

Brainstem Auditory-Evoked Potentials in Iron-Deficiency Anemia

S. Ümit Sarici, MD*, Muhittin A. Serdar, MD[†], M. Rusen Dündaröz, MD*,
Bülent Ünay, MD*, Ridvan Akin, MD*, Gülhis Deda, MD[‡], and Erdal Gökçay, MD*

Slight-to-moderate impairments may be observed in mental and motor developments of infants with iron-deficiency anemia. Brainstem auditory-evoked potentials provide a noninvasive means of examining the auditory aspect of the central nervous system functions. In this study the effect of iron-deficiency anemia on auditory functions was investigated by using brainstem auditory-evoked potentials. Brainstem auditory-evoked potentials of the 20 iron-deficient infants were not significantly different from those of the control group that included 20 healthy age-matched infants. Furthermore, there was not a statistically significant difference between the brainstem auditory-evoked potentials of the study group performed before and 3 months after oral iron therapy. Although we could not demonstrate a hearing loss in infants with moderate iron-deficiency anemia in this study, the relationship between severe iron-deficiency anemia and hearing loss or auditory dysfunction remains to be determined. © 2001 by Elsevier Science Inc. All rights reserved.

Sarici SÜ, Serdar MA, Dündaröz MR, Ünay B, Akin R, Deda G, Gökçay E. Brainstem auditory-evoked potentials in iron-deficiency anemia. *Pediatr Neurol* 2001;24:205-208.

Introduction

Iron deficiency is considered to be the world's most common single-nutrient disorder; an estimated 20% of the world's population has iron-deficiency anemia [1]. In addition to anemia, physical growth and capacity, behavior, and immunoprotective mechanisms may be affected negatively in iron-deficient children, and there are several studies demonstrating the evidence of mental and motor developmental impairments in infants with iron deficiencies [2-6].

Brainstem auditory-evoked potentials provide a noninvasive means of examining the auditory aspect of central nervous system functions. Brainstem auditory-evoked potentials consist of a succession of five or seven waves recorded at the scalp within the first 10 milliseconds of stimulation. Brainstem auditory-evoked potentials represent the progressive activation of different levels of the auditory pathway from the distal part of the acoustic nerve (wave I) to the lateral lemniscus (wave V). The central conduction time (wave I-V interpeak latency) is considered an index of central nervous system development because myelination of nerve fibers and maturation of synaptic relays lead to an exponential reduction in the conduction time. Increases in absolute and interpeak latencies, increases in duration of the waves, and decreases in amplitude of the waves suggest axonal dysmyelination, or asynchronization at the axonal or synaptic levels [7,8].

This study aimed to investigate the effect of iron deficiency on auditory functions in iron-deficient infants by using brainstem auditory-evoked potentials.

Methods and Materials

This study was performed at the Departments of Pediatrics of Gülhane Military Medical Academy and Ankara University School of Medicine. Twenty iron-deficient infants (study group) and 20 healthy infants (control group) were enrolled in the study. Infants with any history of perinatal asphyxia, neonatal hyperbilirubinemia or respiratory disease, central nervous system infection, or congenital middle or external ear lesions were not included in the study. Of the 20 patients in the study group, eight were female and 12 were male with a median age of 14 months old (range = 7-24 months). There were seven female and 13 male infants in the control group, and their median age was 13 months old (range = 6-24 months). Growth parameters in the study and control groups (including weight, height, and head circumference) were recorded.

All patients in the study group met the hematologic criteria required for the diagnosis of iron-deficiency anemia. These patients were given a daily dose of oral iron sulfate (4 mg/kg) for 12 weeks. Informed consent

From the Departments of *Pediatrics and [†]Biochemistry; Gülhane Military Medical Academy; and [‡]Department of Pediatrics; Ankara University School of Medicine; Ankara, Turkey.

Communications should be addressed to:
Dr. Sarici; Department of Pediatrics; Gülhane Military Medical Academy; Etlik 06018; Ankara, Turkey.
Received June 29, 2000; accepted November 27, 2000.

Table 1. Growth parameters of the study and control groups

Parameter	Study Group (n = 20) (mean ± S.D.)	Control Group (n = 20) (mean ± S.D.)	P Value
Weight (kg)	8.4 ± 1.9	8.8 ± 1.7	> 0.05
Height (cm)	70.5 ± 6.2	71.7 ± 7.2	> 0.05
Head circumference (cm)	43.1 ± 1.8	43.8 ± 2.1	> 0.05

was obtained from parents of the patients in the study, and the study was approved by the local ethics committee.

Brainstem auditory-evoked potentials were performed twice, before and after iron supplementation in the study group, and once at the study entry in the control group at the pediatric neurology and electrophysiology laboratory with a Nihon Kohden Neuropack 4 MEB-5304 K04 (Tokyo, Japan). To obtain brainstem auditory-evoked potentials, every patient was sedated with hydroxyzine (1 mg/kg peroral) and taken to a special soundproof, lightproof room that was electrically shielded. Brainstem auditory-evoked potentials were recorded with silver-silver chloride disk electrodes placed, according to the 10-20 international system, on the vertex (active electrode) and earlobe (reference electrode) ipsilateral to the stimulation. The contralateral ear was masked by white noise of 40 dB during stimulation. Each ear was stimulated with a series of square wave rarefaction clicks through headphones at 70 and 90 dB. The repetition rate of stimuli was 15 Hz (15/second), the recording window was 10 milliseconds from click onset, and each trial consisted of 1000-2000 artifact-free clicks. Brainstem auditory-evoked potentials generated were displayed as waveforms on the computer screen of the system, and with the aid of cursors the individual waves of each response were identified and marked, and absolute latency and amplitude for waves I, II, III, IV, and V, and interpeak latencies I-III, III-V, and I-V were transferred to a spreadsheet. The latency and amplitude values obtained for the left and right ears were averaged to represent each case by one value in statistical analysis.

One sample Kolmogorov-Smirnov test was performed to three brainstem auditory-evoked potential measurement groups in the study to determine the distribution of the brainstem auditory-evoked potential values. After determination of normal distribution the pretreatment values were statistically compared with the values after treatment by paired Student *t* test, and the before and after brainstem auditory-evoked potential values of the study group were compared with those of the control group by unpaired Student *t* test.

Results

Study and control groups were fairly comparable with respect to age and gender distribution. None of the patients in the study displayed brainstem auditory-evoked potential findings that were indicative of hearing loss.

There were no significant differences between the study and control groups with respect to growth parameters, including weight, height, and head circumference (Table 1).

Hematologic parameters of the control group were in the normal range (hemoglobin 12.1 ± 0.5 g/dL, hematocrit 36.4 ± 1.4%, mean corpuscular volume 75.1 ± 2.9 fl, red cell distribution width 15.1 ± 1.4%, and ferritin 68.7 ± 29.5 µg/L). There were significant differences in the before and after treatment hematologic parameters of the study group (Table 2).

There were no significant differences among the before treatment, after treatment, and control group brainstem

Table 2. The before and after treatment hematologic parameters of the patients with iron deficiency anemia

Parameter	Before Treatment (n = 20) (mean ± S.D.)	After Treatment (n = 20) (mean ± S.D.)	P Value
Hemoglobin (g/dL)	8.8 ± 1.2	11.9 ± 0.6	< 0.001
Hematocrit (%)	27.9 ± 2.9	35.4 ± 1.8	< 0.001
Mean corpuscular volume (fl)	60.5 ± 3.4	74.6 ± 3.4	< 0.001
Red cell distribution width (%)	20.6 ± 2	16.8 ± 1.3	< 0.001
Ferritin (µg/L)	10.8 ± 5.4	78.2 ± 21.3	< 0.001

auditory-evoked potential values for any of the waves I, II, III, IV, and V, and interpeak latencies I-III, III-V, and I-V at 90 dB (*P* > 0.05) (Table 3, Fig 1).

At 70 dB there were also no significant differences among the before treatment, after treatment, and control group values for any of the same waves and interpeak latencies (*P* > 0.05) (Table 4, Fig 2).

Discussion

Slight-to-moderate impairments may be observed in mental and motor developments of infants with iron-deficiency anemia. Decrease in cerebral iron content resulting from iron-deficiency anemia may decrease the activity of several neurotransmitters, such as dopamine, serotonin, and noradrenaline, by interfering with the iron-dependent enzymes, which are important in synthesis of these particular neurotransmitters [9,10]. There may also be a relationship between behavioral abnormalities and monoamine oxidase deficiency [11,12]. A decrease in the activity of aldehyde oxidase resulting from iron-deficiency anemia may interfere with degradation of serotonin and thus may cause a decrease in cognitive functions [3,13]. These alterations in cognitive processes may be related to the auditory aspect of the central nervous system functions as well. Therefore we sought to determine whether audi-

Table 3. Comparison of the brainstem auditory-evoked potential values (msec) of the study (before and after treatment) and control groups for waves and interpeak latencies (IPL) at 90 dB

	Control (n = 20) (mean ± S.D.)	Before Treatment (n = 20) (mean ± S.D.)	After Treatment (n = 20) (mean ± S.D.)
Wave I	1.59 ± 0.18	1.64 ± 0.23	1.64 ± 0.23
Wave II	2.71 ± 0.27	2.78 ± 0.26	2.79 ± 0.31
Wave III	4.00 ± 0.33	3.99 ± 0.32	3.96 ± 0.35
Wave IV	5.15 ± 0.31	5.11 ± 0.36	5.12 ± 0.34
Wave V	6.02 ± 0.2	5.94 ± 0.38	5.90 ± 0.4
IPL I-III	2.41 ± 0.22	2.35 ± 0.31	2.32 ± 0.33
IPL III-V	2.01 ± 0.3	1.95 ± 0.32	1.95 ± 0.35
IPL I-V	4.43 ± 0.21	4.29 ± 0.36	4.27 ± 0.39

Abbreviation:

IPL = Interpeak latency

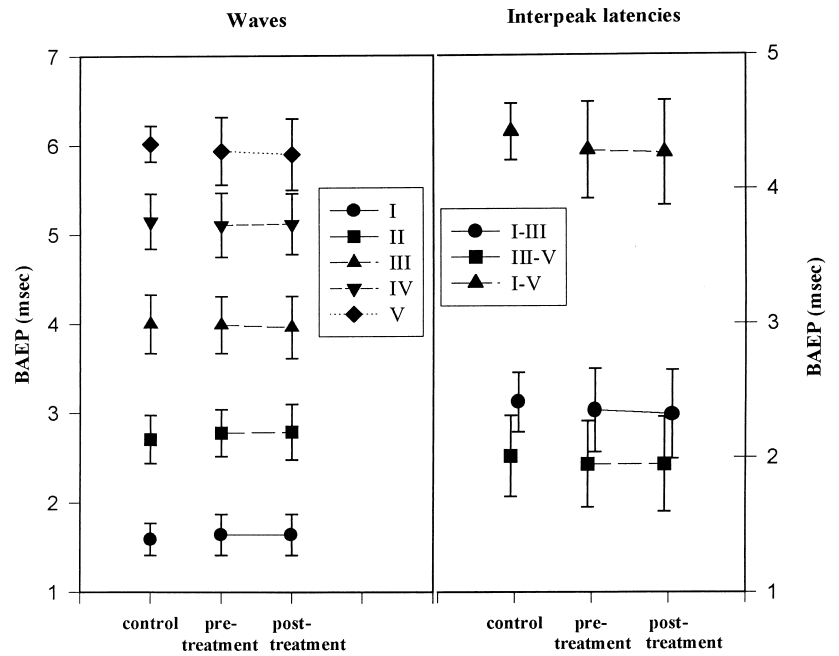


Figure 1. Schematic representation and comparison of the brainstem auditory-evoked potential values of the study (before and after treatment) and control groups for waves I, II, III, IV, and V and interpeak latencies I-III, III-V, and I-V at 90 dB.

tory functions are negatively affected from iron-deficiency.

Iron-deficiency anemia can interfere with intracellular energy production and detoxification mechanisms, leading to a decrease in the activities of succinyl dehydrogenase and peroxidase, iron-containing cochlear enzymes responsible for mitochondrial respiration, and scavenging intracellular free radicals and peroxide molecules. Sun et al. [14] have demonstrated the decreased activity of these enzymes in iron-deficient rats, and they have proposed that iron-deficiency anemia can cause auditory dysfunction by disturbing cell respiration and initiating peroxidative damage to inner ear cells. Microscopic abnormalities in cochlear hair cells were reported in the Corti organs of rats with iron-deficiency anemia [15].

In several experimental animal studies performed with noninvasive electrophysiologic methods assessing audi-

tory brainstem responses a clear relationship between iron deficiency and hearing loss has been established [16-19].

In the only study investigating the effect of iron-deficiency anemia on the auditory systems of human infants, Li et al. [20] demonstrated abnormal brainstem auditory-evoked potential results in 26 of 48 iron-deficient infants. The presence of a peripheral type of impairment was emphasized, especially in high frequencies of auditory function, and a direct relationship between the severity of iron-deficiency anemia and the degree of abnormality of brainstem auditory-evoked potential abnormalities were increases in latencies of waves I and II and in wave I-V interpeak latency. All 48 iron-deficient infants in that study had hemoglobin levels of less than 10.5 g/dL, and 14 patients who had a more severe auditory dysfunction displayed a more severe anemia (hemoglobin less than 9.5 g/dL) when compared with the other 12 patients who had less-severe abnormalities. In 11 patients with a more severe anemia, eight exhibited the most severe brainstem auditory-evoked potential abnormalities, and only six of 37 infants with a moderate anemia (hemoglobin between 9.5 and 10.5 g/dL) had the most severe auditory dysfunction. According to the statistical analysis of the study, the incidence of a severe auditory dysfunction in severe and moderate iron-deficient infants was 88.89% and 35.29%, respectively, and this difference was statistically significant. Only four patients were re-examined after an oral iron therapy of 3 months: a significant improvement in auditory functions of two infants treated successfully; no improvement in one infant; and one patient had already normal before and after treatment brainstem auditory-evoked potential results.

Table 4. Comparison of the brainstem auditory-evoked potential values (msec) of the study (before and after treatment) and control groups for waves and interpeak latencies at 70 dB

	Control (n = 20) (mean ± S.D.)	Before Treatment (n = 20) (mean ± S.D.)	After Treatment (n = 20) (mean ± S.D.)
Wave I	1.67 ± 0.14	1.82 ± 0.27	1.70 ± 0.19
Wave II	2.75 ± 0.1	2.87 ± 0.34	2.82 ± 0.31
Wave III	4.09 ± 0.22	4.04 ± 0.47	4.09 ± 0.37
Wave IV	5.28 ± 0.12	5.26 ± 0.45	5.22 ± 0.39
Wave V	6.03 ± 0.2	6.12 ± 0.45	6.04 ± 0.42
IPL I-III	2.51 ± 0.21	2.23 ± 0.48	2.39 ± 0.33
III-V IPL	1.94 ± 0.28	2.08 ± 0.36	1.95 ± 0.32
I-V IPL	4.46 ± 0.22	4.30 ± 0.44	4.34 ± 0.37

Abbreviation:

IPL = Interpeak latency

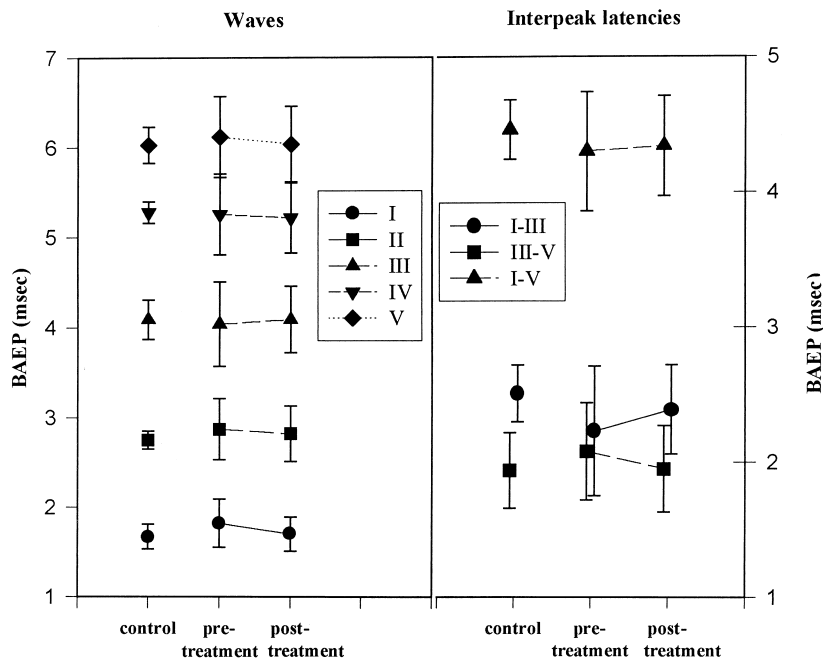


Figure 2. Schematic representation and comparison of the brainstem auditory-evoked potential values of the study (before and after treatment and posttreatment) and control groups for waves I, II, III, IV, and V and interpeak latencies I-III, III-V, and I-V at 70 dB.

We observed no significant differences between the brainstem auditory-evoked potential values of 20 iron-deficient infants and those of the control group, and we could not demonstrate any improvements in auditory functions of the study group after 3 months of treatment despite an excellent hematologic response to oral iron therapy. Sun et al. [16] demonstrated the association of presence of the longer duration of iron-deficiency anemia with the higher incidence of hearing loss and with the more severe abnormalities of stria vascularis and spiral ganglion cells in growing rats in an experimental study. Therefore the duration and depth of anemia might not have been severe enough to cause any electrophysiologic auditory disturbances or hearing loss in our study group in this study.

Contrary to experimental animal studies performed previously, we could not demonstrate hearing loss in infants with moderate-to-severe iron-deficiency anemia. However, the relationship between severe iron-deficiency anemia and hearing loss remains to be determined.

References

[1] Lee GR. Iron deficiency and iron deficiency anemia. In: Lee GR, Bithell TC, Foerster J, Athens JW, Lukens JN, eds. Hematology, 9th ed. Philadelphia: Lea and Febiger, 1993:808-39.

[2] Lozoff B, Brittenham GM, Wolf AW. Iron deficiency anemia and iron therapy effects on infant developmental test performance. *Pediatrics* 1987;79:981-95.

[3] Lozoff B, Wolf AW, Jimenez E. Iron deficiency anemia and infant development: Effects of extended oral iron therapy. *J Pediatr* 1996;129:382-9.

[4] Oski F, Honing A, Helu B. Effect of iron therapy on behavior performance in nonanemic iron deficient infants. *Pediatrics* 1983;71:877-80.

[5] Dallman PR. Manifestation of iron deficiency. *Semin Hematol* 1982;19:19-30.

[6] Oski F. The non-hematologic manifestations of iron deficiency. *Am J Dis Child* 1979;133:315-22.

[7] Jewett DL, Romano MN, Williston JS. Human auditory evoked potentials: Possible brainstem components detected on the scalp. *Science* 1970;167:1517-8.

[8] Moller AR, Janetta PJ. Evoked potentials from the inferior colliculus in man. *Electroencephalogr Clin Neurophysiol* 1982;53:612-20.

[9] Beard JL, Connor JD, Jopnes BC. Brain iron: Location and function. *Prog Food Nutr Sci* 1993;17:183-221.

[10] Dallman PR. Biochemical basis for the manifestation of iron deficiency. *Annu Rev Nutr* 1986;6:13-40.

[11] Youdim MB, Woods HF, Mitchell B, Grahame-Smith DG, Callender S. Human platelet monoamine oxidase activity in iron deficiency anemia. *Clin Sci Mol Med* 1975;48:289-95.

[12] Youdim MB, Grahame-Smith DG, Woods HF. Some properties of human platelet monoamine oxidase in iron deficiency anemia. *Clin Sci Mol Med* 1976;50:479-85.

[13] Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. *N Engl J Med* 1991;325:687-94.

[14] Sun AH, Li JY, Xiao SZ, Li ZJ, Wang TY. Changes in the cochlear iron enzymes and adenosine triphosphatase in experimental iron deficiency. *Ann Otol Rhinol Laryngol* 1990;99:988-92.

[15] Sun AH, Xiao SZ, Zheng Z, Li BS, Li ZJ, Wang TY. A scanning electron microscopic study of cochlear changes in iron-deficient rats. *Acta Otolaryngol (Stockh)* 1987;104:211-6.

[16] Sun AH, Xiao SZ, Li BS, Li ZJ, Wang TY, Zhang YS. Iron deficiency and hearing loss. Experimental study in growing rats. *ORL J Otorhinolaryngol Relat Spec* 1987;49:118-22.

[17] Sun AH, Wang ZM, Xiao SZ, Li ZJ, Zheng Z, Li JY. Sudden sensorineural hearing loss induced by experimental iron deficiency in rats. *ORL J Otorhinolaryngol Relat Spec* 1992;54:246-50.

[18] Sun AH, Wang ZM, Xiao SZ, Li ZJ, Li JY, Kong LS. Red cell basic ferritin concentration in sensorineural hearing loss. *ORL J Otorhinolaryngol Relat Spec* 1991;53:270-2.

[19] Sun AH, Wang ZM, Xiao SZ, et al. Noise-induced hearing loss in iron deficient rats. *Acta Otolaryngol (Stockh)* 1991;111:684-90.

[20] Li YY, Wang HM, Wang WG. The effect of iron deficiency anemia on the auditory brainstem response in infant. *Chung-Hua I Hsueh Tsai Chih* 1994;74:367-9.