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Visual Evoked Potential in Children with Thalassemia

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ABSTRACT

Background and Aim: Beta thalassemia has a spectrum of varied manifestations and complications. Survival is associated with various multisystem complications primarily caused by chronic anemia, iron overload, adverse effects of chelation, and transfusion-associated infections. Thus, a disease that starts merely as hemolytic anemia attains the dimension of a chronic disease with multisystem involvement. Neurological involvement is initially subclinical and can only be detected during neurophysiological or neuroimaging evaluation. Abnormal findings in the visual evoked potential recordings are mainly attributed to deferoxamine neurotoxicity. Aim was to study visual evoked potential in thalassemia children and effect of iron overload on visual evoked potential.

Methods: 30 children with thalassemia on regular transfusion and iron chelation therapy and 30 healthy age and sex matched controls were subjected to visual evoked potential. 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 between cases and controls, there was no significant difference in p100 wave latency of both eyes (p>0.05). On comparing two groups of cases (group I with serum ferritin level<1000ng/ml and group II with serum ferritin level >1000ng/ml) serum ferritin level was significantly associated with greater p100 latency in both right and left eye in group II of cases.

Conclusions: We concluded that in children with thalassemia on regular transfusion and Iron chelation regime, visual evoked potential is normal in comparison to normal control but with progressive increase in serum ferritin level, the latency is increased and is statistically significant.

Keywords: Deferasirox, Ferritin, Visual Evoked Potential, Thalassemia

INTRODUCTION

Thalassemia is among the most widely distributed genetic disorder to cause major public health problem. β Thalassemia is a severe hemolytic anemia occurring as a result of deficient or absent synthesis of beta-globin chain of HbA.[1] 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. There are two clinically important presentation of beta thalassemia. Homozygous beta thalassemia usually results in thalassemia major, a severe anemia which requires regular blood transfusion and iron chelation therapy from early infancy for survival. A milder form of this disorder exists called thalassemia intermedia, which encompasses a wide spectrum of clinical severity, ranging from transfusion independency to the occasional need for transfusion. Thalassemia intermedia may result from a variety of molecular processes, but its milder clinical presentation is usually due to a less marked,

imbalance of the alfa:betaglobin chain ratio.[2] 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.[3] On the other hand, frequent blood transfusions leading to iron overload and chronic nature of the disease have contributed to a whole new spectrum of complications in patients suffering from thalassemia major.[4,5] 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.[6] Over the year several reports have demonstrated involvement of nervous system in beta thalassemia patients.[7] Neurological complications have been attributed to various factors such as chronic hypoxia, bone marrow expansion, iron overload and desferrioxamine neurotoxicity. In most cases neurological involvement does not initially present with relevant signs and symptoms (i.e. subclinical) and can only be detected during neurophysiological or neuroimaging evaluation.[8] There is relatively low awareness of this manifestation due to a very few studies in Indian population. Hence, the need for this study. This study was planned to detect subclinical lesion in beta thalassemia patients by neurophysiological evaluation, enabling early detection of neural pathway impairment and allowing for appropriate management, in order to achieve a better quality life for this patient group.

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 visual evoked potential. Following parameters will be recorded: Latency for P_{100} wave in mill sec (ms) will be recorded for each eye separately on 12 channel EMG machine of NIHON KOHDEN enterprises from Japan.

STATISTICAL ANALYSIS

We analysed the data using SPSS software for windows. We calculated means, standard deviation of quantitative variables in both the groups i.e. cases and controls. We also calculated means and standard deviation of quantitative variables in two groups of cases i.e. group I (serum ferritin level <1000 ng/ml) and group II (serum ferritin level >1000ng/ml). We compare the means by student t-test as relevant to given statistical situation. 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 visual evoked potential, on comparing the results between cases and controls, there was no significant difference in p100 wave latency of both eyes (p>0.05) .In right eye , P100 latency in cases was 110.69ms (SD-0.97) and in controls was 110.64ms (SD-0.94) which was not significant. In left eye, P100 latency in cases was 110.59ms (SD-0.90) and in controls was 110.50ms (SD-0.88) which was also not significant (TABLE 1). On comparing two groups (group I with serum ferritin level<1000ng/ml and group II with serum ferritin level>1000ng/ml), serum ferritin level was associated with greater p100 latency in both right and left eye in group II of cases. In right eye, p100 latency increased from 110.09ms in group I to 110.91ms in group II which was significant (p<0.05). In left eye, p100 latency increased from 109.99ms in group I to 110.81ms in group II which was also significant (p<0.05). (TABLE 2).

TABLE 1: COMPARISION OF VEP : CASES vs CONTROLS

Visual Evoked Potential (P100 Latency)	Cases (n=30)		Controls (n=30)		P Value
	Mean ± SD	Min - Max	Mean ± SD	Min - Max	
Right	110.69 ± 0.97	108.2 - 111.9	110.64 ± 0.94	108.2 - 111.8	0.861
Left	110.59 ± 0.90	109.1 - 111.9	110.50 ± 0.88	109.0 - 111.7	0.696

TABLE 2: RELATION OF VEP WITH SERUM FERRITIN LEVEL IN CASES

VEP(P100 LATENCY)	GROUP I(serum ferritin<1000ng/ml)	GROUP II(serum ferritin>1000ng/ml)	p value
	Mean ± SD	Mean ± SD	
Right	110.088-1.0521	110.905-0.8610	0.039
Left	109.988-0.7661	110.809-0.8541	0.024

DISCUSSION

In the present study conducted on children with thalassemia between 5-18 yrs of age with a mean age of 12.43 yrs. On comparing the results between cases and controls, there was no significant difference in p100 wave latency of both eyes (p>0.05) whereas, Zaferriou et al in 1998 reported abnormal visual evoked potential in 15% of thalassemia patients[9] and Rahiminejad et al in 2009, reported abnormal visual evoked potential in 3.5 % of thalassemia patients[10]. Both of which were attributed to deferoxamine neurotoxicity. This difference could be attributed to the fact that the patients in these studies received deferoxamine as chelation therapy where as our patients received deferasirox. On comparing two groups of cases (group I with serum ferritin level <1000ng/ml and group II with serum ferritin level >1000ng/ml), serum ferritin level was significantly associated with greater p100 latency in both right and left eye in group II of cases where as Rahiminejad et al in2009 reported no relation with the serum ferritin level[10]

CONCLUSION

The results of our study revealed that there was no significant difference on comparing cases with controls in visual evoked potential. On dividing cases into further two groups and comparing serum

ferritin level with visual evoked potential, a significant relation was found. With progressive increase in serum ferritin level, abnormalities were found in visual evoked potential, there was subclinical optic sensory neuropathy. 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. Hence, the use of neurophysiologic monitoring becomes imperative, enabling early detection of neural pathway impairment and allowing appropriate management. Therefore, it is recommended that visual evoked potential should be applied periodically in beta thalassemia patients in order to provide, better quality of life.

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