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BRAINSTEM EVOKED POTENTIAL IN CHILDREN WITH THALASSEMIA

Paediatrics

Banita Negi MD, Junior Resident, Pediatrics, Indira Gandhi Medical College, Shimla, HP, India

Parveen Bhardwaj MD, Professor, Pediatrics , Indira Gandhi Medical College, Shimla, HP, India.

Minoo Sharma* MD, Associate Professor, Physiology, Indira Gandhi Medical College, shimla, HP, India *Corresponding Author

Sudhir Sharma DM, Professor, Neurology, Indira Gandhi Medical College, Shimla, HP, India.

ABSTRACT

Beta thalassemia has a spectrum of varied complications primarily caused by chronic anemia, iron overload, adverse effects of chelation, and transfusion-associated infections. Hearing impairment is one of the complications. Our aim was to study brainstem evoked potential in thalassemia children and effect of iron overload on brainstem evoked potential. Study was conducted in 30 children with thalassemia and 30 healthy age and sex matched controls. Both groups were subjected to brainstem evoked potential. On comparing the results between cases and controls, we found that, latency and interpeak latency of waves V, IV, I-III, III-V and I-V were significantly prolonged in cases as compared to controls. On comparing serum ferritin level with brainstem evoked potential between two groups of cases (group I with serum ferritin level<1000ng/ml and group II with serum ferritin level>1000ng/ml) significant relation was found. With progressive increase in serum ferritin level, latency and interpeak latency of waves in group II of cases were increased in brainstem evoked potential. We concluded that in children with thalassemia on regular transfusion and iron chelation regime, in brainstem evoked potential, latency and interpeak latency of waves were significantly prolonged in cases as compared to controls. A significant relation was found on comparing serum ferritin level with brainstem evoked potential between two groups of cases. With progressive increase in serum ferritin level, abnormalities were found in brainstem evoked potential.

KEYWORDS

Deferasirox, Ferritin, Brainstem evoked potential, Thalassemia

INTRODUCTION

Thalassemia is among the most widely distributed genetic disorder to cause major public health problem. Various organ disorders either as a result of the disease or the treatment may be affected by chronic anemia[1,2] Arrhythmias, heart failure, osteoporosis, bone pain, and bone changes, bile stone formation, increased risk of viral hepatitis, delayed puberty, cirrhosis, growth retardation, developmental delay, diabetes mellitus and hypothyroidism are the common complications.[3] Various factors such as chronic hypoxia, bone marrow expansion, iron overload and desferrioxamine neurotoxicity have been attributed to neurological complications. In most cases neurological involvement does not initially present with relevant signs and symptoms (i.e subclinical) and can only be detected by neurophysiological evaluation or neuroimaging.[4] Hearing impairment is one of the complication that may occur in thalassemic patients.[5] In thalassemia hearing impairment is correlated to chronic anemia,[6] iron overload,[6-8] extramedullary hematopoiesis,[9] and the side effect of desferoxamine chelation therapy.[8, 10-14] To detect hearing impairment various diagonostic tools are used, one of them is brainstem auditory evoked potential (BAEP). [15-18] This study was planned for early detection of neural pathway impairment in beta thalassemia patients and allowing for appropriate management.

Subjects and 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 case 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 brainstem evoked potential. Absolute latencies of waves I, II, III, IV, and V and interpeak latencies between waves I–III, III–V, and I–V will be recorded for each ear separately on 12 channel EMG machine of NIHON KOHDEN enterprises from Japan. 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:

In 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. In brainstem evoked potential, when cases and controls were compared, we found that, in right ear, there was significant difference in the latency of wave V and interpeak latency of wave I-III. Latency of wave V in control was 5.45ms(SD-0.07) and in cases was 5.50ms(SD-0.07) which was significantly increased ($p<0.05$). Interpeak latency of wave I-III in control was 2.06 ms (SD- 0.07) and in cases was 2.11ms(SD-0.07) which was also significantly increased ($p<0.05$). In left ear, there was significant difference in the latency of wave IV and interpeak latency of wave III-V and wave I-V. Interpeak latency of wave I-V in control was 3.74 ms (SD-0.02) and in cases was 3.75 ms (SD-0.02) which was significantly increased ($p<0.05$). Interpeak latency of wave III-V in control was 1.92ms (SD-0.02) and in cases in was 1.94 ms (SD-0.02) which was also significantly increased ($p<0.05$). Latency of wave IV in control was 4.51ms (SD-0.04) and in cases was 4.54ms (SD-0.03) which was significantly increased ($p>0.05$) whereas there was no significant difference in absolute latency and interpeak latency of other waves of left and right ear ($p>0.05$). (Table 1). On comparing serum ferritin level with brainstem evoked potential between two groups of cases (group I with serum ferritin level<1000ng/ml and group II with serum ferritin level>1000ng/ml). In right ear, serum ferritin level was significantly associated with greater latency of wave II in group II of cases. The latency increased from 2.36ms (SD-0.04) in group I to 2.45ms(SD-0.06) in group II ($p<0.05$) However, in left ear, it was also

significantly associated with greater interpeak latency of wave I-III in group I. Interpeak latency of wave I-III increased from 1.88 ms (SD-0.05) in group II to 1.94ms(SD-0.02) in group I ($p<0.05$). (Table 2). Latency and interpeak latency of other waves did not differ significantly with the level of serum ferritin ($p>0.05$) (Table 2).

Table 1: Comparision Of BAEP : Cases Vs Controls

Brainstem Evoked Potential		Cases (n=30)	Controls (n=30)	P Value
		Mean ± SD	Mean ± SD	
Right	I	1.44 ± 0.02	1.43 ± 0.03	0.137
	II	2.42 ± 0.07	2.40 ± 0.08	0.290
	III	3.48 ± 0.05	3.47 ± 0.05	0.495
	IV	4.60 ± 0.04	4.59 ± 0.05	0.437
	V	5.50 ± 0.07	5.45 ± 0.07	0.011
	I-III	2.11 ± 0.07	2.06 ± 0.07	0.020
	III-V	1.83 ± 0.03	1.82 ± 0.03	0.267
	I-V	3.79 ± 0.05	3.78 ± 0.05	0.410
Left	I	1.53 ± 0.03	1.52 ± 0.03	0.165
	II	2.47 ± 0.04	2.45 ± 0.05	0.230
	III	3.44 ± 0.02	3.43 ± 0.03	0.063
	IV	4.54 ± 0.03	4.51-0.04	0.019
	V	5.33 ± 0.07	5.32 ± 0.06	0.487
	I-III	1.89 ± 0.06	1.88 ± 0.06	0.310
	III-V	1.94 ± 0.02	1.92 ± 0.02	0.001
	I-V	3.75 ± 0.02	3.74 ± 0.02	0.011

Table 2: Relation Of BAEP With Serum Ferrit in Level In Cases

Brainstem Evoked Potential		GROUP I(serum ferritin<1000ng/ml)	GROUP II(serum ferritin>1000ng/ml)	p value
		Mean ± SD	Mean ± SD	
Right	I	1.43±0.01	1.44±0.02	0.156
	II	2.35±0.03	2.44±0.06	0.001
	III	3.46±0.06	3.40±0.04	0.513
	IV	4.62±0.04	4.59±0.04	0.093
	V	5.49±0.05	5.49±0.07	0.911
	I-III	2.11±0.10	2.11±0.05	0.995
	III-V	1.85±0.04	1.82±0.02	0.081
	I-V	3.79±0.04	3.79±0.57	0.992
Left	I	1.54±0.02	1.52±0.02	0.377
	II	2.47±0.04	2.46±0.04	0.396
	III	3.44±0.01	3.43±0.02	0.399
	IV	4.53±0.02	4.53±0.02	1
	V	5.33±0.02	5.32±0.07	0.902
	I-III	1.93±0.06	1.87±0.05	0.016
	III-V	1.94±0.02	1.94±0.02	0.958
	I-V	3.74±0.01	3.75±0.01	0.157

DISCUSSION:

In the present study , conducted on children with thalessemia between 5-18 yrs of age with a mean age of 12.43 yrs. When cases and controls were compared, we found that, in right ear, there was significant difference in the latency of wave V and interpeak latency of wave I-III. Latency of wave V in control was 5.45ms(SD-0.07) and in cases was 5.50ms(SD-0.07) which was significantly increased ($p<0.05$). Interpeak latency of wave I-III in control was 2.06 ms (SD- 0.07) and in cases was 2.11ms(SD-0.07) which was also significantly increased ($p<0.05$). In left ear, there was significant difference in the latency of wave IV and interpeak latency of wave III-V and wave I-V. Interpeak latency of wave I-V in control was 3.74 ms (SD-0.02) and in cases was 3.75 ms (SD-0.02) which was significantly increased ($p<0.05$). Interpeak latency of wave III-V in control was 1.92ms (SD-0.02) and in cases in was 1.94 ms (SD-0.02) which was also significantly increased ($p<0.05$). Latency of wave IV in control was 4.51ms (SD-0.04) and in cases was 4.54ms (SD-0.03) which was significantly increased ($p>0.05$) whereas there was no significant difference in absolute latency and interpeak latency of other waves of left and right ear ($p>0.05$) . On comparing the results with other studies, Wong et al in 1993, reported mild sensorineural hearing impairment in 12% of thalassemia patients which was realted to long use of desferoxamine.[19] Zafeiriou et al in 1998 reported abnormal brainstem evoked potential in 25% of thalassemia patients[20]. Subclinical involvement of auditory pathway was stastically associated with higher mean daily desferoxamine doses and longer duration of desferioxamine. Triantafyllou et al reported abnormal brainstem evoked potential in 25% of thalassemia patients which was related either to desferoxamine neurotoxicity or to iron overload[21]. Our results could be explained on the basis of its significant relation with serum ferritin level: In right ear, serum ferritin level was significantly associated with greater latency of wave II in group II of cases. The latency increased from 2.36ms (SD-0.04) in group I to 2.45ms(SD-0.06) in group II ($p<0.05$) However, in left ear, it was also significantly associated with greater interpeak latency of wave I-III in group I. Interpeak latency of wave I-III increased from 1.88 ms(SD-0.05) in group II to 1.94ms(SD-0.02) in group I ($p<0.05$). This was an isolated finding and difficult to explain hence, further studies are needed to explain this. Latency and interpeak latency of other waves did not differ significantly with the level of serum ferritin ($p>0.05$). All the patients were without symptoms of hearing impairment. No studies are available to support this data. Waves of brainstem evoked potential arises from different sites on the stimulation of auditory neural pathway. Wave I arises from peripheral auditory nerve close to chochlea, wave II arises from the same generator as wave I, wave III from superior olivary nucleus, IV and V from lateral leminiscus and superior colliculus respectively. Prolonged I-III interpeak latency demonstrates defect in brainstem auditory conduction system between N.VIII close to the cochlea and lower portion of the pons. Whereas prolonged I-III and III-V interpeak latencies demonstrates diffused lesion in brainstem auditory pathways. Prolonged I-V interpeak latency demonstrates several dysfunction of acoustic nerve or brainstem, but the localization of the lesion could not be specified. Prolongation of wave possibly indicate that the timing of neuronal activity is delayed uniformly across the cell population. It indicates dysfunction not complete loss of activity; in a part of infratentorial auditory pathway.

So, from this study it was concluded that in brainstem evoked potential, latency and interpeak latency of waves V, IV, I-III, III-V and I-V were significantly prolonged in cases as compared to controls, which indicate subclinical whole auditory pathway dysfunction. On dividing cases into further two groups i.e group I with serum ferritin <1000ng/ml and group II with serum ferritin>1000 ng/ml and comparing serum ferritin level with brainstem evoked potential, a significant relation was found. With progressive increase in serum ferritin level, abnormalities were found in brainstem evoked potential, there was subclinical whole auditory pathway dysfunction. Iron overload due to frequent blood transfusion have contributed to new spectrum of complications. Hence, the use of brainstem evoked potential becomes imperative, enabling early detection of subclinical whole auditory pathway impairment and allowing appropriate management. Therefore, it is recommended that brainstem evoked potential should be applied periodically in beta thalassemia patients in order to detect neuropathy at an early stage and better quality of life.

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