

Evaluation of brainstem auditory-evoked potentials in infants with iron deficiency anemia

Demir eksikliği anemisi olan infantlarda beyin sapı işitsel uyarılmış potansiyel yanıtlarının değerlendirilmesi

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Abstract

Purpose: To evaluate and compare the brain functions of infants with and without Iron Deficiency anaemia (IDA) electrophysiologically with brainstem auditory potentials (BAEPs).

Materials and methods: BAEP tests were performed on 26 healthy infants and 26 infants with iron deficiency anaemia, aged 6-24 months, who were followed through the Paediatric Haematology Department at SDU Faculty of Medicine. Children were classified as anaemic if their haemoglobin (Hb) level fell below -2 standard deviations for their age. All patients diagnosed with iron deficiency anaemia received 5 mg/kg/day of divalent iron glycine sulphate complex in three doses daily for a duration of 12 weeks, to be taken on an empty stomach. Both group were orally administered Chloral hydrate at a dosage of 50 mg/kg prior to the BAEP test to induce sedation. The BAEP was recorded at a sound intensity level of 90 decibels, with a frequency of 10 Hertz, and with click stimuli ranging from 1000 to 2000. The BAEP test was administered to the IDA group before and after treatment, as well as to the control group, with a 3-month interval between tests.

Results: 14 (53.8%) of the IDA patients were males, and 16 (61.5%) of the control group were females. Patients with IDA had an average age of 14.4±3.09 months, while the control group patients have an average age of 11.2±4.04 months. Patients with iron deficiency anaemia had lower pre-treatment levels of Hb, Hct, MCV, MCH, MCHC, transferrin saturation percentage, and ferritin compared to the control group, whereas platelet and RDW values were greater ($p<0.05$). The study compared the Brainstem Auditory Evoked Potential (BAEP) values of patients with Iron Deficiency Anaemia (IDA) before treatment with those of control patients. The results indicated that the III-V interval, showing nerve conduction time, was significantly prolonged in the pre-treatment BAEPs ($p=0.002$). There was no significant difference in interpeak latencies between the control group and patients with iron deficiency anaemia (IDA) following therapy ($p<0.05$). Significant differences were found in the I-III, III-V, and I-V interpeak latencies of individuals with iron deficiency anaemia before and after treatment ($p<0.05$).

Conclusion: Iron deficiency anaemia appears to affect the functional development of the auditory system. Untreated iron deficiency anaemia, especially in infancy, may have long-term effects on the central auditory system. Consequently, this can result in changes in the maturation of neuro-functional.

Keywords: Iron deficiency anaemia, myelination, BAEP.

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Öz

Amaç: Demir eksikliği anemisi (DEA) olan ve olmayan bebeklerin beyin fonksiyonlarını beyin sapı işitsel potansiyelleri (BAEPs) ile elektrofizyolojik olarak değerlendirmek ve karşılaştırmaktır.

Gereç ve yöntem: SDÜ Tıp Fakültesi Pediatrik Hematoloji Bilim Dalı'nda takip edilen, yaşları 6-24 aylık, 26 DEA'lı olan ve 26 DEA'lı olmayan sağlıklı çocuğa BAEP testi uygulandı. Hemoglobün (Hb) değeri yaşına göre -2SD'nin altında olan çocuklar anemik olarak kabul edildi. DEA'lı tüm hastalara aç karnına 12 hafta boyunca 3 dozda 5 mg/kg/gün iki değerlikli demir glisin sülfat kompleksi verildi. Sedasyon için testten önce kloral hidrat (50 mg/kg/doz) oral olarak verildi. BAEP, 90dB, frekans 10 Hz ve 1000-2000 klik uyarılarla kaydedildi. Bu test, DEA grubuna tedaviden önce ve sonra olmak üzere iki kez, kontrol grubuna ise 3 ay arayla iki kez uygulandı.

Bulgular: DEA hastalarının 14'ünü (%53,8) erkekler, kontrol grubunun 16'sını (%61,5) kadınlar oluşturdu. DEA'lı hastaların yaş ortalaması 14,4±3,09 ay, kontrol grubu hastalarının yaş ortalaması ise 11,2±4,04 aydır. DEA'lı hastaların tedavi öncesi Hb, Hct, MCV, MCH, MCHC, transferrin saturasyon yüzdesi ve ferritin değerleri kontrol grubundan daha düşükkün, trombosit ve RDW değerleri daha yüksektir ($p<0,05$). DEA'lı grubunun tedavi öncesi ile kontrol grubunun interpike latansları karşılaştırıldığında, DEA'lı grubun III-V interpike latansında uzama tespit edilmiştir ($p=0,002$). Kontrol grubunun ve DEA'lı grubun tedavi sonrası interpike latansları karşılaştırıldığında, interpike latans değerlerinde anlamlı fark tespit edilmedi ($p>0,05$). DEA hastaların tedavi öncesi ve tedavi sonrası I-III, III-V ve I-V interpike latans değerlerinde anlamlı fark tespit edildi ($p<0,05$).

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Sonuç: Demir eksikliği anemisinin işitsel sistemin fonksiyonel gelişimini etkilediği görülmektedir. Tedavi edilmeyen demir eksikliği anemisi, özellikle bebeklik döneminde, merkezi işitme sistemi üzerinde uzun vadeli etkileri olabilir. Bu durum nöro-fonksiyonel yapıların maturasyonunda değişikliklere yol açabilir.

Anahtar kelimeler: Demir eksikliği anemisi, miyelinizasyon, BAEP.

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Introduction

Iron deficiency is the predominant nutritional problem globally. This inadequacy persists as a significant public health issue worldwide, particularly notable in countries with low to middle socioeconomic levels [1, 2]. The global prevalence of anaemia in children aged 6-59 months is over 40% [3]. The prevalence of anaemia in children in Türkiye ranges from 15.2% to 62.5% [4]. Anaemia is defined as a haemoglobin (Hb) level that is more than 2 standard deviations below the average for the age of the individual [5]. Infants and young children are susceptible to iron deficiency anaemia because of their rapid growth, whereas adolescent girls are at risk due to menstrual blood loss [6]. Iron is present in the composition of our body's haemoglobin, myoglobin, and other enzymes. Iron is involved in various crucial tasks such oxygen transfer, adenosine triphosphate (ATP) and deoxyribonucleic acid (DNA) synthesis, mitochondrial activities, myelination, neurotransmitter regulation, and serotonin production [7]. Research has demonstrated that infants with iron deficiency (ID) perform worse in mental and motor development assessments compared to infants with adequate iron levels [8]. Iron is essential for the production of myelin. Research on rats has demonstrated that iron deprivation leads to hypomyelination. Iron deficiency has a long-term impact on neuronal conduction and the development of the central nervous system. Myelination or nerve conduction speed decreases as interpeak latencies increase. Reduced interpeak latency is linked to improved myelination [9, 10]. The Brainstem Auditory Evoked Potential (BAEP) test evaluates the auditory pathways in the brainstem of young children, which cannot be assessed through behavioural audiological testing. This study aims to evaluate and compare the brain functions of infants with and without iron deficiency anaemia (IDA) using brainstem auditory potentials (BAEPs).

Materials and methods

This study was conducted between 1.07.2002 and 1.06.2004 at the haematology outpatient clinic of Süleyman Demirel University (SDU) Faculty of Medicine, Department of Child Health and Diseases.

Thirty-four infants between the ages of 6 months and 24 months diagnosed with iron deficiency anaemia and 26 healthy infants in the same age group without iron deficiency or anaemia were included in the research. The study excluded those who had a history of prenatal asphyxia, neonatal hyperbilirubinemia needing treatment, central nervous system infection, preterm, family history of hearing loss, low birth weight, malnutrition, and external auditory canal and middle ear abnormalities. Individuals within a specific age range were classified as having iron deficiency anaemia (IDA) if their haemoglobin (Hb) level was below -2 standard deviations and their ferritin level was below 10ng/ml [5]. The same laboratory tests were performed on the control group at the beginning of the study. The patients were categorised into two groups: the group with IDA (N: 34) and the group without IDA (N: 26). The IDA group received daily oral ferrous sulphate (ADEKA Pharmaceuticals Industry and Trade Inc., Samsun, Türkiye) at a dosage of 5mg/kg per dose for a duration of 12 weeks.

BAEP measurements were conducted twice in each group. BAEP testing was conducted at the study's beginning and again 12 weeks later. BAEPs were recorded and processed with the Nihon Kohden MEB-5504 device in a quiet and poorly light room. Both groups were orally administered 50mg/kg/dose of Chloral hydrate (Galenik Pharmaceuticals and Chemical Substances Domestic and Foreign Industry Trade Inc., İzmir, Türkiye) before the test for sedation. It was dissolved in water. Chloral hydrate sedation does not affect

BAEP parameters [11]. The active electrode was positioned on the earlobes, the vertex reference electrode on the vertex, and the neutral electrode on the forehead. The stimulus was shown to both ears at the same time. The stimulus strength was set at 90 decibels, the frequency at 10 Hertz, and the analysis time at 10 milliseconds. 1000-2000 clinical stimuli were used for each test. The potentials were visualised as a waveform on the monitor, and

the I, II, III, IV, and V waves were identified using a cursor. Absolute interpeak latencies (IPL) were then determined. The BAEP recordings were evaluated based on the latency and interpeak latency of the waves. A single value was calculated by averaging the latency values obtained for both the left and right ears. The procedure of our study is summarised in Figure 1.

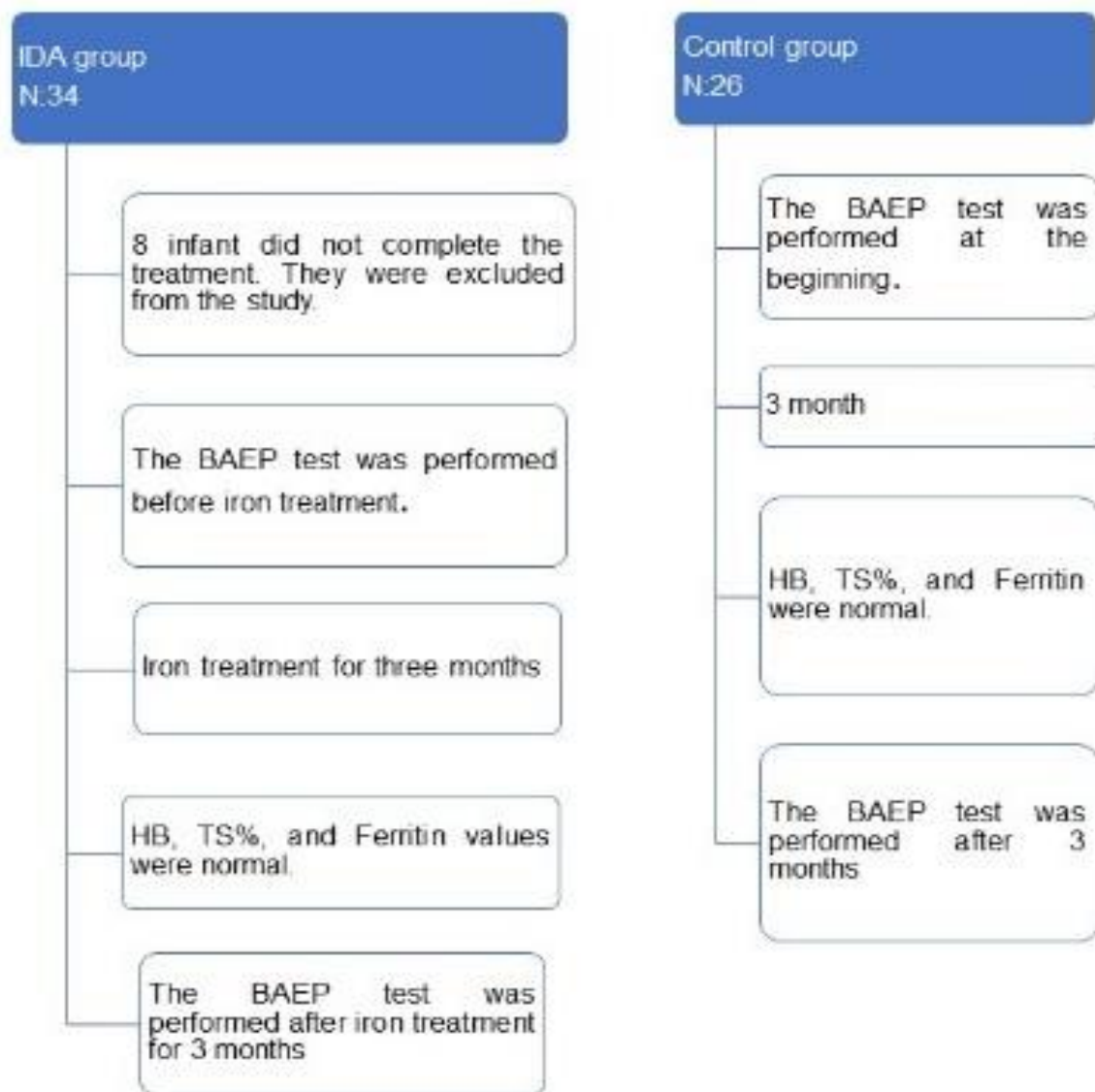


Figure 1. The procedure of our study

Statistical analyses

The study was conducted on a computer using the SPSS 15.0 (Statistical Package for the Social Sciences) statistical package program. In the survey, descriptive statistics of categorical variables were given with frequency and percentage, and descriptive statistics of continuous variables were given with mean and standard deviation values. Kurtosis and Skewness values were calculated to determine whether the BAEP values of the groups with and without iron deficiency anaemia fit the normal distribution. As a result of the calculations, it was resolved that the kurtosis and skewness values of the BAEP values were between +2 and -2, as required in the literature. Pre-treatment and post-treatment values were analysed with paired samples t test. The before and after treatment brainstem auditory evoked potential values of the IDA group were compared with those of the control group without IDA using an Independent Samples t-test. In all statistical analyses, if the p -value was below 0.05, it was considered statistically significant.

Informed consent was obtained from each parent participating in the study. The study was conducted by the rules of the Declaration of Helsinki. The SDU Research Fund supported this work under project number 605. The study was produced from the undergraduate thesis prepared before 2020. Suleyman Demirel University Clinical Research Ethics Committee approved of the study protocol before starting up the study.

Results

Eight patients in the IDA group were excluded from the study because they did not use iron therapy regularly. The study was completed with 26 children in the IDA group and 26 children in the control group without IDA and ID. The average age in the IDA group was 14.4 ± 3.09 months, and the average age in the control group was 11.2 ± 4.04 months. There is a significant difference in the haematological test findings between the two groups at the start of the trial. Before starting therapy, patients with iron deficiency anaemia had lower levels of Hb, Hct, MCV, MCH, MCHC, transferrin saturation percentage, and ferritin compared to the control group ($p=0.001$). Platelet and RDW values shown an increase in comparison ($p=0.013$, $p=0.001$) (Table 1).

Comparing the Hb, Hct, MCV, MCHC, transferrin saturation percentage, and ferritin results of the IDA group before and after therapy showed that they were lower before treatment ($p=0.001$). Platelet and RDW values were considerably elevated compared to other values ($p=0.023$, $p=0.001$) (Table 2).

The analysis revealed that the average before-treatment III-V interpeak latency for the iron deficiency anaemia group was 2.19 ± 0.11 , whereas the IIII-V interpeak latency average for the control group was 2.06 ± 0.16 . A significant difference was found in the before-treatment mean III-V interpeak latency values between the iron deficient anaemia group and the control group $p=0.002$ as shown in Table 3.

Table 1. Hematological test results of IDA and control groups at the beginning of the study

	Group with IDA N=26 Mean \pm SD	Control Group N=26 Mean \pm SD	t	p value
Hemoglobin (g/dl)	9.5 \pm 0.50	12.2 \pm 0.38	-21.078	0.001*
HCT	29.5 \pm 2.14	36.1 \pm 1.7	-11.284	0.001*
MCV	62.4 \pm 6.39	78.7 \pm 3.1	-11.640	0.001*
MCHC	31.6 \pm 2.06	36.7 \pm 1.20	-10.784	0.001*
RDW	16.5 \pm 2.38	13.7 \pm 0.63	5.485	0.001*
Platelet	488x10 ³ \pm 162	392x10 ³ \pm 98	2.588	0.013*
TF%	4.20 \pm 2.64	27.60 \pm 5.93	-17.837	0.001*
Ferritin (mg/L)	4.97 \pm 2.51	27.80 \pm 11.4	-9.936	0.001*

*= $p < 0.05$, Independent samples t test was conducted on independent groups, t was the test value of the independent samples
N=Number of patients, SD=Standard Deviation, IDA=Iron deficiency anaemia, MCV=Mean Corpuscular Volume, TF=Transferrin Saturation
MCHC=Mean Corpuscular Hemoglobin Concentration, RDW=Red cell Distribution Width

Table 2. Haematological test results of the IDA group before and after treatment

	IDA Group Before Treatment N=26 Mean±SD	IDA Group After Treatment N=26 Mean±SD	t	p-value
Haemoglobin (g/dl)	9.5±0.50	13.1±5.07	-3.633	0.001*
HCT	29.5±2.14	36.1±1.69	-10.601	0.001*
MCV	62.4±6.39	78.5±3.27	-12.016	0.001*
MCHC	31.6±2.06	34.3±1.18	-6.258	0.001*
RDW**	16.5±2.38	13.7±0.74	5.021	0.001*
Platelet	488x10 ³ ±162	392x10 ³ ±98	2.425	0.023*
TF%	4.20±2.64	26.6±3.11	-30.875	0.001*
Ferritin (mg/L)	4.97±2.51	24.3±10.6	-9.217	0.001*

*= $p < 0.05$, Paired Samples T-test was conducted on dependent groups, t was the test value of the paired samples
N=Number of patients, SD=Standard Deviation, IDA=Iron deficiency anaemia, MCV=Mean Corpuscular Volume, TF=Transferrin Saturation
MCHC=Mean Corpuscular Hemoglobin Concentration, RDW=Red cell Distribution Width

Table 3. Brainstem evoked potentials at 90 dB of IDA and control groups at the beginning of the study

	Group with IDA N=26 Mean±SD	Control Group N=26 Mean±SD	t	p value
Wave I	1.54±0.10	1.56±0.13	0.787	0.435
Wave III	3.79±0.20	3.75±0.30	-0.543	0.589
Wave V	5.88±0.23	5.91±0.27	0.452	0.654
IPL I - III	2.25±0.15	2.18±0.27	-1.067	0.291
IPL III - V	2.19±0.11	2.06±0.16	-3.316	0.002*
IPL I - V	4.33±0.23	4.34±0.25	0.115	0.909

*= $p < 0.05$, $p < 0.05$ was considered statistically significant
Independent samples t test was conducted on independent groups, t was the test value of the independent samples. N=Number of patients
IDA=Iron deficiency anaemia, IPL=Interpeak latencies, SD=Standard Deviation

The analysis showed that there was no significant difference in the average BAEP values between the iron deficient anaemia group after treatment and the control group ($p > 0.05$) (Table 4).

The mean interpeak latency values for peak I-III, III-V, and I-V in the iron deficiency anaemia

group were 2.25±0.15, 2.19±0.11, and 4.33±0.23 before treatment, and 2.17±0.15, 2.04±0.19, and 4.22±0.20 after treatment, respectively. The mean interpeak latency differences of peak I-III, III-V, and I-V in the iron deficient anaemia group before and after therapy show statistical significance ($p < 0.05$) as indicated in Table 5.

Table 4. Brainstem evoked potentials at 90 dB of IDA and control groups at the end of the study

	Group with IDA N=26 Mean±SD	Control Group N=26 Mean±SD	t	p value
Wave I	1.58±0.94	1.56±0.13	-0.424	0.673
Wave III	3.75±0.30	3.75±0.30	0.000	0.999
Wave V	5.93±0.20	5.91±0.25	-0.402	0.689
IPL I - III	2.17±0.15	2.18±0.27	0.253	0.801
IPL III - V	2.04±0.19	2.09±0.09	1.234	0.223
IPL I - V	4.22±0.20	4.30±0.24	1.210	0.232

$p < 0.05$ was considered statistically significant
Independent samples t test was conducted on independent groups, t was the test value of the independent samples. N=Number of patients
IDA=Iron deficiency anaemia, IPL=Interpeak latencies, SD=Standard Deviation

Table 5. Brainstem evoked potentials at 90 dB of the IDA group before and after treatment

	IDA Group Before Treatment N=26 Mean±SD	IDA Group After Treatment N=26 Mean±SD	t	p value
Wave I	1.54±0.10	1.58±0.94	-1.774	0.088
Wave III	3.79±0.20	3.75±0.30	0.601	0.553
Wave V	5.88±0.23	5.93±0.20	-1.105	0.280
IPL I - III	2.25±0.15	2.17±0.15	2.100	0.046*
IPL III - V	2.19±0.11	2.04±0.19	4.200	0.001*
IPL I - V	4.33±0.23	4.22±0.20	2.156	0.041*

*= $p < 0.05$, $p < 0.05$ was considered statistically significant

Paired Samples T-test was conducted on dependent groups, t was the test value of the paired samples
N=Number of patients, IDA=Iron deficiency anaemia, IPL=Interpeak latencies, SD=Standard Deviation

Discussion

This study assessed the brainstem auditory responses of children aged 6-24 months with and without iron deficiency anaemia (IDA) using the Brainstem Auditory Evoked Potential (BAEP) test, a non-invasive procedure. We examined and compared the Brainstem Auditory Evoked Potentials (BAEPs) of both groups at 90 dB at the start and conclusion of the trial. At the beginning of the trial, the IDA group showed significantly extended III-V interpeak latencies ($p < 0.05$). After three months of iron treatment, the anomalies in Brainstem Auditory Evoked Potentials (BAEP) in the group with Iron Deficiency Anaemia (IDA) improved as the haematological parameters improved. Oligodendrocytes require iron for the production of myelin. The development of the brainstem auditory pathways continues until the age of two. Research has demonstrated that iron insufficiency and iron deficiency anaemia have a detrimental impact on myelin production. We theorise that the results of our investigation could be attributed to the delayed secondary myelination caused by iron shortage. We believed that conduction was delayed as a result of iron deficient anaemia, resulting in extended III-V interpeak delays.

Sundagumaran and Seethapathy [12] conducted Auditory Brainstem Response (ABR) tests at 70, 50, and 30 dB to patients with and without iron deficient anaemia. The group with anaemia showed extended III-V and I-V interpeak latencies at 50 and 30 dB. Extended III-V interpeak latencies were observed, consistent with our research findings. The authors suggested that the extended ABR III-V interval could be attributed to delayed

myelination. They did not investigate brainstem auditory responses post-treatment, unlike our investigation.

Zheng et al. [13] conducted a Brainstem Auditory Evoked Potential (BAEP) investigation on 48 infants with Iron Deficiency Anaemia (IDA) aged 6 to 36 months, finding abnormal results in 26 cases. Like our research, they found that brainstem auditory responses showed enhancement following iron treatment in four instances.

Sarici et al. [14] in their study, categorised infants aged 6 to 24 months into two groups: one with iron deficient anaemia and the other as a control group. The brainstem auditory-evoked potential values showed no significant differences between the before-treatment and control group. Additionally, there was no statistically significant variance observed in the BAEP of the study group before and after a three-month period of oral iron therapy. They attributed the lack of difference in BAEP results to the mild to moderate severity of iron deficiency anemia in their patients. In our study showed improvements in Brainstem Auditory Evoked Potential (BAEP) values following three months of iron treatment in patients with iron deficiency anaemia.

Küreççi et al. [15] in their study, categorised infants aged 6-24 months into three groups: iron deficit, iron deficiency anaemia, and a control group. The BAEP test was performed to all three groups both before and after the treatment. No differences in peak interpeak latencies were found between the groups before and after therapy. They clarified that they did not observe

any distinction due to the mild and moderate iron status in the iron deficiency and iron deficiency anaemia groups.

Roncagliolo et al. [16] analysed the brainstem auditory responses of 6-month-old infants with and without iron deficiency anaemia using the ABR test before treatment and at 6, 12, and 18 months after treatment. While the haematological indicators showed improvement following therapy in the group with anaemia, it was found that the dysfunction in brainstem auditory responses persisted at the 12th and 18th months. Their investigation did not find any enhancement in brainstem auditory responses following iron therapy. Chloral hydrate was used for sedation in our research. Roncaglio et al. [16] measured ABR values during natural sleep without sedation. Methodological differences may exist between our study and their investigation. As we did not investigate the long-term effects of iron deficiency anaemia using the BAEP test in our study, we are unable to provide information on its long-term consequences.

Research indicates that while medication can improve haematological parameters in infants with iron deficient anaemia, long-term motor, sensory, behavioural, and cognitive abnormalities persist [17-20]. Studies have shown that individuals who had iron deficiency anaemia during infancy had worse scores on behavioural performance tests [21]. Neuro-behavioral development, gross motor skills, fine motor skills, and compliance development performance values were poorer in children with iron deficiency compared to those without. An inverse relationship has been discovered between iron deficient anaemia and neurobehavioral development [13]. Studies on animals have demonstrated that a lack of iron in the early stages of life can have lasting impacts on the central nervous system [22].

Lou et al. [23] an investigation revealed that infants born with low ferritin levels and anaemia at 10 months of age exhibited a prolonged III-V interpeak latency.

Amin and et al. [24] studied the relationship between cord serum ferritin levels and auditory brainstem evoked response (ABR) interpeak latencies in infants born at or after 35 weeks of gestational age (GA). Infants with low iron levels (cord serum ferritin: 11-75 ng/mL) were

compared to those with normal iron levels (>75 ng/mL). Findings showed that children with latent iron deficit had notably extended interpeak latencies, indicating a link between prenatal iron shortage and atypical auditory neural myelination in infants born at or after 35 weeks gestational age. Their findings supported our study's results.

Elalfy et al. [25] conducted a study with 50 participants diagnosed with iron deficiency anaemia (IDA) and 50 healthy mothers chosen as controls. They conducted Auditory Brainstem Response (ABR) tests on babies within 48 hours after birth and then repeated the procedures at 3 months. The study revealed that neonates of mothers with iron deficiency anaemia (IDA) had higher ABR interpeak latencies compared to the control group. The study found a significant association between ABR test outcomes and the extent of iron insufficiency in mothers and babies. In our study, similar to their results, I-III, III-V and I-V inter-peak latencies were significantly prolonged in the group with iron deficiency anaemia before treatment compared to after treatment ($p<0.05$).

Iron requirements are most significant during the initial 1000 days of life. Infants aged 6 to 24 months are particularly susceptible to iron insufficiency and iron deficiency anaemia. The initial 1000 days of life are the most critical period for the risk of iron deficiency and its lasting neurological effects. Iron plays a role in brain energy metabolism, neurotransmitter metabolism (particularly dopamine and serotonin), myelin production, and memory processes. Iron is essential for typical neurodevelopment, as evidenced by numerous animal investigations [26]. During this period, it is advisable to conduct comprehensive screening for all infants around 12 months of age, incorporating assessments such as hemoglobin testing and evaluation of iron levels, such as ferritin. These recommendations are predominantly based on expert guidance and clinical assessment [27].

Our study's limitation is that we conducted before and after treatment monitoring of our groups for 3 months and conducted BAEP tests. We could not investigate the prolonged impacts of iron deficient anaemia on brainstem auditory responses. The number of infants in the group could have been slightly higher. The patient

sample size within the groups have been slightly increased.

In conclusion, iron deficiency anaemia adversely affects brainstem auditory responses, although the exact cause is not yet known. Further comprehensive research is required to elucidate the connection between iron deficiency, iron deficiency anaemia, and auditory functions.

Conflict of interest: No conflict of interest was declared by the authors.

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The authors' contributions to the article

H.A., G.A. and B.T. constructed the main idea and hypothesis of the study. H.A., B.T. and G.A. developed the theory and arranged/edited the material and method section. H.A. and G.A. have evaluated the data in the results section. G.A. has done the BAEP analysis and evaluation of the data-discussion section of the article written by H.A., and G.A. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.