International Journal of Research in Medical Sciences
Negi B et al. Int J Res Med Sci. 2018 Jun;6(6):2138-2142
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20182302

Original Research Article

Nerve conduction study in children with thalassemia

Banita Negi[1], Parveen Bhardwaj[1], Minoo Sharma[2]*, Sudhir Sharma[3], Neelam Grover[1]

[1]Department of Pediatrics, [2]Department of Physiology, [3]Department of Neurology, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India

Received: 10 April 2018
Accepted: 01 May 2018

***Correspondence:**
Dr. Minoo Sharma,
E-mail: minoo01sharma@gmail.com

ABSTRACT

Background: Regular blood transfusion and iron chelation therapy has increased life span of children with Thalassemia and with prolongation of life expectancy the toxic effect of iron on nervous system are being increasingly reported. Aim was to study nerve conduction study in thalassemia children and effect of iron overload on NCV.
Methods: 30 children with thalassemia on regular transfusions and iron chelation therapy and 30 healthy age and sex matched controls were subjected to nerve conduction study on three motor and sensory nerves. Statistical analysis used: means of quantitative variables were calculated in two groups and compared with student t- test. A p-value of <0.05 was taken as significant.
Results: On comparing the results the between cases and controls, we found that, there was no significant difference in the distal latency, amplitude and nerve conduction velocity of all three motor nerves and sensory nerves which were evaluated. Cases were further divided in to two groups depending upon serum ferritin level of < and >1000ng/ml. On comparing these two groups it was noted that distal latency was increased, nerve conduction velocity was slow in all the motor nerves (i.e. median, ulnar and tibial nerves) and sensory nerves (i.e. median, ulnar and sural nerves) in group with serum ferritin level >1000ng/ml and these findings were statistically significant.
Conclusions: We concluded that in children with thalassemia on regular transfusion and Iron chelation regime, nerve conduction study is normal in comparison to normal control but with progressive increase in serum ferritin level, the latency and conduction velocity is decreased and is statistically significant.

Keywords: Deferasirox, Ferritin, Nerve conduction study, Thalassemia

INTRODUCTION

Beta- thalassemia is an inherited disorder of hemoglobin characterized by an absence or reduced synthesis of beta globin chain. The net result is an excess of alfa chains, which precipitate and destroy the red cell precursors, leading to anemia, skeletal changes, splenomegaly and numerous other complication. Beta thalassemia major was first described in 1925 by Thomas Cooley and Lee.[1]

In those days, thalassemia major patients rarely used to survive the first decade of life. Following the introduction of regular transfusion regimens in the 1960's, initially by Orsini, and later by Wolman and Piomelli, thalassemics survived into 2nd and 3rd decades.[2-5] As a result of this improved survival due to transfusion therapy, the problems of transfusional hemosiderosis became conspicuous. The combination of transfusion and chelation therapy has dramatically extended the life expectancy of these patients, thus transforming thalassemia from a rapidly fatal disease of childhood to a chronic illness compatible with a prolonged life.[6]

Heart failure, arrhythmias, osteoporosis, bone pain, and bone changes, bile stone formation, increased risk of viral hepatitis, cirrhosis, delayed puberty, growth retardation;

developmental delay, diabetes mellitus and hypothyroidism are the common complications.[7] Over the years, several reports have demonstrated involvement of nervous system in beta thalassemia patients.[8] There is relatively low awareness about nervous system involvement in thalassemia and scanty literature in this field, especially in pediatric age group and in Indian population so the need for this study was felt.

METHODS

This study was cross sectional observational study conducted in a tertiary teaching hospital done over a period of one year from 1st July 2015 to 30th June 2016. The inclusion criteria for the case group was to include all beta thalassemia patients clinically diagnosed and confirmed by Hb electrophoresis with age >5 years of age. All thalassemic patients with preexisting neurological disease or congenital malformation and with vision and hearing problems were excluded. Age and sex matched healthy children attending pediatric OPD were included as control group. As per the inclusion criteria 30 thalassemic children were included in the control group and 30 age and sex matched children comprised the control group. Informed consent was taken from the parents or guardians of the beta thalassemia patients and the control group included in the study. All cases and control subjects were assessed clinically and were subjected to investigations like complete haemogram, Serum ferritin levels, Liver function test, Renal function test, Blood sugar level, vision and hearing evaluation. All cases and control subjects were evaluated for nerve conduction study on 12 channel EMG machine of NIHON KOHDEN enterprises from Japan. For motor nerve conduction-median, ulnar and tibial nerves were evaluated. For sensory nerve conduction- median, ulnar and sural nerve were evaluated. These nerves were evaluated for latency, amplitude and nerve conduction velocity (NCV).

A statistical analysis of the data was done using SPSS software for windows. A p -value of <0.05 was treated as statistically significant.

RESULTS

The present study, analysis was done on 30 thalassemia patients and 30 age and sex matched controls aged >5 years with mean age of 12.43 yrs (SD 5.19). Both cases and controls consisted of 20 (66.7%) males and 10 (33.3%) females, with a male to female ratio of 2:1. The haemoglobin values in cases ranged between 9.0-10.8 (mean-9.88, SD-0.55). Patients were transfused with packed red blood cells at intervals of 3-4 weeks with the goal being to maintain a hemoglobin level of >9g/dl as per the departmental protocol. The serum ferritin level in cases was less than 1000 ng/ml in 8 patients (26.7%), between 1000-2000ng/ml in 20 patients (66.7%) and more than 2000 ng/ml in 2 patients (6.7%). (Mean-1373 with SD-474.48). These patients also received deferasirox at a dose ranging between 20mg/kg/d to 40mg/kg/d depending on serum ferritin level i.e. >1000ng/ml. It was given once daily on an empty stomach as per protocol of the department. 15 patients (50%) received deferasirox @ 20-30mg/kg/day, 8 patients (26.7%) received defersirox @30-40mg/kg/day and 6 patients were not on deferasirox as the serum ferritin level was less than 1000ng/ml.

Nerve conduction study was done in all cases and controls and three motor nerves (i.e. median, ulnar and tibial nerves) and three sensory nerves (i.e. median, ulnar and sural nerves) were evaluated for distal latency, amplitude and nerve conduction velocity. On comparing the results the between cases and controls, we found that, there was no significant difference in the distal latency, amplitude and nerve conduction velocity of all three motor nerves and sensory nerves which were evaluated as shown in Table 1 and 2 respectively.

Table 1: Nerve conduction study in motor nerves.

Motor Nerves			Cases (N=30)		Controls (N=30)		P Value
			Mean ± SD	Min - max	Mean ± SD	Min - max	
Median	Wrist	Latency	3.36±0.65	2.3 - 4.3	3.27±0.67	2.2 - 4.2	0.626
		Amplitude	6.05±2.91	2.4 - 10.0	5.97±2.87	2.4 - 9.9	0.915
		NCV	49.85±5.35	41.2 - 61.9	49.73±5.28	41.1 - 61.0	0.934
	Elbow	Latency	6.39±1.24	4.7 - 8.2	6.31±1.26	4.6 - 8.1	0.789
		Amplitude	5.72±2.97	2 - 10	5.63±2.94	2 - 10	0.906
Ulnar	Wrist	Latency	5.62±0.53	1.7 - 3.4	5.54±0.55	1.6 - 3.3	0.569
		Amplitude	8.37±2.26	4.6 - 10.9	8.27±2.26	4.5 - 10.9	0.869
		NCV	49.17±4.59	44.4 - 60.9	49.02±4.60	44.0 - 60.8	0.924
	Elbow	Latency	6.21±1.21	4.0 - 7.5	6.11±1.21	3.9 - 7.4	0.750
		Amplitude	8.72±2.82	5.1- 11.4	8.63±2.82	5.0 - 11.4	0.898
Tibial	Ankle	Latency	3.47±0.94	2.6 - 5.4	3.36±0.95	2.5 - 5.3	0.653
		Amplitude	11.96±4.42	5.5 - 18.5	11.92±4.43	5.4 - 18.4	0.975
		NCV	56.07±5.84	46.5 - 68.4	56.01±5.88	46.4 - 68.4	0.969
	Poptileal	Latency	8.77±2.93	4.7 - 12.4	8.67±2.93	4.6 - 12.2	0.888
		Amplitude	8.99±1.44	7.0 - 10.9	9.31±2.29	6.9 - 16.2	0.515

Latency in millisecond, Amplitude in millivolt, Nerve conduction velocity(NCV) in meter/second

Table 2: Nerve conduction study in sensory nerves.

Sensory nerve		Cases (n=30)		Controls (n=30)		P Value
		Mean ±SD	Min - Max	Mean ± SD	Min - Max	
Median	Latency	2.15±0.31	1.6 - 2.6	2.03±0.31	1.5 - 2.5	0.152
	Amplitude	43.81±13.29	30.0 - 65.0	43.70±13.20	30.0 - 64.6	0.974
	NCV	53.49±1.79	50 - 57	53.56±1.85	50 - 57	0.871
UNLAR	Latency	2.08±0.52	1.3 - 2.9	2.00±0.52	1.2 - 2.8	0.551
	Amplitude	37.43±13.51	5.5 - 67.4	39.26±12.69	23.0 - 67.3	0.590
	NCV	46.27±2.87	41 - 54	46.12±2.80	41 - 54	0.845
SURAL	Latency	2.43±0.56	1.7 - 3.2	2.35±0.55	1.6 - 3.1	0.541
	Amplitude	12.90±5.26	7.4 - 21.8	13.27±5.36	7.3 - 21.7	0.792
	NCV	48.30±3.11	44 - 53	48.16±3.04	44 - 53	0.864

Latency in millisecond, Amplitude in microvolt, Nerve conduction velocity (NCV) in meter/second

Table 3: Nerve conduction studies in relation to serum ferritin levels (motor nerves).

NCS (motor nerve)			Group I (serum ferritin<1000ng/ml)	Group II (serum ferritin>1000ng/mL)	P value
			Mean ± SD	Mean ± SD	
Median	Wrist	Latency	2.938-0.5363	3.509-0.6331	0.031
		Amplitude	3.725-2.3837	6.891-2.6488	0.006
		NCV	55.113-5.662	47.932-3.7947	<0.001
	Elbow	Latency	5.475-1.0727	6.727-1.1403	0.012
		Amplitude	3.27-2.421	6.61-2.667	0.004
Unlar	Wrist	Latency	2.100-0.5904	2.805-0.3709	0.001
		Amplitude	6.025-2.0548	9.218-1.6755	<0.001
		NCV	54.175-6.3295	47.305-1.6079	0.018
	Elbow	Latency	4.975-1.2848	6.664-0.8232	<0.001
		Amplitude	6.213-2.2300	9.632-2.4567	0.002
Tibial	Ankle	Latency	3.100-0.9258	3.600-0.9284	0.202
		Amplitude	8.313-4.3222	13.282-3.7295	0.004
		NCV	59.988-2.2863	54.650-6.1097	0.002
	Poptileal	Latency	6.338-2.8410	9.659-2.4591	0.004
		Amplitude	7.775-1.1311	9.427-1.2896	0.003

Latency in millisecond, Amplitude in millivolt, Nerve conduction velocity(NCV) in meter/second

Table 4: Nerve conduction studies in relation to serum ferritin levels (sensory nerves).

NCS (sensory)		Group I (serum ferritin<1000ng/ml)	Group II (serum ferritin>1000ng/ml)	p value
		Mean ± SD	Mean ± SD	
Median	Latency	1.854-0.2873	2.257-0.2461	0.001
	Amplitude	53.838-15.1565	40.164-10.7370	0.01
	NCV	53.57-2.176	53.45-1.678	0.873
UNLAR	Latency	1.625-0.3991	2.243-0.4647	0.002
	Amplitude	28.263-7.1476	40.763-13.8304	0.022
	NCV	48.50-2.934	45.45-2.434	0.008
SURAL	Latency	2.000-0.5014	2.590-0.4984	0.008
	Amplitude	10.038-4.8565	13.945-5.1066	0.071
	NCV	50.49-2.574	47.50-2.944	0.017

Latency in millisecond, Amplitude in microvolt, Nerve conduction velocity(NCV) in meter/second

In order to find effect of ferritin level on nerve conduction cases were stratified in to two groups depending upon their serum ferritin level, Group A consisting of 8 cases with serum ferritin level<1000ng/ml

and Group B consisting of 22 cases with serum ferritin level >1000ng/ml.

On comparing these two groups it was noted that distal latency was increased, nerve conduction velocity was slow in all the motor nerves (i.e. median, ulnar and tibial nerves) and sensory nerves (i.e. median, ulnar and sural nerves) in group I with serum ferritin level >1000ng/ml and these findings were statistically significant. Amplitude was increased in all the three motor nerves and two of the sensory nerves (ulnar and sural) ($p< 0.05$) in group with serum ferritin of >1000ng/ml (Table 3 and 4).

DISCUSSION

In the present study conducted on children with thalessemia between 5-18 yrs of age with a mean age of 12.43 yrs. On comparing the results between cases and controls, we found that, there was no significant difference in the distal latency, amplitude and nerve conduction velocity of all three motor nerves (i.e. median, ulnar and tibial nerves) and sensory nerves (i.e. median, ulnar and sural nerves) which were evaluated, whereas Wong et al, performed NCS in 34 thalassemia patients and reported sensory neuropathy in 21% patients which was attributed to DFO neurotoxicity.[9] Zafeiriou et al, examined 40 patients of beta thalassemia and reported neuropathy in 25% of thalassemia patients which was also related to longer mean duration of DFO therapy.[10] This difference could be attributed to the fact that the patients in these studies received DFO as chelation therapy which was the drug of choice for iron chelation in that era where as our patients received deferasirox.

Papanastasiou et al, in their study on 53 beta thalassemia patients reported mild sensory and motor polyneuropathy in 22% of thalassemic patients which was related to age and appeared around 2nd and 3rd decade of life and was attributed to prolonged exposure to chronic hypoxia as a significant positive correlation was observed between the mean conduction velocity of the tibial and peroneal nerves and the mean haematocrit value.[11] Stamboulis et al, in their study on thirty six patients found sensory axonal neuropathy in 52.7% of the cases. The mean age of the cases was 29.2 years ±8.2. They concluded that sensory neuropathy in their patients was due to chronic hypoxia resulting from prolonged severe anemia.[12] This difference could be explained by the fact that the patients in these studies were in the second and third decade of life, whereas our patients were mostly in the pediatric age group with a mean age of 12.43yrs.

In our study when we subdivided case in to two groups depending upon serum ferritin level of < and >1000ngm/ml respectively. We found that with progressive increase in serum ferritin level, distal latency was increased, nerve conduction velocity was slow in all the motor nerves (i.e. median, ulnar and tibial nerves) and sensory nerves (i.e. median, ulnar and sural nerves) and these findings were statistically significant. This may be due to direct toxic effect of excessive iron on nerve, Wong et al, reported a significant association between subclinical toxicity to the peripheral or central nervous systems and serum ferritin level.[9]

In group with serum ferritin of >1000ng/ml, amplitude was increased in all the three motor nerves and two of the sensory nerves (ulnar and sural) ($p < 0.05$). A finding also reported by Sawaya et al, who found significant association of serum ferritin level with higher amplitude in sural nerve.[13] This may be because of degeneration followed by reinnervation via collateral sprouting which can cause an increase in amplitude.

CONCLUSION

So, from this study it was concluded that children of thalessemia on long term blood transfusion therapy and iron chelation may have normal nerve conduction but with progressive increase in serum ferritin level of more than 1000ng/ml, abnormalities were found in NCS as compared to patients with serum ferritin level less than 1000ng/ml.

Combination of transfusion and chelation therapy has dramatically extended the life expectancy of beta thalassemia patients. Frequent blood transfusions leading to iron overload have contributed to new spectrum of complications including neuropathies. Hence, the use of neurophysiologic monitoring becomes imperative, enabling early detection of neural pathway impairment and allowing appropriate management. Therefore, it is recommended that NCS should be applied periodically in beta thalassemia patients in order to detect neuropathy at an early stage and better quality of life.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Cooley T, Lee P. A series of cases of splenomegaly in children with anemia and peculiar bone changes. Trans Am Pediatr. 1925;37:29.
2. Orsini A, Boyer G. Thalassemia in Marseille; data on the frequency and observations on some clinical therapeutic and assisitential aspects. The social problem of microcythemia and Cooley's disease. Rome, 1961.
3. Wolman LJ. Transfusion therapy in Cooley's anemia. Growth and health as related to long range hemoglobin level. Ann N Y Acad Sci. 1964;119:736.
4. Wolman LJ, Ortolani M. Some clinical features of Cooley's anemia patients as related to transfusion schedules. Ann N Y Acad Sci. 1969;105:407-14.

5. Piomelli S, Danoff SJ, Becker MH, Lipera MJ, Travis SF. Prevention of bone malformations and cardiomegaly in Cooley's anemia by early hypertransfusion regimen. Annals New York Academy Sciences. 1969 Nov 1;165(1):427-36.
6. Khan DI. Thalassemia: Still a challenge. Gomal J Med Sci. 2006;4:47-8.
7. Cunningham MJ, Shankaran VG, Nathan DG, orkin SH. The Thalassemia. In: Orkin SH, Nathan DG, Ginsberg D, Look AT. Nathan and Oski's Hematology of infancy and childhood, 7th ed, Philadelphia: Sounders Elsevier;2009:1015-1109.
8. Moorjani JD, Chithira I. Neurotic manifestations in adolescents with thalassemia major. Indian J Pediatr. 2006;73:603-7.
9. Wong V, Li A, Lee A. Neurophysiological study of betathalassemia patients. J Child Neurol. 1993;8:330-5.
10. Zafeiriou DI, Kousi AA, Tsantali CT, Kontopoulos EE, Augoustidou-Savvopoulou PA. Neurophysiologic evaluation of long-term desferrioxamine therapy in beta-thalassemia patients. Pediatric Neurology. 1998;18:420-24.
11. Papanastasiou D, Papanikolaou D, Magiakau AM, Beratis NG, Tzebelikos E, Papapetropoulos T. Peripheral neuropathy in patients with b-thalassemia. J neurol Neurosurg Psychiatry. 1991;54:997-1000.
12. Stamboulis E, Vlachou N, Drossou M, Tsaftaridis P, Koutsi G, Katsaros N, Economou-Petersen E, et al. Axonal sensorimotor neuropathy in patients with beta-thalassemia. J Neurol Neurosurg Psychiatry. 2004;75:1483-6.
13. Sawaya RA, Zahed L, Taher A. Peripheral neuropathy in thalassaemia. Ann Saudi Med. 2006;26(5):358-63.

Cite this article as: Negi B, Bhardwaj P, Sharma M, Sharma S, Neelam Grover N. Nerve conduction study in children with thalassemia. Int J Res Med Sci 2018;6:2138-42.