives: To describe characteristics of adults with thalassemia as well as treatment modalities, disease and treatment-related complications, and socioeconomic information of the patients.

Methods: We preformed a retrospective analysis of 14 adult patients › 35 years of age with TM and TI who were treated at our institute, a single center specializing in the care of adult thalassemia patients living in Israel, between the years 2006 and 2016.

Results: The median age of patients was 37 years and most patients were transfusion-dependent. The median number of chelation therapeutic lines was three, and 85.7% of patients were treated at one point by combination chelation therapy. Most patients suffered from at least some form of endocrine dysfunction (n=12), and four patients developed overt heart failure. Of the patients, 85% had completed at least a high school education, 78% were employed, and 64.2% were married.

Conclusions: Prolonged survival of thalassemia patients in recent years has been accompanied by a new set of challenges for both the patients and the treating staff. Further research is warranted to improve both medical management and the socioeconomic well-being of this unique group of adult thalassemia patients.

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KEY WORDS: thalassemia, adults, treatment, complications, socioeconomic status (SES)

Survival of patients with beta thalassemia major (TM) and beta thalassemia intermedia (TI) has improved significantly over the past few decades due to improved availability of medical services, growing knowledge of the pathogenesis of disease symptoms, novel treatments and advancing technology. Treatment of thalassemia patients in a specialized center has been shown to have considerable influence on patient survival [1].

Regular red blood cell transfusions effectively prevent several complications of beta thalassemia, including facial malformations and high-output heart failure. However, the consequence of regular blood transfusions is deposition of iron in major organs, mainly in the liver, endocrine glands, and the heart. These complications have become a major cause of morbidity and mortality of beta thalassemia patients [2,3]. A significant improvement in the management of complications of iron overload has been achieved following the introduction of iron chelation therapy [4] with deferioxamine, which is administered parenterally, as well as deferiprone and deferasirox, which are given orally. Chelation therapy with deferioxamine has been shown to improve survival [5,6], and further improvements have been achieved over the past 10 years with the use of deferiprone, as well as combination therapy with deferiprone and deferioxamine [7-10].

The newer oral agent, deferasirox, offers an additional option for chelation with the increased advantage of once daily administration. Recent advances in monitoring of chelation therapy efficacy include various magnetic resonance imaging (MRI) techniques, enabling the measurement and monitoring of the amount of iron in major organs as well as labile plasma iron (LPI), which is responsible for catalyzing the generation of reactive oxygen species (Fenton reaction) [11-16]. The effective treatment and monitoring of iron overload has resulted in a significant improvement of the survival of the multi-transfused patients [4]. Additional improvements in the care of the beta thalassemia patients include advances in the management of hepatitis C, early diagnosis and management of diabetes, and other endocrinopathies, as well as careful surveillance for serious life-threatening infections. In addition to improved patient survival, there has also been a reduction in the rate of affected newborns, owing to population screening, genetic counseling, and the availability of prenatal diagnosis.

Therefore, presently, the number of older thalassemia patients with more data on their survival is increasing. Since traditionally most of the patients worldwide are treated in pediatric clinics by pediatricians, there is still limited data on the morbidity and complications of adult patients with TM and TI.

The aim of the present study is to describe the clinical and socioeconomic profile of patients with TM and TI who are older than 35 years and being treated in a dedicated adult thalassemia center in Israel.

*The first and second authors contributed equally to this study

Table 1. Patient characteristics

No.	Gender	Age (years)	Ethnicity	Genotype	Education	Employment	Marital status
1	F	51	A	NA	E	N	M
2	M	36	J	IVS16/IVS16	A	Y	S
3	M	43	S	NA	A	Y	M
4	F	42	J	IVS16/IVS16	H	Y	M
5	M	36	J	IVS15/IVS15	A	Y	M
6	F	37	A	IVSI110/IVSI110	H	N	M
7	M	39	J	IVS15/IVS15	H	Y	M
8	M	39	A	IVSI110/IVSI110	E	Y	M
9	M	42	J	Codon44/codon44	H	Y	S
10	F	37	A	NA	H	Y	S
11	M	44	J	IVSII1,2/IVSII1,2	H	Y	M
12	M	36	A	IVSI6/IVSI110	H	N	S
13	F	35	A	NA	H	Y	S
14	F	35	A	IVSI6/IVSI110	H	Y	M

Gender: F = female, M = male; Ethnicity: A = Arabic, J = Jewish, S = Samaritan; Genotype: NA = not available; Education: E = elementary , H = high school, A = academic; Employment: Y = yes, N = no; Marital status: M = married, S = single

PATIENTS AND METHODS

PATIENTS

Data from medical charts of all adult patients with TI and TM followed and treated between the years 2006 and 2016 in a dedicated thalassemia clinic at the Rabin Medical Center (Beilinson Campus) in Israel were analyzed (single center experience).

Eligibility criteria for this retrospective analysis included: TM and TI patients diagnosed by complete blood count and hemoglobin electrophoresis and age ≥ 35 years.

METHODS

Data recorded from charts included demographic characteristics (i.e., gender, date of birth, ethnicity, educational and occupational status), disease and treatment characteristics (e.g., type of thalassemia mutation, splenectomy, transfusion frequency, chelation therapy history), laboratory data (including hemoglobin [Hb] level, mean corpuscular volume [MCV], erythropoietin level, lactate dehydrogenase [LDH] value, indirect bilirubin [ID-BIL] level, uric acid level), and target organ complications (including endocrinopathies and liver and heart disease). Liver iron load was defined as evidence of iron accumulation by T2* MRI. Myocardial iron overload was defined as established cardiac disease requiring cardio-active drugs with ferritin levels higher than 2000 and no cardiac anatomical pathology. All cardiac events occurred in the 1990s when the T2* MRI technique was not available for clinical use.

Table 2. Treatment modalities

No.	Transfusion starting age (years)	Chelation treatment: number of lines	Treatment (line)			
			DFO	DFP	DFO+DFP	DFX
1	› 20	3		1,3		2
2	› 20	2		2		1
3	› 20	1				1
4	By demand	3		2		1.3
5	‹ 3	2	1			2
6	‹ 3	5	1	2,4	5*	3
7	‹ 3	5	1	4	2	3.5
8	‹ 3	1			1	
9	‹ 3	3	1		2	3
10	‹ 3	3	1		2	3
11	‹ 3	6§	1	4	2*	3.5
12	‹ 3	4	1		2.4*	3
13	‹ 3	5	1	4	2.5*	3
14	‹ 3	4‡	1.2 (IV)			3

DFO = deferioxamine, DFP = deferiprone, DFX = deferasirox
*IV DFO; §current treatment: DFP+DFX; ‡current treatment: IV DFO+DFX

STATISTICAL ANALYSIS

Descriptive statistical analysis was conducted for demographic variables, clinical features, laboratory results, and treatment variables. Mann–Whitney test was used to compare patients with TI and patients with TM. Statistical analysis was performed using SPSS software version 16 (SPSS Inc., Chicago, IL, USA). This retrospective study was approved by the institutional review board of our institution in accordance with the Declaration of Helsinki.

RESULTS

Between the years 2006 and 2016, 62 adult patients older than 18 years with TM and TI were followed and treated at our center. Out of these 62 patients, 14 (TM = 10 and TI = 4) were older than 35 years and were included in the present study.

Baseline characteristics of the patients are presented in Table 1. The median age of patients was 37 years (range 35–51), 66% males and 50% of Arab ethnicity. Most of the patients had at least a high school education (85%) and 78% were employed.

Treatment modalities are presented in Table 2. Thirteen patients (all TM patients and 3 out of the 4 TI patients) were treated regularly with blood transfusions. The remaining patient received blood transfusions only on demand. All patients received chelation treatment.

Median Hb levels and MCV levels were lower in patients with TI compared to TM (8.1 vs. 10 g/dl, $P = 0.002$ and 72.4 vs. 84 fl, $P = 0.004$, respectively). Median erythropoietin levels

in the transfused patients were 43.3 mIU/ml (normal range 2.6–18.5), reflecting the reduced red blood cell production.

Median LDH levels and ID-BIL levels were higher in patients with TI compared to TM (603 vs. 330 u/L, $P = 0.004$ and 2.02 vs. 1.1 mg/dl, $P = 0.06$, respectively) indicating increased hemolysis. Median uric acid levels were higher in patients with TI compared to TM (7.7 vs. 4.2 mg/dl, $P = 0.0004$). One TI patient had symptomatic gout.

All patients underwent splenectomy and therefore all had secondary thrombocytosis.

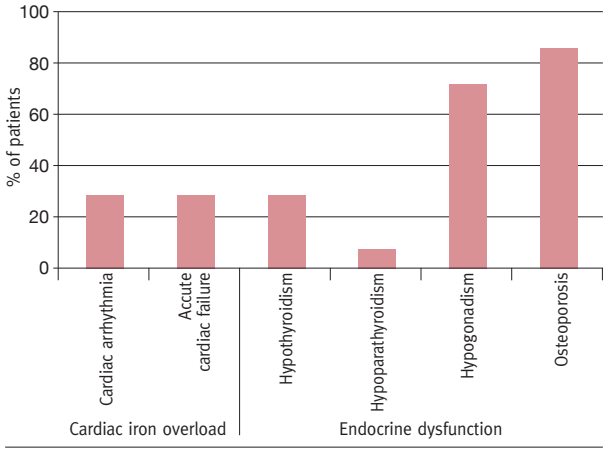
All but two patients were treated with at least two different chelation modalities during follow-up in our center. One option was single agent treatment, such as subcutaneous or intravenous deferioxamine, deferiprone, or deferasirox. Another option included combination therapy options, including oral, subcutaneous, and intravenous therapy. The median number of chelation treatment lines was three. All the patients who were treated with chelation treatment suffered from at least one adverse event related to the chelation treatment, necessitating at least temporary discontinuation, and in most cases substitution of treatment during the follow-up period was needed.

The median number of adverse events resulting in therapy replacement or dose adjustment was 1.5 per patient. Nine patients (64.2%) were reported to have good compliance with current chelation therapy according to physician evaluation and persistent non-elevated ferritin levels.

A major cause for switching therapy was treatment failure, defined as clinical or laboratory signs of iron overload (with elevated ferritin levels and acute episodes of heart failure). Seven patients had consistently high ferritin levels requiring change of treatment. Four of these patients, 28% of all patients, also had clinical signs of iron overload, manifested as episodes of acute heart failure. These events occurred during the late teen ages, while they were still treated by the pediatric hematologists. All four were treated with subcutaneous deferioxamine and had ferritin levels consistently higher than 1500 ng/ml, which suggests poor compliance. All four were admitted for emergency treatment with intravenous deferioxamine. Treatment was combined with deferiprone in two patients. With this intensified iron chelation therapy clinical symptoms improved, and heart function was normalized according to echocardiography in all cases. These cardiac events occurred during the 1990s when the T2* MRI technique was not available for clinical use. Heart T2* MRI results examined for all patients were within normal range for all but one patient.

Of the four patients with overt heart failure, three had episodes of cardiac arrhythmia ranging from atrial fibrillation to sustained ventricular tachycardia (VT). All three were treated with oral anticoagulants. An additional patient without overt heart failure suffered from cardiac arrhythmia (sustained VT). Figure 1 shows the relative rates of symptomatic cardiac iron overload and endocrine dysfunction in the cohort.

Figure 1. Symptomatic cardiac iron overload and endocrine dysfunction in the cohort



Three patients (21.4%) had significant liver iron overload according to liver T2* MRI, necessitating chelation treatment intensification.

Three patients (21%) were hepatitis C virus carriers. Two of them received anti-viral treatment, and only one responded to treatment, achieving polymerase chain reaction negativity. Four TM patients (40%) were hypothyroid; two of them were treated with thyroid hormone replacement, the other two had sub-clinical hypothyroidism. None of the patients had diabetes that required hypoglycemic agents. None of the patients had hypertension. All TM patients had hypogonadism. All females had amenorrhea and were treated with hormone replacement therapy, and none of them tried to conceive. Six of the seven male TM patients were treated with monthly testosterone injections, and three of them fathered children.

All TM patients had osteoporosis that was treated with hormonal therapy (testosterone or hormone replacement therapy) in addition to calcium and vitamin D supplements. Three TI patients (75%) had metabolic bone disease. Two had osteoporosis and one had osteopenia. One patient required surgical repair of a femur neck fracture following minor trauma. All TI patients were treated with calcium and vitamin D supplements.

None of the patients underwent allogeneic hematopoietic stem cell transplantation and none developed secondary malignancy during follow-up.

DISCUSSION

In the past, patients with transfusion dependent beta thalassemia were not expected to survive to adulthood. Therefore, since the 1970s the management of these patients has traditionally been conducted in specialized pediatric units. However, improvements in patient care and treatment modalities have enabled a growing number of thalassemia patients to reach adulthood. An Italian multicenter study that has been going on

for the past 26 years and includes almost 1,000 patients born since 1960 demonstrated that in 2009, 60% of the patients were older than 30 years (unpublished data, Borgna-Pignatti) [17]. Survival was increased in patients born in more recent years, mainly for females, who were less likely to die than males (relative risk = 0.65). Similar results have been reported for patients in the United Kingdom and Cyprus [4,18]. Indeed, medical advances are now enabling up to 90% of the pediatric population with special healthcare needs to survive to adulthood [19]. Transition from pediatric care to adult services has recently become an important issue for the thalassemia community. Organized multidisciplinary transition programs could ease this process and improve the medical outcome of the patients [20].

Although there have been several other studies describing the experience of dedicated centers treating adult thalassemia patients, most have focused on survival outcomes only [1,8,17]. Despite the relatively small number of patients in the present study, we explored multiple facets of the adult thalassemia patients, describing information regarding disease-related data, therapeutic history, and socioeconomic information in this unique population of adult thalassemia patients.

In the present study, we have retrospectively analyzed data regarding 14 patients with TM (n=10) and TI (n=4) treated in a single center in Israel in recent years. Median age was 37 years and most patients had completed at least a high school education, and were employed (85% and 78%, respectively). These statistics are in concordance with information presented in an adult Greek population with thalassemia, where 71.6% of the study population patients were employed and 75% had a Bachelor's degree [21]. A Canadian–American [22] study found a similar rate of employment in the adult thalassemia population (70%) with lower rates of completion of high school (60%) compared to our findings. While 64.2% of patients in our study were married, only 25% of the female population in a study describing marriage and child bearing in an Iranian thalassemia center were married [23]. Of note, none of our female TM patients had regular menses and none conceived. Nevertheless, taken together, these findings are indicative of a high rate of functional capacity maintained throughout early life in the modern era of thalassemia management, enabling successful incorporation of these patients into the adult milieu. This finding is quite remarkable, especially in light of the considerable healthcare burden inflicted upon thalassemia patients. In one study, the average time dedicated to healthcare related tasks per month was 271 hours [24]. Furthermore, in a recent report from Greece, approximately one out of four adult TM patients was prone to develop a psychiatric disorder according to the General Health Questionnaire (GHQ-28) screening tool [25]. We noticed a considerable heterogeneity regarding the thalassemia genotype in our study, reflecting the ethnic diversity observed in the Israeli population monitored in our center [Table 1].

As expected, median Hb levels were lower in the TI patients compared to the TM patients (8.1 g/dl and 10 g/dl, respectively), most likely reflecting the increased transfusion rate of the TI patients. Most of the patients, 13 out of 14, in both groups were transfusion-dependent [Table 2]. This finding is in line with the Canadian–American study in which 69.5% of the patients required at least eight transfusions per year [22].

The median number of chelation therapeutic lines in our study group was three, and 85.7% of patients were treated at one point by combination chelation therapy. While 100% of our study population was currently using chelator therapy, the Canadian–American study reported on lower figures of 72.3% [22].

As expected, many of our patients experienced some form of target-organ damage. In a Greek population-based study, 77.6% of the study population had significant complications [21]. Four patients in our study population had overt heart failure and three out of the four had arrhythmias, either atrial or ventricular, which were all treated with anticoagulants. Although cardiac function normalized with chelation therapy intensification in all four patients, only three had normalization of T2* cardiac MRI. Cardiac manifestations have been shown to confer the most important influence on survival outcome in thalassemia patients.

CONCLUSIONS

In conclusion, advances in the treatment of thalassemia patients have enabled the majority of these patients survival into adulthood. However, this development has brought with it a new set of challenges for both the patient and the treating staff. Our present study delineates the many challenges faced while treating adult patients with TI and TM in the modern era. Although adult thalassemia patients and their caregivers are faced with the continued struggle with disease-related and treatment-related complications, our study emphasizes that most patients are able to lead socially active, productive lives, as indicated by a high rate of higher education, employment, and marriage in our population. However, since a non-negligible number of adult thalassemia patients had decreased functional capacity in our study, further research should focus on identifying the etiology of decreased functional capacity in some of the adult thalassemia patients, and finding ways to improve the situation. Our data emphasize the unmet needs for long term surveillance for identification of organ-specific risk factors and early disease manifestations as well as the needs for global transition from pediatric to adult medicine and from pediatric clinics to dedicated comprehensive adult thalassemia clinics.

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References

1. Forni GL, Puntoni M, Boeri E, Terenzani L, Balocco M. The influence of treatment in specialized centers on survival of patients with thalassemia major. *Am J Hematol* 2009; 84 (5): 317-18.
2. Borgna-Pignatti C. Modern treatment of thalassaemia intermedia. *Br J Haematol* 2007; 138 (3): 291-304.
3. Rachmilewitz EA, Giardina PJ. How I treat thalassemia. *Blood* 2011; 118 (13): 3479-88.
4. Modell B, Khan M, Darlison M, et al. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2008; 10: 42.
5. Modell B, Letsky EA, Flynn DM, Peto R, Weatherall DJ. Survival and desferrioxamine in thalassaemia major. *Br Med J (Clin Res Ed)* 1982; 284 (6322):1081-4.
6. Zurlo MG, De Stefano P, Borgna-Pignatti C, et al. Survival and causes of death in thalassaemia major. *Lancet* 1989; 2 (8653): 27-30.
7. Borgna-Pignatti C, Cappellini MD, De Stefano P, et al. Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. *Blood* 2006; 107 (9): 3733-7.
8. Ladis V, Chouliaras G, Berdoukas V, et al. Relation of chelation regimes to cardiac mortality and morbidity in patients with thalassaemia major: an observational study from a large Greek unit. *Eur J Haematol* 2010; 85 (4): 335-44.
9. Lai ME, Grady RW, Vacquer S, et al. Increased survival and reversion of iron-induced cardiac disease in patients with thalassemia major receiving intensive combined chelation therapy as compared to desferoxamine alone. *Blood Cells Mol Dis* 2010; 45 (2): 136-9.
10. Maggio A, Vitrano A, Capra M, et al. Improving survival with deferiprone treatment in patients with thalassemia major: a prospective multicenter randomised clinical trial under the auspices of the Italian Society for Thalassemia and Hemoglobinopathies. *Blood Cells Mol Dis* 2009; 42 (3): 247-51.
11. Anderson LJ, Holden S, Davis B, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J* 2001; 22 (23): 2171-9.
12. Au WY, Lam WW, Chu WW, et al. Organ-specific hemosiderosis and functional correlation in Chinese patients with thalassemia intermedia and hemoglobin H disease. *Ann Hematol* 2009; 88 (10): 947-50.
13. Hekmatnia A, Radmard AR, Rahmani AA, Adibi A, Khademi H. Magnetic resonance imaging signal reduction may precede volume loss in the pituitary gland of transfusion-dependent beta-thalassemic patients. *Acta Radiol* 2010; 51 (1): 71-7.
14. Noetzli LJ, Papudesi J, Coates TD, Wood JC. Pancreatic iron loading predicts cardiac iron loading in thalassemia major. *Blood* 2009; 114 (19): 4021-6.
15. Papakonstantinou O, Ladis V, Kostaridou S, et al. The pancreas in beta-thalassemia major: MR imaging features and correlation with iron stores and glucose disturbances. *Eur Radiol* 2007; 17 (6): 1535-43.
16. Pootrakul P, Breuer W, Sametband M, et al. Labile plasma iron (LPI) as an indicator of chelatable plasma redox activity in iron-overloaded beta-thalassemia/HbE patients treated with an oral chelator. *Blood* 2004; 104 (5): 1504-10.
17. Borgna-Pignatti C. The life of patients with thalassemia major. *Haematologica* 2010; 95 (3): 345-8.
18. Telfer PT, Warburton F, Christou S, et al. Improved survival in thalassemia major patients on switching from desferrioxamine to combined chelation therapy with desferrioxamine and deferiprone. *Haematologica* 2009; 94 (12): 1777-8.
19. American Academy of Pediatrics; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. A consensus statement on health care transitions for young adults with special health care needs. *Pediatrics* 2002; 110 (6 Pt 2): 1304-6.
20. Yacobovich J, Tamary H. Thalassemia major and sickle cell disease in adolescents and young adults. *Acta Haematol* 2014; 132 (3-4): 340-7.
21. Vardaki MA, Philalithis AE, Vlachonikolis I. Factors associated with the attitudes and expectations of patients suffering from beta-thalassaemia: a cross-sectional study. *Scand J Caring Sci* 2004; 18 (2): 177-87.
22. Pakbaz Z, Treadwell M, Kim HY, et al. Education and employment status of children and adults with thalassemia in North America. *Pediatr Blood Cancer* 2010; 55 (4): 678-83.
23. Zafari M, Kosaryan M. Marriage and child bearing in patients with transfusion-dependent thalassemia major. *J Obstet Gynaecol Res* 2014; 40 (8): 1978-82.
24. Compagno LM. Caring for adults with thalassemia in a pediatric world. *Ann N Y Acad Sci* 2005; 1054: 266-72.
25. Vlachaki E, Neokleous N, Paspali D, et al. Evaluation of mental health and physical pain in patients with β-thalassemia major in Northern Greece. *Hemoglobin* 2015; 39 (3): 169-72.

Capsule

Cells that fix the heart

The adult heart is thought to lack the capacity to self-repair. Any injury after, say, a heart attack, causes scarring and may result in heart failure. In some animals, particularly when very young, heart muscle regeneration does occur. Even in adult mammals, new heart muscle cells (cardiomyocytes) can arise, but they are rare. Most maturing mammalian cardiomyocytes become binucleated and polyploid, and these seem to be incapable of regeneration. **Patterson** and co-authors found that a few "normal" mononucleated diploid cardiomyocytes (MNDCMs) occur in mice. Some individuals have more MNDCMs than others, and these individuals are better able to recover after heart injury. A gene called *Tnni3k* limits the number of MNDCMs, and it is this that appears to control the capacity for recovery after heart injury.

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"The art of medicine consists in amusing the patient while nature cures the disease"

François-Marie Arouet, (1694–1778), known by his nom de plume, Voltaire, was a French Enlightenment writer, historian, and philosopher famous for his wit, his attacks on the established Catholic Church and Christianity as a whole, and his advocacy of freedom of religion, freedom of speech, and separation of church and state

"Wherever the art of medicine is loved, there is also a love of humanity"

Hippocrates of Kos, (c. 460–c. 370 BCE), also known as Hippocrates II, was a Greek physician of the Age of Pericles (Classical Greece), and is considered one of the most outstanding figures in the history of medicine. He is sometimes referred to as the "Father of Medicine" in recognition of his lasting contributions to the field as the founder of the Hippocratic School of Medicine