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ASSESSMENT OF THE AUTONOMIC AND PERIPHERAL NERVE FUNCTION IN PATIENTS WITH THALASSAEMIC SYNDROME IN A TERTIARY CARE HOSPITAL - A CROSS SECTIONAL STUDY

Cardiology

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ABSTRACT

INTRODUCTION: β-thalassaemia is an inherited disorder of haemoglobin characterized by an absence or reduced synthesis of the β-globin chain. The net result is an excess of α-chains, which precipitate and destroy the red cell precursors, leading to anaemia, skeletal changes, splenomegaly and numerous other complications. Treatment is by regular blood transfusion coupled with iron chelation therapy to prevent iron accumulation and organ damage.

AIM: To assess the autonomic and peripheral nerve function in patients with thalassaemic syndrome.

MATERIAL AND METHODS: Patients attending the Thalassaemia Clinic of Medical College Hospital, Kolkata. Indoor patients from Medicine ward and Institute of Haematology and Transfusion Medicine wards of Medical College Hospital, Kolkata from 1st May 2008 to 30th April 2009. After inclusion patients were divided into following groups: Group1 **(THAL1)**: Patients requiring regular blood transfusion and are either receiving inadequate iron chelation or no iron chelation at all. Group2 **(THAL2)**: Patients who require regular blood transfusion and are receiving adequate iron chelation. Group3 **(THAL3):** Patients who do not require regular blood transfusion

RESULT: The median value of distal latency of right common peroneal nerve is slightly increased in all 3 groups. The normal value should be < 4.55ms, thus increase in distal latency is seen in all 3 groups. The median values of distal latency of left common peroneal nerve as well as distal latency of common peroneal nerve as a whole is within normal limits. Distal latency of common peroneal nerve (**p value=0.012**). Proximal latency of left common peroneal nerve(**p value=0.013**). Proximal latency of common peroneal (**p value=0.001)**

CONCLUSION: There is demyelinating type of neuropathy of right common peroneal nerve of all the groups. This indicates presence of motor peripheral neuropathy in patients of thalassaemia. All other latencies and amplitudes of both motor and sensory nerves are within normal limits. There were statistically increased motor latencies in patients receiving iron chelation therapy with adequate chelation when compared to the other groups, although the overall latency was within acceptable limits of the laboratory standards. This may be due to subclinical affection of the motor nerves in the form of demyelination. Therefore, the role of toxic effects of iron chelator on peripheral nerves needs to be studied further.

KEYWORDS

Thalassaemia, Blood Transfusion, Motor Peripheral Neuropathy, Toxic Effects.

INTRODUCTION

The thalassaemia syndromes are inherited disorders of α- or β-globin biosynthesis. The reduced supply of globin diminishes production of hemoglobin tetramers, causing hypochromia and microcytosis. Unbalanced accumulation of the α and β subunits occurs because the synthesis of the unaffected globins proceeds at a normal rate[1]. There is ineffective erythropoiesis and hemolysis[2].

β-thalassaemia is an inherited disorder of haemoglobin characterized by an absence or reduced synthesis of the β-globin chain. The net result is an excess of α-chains, which precipitate and destroy the red cell precursors, leading to anaemia, skeletal changes, splenomegaly and numerous other complications. Treatment is by regular blood transfusion coupled with iron chelation therapy to prevent iron accumulation and organ damage.

In West Bengal, thalassaemic syndrome is complicated by presence of Hemoglobin-E, which can present with any of the above forms. The E-β thalassaemia group forms the major bulk of population attending the Thalassaemia Clinic and Day Care for regular blood transfusion.

With intensive and early blood transfusion and iron chelation therapy the immediate prognosis of the thalassemic patients has improved considerably in recent times. As the life expectancy of the patients is increasing, the long term complications of both the disease and the treatment, are beginning to show up[3].

Apart from the well known problems of growth, infertility, endocrinopathies and cardiac failure[2], incidence of autonomic and peripheral nerve dysfunction has been reported in various studies. This may be attributed to chronic hypoxia, bone hyperplasia causing nerve compression due to extramedullary erythropoiesis 10 or to the treatment leading to iron overload[4].

A few studies have evaluated the presence of any neuromuscular complications. Focal neurological episodes, nerve deafness, as well as the presence of a myopathic syndrome have been documented in a few cases. More recently, Papanastasiou et al [5] demonstrated an age-related peripheral neuropathy in patients with β-thalassaemia, which might at least partly, be due to chronic anaemia.

The neurotoxic effects of iron chelation therapy have also been documented in a few studie. Some showed that desferrioxamine may cause ocular and acoustic nerve complications, in a dose-related fashion. Most of the studies that have appeared in the literature concerning the effects of thalassaemia and its treatment on the peripheral nerves, have shown a predominantly sensory peripheral neuropathy.

Many papers do mention sensory, motor and mixed peripheral neuropathy and its symptoms as a side effect of desferrioxamine therapywhile some studies suggest that adequate iron chelation have a protective role in preventing neuropathy[6].

The role of chronic ischaemia in the development of neuropathy has been demonstrated both in experimental studies and in clinical situations where ischaemia or hypoxia is present. The nerve ischaemia usually results in axonal damage. The large sensory myelinated fibres seem to be more severely affected and could also be attributed to chronic hypoxia of the nerves resulting from long standing anaemia. The higher prevalence of neuropathy in older patients and in patients with a low haematocrit is in agreement with this hypothesis.

There are evidences of nerve dysfunction due to entrapment following bony expansion as a result of extramedullary haematopoesis in patients of thalassaemia who may respond to surgical decompression[7].

In this study we examined the autonomic and peripheral nerve function parameters by history, clinical examination, autonomic testing using continuous ECG tracing and nerve conduction studies[8].

AIMS AND OBJECTIVES:

AIM: To assess the autonomic and peripheral nerve function in patients with thalassaemic syndrome.

SPECIFIC

1. 1.To assess the autonomic and peripheral nerve status of thalassemic patients with the help of ECG and nerve conduction velocity study.
2. To compare the peripheral nerve dysfunction of patients with thalassemic syndrome who have received regular blood transfusion with adequate iron chelation therapy for more than 5 years with those

a) who have received regular blood transfusion for more than five years with

- No iron chelation therapy
- Inadequate iron chelation therapy

b) who do not require regular blood transfusion

MATERIALS AND METHODS:

Study Area-

Medical College and Hospital, Kolkata.

Study Population-

Patients attending the Thalassaemia Clinic of Medical College Hospital,Kolkata. Indoor patients from Medicine ward and Institute of Haematology and Transfusion Medicine wards of Medical College Hospital, Kolkata.

Study Period- 1st May 2008 to 30th April 2009

Sample Size- Total of 43 subjects divided into 3 groups.

Sample Design-

Exclusion Criteria:

a) Blood transfusion less than five years in Group1 and Group2
b) Diabetes Mellitus, clinical features suggestive of Vitamin B-Complex deficiency, Chronic Renal Failure, Chronic Liver Disease, Hypothyroidism, history suggestive of toxic substance exposure and family history of peripheral nerve dysfunction.

Before inclusion every patient gave an informed consent.

After inclusion patients were divided into following groups:
Group1 (THAL1) : Patients requiring regular blood transfusion and are either receiving inadequate iron chelation or no iron chelation at all.
Group2 (THAL2): Patients who require regular blood transfusion and are receiving adequate iron chelation.
Group (THAL3): Patients who do not require regular blood transfusion

Study Design- Hospital based cross-sectional study

RESULT AND DISCUSSION

The 3 groups of the study are mentioned as:
THAL1: Patients requiring regular blood transfusion and are either receiving inadequate iron chelation or no iron chelation at all
THAL2: Patients who require regular blood transfusion and are receiving adequate iron chelation.
THAL3: Patients who do not require regular blood transfusion With advancement in medicine, there is early diagnosis of thalassaemic patients. There is early institution of blood transfusion along with iron chelation which has improved the immediate prognosis of the disease. Since the life expectancy of these patients has increased, the long term complications of the disease and its treatment has started to show up.

Firat Kardelen et al[9] have demonstrated that patients of thalassaemia major have autonomic dysfunction as evidenced by significant reduction in heart rate variability during deep breathing. They concluded that heart rate variability in preclinical phase of cardiac involvement is a measure of early cardiac autonomic neuropathy without any other evidence of autonomic and peripheral nerve dysfunction in asymptomatic patients.

In our study, we have not only studied the heart rate variability but also other autonomic parameters.

We found that:

1. Heart rate variation with deep breathing was reduced in all the 3 groups showing autonomic dysfunction. This finding is consistent with the previous study. The variation was maximum in group THAL2, although not statistically significant, showing that blood transfusion and adequate iron chelation therapy may have got some protective effect as that group was least affected.
2. E:I ratio is also decreased in all the 3 groups also support the above finding of autonomic dysfunction. The ratio was maximum in THAL2, but not statistically significant, again showing that blood transfusion along with adequate iron chelation may have got some protective effect as that group was least affected.
3. The heart rate increase 15 seconds after standing was normal in all the 3 groups but the increase was maximum in THAL2, although not statistically significant, again showing group with blood transfusion with adequate iron chelation is least involved.
4. The ratio of RR interval at 30s:15s after standing was also normal in all the 3 groups but it was least in THAL1 and comparable in THAL2 and THAL3. Although the ratio is normal but the trend of THAL1 getting maximally involved suggest that it may be associated with both chronic hypoxia and iron overload.
5. The ratio of maximum : minimum RR interval during valsalva manoeuvre also show autonomic dysfunction. The maximally affected group here is THAL3, although not statistically significant, suggesting that chronic hypoxia may play an important role in the pathogenesis of autonomic dysfunction. The patients of this group have a low mean haemoglobin level and they remain asymptomatic without any transfusion for long duration leading to chronic hypoxia and may be an important contributing factor.
6. There was no significant postural drop in blood pressure.

None of the autonomic parameters showed any statistically significant intergroup variation.

Thus most of the patients belonging to all the 3 groups had autonomic dysfunction as evidence by decreased heart rate variability and decreased RR ratios (E:I with deep breathing and maximum : minimum with Valsalva manoeuvre) without any significant postural drop in blood pressure or abnormal heart rate change on standing.

Thus these findings may suggest early autonomic neuropathy in thalassaemic patients irrespective of the transfusion requirement and treatment given. But the involvement seems to be least in those thalassaemic patients who receive regular blood transfusion and are adequately chelated, though the difference observed is not statistically significant.

Patients suffering from thalassemia may complain of paresthesias distally in the lower extremities along with symptoms suggestive of peripheral neuropathy. Literature suggests that few even lose the deep tendon reflexes in the legs.

In our study we found that:

In the motor peripheral nerves –

a) The distal latency of right peroneal nerve was increased in all the 3 groups suggesting a peripheral motor neuropathy probably a demyelinating type.
b) The latencies and amplitudes of all the other nerves studied were within normal limits.
c) There was a statistically significant intergroup variation of the latencies of median, ulnar, common peroneal and tibial nerves.

In all the above cases the latency of the motor nerve was generally increased in THAL2 group in comparison to the other groups. However the overall latency was normal limits of our accepted laboratory standards. The increase in latency in this group suggests that there might be some subclinical demyelinating type of affection of motor nerves. Interestingly this group receives regular blood transfusion and adequate iron chelation therapy. These findings are similar to the findings of R A Sawaya et al[6] who did not find any increase in latency of motor nerves. But here we have found a modest increase in the distal latency of common peroneal nerve suggesting demyelination. E Stamboulis et al[4] had documented increase in motor distal latency of ulnar nerve but the latencies of ulnar nerve in our study is within normal limits. The significant association of iron chelator in our study may suggest the role of toxic drug effect in this affection although subclinical. This is consistent with the findings of Levine et al[10] who demonstrated association between sensorimotor neuropathy and desferrioxamine. R Elbera et al[11] and N F Olivieri[12] et al in their independent studies showed neurological side effects of desferrioxamine in the form of sensorineural hearing loss.

The motor amplitudes, although within normal limits,when compared within the groups were reduced in the THAL2 group in the median and peroneal nerves. It was also reduced in THAL1 group in the ulnar nerves while it was equal in all 3 groups in tibial nerve .This trend of decrease in amplitude suggest subclinical axonal type of neural affection. Surprisingly THAL1 and THAL2 both require regular blood transfusion. This finding may be attributed to iron overload or effect of drug to overcome iron overload.

d. The nerve conduction velocities were normal but had statistically significant variation in the The motor conduction velocities were normal which is contrary to the findings of Papanastasiou et al[5] who demonstrated the presence of predominantly motor peripheral neuropathy. The NCV, although within normal limits, the minimum NCV was for THAL2 for all the four motor nerves studied. This variation was statistically significant in the above 2 motor nerves. This reduction may be at least partially be attributed to the iron chelation therapy received in this group leading to or at least tending to subclinical motor neuropathy.

In the sensory peripheral nerves –

a. The values of latencies and amplitudes in all nerves studied were within normal limits.
b. There was significant intergroup variation of latencies of median and ulnar nerve: In our study, in contrast to the previous studies there was no evidence of sensory neuropathy in the study population.
c. There was no significant intergroup variation of amplitude in the sensory nerves.

The above findings are in contrast to the studies by E Stamboulis et al[4] who found that majority of his patient suffered from mild sensory axonal polyneuropathy. Even Papanastaiou et al[5] in his study found a significant sensory involvement. R A Sawaya[6] in his study also found majority of the patient having sensory neuropathy. But in our study we could not derive a significant association of thalassaemia as the median values of all sensory parameters were well within normal limits.

CONCLUSION:

This study can be summarised as follows:

1. There is autonomic dysfunction in patients of thalassaemia, irrespective of the type of haemoglobinopathy and transfusion requirement. This autonomic dysfunction is seen in patients who do not require regular blood transfusion as well as those who require regular blood transfusion with or without iron chelation therapy. Chronic hypoxia leading to ischaemic changes of the nerve fibres may be the etiologic factor for this affection.
2. Although statistically not significant, this dysfunction was least in the group receiving iron chelation therapy. The protective role of iron chelation therapy in the development of autonomic dysfunction needs to be further studied in a larger population.
3. The patients should be tested for other autonomic parameters like SSRT (Symphathetic or Galvanic Skin Resistance Test),QSART(Quantitative Sudomotor Axon Reflex Test), TST(Thermoregulatory Skin Test) and others as these small fibres cannot be studied by standard nerve conduction studies.
4. There is demyelinating type of neuropathy of right common peroneal nerve of all the groups. This indicates presence of motor peripheral neuropathy in patients of thalassaemia. All other latencies and amplitudes of both motor and sensory nerves are within normal limits.
5. There were statistically increased motor latencies in patients receiving iron chelation therapy with adequate chelation when compared to the other groups, although the overall latency was within acceptable limits of the laboratory standards. This may be due to subclinical affection of the motor nerves in the form of demyelination. Therefore the role of toxic effects of iron chelator on peripheral nerves needs to be studied further.
6. These patients especially those whose peripheral nerve parameters are within normal limits at present, need to be followed up for the development of overt neuropathy in future.

The general features between the 3 groups were as shown in **TABLE A** with values representing mean ± standard deviation:

TABLE A	AGE (years)	SEX		Hb (gm /dl)	SERUM FERRITIN (ng/ml)	TRANSFUSION REQUIREMENT (per year)	AVERAGE AGE OF FIRST TRANSFUSION (yr)
GROUPS		M	F				
THAL1	22.3± 10.2	15	7	6.8± 0.7	1796.5± 625.2	12.5±3.6	6.3±6.1
THAL2	20.9± 4.2	9	3	7.6± 1.1	631.2± 217.9	9.0±2.9	5.3±2.8
THAL3	20.2± 4.1	6	3	7.4± 0.4	363.4± 99.1	0.8±0.3	14±4.2

The type of haemoglobinopathy and splenectomy status was as shown in **TABLE B**

TABLE B	TYPE OF HAEMOGLOBINOPATHY				SPLENECTOMY		
GROUPS	β-THALASSAEMIA MAJOR	%	E-β THALASSAEMIA	%	DONE	NOT DONE	% SPLENECTOMY
THAL1	4	18.18	18	81.82	6	16	27.27
THAL2	5	41.67	7	48.33	3	9	25
THAL3	0	0	9	100	0	9	0

TABLE C	TYPE OF IRON CHELATION THERAPY			
GROUPS	DESFERAL	KELFER	DESIROX	NONE
THAL1	3	7	3	9
THAL2	7	4	1	0
THAL3	0	0	0	9

The Autonomic Parameters Were:

TABLE 1	HR VARIATION WITH DEEP BREATHING		E:I (MAX:MIN RR) WITH DEEP BREATHING		HR INC 15S AFTER STANDING		RR30S:15S AFTER STANDING		RR(MAX:MIN) VALSALVA	
GROUPS	MED	RANGE	MED	RANGE	MED	RANGE	MED	RANGE	MED	RANGE
THAL1	10	12	1.1135	0.26	14.5	28	1.041	0.27	1.1538	0.2455
THAL2	13	12	1.159	0.306	18	16	1.06175	0.1034	1.156	0.137
THAL3	11	21	1.156	0.52	18	64	1.067	0.21	1.1	0.349
P VALUE	0.288		0.081		0.261		0.309		0.233	

CHANGE IN BLOOD PRESSURE 2 MINS AFTER STANDING:

TABLE 2	SYSTOLIC BLOOD PRESSURE		DIASTOLIC BLOOD PRESSURE	
GROUPS	MEDIAN	RANGE	MEDIAN	RANGE
THAL1	11	24	4.5	20
THAL2	5	20	5	20
THAL3	10	20	0	20
P VALUE	0.1		0.917	

Peripheral Nerve Function Parameters Were:

Motor Median Nerve: Latencies

TABLE 3	RT MEDIAN DISTAL		LT MEDIAN DISTAL		MEDIAN DISTAL		RT MEDIAN PROXIMAL		LT MEDIAN PROXIMAL		MEDIAN PROXIMAL	
GROUPS	MED	RANGE	MED	RANGE	MED	RANGE	MED	RANGE	MED	RANGE	MED	RANGE
THAL1	2.65	1.42	2.655	1.64	2.65	1.64	6.325	2.42	6.205	3.26	6.455	2.65
THAL2	3.175	1.4	2.97	1.66	3.07	1.66	6.685	1.7	7	2.65	6.76	2.65
THAL3	2.7	1.8	2.71	1.55	2.705	1.8	6.25	2.65	6.56	2.52	6.25	3.26
P VALUE	**0.005**		0.113		**0.001**		0.079		0.059		**0.005**	

Ulnar Nerve: Latencies

TABLE 5	RIGHT ULNAR DISTAL		LEFT ULNAR DISTAL		ULNAR DISTAL		RIGHT ULNAR PROXIMAL		LEFT ULNAR PROXIMAL		ULNAR PROXIMAL	
GROUPS	MED	RANGE	MED	RANGE	MED	RANGE	MED	RANGE	MED	RANGE	MED	RANGE
THAL1	1.98	1.45	2.04	1.27	1.99	1.45	5.675	3	5.665	2.92	5.665	3.21
THAL2	2.38	1.26	2.55	1.37	2.44	1.5	6.315	1.98	6.315	2.48	6.315	2.6
THAL3	2.08	1.58	2.08	1.35	2.08	1.61	5.73	3.43	5.94	2.41	5.835	3.43
P VALUE	0.187		**0.031**		**0.002**		0.063		0.222		**0.014**	

Tibial Nerve: Latencies

TABLE 9	RT TIBIAL DISTAL		LT TIBIAL DISTAL		TIBIAL DISTAL		RT TIBIAL PROXIMAL		LT TIBIAL PROXIMAL		TIBIAL PROXIMAL	
GROUPS	MED	RANGE	MED	RANGE	MED	RANGE	MED	RANGE	MED	RANGE	MED	RANGE
THAL1	3.745	2.41	3.65	2.55	3.695	2.65	11.305	5.31	11.25	5.41	11.25	5.52
THAL2	4.44	1.84	4.43	1.62	4.43	2.09	12.315	3.84	12.98	3.63	12.795	3.97
THAL3	4.27	1.88	4.38	0.58	4.325	1.88	12.31	3.85	12.5	2.71	12.405	3.86
P VALUE	**0.046**	**0.015**	**<0.001**	**0.043**	**0.007**	**<0.001**						

Sensory Median Latencies

TABLE 12	RT MEDIAN		LT MEDIAN		MEDIAN	
GROUPS	MEDIAN	RANGE	MEDIAN	RANGE	MEDIAN	RANGE
THAL1	2.285	2.88	2.18	3.16	2.265	3.16
THAL2	2.55	1.42	2.675	1.04	2.58	1.42
THAL3	2.67	3	2.58	2.95	2.58	3
P VALUE	**0.027**		**0.056**		**0.006**	

Ulnar Nerve: Latency

TABLE14	RT ULNAR		LT ULNAR		ULNAR	
GROUPS	MEDIAN	RANGE	MEDIAN	RANGE	MEDIAN	RANGE
THAL1	1.94	2.54	2	2.96	1.98	2.96
THAL2	2.14	0.95	2.25	1.05	2.23	1.05
THAL3	2.21	2.9	2.08	3	2.165	3
P VALUE	**0.029**	**0.038**	**0.002**			

Sural Nerve: Latency

TABLE 16	RT SURAL		LT SURAL		SURAL	
GROUPS	MEDIAN	RANGE	MEDIAN	RANGE	MEDIAN	RANGE
THAL1	1.79	28.45	1.855	5.34	1.83	28.45
THAL2	2.125	2.54	2.275	2.25	2.225	2.54
THAL3	2.13	3.4	2	4.8	2.05	4.8
P VALUE	0.344		0.268		0.121	

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