The Egyptian Journal of Hospital Medicine (January 2022) Vol. 86, Page 391-397

Frequency of Neurological Manifestations in β-Thalassaemic Patients in Zagazig University Hospitals

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ABSTRACT

Background: Beta thalassemia syndrome is a hereditary disorder characterized by reduced or absent synthesis of the beta chains of hemoglobin that disturbs the normal shape of red blood cells. Chronic hypoxia of the nerves resulting from severe anemia may contribute to the pathogenesis of the peripheral neuropathy in patients with β-thalassemia. The aim of this study was to find out the frequency of neurological manifestations in β- thalassemia patients and to determine the contributing factors that lead to these manifestations.

Patients and Methods: This study was prospective cross sectional study conducted during the period from June 2019 to December 2020. This study was carried out on 120 thalassemia patients (67 males and 53 females), with ages ranged from 11 to 22 years old with a mean age of 16.45+3.31 years.

Results: About 31.7% of the studied cases had neurological manifestations. Tingling and numbness were the main neurological symptoms among cases (24.1% and 23.3% respectively) followed by headache (21.7%), joint and muscle pain (20.8%) and tremors in hands (3.3%). Hypotonia was found in 25 cases (20.8%). Grade 4 muscle power was reported in 13 cases (10.8%) and normal (grade 5) muscle power was reported in 107 cases (89.1%). Deep tendon reflexes were normal in (89.2%) cases, while (10.8%) cases had brisk deep tendon reflexes.

Conclusion: Frequency of neurological manifestations in beta thalassemia patients was 31.7%. About 26.3% of them had abnormal nerve conduction study (NCS). Age >16 years old, short stature, prolonged duration of the disease, transfusion frequency >10 times/year, delayed puberty and jaundice were risk factors for neurological manifestations in our studied cases.

Keywords: β-Thalassaemic Patients, Frequency, Neurological Manifestations.

INTRODUCTION

Thalassemia is an inherited blood disorder in which the body makes an abnormal form of hemoglobin. It is an autosomal recessive inheritance disease characterized by inability to produce one or more of globin chains forming hemoglobin molecule **(1)**. Thalassemia is, more common in Mediterranean and Southeast Asia regions, Iran and Pakistan **(2)**.

β-Thalassemia caused by genetic abnormalities in β-globin chains synthesis resulting in an excess of α-globin chains that precipitate in and destroy red cell precursors. Imbalanced globin synthesis results in the chronic hemolytic anemia and ineffective erythropoiesis that causes chronic hypoxia in patients with thalassemia **(3)**.

There are two clinically important presentations of β-thalassemia. Homozygous β-thalassemia usually results in thalassemia major, a severe anemia which requires regular blood transfusions and iron chelation therapy for survival. A milder form of the disorder exists, called thalassemia intermedia, with milder clinical presentation with less marked imbalance of the α:β globin chain ratio **(4)**.

Anemia, hemosiderosis and iron chelation therapy may be the main three factors responsible for the neurological changes in β- thalassemic patients **(5)**. Neurological manifestations also have been attributed to various factors such as, chronic hypoxia, bone marrow expansion, iron overload and desferrioxamine neurotoxicity, and also nutrition deficiency. Chronic hypoxia of the nerves resulting from severe anemia may contribute to the pathogenesis of the peripheral neuropathy in patients with β-thalassemia **(6, 7)**.

Iron overload in many body organs, due to chronic hemolysis and repeated blood transfusion, may be the cause of cellular damage and neurotoxicity by the way of free radicals **(8)**. Erythropoietic tissue masses occur as a compensatory mechanism to overcome chronic hemolysis. Paraspinal masses may cause spinal cord compression and neurological changes due to the compression. The size and location of lesions as well as the extent of spinal cord involvement determine the severity, and multiplicity of signs and symptoms **(9)**.

The aim of this study was to find out the frequency of neurological manifestations in β-thalassemia and to determine the contributing factors that lead to these manifestations.

SUBJECTS AND METHODS

This was a prospective cross sectional study, which was conducted at the outpatient clinics of Haematology Unit of Pediatric Department and Neurology

Received: 25/08/2021
Accepted: 21/10/2021

Department, Faculty of Medicine, Zagazig University, during the period from June 2019 to December 2020.

Sample size:

The study included 120 Egyptian children with β-thalassemia major using EpIsnfo 7, at power 80% and confidence level 95%. The cases were above 10 years old (67 males and 53 females) with ages ranged from 11-22 years (mean age±standard deviation 16.45±3.31). The study participants were selected randomly from the outpatient clinic of Hematology Unit of Pediatric Department in Zagazig University Hospitals. The age group was divided into cases above 10 years and below 16 years and cases ≥ 16 years.

Sampling technique:

Comprehensive sampling during period of data collection. All eligible children with B-thalassemia, receiving long-term blood transfusion and undergoing iron chelation therapy participated in this research study to get the previously calculated sample.

Inclusion criteria: Patients with β-thalassemia (major, intermedia and minor). Sex: Both genders are involved, and age: Above 10 years old.

Exclusion criteria: History of congenital malformation or perinatal complications as hypoxic ischemic encephalopathy or traumatic birth injury. Family history of neurological diseases. Acute febrile illness within 3 weeks prior to enrollment. A serious concurrent illness. Patients with comorbidities associated with neuropathy (diabetes mellitus, leg ulcers, thrombosis) were excluded. Patients with vision and hearing problems, and patients unwilling to give consent to participate in the study.

All patients underwent the following:

- A questionnaire interview for collection of personal data, sociodemographic data and complete history taking with particular emphasis on age, sex, consanguinity, duration of illness, family history of β-thalassemia and family history of any neurological symptoms.
- History of concomitant medical conditions e.g. viral hepatitis (HBV, HCV), splenectomy (date and indications). History of blood transfusion including age of onset, duration and frequency of transfusion. History of iron chelation therapy (type, age of onset, duration, dose, adverse effects and compliance).
- Other drugs therapy e.g. hydroxyurea, vitamins .

Complete general and neurological examination:

Clinical examination:

1. General clinical examination: Complete clinical examination was done to every case carefully. General examination including assessment of vital signs, presence of pallor, jaundice, mongoloid facies, spleen and liver status.
2. Anthropometric measurements: Weight in kilograms, height in meters, and Body Mass Index (BMI). BMI = weight (kg)/height (m^2).
3. Skeletal and abdominal features of B-thalassemia.

Neurological examination:

Neurological examination including assessment of mentality changes, speech, cranial nerves, motor system, coordination, sensory system, head, back, spine and gait. Neurological manifestations as headache, tingling, numbness, pain related to legs or feet, hypotonia in upper limb or lower limb, neuropathy, muscle power and deep tendon reflexes were important during examination.

Motor power; Grade 4: Good, active movement against gravity with some resistance, Grade 5: Normal, active movement with full resistance.

Deep tendon reflexes grades; 0: No response, absent, 1: Somewhat diminished, low normal, 2: Average, expected response, normal, 3: Brisker than average, slightly hyperreflexic, 4: Very brisk, hyperactive, with clonus **[10].**

Laboratory Investigations:

Routine laboratory investigations for the thalassemic patients including complete blood picture, liver functions, renal functions, serum ferritin, total serum bilirubin and direct serum bilirubin, serum albumin and total protein were done.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis:

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 22). According to the type of data qualitative were represented as number and percentage and quantitative data were represented by mean ± SD, median, and range. Difference and association of qualitative variable were tested by Chi square test (X^2). Differences between parametric quantitative independent groups were tested by Mann-Whitney test. P value was set at **<0.05** for significant results and **<0.001** for high significant result.

RESULTS

This table shows that age at presentation of the disease ranged from 1 to 5 years with mean 1.47 ± 0.76. Duration of the disease ranged from 9.50 to 22 years with mean 15.6 ± 3.36. Transfusion frequency ≥ 10 times/year was in about 80.8% and <10 times/year in 19.2% of cases. About 61.7% of cases received blood transfusion every 2 weeks. Splenectomy was done in 29.9% of cases at mean age of 4.33 years. About 29.2% were short stature **(Table 1)**.

Table (1): Baseline clinical data among studied cases

Baseline clinical data	The studied cases (N=120)	
	Number	Percent
Age at presentation (years)		
Mean ± SD	1.47 ± 0.76	
Median (Range)	1 (1 – 5)	
Duration of disease (years)		
Mean ± SD	15.6 ± 3.36	
Median (Range)	16 (9.50 – 22)	
Frequency of blood transfusion per week		
Every 2 weeks	74	61.7%
Every 3 weeks	31	25.8%
Every 4 weeks	15	12.5%
Transfusion Frequency (times/year)		
<10 times/year	23	19.2%
≥10 times/year	97	80.8%
HCV		
present	27	22.5%
Delayed puberty		
Present	36	30%
Splenectomy		
Yes	35	29.2%
Age at splenectomy (years)	(N=35)	
Mean ± SD	4.33 ± 1.28	
Median (Range)	4 (2.50 – 8)	
Short stature No Yes Clinical manifestations	 85 35	 70.8% 29.2%
Pallor	96	80%
Jaundice	85	70.8%
Mongoloid facies	87	72.5%
Splenomegaly	85	70.8%
Hepatomegaly	63	52.5%

HCV: Hepatitis C virus

Mean level of serum ferritin was 2580.85 ng/ml and 55.8% of cases had levels ≥2000 ng/ml. The mean levels of all laboratory data were within normal ranges except serum ferritin, total serum bilirubin (TSB), direct serum bilirubin (DSB) and urea levels exceeding the reference range and hemoglobin below normal level **(Table 2)**.

Table (2): Hematological and Biochemical profile of the studied cases

Hematological and Biochemical profile	Mean ±SD (N=120)
Hb (g/dl)	7.62 ±0.96
Serum ferritin (ng/ml)	2580.85 ±71.49
Total iron (ug/dl)	180.31 ±21.71
Total protein (g/dl)	7.40 ±0.81
Serum albumin (g/dl)	4.34 ±0.44
TSB (mg/dl)	1.53 ±0.17
DSB (mg/dl)	0.35 ±0.07
ALT (U/L)	32.64 ±5.80
AST (U/L	34.78 ±4.58
Urea (mg/dl)	28.10 ±5.28
Serum creatinine (mg/dl)	0.48 ±0.16
	N (%)
Serum ferritin	
<2000 ng/ml	53 (44.2%)
≥2000 ng/ml	67 (55.8%)

Hb: Hemoglobin: TSB: Total serum bilirubin; DSB: Direct serum bilirubin; ALT: Alanine aminotransferase; AST: Aspartate

aminotransferase

This table shows that deferasirox was the most common used drug. The most common side effects of chelation drugs were nausea and vomiting. Good compliance to chelation therapy was reported in 77.5% of the cases **(Table 3)**.

Table (3): Iron chelation distribution and side effects of chelation among studied cases

Iron chelation distribution and side effects of chelation	The studied cases (N=120)	
	Number	Percent
Iron chelation therapy		
Deferoxamine	32	26.7%
Deferasirox	55	45.8%
Deferiprone	19	15.8%
Combined	14	11.7%
Side effect of chelation		
Scars	31	25.8%
Nausea and vomiting	38	31.7%
Arthralgia	9	7.5%
Compliance		
Good	93	77.5%
Poor	27	22.5%

This table shows that 31.7% of the studied cases had neurological manifestations. Tingling and numbness were the main neurological symptoms among cases. Hypotonia was found in 25 cases. Normal (grade 5) muscle power was reported in 107 cases. 10.8% cases had brisk deep tendon reflexes **(Table 4)**.

Table (4): Frequency of neurological manifestations among studied cases

Neurological manifestations	The studied group (N=120)	
	Number	Percent
Overall neurological manifestations	38	31.7%
Symptoms: Headache	26	21.7%
Tingling	29	24.1%
Numbness	28	23.3%
Pain	25	20.8%
Tremors in hands	4	3.3%
Signs: Hypotonia	25	20.8%
Motor power		
Grade 4 Grade 5	13 107	10.8% 89.1%
Deep tendon reflexes		
Grade 2	107	89.2%
Grade 3	13	10.8%

There was a significantly higher mean age in patients with neurological manifestations compared to those without. All subjects with neurological manifestation aged above 16 years old. Neurological manifestations were highly significantly more in short stature subjects **(Table 5)**.

Table (5): Relation between neurological manifestation and sociodemographic data among the studied cases

Sociodemographic data	Neurological manifestation				p-value (Sig.)
	Absent (N=82)		Present (N=38)		
	No.	%	No.	%	
Sex					
Male	44	53.7%	23	60.5%	0.481
Female	38	46.3%	15	39.5%	
Age (years)					
Mean±SD	15.09 ± 3.12		19.25 ± 1.35		<0.001**
Median (Range)	15 (11 – 22)		19 (16 – 22)		
Age group					
<16 years	47	57.3%	0	0%	<0.001**
≥16 years	35	42.7%	38	100%	
Consanguinity (1st degree)					
Negative	79	96.3%	33	86.8%	0.248
Positive	3	3.7%	5	13.2%	
Similar condition in family					
Absent	78	95.1%	34	89.5%	0.523
Present	4	4.9%	4	10.5%	
Short stature					
No	66	81.5%	18	48.7%	<0.001**
Yes	16	18.5%	20	51.3%	

: Highly significant, Patients with neurological manifestations have significantly prolonged duration of the disease, frequent transfusion ≥10 times/year and presence of jaundice, mongoloid facies, delayed puberty. But there was no significant relations as regards HCV **(Table 6).

Table (6): Relation between neurological manifestation and clinical data among the studied cases

Clinical data	Neurological manifestation					p-value (Sig.)
	Absent (N=82)			Present (N=38)		
	No.	%		No.	%	
Age at presentation (years)						
Mean±SD	1.32 ± 0.58			1.79 ± 0.97		0.006*
Median (Range)	1 (1 – 4)			2 (1 – 5)		
Duration of disease (years)						
Mean±SD	13.91 ± 3.30			17.58 ± 1.78		<0.001**
Median (Range)	14 (9.50 – 24)			18 (13 – 21)		
Frequency of blood transfusion per week						
Every 2 weeks	51	63%		23	60.5%	0.447
Every 3 weeks	22	27.2%		9	23.1%	
Every 4 weeks	9	10.9%		6	15.8%	
Transfusion Frequency (times/year)						
<10 times/year	22	27.2%		1	2.6%	0.001*
≥10 times/year	60	73.2%		37	97.4%	
HCV						
Absent	64	78%		29	76.3%	0.333
Present	18	22%		9	23.7%	
Delayed puberty	4	4.9%		32	84.2%	<0.001**
Splenectomy						
No	58	70.7%		27	71.1%	0.928
Yes	24	29.3%		11	28.9%	
Age at splenectomy (years)						
Mean±SD	4.50 ± 1.35			4 ± 1.15		0.398
Median (Range)	4 (2.50 – 8)			4 (3 – 6)		
Jaundice						
Absent	27	32.9%		8	21.1%	<0.001**
Present	55	67.1%		30	78.9%	
Mongoloid facies						
Absent	32	39 %		1	2.6%	<0.001**
Present	50	61.7%		37	97.4%	

*: Significant, **: Highly significant

This table shows no significant relation between presence of neurological manifestations and type of iron chelation therapy **(Table 7)**.

Table (7): Relation between neurological manifestation and iron chelation therapy

Iron chelation therapy	Neurological manifestation					p-value (Sig.)
	Absent (N=82)			Present (N=38)		
	No.	%		No.	%	
Deferoxamine	18	22 %		14	36.8%	0.135
Deferasirox	43	52.4%		12	31.6%	
Deferiprone	13	15.9%		6	15.8%	
Combined	8	9.8%		6	15.8%	

DISCUSSION

Our results showed that the age of all studied patients ranged from 11 to 22 years with a mean value 16.45 years. β-thalassemia patients consisted of 67 (55.8%) males and 53 (44.2%) females with male sex predominance. This result is in agreement with **Kaushik *et al.*** [12] who reported in their study that mean (SD) age of enrolled patients (n = 50) was 10.5 (4.5) years with a male predominance [36 (72%)]. On contrast, **El-Tagui *et al.*** [13] in their study to evaluate the frequency of polyneuropathy in adolescents and young adults with beta thalassemia, reported that their studied patients included 22 (36.7%) males, with a male to female ratio of 0.6.

As regards to growth parameter and anthropometric characters among our studied cases, weight of the cases ranged from 28 to 70 Kg with mean 50.75 Kg. Height of the studied cases ranged from 138 to 157 centimeters with mean 159.19 cm. About 35 studied cases (29.2%) were short stature. Body Mass Index (BMI) of our studied cases ranged from 14.70 to 27.80 with mean 21.99. These results were in agreement with **Cheung *et al.*** [14] who reported that compared with controls, thalassemia patients were lighter (48.2 ± 8.9 kg vs 58.0 ± 12.1 kg, P < 0.001) and had a smaller body mass index (19.2 ± 2.3 kg/m^2 vs. 21.7 ± 3.7 kg/m^2, P=0.004).

In the current study mean level of serum ferritin was 2580.85 ng/ml with range from 168-8970 ng/ml and 55.8% of cases had levels ≥2000 ng/ml. Our results were in agreement with **Ari *et al.*,** [15] who reported that mean serum ferritin level was 1842±1049 ng/mL among their thalassemia patients.

In this study we found that, complications were significantly associated with thalassemia cases like hepatomegaly in 52.5%, splenomegaly in 70.8%, delayed puberty in 30%, HCV infection in 22.5% and short stature in 29.2%%. This can be explained by **Origa** [16], who reported that excess iron is extremely toxic to all body tissues, leading to significant morbidity and mortality among β-thalassemia patients as well as other iron-overload conditions where it causes serious and irreversible biological damage, such as cirrhosis, liver fibrosis, heart disease, and endocrine abnormalities.

All our patients have used chelation therapy due to high serum ferritin. About 26.7% of the patients used deferoxamine, 45.8% used deferasirox, 15.8% used deferiprone and 11.7% used combined drugs. Good compliance to chelation therapy was reported in 77.5% of the cases. In our study, the most common side effect of chelation was nausea and vomiting, followed by scars then arthralgia. **Putri *et al.*** [17] in study on sixty patients with major beta-thalassemia reported that Fifty-six (93.3%) subjects received iron chelation therapy; 21 subjects were given deferasirox, 30 subjects received deferiprone, 5 subjects used desferal. Also, **Kaushik *et al.*** [12] reported in their study that mean (SD) of hemoglobin was 8.9 (1.2) g/dl and majority of children were on deferasirox [30 (60%)].

The current study showed that 31.7% of the studied cases had neurological manifestations. Tingling and numbness were the main neurological symptoms among cases (24.1% and 23.3% respectively) followed by headache (21.7%), joint and muscle pain (20.8%) and tremors in hands (3.3%). Hypotonia was found in 25 cases (20.8%). Muscle power of grade four was reported in 13 cases (10.8%) and normal muscle power was reported in 107 cases (89.1%). Deep tendon reflexes were normal in (89.2%) cases, while (10.8%) cases had brisk deep tendon reflexes. **El-Tagui *et al.*** [13] found twenty-nine (48.3%) patients suffered from paresthesia and 22 (36.7%) complained of recurrent numbness. Also, they reported that neurological examination was normal in 25 thalassemic patients (41.7%). **Sawaya *et al.*** [4] in study on 30 patients with thalassemia found five patients (17%) had absent deep tendon reflexes in the knees and ankles, six patients (20%) had depressed reflexes and 17 patients (57%) had normal reflexes. Gait and tandem walking were normal in all the patients except the patient with the peroneal nerve lesion.

The current results disagree with **Işıkay *et al.*** [3] who found in their study on 154 thalassemia patients and 100 control cases that neurological examination did not indicate any abnormalities in any of the participants. Any evidence of large-fiber neuropathy was not present in any of the participants. Also disagrees with **Kaushik *et al.*** [12] who concluded in their study on children aged 5–15 years with transfusion-dependent thalassemia major that none of the children had either clinical or electrophysiological evidence of peripheral neuropathy.

Stamboulis *et al.* [7] reported that 25% of patients with β-thalassemia had neurological symptoms, 22% had neurological signs of neuropathy such as, hypoesthesia of the feet, weakness of the extensor digitorum brevis, and reduced knee. In contrast, **Zafeiriou *et al.*** [18] reported that 10 % of patients had clinical evidence of a sensory neuropathy (absent or diminished deep tendon reflexes and loss of sensation

in a stock-glove distribution) and additionally 25 % had decreased sensory conduction velocities, and only 10 % also had decreased motor NCVs.

As regards to age of studied cases with neurological manifestation, there was significantly higher mean age in patients with neurological manifestations compared to those without. All subjects with neurological manifestation aged above 16 years old. These data are in agreement with **Papanastasiou *et al.*** [19] who carried study on 53 thalassemia patients with a mean age of 17 years and defined that neuropathy was appearing during the second and third decades of life.

The results of this study showed a highly significant increase in weight, height, Body Mass Index (BMI) in studied patients with neurological manifestations compared to those without. About 51.3% of cases with neurological manifestations had short stature compared to those without.

Patients with neurological manifestations had significantly prolonged duration of the disease, frequent transfusion ≥10 times/year and presence of jaundice, mongoloid facies, delayed puberty, and hepatomegaly. But there was no significant relations as regards HCV, splenomegaly, age at splenectomy, the level of serum ferritin, and the type of chelation therapy

Sawaya *et al.* [4] reported that thalassemia patients who received blood transfusions and desferrioxamine had better nerve function than those who did not receive, irrespective of the dose of desferrioxamine. The neuropathy was worse for older patients, irrespective of sex in that study which was similar to our results. This result disagrees with **El-Tagui *et al.*** [13] who found that patients with electrophysiological proof of peripheral motor neuropathy showed elevated serum ferritin, and those with severe iron overload (serum ferritin C 2000 ng/ml) are at higher risk. Also they showed that peripheral neuropathy correlated positively with transfusion frequency and serum ferritin; highlighting an association between severe iron overload and motor neuropathy.

CONCLUSION

Frequency of neurological manifestations in beta thalassemia patients among 120 Egyptian children in the outpatient clinic of Hematology Unit of Pediatric Department and Neurology Department, Faculty of Medicine, Zagazig University is 31.7%.

Age >16 years old, short stature, prolonged duration of the disease, transfusion frequency > 10 times/year, delayed puberty and jaundice were risk factors for neurological manifestations in our studied cases.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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