EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 12
341-344
Year: 2021

EFFECT OF DEGREE OF IRON OVERLOAD ON BRAINSTEM AUDITORY EVOKED POTENTIAL IN THALASSEMIA PATIENTS ON IRON CHELATION THERAPY.

Mridul Yadav[1]*, Jyoti Yadav[2], Shelja Deswal[3] and Pankaj Abrol[4]

[1]Associate Professor, Department of Physiology, Pt. BDS PGIMS Rohtak, Haryana, India.
[2]Senior Prof. & Head, Department of Physiology, Pt. BDS PGIMS Rohtak, Haryana, India.
[3]Assistant Professor, Department of Physiology, Pt. BDS PGIMS Rohtak, Haryana, India.
[4]Professor & Head, Department of Pediatrics, SGT Medical College Hospital & Research Institute, Budhera, Gurugram, Haryana, India.

***Corresponding Author: Dr. Mridul Yadav**
Associate Professor, Department of Physiology, Pt. BDS PGIMS Rohtak, Haryana, India.

Article Received on 02/06/2021 **Article Revised on 02/11/2021** **Article Accepted on 23/11/2021**

ABSTRACT
Thalassemia is a genetic disease requiring long term blood transfusions. This results in iron overload in these patients which is a challenging problem despite iron chelation therapy. The purpose of this study was to detect any correlation between the degree of iron overload and subclinical involvement of auditory pathway by doing brainstem auditory evoked potential (BAEP). Forty five patients of thalassemia major were divided into three groups (I, II &III) based on their iron chelation therapy as desferrioxamine, combination of desferrioxamine & deferiprone and only deferiprone respectively. Each group was further divided into subgroups 'a' and 'b' having serum ferritin levels less than 5000 ng/mL and more than 5000 ng/ mL respectively. Brainstem auditory evoked potentials were recorded by using RMS EMG EP MK2 and correlated with serum ferritin levels of subgroups a and b within each group. We found that there was no significant correlation between degree of iron overload and absolute latencies and interpeak latencies of auditory evoked potentials in any of the groups, Our findings indicate that high levels of serum ferritin do not affect BAEP in thalassemia patients.

KEYWORDS: Thalassemia, Brainstem auditory evoked potentials, serum ferritin.

INTRODUCTION
The term thalassemia is derived from the Greek word "Thalassa" which means "the sea" as the patients of thalassemia were initially identified in the areas around the Mediterranean sea. Thalassemia is common among people originating from Africa, Asia & the Mediterranian Sea or the Middle East. It is common in this region as these are endemic in malaria and it helps to protect carriers against malaria. The children suffering from thalassemia require long term blood transfusion therapy to maintain their blood hemoglobin levels.[1] Although transfusion therapy can enhance the quality of life and prolong survival in thalassemia patients,[2],[3] there is no physiological mechanism for excretion of iron. These children eventually develop iron overload due to repeated transfusions and increased absorption from gastrointestinal tract. The excess iron is stored in various tissues of the body as ferritin and hemosiderin which can result in organ failure and eventually death.[4] For better clinical management of iron overload in thalassemia chelation therapy has become an essential part.[5] But management of iron overload in thalassemia patients still remains a challenge due to various factors including availability of iron chelating agents and poor compliance.[6] Iron overload has been documented to affect auditory pathway. Sensorineural hearing loss has occurred with unusual frequency in patients with hemochromatosis,[7] as well as in patients with transfusional iron overload who have received little or no deferoxamine as chelation therapy.[8] Therefore the present study was planned to find if there is correlation between the degree of iron overload and absolute latencies and interpeak latencies of BAEP.

MATERIAL AND METHODS
The present study was conducted in the Department of Physiology & in the Department of Paediatrics, Pt. B. D. Sharma Post Graduate Institute of Medical Sciences, Rohtak, in 45 patients of thalassemia .All the patients of thalassemia were more than 5 years of age clinically diagnosed and confirmed by Hb Electrophoresis attending the Thalassemia Day Care centre. Patients with history of neurological disease, intake of drugs with known auditory neurotoxicity, patients of diabetes mellitus and with conductive deafness were excluded from the study. The patients receiving iron chelation therapy for more than 6 months were enrolled in the study. They were divided into three groups of 15 patients

each. The first group (Group I) included patients of thalassemia receiving DFO therapy (Injection Desferrioxamine) for more than 6 months. The second group (Group II) received DFO and Deferiprone on every alternate day. The third group (Group III) included patients receiving Deferiprone alone (oral chelating agent). The data was collected which included name, age, sex, Hb, serum ferritin, duration of chelation therapy and dose of chelation therapy at the time of audiologic test. Each group was further divided in two subgroups 'a' and 'b' according to the level of serum ferritin i.e. less than 5000 and more than 5000 ng/mL. The procedure was explained to the patients and their parents and informed consent was taken.

Brainstem Auditory Evoked Potential (BAEP)

BAEP recording was done by using RMS EMG EP MK2 machine. Hearing threshold of 25 dB was considered as normal according to WHO classification of hearing impairment. Click stimuli at the rate of 11.1/sec with intensity of 70 dB above normal hearing threshold were presented to both ears monaurally, in the form of 0.1 ms square pulses through shielded headphones with alternating polarity.[9] During stimulation, other ear was masked by 40 dB sound. Total 2000 stimulations were applied.

Serum Ferritin

Serum ferritin estimation was done by ADVIA Centaur CP Ferritin assay which is a two-site sandwich immunoassay using direct chemiluminometric technology.[10]

RESULTS

Table 1: Comparison of absolute latencies and interpeak latencies of right ear with S. ferritin levels within Group I, Group II and Group III.

Latency (msec)	Gp Ia ≤ 5000ng/mL (mean ± SD)	Gp Ib > 5000ng/mL (mean ± SD)	p value	Gp IIa ≤ 5000ng/mL (mean ± SD)	Gp IIb > 5000ng/mL (mean ± SD)	p value	Gp IIIa ≤ 5000ng/mL (mean ± SD)	Gp IIIb > 5000ng/mL (mean ± SD)	p value
Wave I	2.02 ± 0.60	1.94 ± 0.63	>0.05	1.74 ± 0.27	1.67 ± 0.42	>0.05	1.5 4 ± 0.19	1.42 ± 0.19	>0.05
Wave II	2.75 ± 0.36	2.59 ± 0.41	>0.05	2.86 ± 0.37	2.77 ± 0.62	>0.05	2.60 ± 0.23	2.37 ± 0.15	>0.05
Wave III	3.785 ± 0.42	3.59 ± 0.30	>0.05	3.56 ± 0.33	3.61 ± 0.38	>0.05	3.52 ± 0.28	3.5 ± 0.56	>0.05
Wave IV	4.90 ± 0.30	4.58 ± 0.42	>0.05	4.81 ± 0.38	4.69 ± 0.33	>0.05	4.78 ± 0.34	4.54 ± 0.41	>0.05
Wave V	5.75 ± 0.50	5.71 ± 0.5	>0.05	5.78 ± 0.49	5.61 ± 0.25	>0.05	5.56 ± 0.45	5.10 ± 0.42	>0.05
I – III	2.0 ± 0.13	2.1 ± 0.23	>0.05	1.96 ± 0.19	1.93 ± 0.09	>0.05	1.99 ± 0.30	2.07 ± 0.37	>0.05
I – V	3.93 ± 0.70	4.21 ± 0.30	>0.05	3.97 ± 0.39	3.93 ± 0.18	>0.05	4.01 ± 0.40	3.65 ± 0.21	>0.05
III- V	2.0 ± 0.71	2.11 ± 0.48	>0.05	2.02 ± 0.42	2.00 ± 0.19	>0.05	2.00 ± 0.53	1.58 ± 0.15	>0.05

p value not significant (>0.05) on comparison of Gp Ia with Ib; Gp IIa with IIb; Gp III a with IIIb

Table 2: Comparison of absolute latencies and interpeak latencies of left ear with S. ferritin levels within Group I, Group II and Group III

Latency (msec)	Gp Ia ≤ 5000ng/mL (mean ± SD)	Gp Ib > 5000ng/mL (mean ± SD)	p value	Gp IIa ≤ 5000ng/mL (mean ± SD)	Gp IIb > 5000ng/mL (mean ± SD)	P value	GpIIIa ≤ 5000ng/mL (mean ± SD)	Gp IIIb > 5000ng/mL (mean ± SD)	p value
Wave I	1.63 ± 0.21	1.35 ± 0.23	>0.05	1.43 ± 0.20	1.47 ± 0.17	>0.05	1.51 ± 0.17	1.58 ± 0.22	>0.05
Wave II	2.68 ± 0.40	2.35 ± 0.27	>0.05	2.42 ± 0.30	2.52 ± 0.30	>0.05	2.55 ± 0.23	2.59 ± 0.38	>0.05
Wave III	3.53 ± 0.44	3.51 ± 0.42	>0.05	3.38 ± 0.44	3.43 ± 0.33	>0.05	3.63 ± 0.34	3.52 ± 0.31	>0.05
Wave IV	4.74 ± 0.41	4.75 ± 0.04	>0.05	4.45 ± 0.46	4.56 ± 0.39	>0.05	4.48 ± 0.15	5.79 ± 0.47	>0.05
Wave V	5.56 ± 0.40	5.82 ± 0.46	>0.05	5.39 ± 0.34	5.41 ± 0.36	>0.05	5.36 ± 0.14	5.34 ± 0.33	>0.05
I – III	1.92 ± 0.35	2.15 ± 0.19	>0.05	1.95 ± 0.27	1.99 ± 0.40	>0.05	2.13 ± 0.30	1.94 ± 0.35	>0.05
I – V	3.86 ± 0.39	4.47 ± 0.69	>0.05	3.97 ± 0.29	3.95 ± 0.45	>0.05	3.86 ± 0.27	3.74 ± 0.33	>0.05
III- V	2.00 ± 0.36	2.31 ± 0.88	>0.05	2.01 ± 0.28	1.95 ± 0.29	>0.05	1.72 ± 0.36	1.78 ± 0.22	>0.05

p value not significant(>0.05) on comparison of Gp Ia with Ib; Gp IIa with IIb; Gp III a with IIIb

DISCUSSION

Transfusion therapy in thalassemia patients alleviates anemia and its sequele but it leads to massive tissue deposition of iron and eventually to organ failure.[11] Each unit of red cells contains 200 to 250 mg of elemental iron. Thus patients on chronic transfusion therapy by the age of 12 will have stored 55 or more grams of excess iron.[12] Moreover, the patients with ineffective erythropoiesis absorb iron from the gastrointestinal tract at an increased rate further adding to their iron burden.[13] Oral iron chelation with deferiprone has shown poor efficacy when used alone.[14] Also failure of many patients to comply with cumbersome administration of DFO is an obstacle to proper management of iron overload.[15]

In our study when we compared the auditory evoked potentials of patients with levels of serum ferritin less

than 5000ng /mL with those with serum ferritin levels more than 5000ng/mL, i.e. comparing Gp Ia with Ib; Gp IIa with IIb and Gp IIa with IIb, it was observed that there is no statistically significant difference between them in both the ears despite the mode of iron chelation therapy. In all the three groups (I, II and III) there was no correlation between the serum ferritin levels and the absolute latencies and interpeak latencies. The observations of our study are similar to Wang et al who found no relationship between serum ferritin levels and neurotoxicity of auditory system.[16] Our result was similar to that of Aregioulu et al who observed that there was no difference in patients with neurosensory hearing loss and those with normal hearing in regard to serum ferritin levels.[17] Triantafyllou et al observed that disturbances in evoked potentials were found in patients with serum feritin levels above 2000 ng or under 1500ng.[18] Our findings differed with that of a study done by Das et al where umblical cord serum ferritin levels in new borns were correlated with latencies of waves in BAEP and it was observed that low ferritin levels cause prolongation in the latency of wave V of AEP and affects central conduction of waves.[19] Porter et al also observed that when the degree of iron overload was looked at, a lower serum ferritin was also a risk factor for sensorineural hearing loss.[20] In another study significant sensorinueral hearing loss was seen in patients with lower iron overload.[21] This discrepancy between our data and the other data may be related to our patients' younger age and meticulous control of these patients in other studies. It seems likely that the causative factors in their patients were, as they suggest bony hypertrophy that affected the internal auditory canal, iron deposition or chronic hypoxia. Our patients had no evidence of bony hypertrophy that affected the region of the internal auditory canal and they had received an adequate number of transfusions before thus making chronic hypoxia an unlikely cause. Iron chelating agent DFO has also been found to exhibit ototoxic effects.[22][23] The absence of sensorineural hearing loss in patients with serum. ferritin level more than 2000 ng/ml at the time of maximum dosage of DFO suggests that a high degree of iron overload protects against ototoxic effects of DFO.[20] When we compared the serum ferritin level in the three groups it was lowest for the patients on DFO suggesting that DFO is a better chelating agent than deferiprone and the combination of two.

CONCLUSION

This study was done to observe the effect of degree of iron overload on BAEP but not to compare the effects of different modalities of iron chelation therapy on BAEP. Though in our study no correlation was found between serum ferritin levels and BAEP but other studies have shown that iron chelating agents as well as high and low serum ferritin levels cause hearing loss and have sublinical effects on auditory pathway; it would be pertinent to do the multifactorial analysis of hearing loss in thalassemia patients and meticulously follow them up to adjust the dose and mode of chelation for the best outcome.

REFERENCES

1. Cohen AR, Mijanin J, Schwartz E: Rapid removal of excessive iron with daily, high dose intravenous chelation therapy. J Pediatr, 1989; 115: 151-5.
2. Giardiana PJV, Ehlers KH, Engle MA: The effect of subcutaneous desferrioxamine on the cardiac profile of thalassemia major: A five-year study. Ann NY Acad Sci, 1985: 445 282-92.
3. Giardiana PJ, Grady RW, Ehlers KH: Current therapy of Cooley's anaemia. A decade of experience with subcutaneous desferrioxamine.Ann NY Acad Sci, 1990; 612: 275-85.
4. Engle M A: Cardiac involvement in Cooey's anemia. Ann NY Acad Sci 119:694-702. 1964.
5. Brittenham GM, Griffith PM, Nienhuis AW: Efficacy of desferrioxamine in preventing complications of iron overload in patients with thalassemia major. N Eng J Med, 1994; 331:567-73.
6. Shah FT, Sayani F, Trompeter S, Draser E. Challenges of blood transfusions in β-thalassemia. Blood Review.
7. Rance G, Chisari D. Auditory neuropathy in a patient with hemochromatosis. J Otol, 2016; 11(4): 185-91.
8. De Virgiliis S, Argiolu F, Sanna G.. Auditory involvement in thalassemia major. Acta Haematol, 1979; 61: 209-15.
9. Tandon OP. average evoked potentials-clinical application of short latency responses. Indian J Physiol Pharmacol, 1998; 42(2) : 172-88.
10. Simes MA, Jr JE, Addiego. Feritin in serum: Diagnosis of iron overload in infants and children. 1974; 43: 581-3.
11. Elis JT, Schulman I, Smith CH. Generalised siderosis with fibrosisofliver and pancreas in Cooley's anemia. Am J Pathol, 1954; 30: 287.
12. Giardina PJ, Grady R W. Chelation therapy in β-Thalassemia: The Benefits and Limitations of Desferrioxamine. Seminars in Hematology,1995; 32(4): 304-12.
13. Graziano JH, Cerami A. Chelation therapy for the treatment of thalassemia. Semin Hematol, 1977; 14(1):127-34.
14. Daar S, Patahre AV. Combined therapy with desferrioxamine and deferiprone in beta thalassemia major patients with transfusional iron overload. Ann Hematol, 2006; 85(5): 315-9.
15. Haghpanah S, Zarei T, Zahedi Z. Compliance and satisfaction with deferasirox (Exjade®) compared with deferoxamine in patients with transfusion-dependent beta-thalassemia. Hematology, 2014; 19(4): 187-91.
16. Wong V, Li A, Lee A.C.W. Neurophysiologic Study of β-Thalassemia Patients. J Child Neurol, 1993; 8: 330-5.

17. 17. Argiolu F, Diana G, Avignone A, Cao A, Di Ninni S. Hearing impairment during DFO therapy for thalassemia major. J Pediat, 1991; 118: 826-7.
18. Triantafyllou N, Fisfis M, Sideris G, Triantafyllou D, Rombos A, Vrettou H et al . Neurophysiological and neurootological study of homozygous β thalassemia under long term DFO treatment. Acta Neurol Scand, 1991; 83: 306-8.
19. Das S, Chakraborty S, Gupta C : Effect of Umbilical Cord Ferritin Level on Auditory Brainstem Response Threshold in Newborns. Iranian Journal of Otorhinolaryngology, 2020; 32(2): 73-8.
20. Porter JB, Jaswon MS, Huchns ER, East LA. Desferrioxamine ototoxicity: Evaluation of risk factors in thalassemia patients guidelines for safe dosage. Br. J Hematol, 1989; 73: 403-9.
21. Albera R, Pia F, Morra B, Lacilla M, Bianco L. Hearing loss and desferrioxamine in homozygous beta-thalasemia. Audiology, 1988; 27(4): 207-14.
22. Sacco M, Melelco D, Trcario N, Greco MIani A, Serra E, Parlantore L. Evaluation of DFO ototoxicity in thalassemia patients. Minerva Pediatr, 1994; 46: 225-30.
23. Karimi M, Asadi-Pooya AA, Khademi B, Asadi-Pooya K, Yamohammadi H. Evaluation of the incidence of sensorineural hearing loss in beta-thalassemia major patients under regular chelation therapy with DFO. Acta Hematol, 2002; 108: 79-83.