Effects of iron deficiency versus iron deficiency anemia on brainstem auditory evoked potentials in infancy

A. Emin Kürekçi[1], S. Ümit Sarıcı[1], Abdulbaki Karaoğlu[1], Ü. Hıdır Ulaş[2]
A. Avni Atay[1], Muhittin A. Serdar[3], Rıdvan Akın[1], Okan Özcan[1]
Departments of [1]Pediatrics, [2]Neurology, and [3]Clinical Biochemistry, Gülhane Military Medical Academy, Ankara, Turkey

SUMMARY: Kürekçi AE, Sarıcı SÜ, Karaoğlu A, Ulaş ÜH, Atay AA, Serdar MA, Akın R, Özcan O. Effects of iron deficiency versus iron deficiency anemia on brainstem auditory evoked potentials in infancy. Turk J Pediatr 2006: 48; 334-339.

There has been little or no evidence of brainstem auditory evoked potentials (BAEPs) among infants with iron deficiency (ID) that is not severe enough to cause anemia. To our knowledge, the effect of ID on auditory functions and/or potentials has not been investigated previously, though it seems reasonable that it should be associated with BAEP measures intermediate between those observed in iron deficiency anemia (IDA) and in iron sufficiency, considering the role of iron in myelin formation and maintenance. We therefore aimed in this study to investigate the effect of ID on BAEPs by comparing three groups of infants with ID, IDA and iron sufficiency (control) both before and after iron treatment (in iron-deficient groups). Three groups of infants (IDA, n=25; ID, n=24; Control, n=44) were compared on the basis of hematological laboratory parameters and BAEP measurements both at entry into and after (12 weeks treatment with oral iron in IDA and ID groups) the study. BAEP measurements recorded at 85 dB both at entry into and after the study were not significantly different among the groups, although a sufficient response to iron treatment was achieved in iron-deficient groups (Group I and Group II). The only positive finding determined in our study was a slight decrease in latencies obtained at the end of the study when compared to the pre-study values in all three groups of the study in accordance with the expected age-dependent developmental changes. Although no negative electrophysiological effect of ID on brainstem auditory functions was found in the present study, further longer term (late childhood or adult) studies are necessary to elucidate the relationships among anemia (maybe other than IDA), ID and auditory functions, and clinical implications of hearing loss (if any) should be questioned.

Key words: iron deficiency, iron deficiency anemia, hearing, brainstem auditory evoked potentials, infant, children.

In addition to various mental and motor developmental impairments[1,2,3], iron deficiency anemia (IDA) may cause hearing abnormalities[4,5]. Hearing abnormalities caused by IDA are best demonstrated by recording brainstem auditory evoked potentials (BAEPs)[4,6]. A causal relationship between the severity of IDA and extent of hearing abnormalities has been suggested[7,8]. Furthermore, treatment of IDA with iron improves abnormalities in BAEPs[9] and even visual evoked potentials[10]. Iron supplementation even to full-term healthy infants has resulted in better developmental and behavioral test scores[11] and higher visual acuity[12] at the end of the first year of life.

However, there has been little or no evidence of BAEPs among infants with iron deficiency (ID) that is not severe enough to cause anemia. To our knowledge, the effect of ID on auditory functions and/or potentials has not been investigated previously, though it seems reasonable that it should be associated with BAEP measures intermediate between

those observed in IDA and in iron sufficiency, considering the role of iron in myelin formation and maintenance. We therefore aimed in this study to investigate the effect of ID on BAEPs by comparing three groups of infants with ID, IDA and iron sufficiency (control) both before and after iron treatment (in iron-deficient groups).

Material and Methods

This study was performed at the Department of Pediatrics of Gülhane Military Medical Academy between October 2002 and February 2004. All iron-deficient (either only ID or IDA) infants of 6 to 24 months of age diagnosed and followed up during the study period on an outpatient basis were included in the study. Patients admitted with symptoms associated with anemia or those admitted with various complaints other than anemia and found anemic or iron deficient during physical and laboratory examination were included, and the following hematological laboratory investigations were performed: a venous complete blood count including hemoglobin (Hb), mean corpuscular volume (MCV) and red cell distribution width (RDW), serum ferritin, and free erythrocyte protoporphyrin (FEP) when possible. Patients with a serum Hb level of <11.0 g/dl, MCV of <70 fl, RDW of ≥16%, serum ferritin level of <12 mg/L and FEP of ≥1.77 μmol/L/100 μg/dl erythrocytes were deemed to have IDA[4,13,14] and constituted Group I (IDA group, n=32), whereas those with a serum Hb level of ≥11.5 g/dl, MCV of <70 fl, RDW of ≥16%, and serum ferritin level of <12 mg/L were deemed to be iron-deficient[4,13,14] and constituted Group II (ID group, n=35). During the study period one respective healthy infant for a study patient was chosen as the control case, and these cases constituted the control group (Group III, totally 65 cases). All the cases in the control group had the same laboratory investigations at the study entry, and those with any clues suggesting either ID or IDA were excluded from the study.

The study groups (Group I and Group II) were treated with a daily dose of oral iron sulfate (5 mg/kg) for 12 weeks, and the study was terminated afterwards.

In all three groups, BAEP measurements were made twice – at the entry into the study and 12 weeks after the start of the study. In all cases, a complete ear and hearing examination was performed before the study to exclude any outer and middle ear pathologies. The potentials were recorded as described in detail elsewhere[4,6]. BAEP measurements were performed without any pharmacological sedation after feeding during spontaneous sleep. Absolute latencies for waves I, III and V, and interpeak latencies I-III, III-V and I-V were recorded. Latency values obtained for left and right ears were averaged to represent one value in each case. Decreases in absolute waves and interpeak latencies were calculated by subtracting the first measurement from the second for each wave and interpeak latency. The same hematological laboratory investigations performed at entry into the study were repeated in all three groups at the end of the study (after 12 weeks of iron treatment for the two study groups).

Informed parental consent was obtained for each infant, especially for those in the control group, and the study was approved by the local ethics committee.

Laboratory characteristics, absolute wave latencies and interpeak latencies of the three groups in the study were compared using ANOVA test with post-hoc multiple comparison of Tukey or Tamhane tests.

Results

The study was completed with 25, 24 and 44 cases in the IDA (Group I), ID (Group II) and control (Group III) groups, respectively, as 7, 11 and 21 cases from the three groups, respectively, either were excluded from the study due to various reasons, such as diagnosis of chronic diseases during the study period, or they could not complete the study because some parents did not wish to continue.

There were 12, 10 and 21 male infants in the study groups, respectively. Mean age of the cases in the three groups were 14.6±3.7, 13.2±2.6, and 13.1±2.7 months (range=8-24 months), respectively.

At the study entry, there were significant differences among the hematological parameters of the three groups. MCV and ferritin values were significantly lower and RDW values significantly higher in the IDA and ID groups when compared to the control group. Hb values were significantly lower in Group I when compared to the other two groups (Table I).

Table I. Hematological Parameters of the Study and Control Groups at Entry into the Study*

Hematological parameter	Group I (Iron deficiency anemia) (n=25)	Group II (Iron deficiency) (n=24)	Group III (Control) (n=44)	p value
Hemoglobin (g/dl)	8.1 ± 1.1	11.9 ± 0.5	12.5 ± 0.8	I-II=<0.001 I-III=<0.001 II-III=0.058
Mean corpuscular volume (fl)	62 ± 7	66 ± 8	84 ± 5	I-II=0.06 I-III=<0.001 II-III=<0.001
Red cell distribution width (%)	19 ± 3	18 ± 4	12 ± 3	I-II=0.326 I-III=<0.001 II-III=<0.001
Ferritin (mg/L)	5 ± 4	6 ± 4	22 ± 7	I-II=0.386 I-III=<0.001 II-III=<0.001

*Values are given as mean ± SD.

BAEP measurements recorded at 85 dB both at entry into and after the study were not significantly different among the groups (Tables II and III). There were slight decreases in latencies measured after the study, though not significant, in each of the three groups when compared to the pretreatment values (Fig. 1).

After 12 weeks of oral iron treatment in iron deficiency groups (IDA and ID groups) satisfactory responses were achieved, and there were no significant differences among the groups with respect to hematological parameters measured at the end of the treatment (Table IV).

Table II. Brainstem Auditory Evoked Potentials of the Study and Control Groups Recorded at 85 dB at Entry into the Study*

Absolute wave latency or interpeak latency (IPL)	Group I (Iron deficiency anemia) (n=25)	Group II (Iron deficiency) (n=24)	Group III (Control) (n=44)	p value
Wave I	1.84 ± 0.08	1.78 ± 0.08	1.82 ± 0.06	>0.05
Wave III	4.42 ± 0.07	4.68 ± 0.06	4.65 ± 0.05	>0.05
Wave V	5.94 ± 0.05	5.9 ± 0.08	5.96 ± 0.06	>0.05
IPL I-III	3.14 ± 0.07	3.22 ± 0.07	3.25 ± 0.06	>0.05
IPL III-V	2.16 ± 0.05	2.12 ± 0.06	2.18 ± 0.07	>0.05
IPL I-V	5.05 ± 0.06	4.95 ± 0.08	5.1 ± 0.05	>0.05

*Values (msec) are given as mean ± SD.

Table III. Brainstem Auditory Evoked Potentials of the Study and Control Groups Recorded at 85 dB at the End of the Study*

Absolute wave latency or interpeak latency (IPL)	Group I (Iron deficiency anemia) (n=25)	Group II (Iron deficiency) (n=24)	Group III (Control) (n=44)	p value
Wave I	1.8 ± 0.06	1.76 ± 0.07	1.78 ± 0.05	>0.05
Wave III	4.24 ± 0.08	4.3 ± 0.07	4.34 ± 0.06	>0.05
Wave V	5.8 ± 0.06	5.74 ± 0.06	5.7 ± 0.07	>0.05
IPL I-III	3.04 ± 0.06	3.08 ± 0.06	3.1 ± 0.07	>0.05
IPL III-V	2.08 ± 0.06	2.06 ± 0.05	2.1 ± 0.06	>0.05
IPL I-V	4.9 ± 0.04	4.88 ± 0.06	4.92 ± 0.06	>0.05

*Values (msec) are given as mean ± SD.

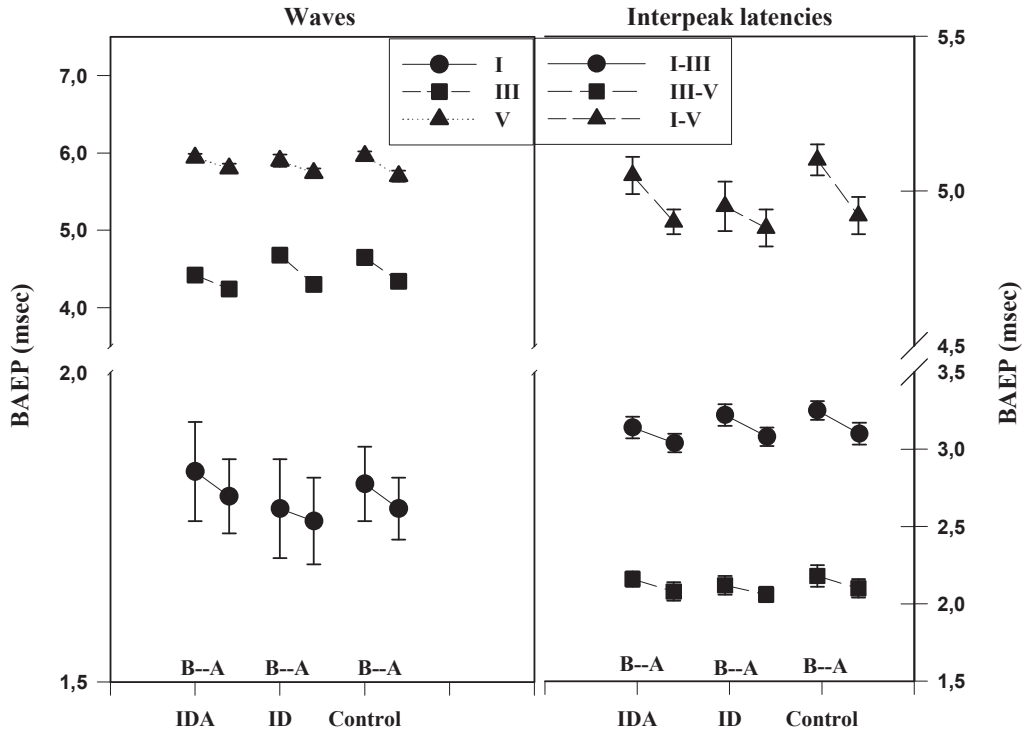

Fig. 1. Schematic demonstration of the absolute wave and interpeak latencies in the study and control groups recorded at 85 dB at entry into and after the study (B; before, A; after the study).

Table IV. Hematological Parameters of the Study and Control Groups at the End of the Study*

Hematological parameter	Group I (Iron deficiency anemia) (n=25)	Group II (Iron deficiency) (n=24)	Group III (Control) (n=44)	p value
Hemoglobin (g/dl)	12.8 ± 0.8	13.4 ± 0.7	13.2 ± 0.5	>0.05
Mean corpuscular volume (fl)	82 ± 5	85 ± 6	86 ± 7	>0.05
Red cell distribution width (%)	14 ± 4	13 ± 5	13 ± 4	>0.05
Ferritin (mg/L)	22 ± 6	28 ± 4	19 ± 8	>0.05

*Values are given as mean ± SD.

Discussion

The association between IDA and hearing loss and/or BAEP abnormalities was first questioned in a study from China[7]. In that study, 48 infants with ID were compared with 30 healthy control infants, and a direct relationship between the severity of IDA and the degree of BAEP abnormality was reported. Although response to iron treatment was evaluated in only four infants in that study[7], a positive effect of iron treatment on BAEP abnormalities in IDA was later demonstrated in an experimental study[9]. However, in a further study conducted at our center neither abnormality nor any improvement in response to oral iron treatment in BAEP measurements in infants with IDA in comparison to healthy control infants could be detected[6]. Our explanation was that mild to moderate anemia might not be severe enough to cause any electrophysiologically demonstrated hearing loss. However, another study performed in Chile has shown that early (at 6 months of age) IDA caused a significant BAEP abnormality (longer central conduction times) both at 6 months of age and at 12 and 18 months of age even after appropriate treatment of IDA[4]. According to the authors, ID could interfere directly with neurotransmission

in the auditory pathway or indirectly by altering certain processes that modulate brainstem auditory activity. The same group also revealed in an animal model that IDA in infancy has some effects that cannot readily be corrected with treatment[15]. Authors have questioned how longer term effects of IDA would be on BAEPs of infants with IDA, and investigated the BAEP responses of previously studied and treated infants in their first study[4] at four years of age[5]. Interestingly former (infantile) IDA children still had BAEP abnormalities demonstrated by significantly longer absolute latencies for all BAEP waves and interpeak latencies (except for I-III interval) at four years. The authors have postulated that these abnormalities are due to impaired myelination since iron is required for the functioning of several neurotransmission systems, myelination, and neuronal metabolic activity. According to their explanation, iron is intimately involved in oligodendrocyte function and the associated production and maintenance of myelin[16,17]. Thus, disruption in the availability of iron should impede myelination since oligodendrocytes have a primary role in myelin production and they depend on iron availability for normal function[18]. When we compare their hypothesis to our findings (if it had been true), we would have had abnormal BAEP findings in both IDA and ID groups if iron deficiency were responsible for BAEP abnormalities. However, we could not demonstrate any abnormalities (increases in latencies) in either the IDA or ID groups, in which iron deficiency was the rule. Also in accordance with our previous study[6], there were no significant differences among the IDA, ID and control groups with respect to BAEP values obtained before and after the study. This is also in concert with why formerly iron-deficient infants do not exhibit any significant hearing loss despite prominent electrophysiological brainstem auditory abnormalities.

The only positive finding in our study was a slight decrease in latencies obtained at the end of the study when compared to the pre-study values in all three groups in the study. This is an expected finding since myelination is an age-dependent process, and progressively shorter latencies until adult levels are achieved by increasing speed of transmission through sensory pathways, resulting in large part from increased myelination[19,20,21].

In conclusion, we could not detect any significant differences in brainstem auditory potentials of infants with IDA and ID when compared to healthy control infants. Furthermore, appropriate iron treatment of these iron-deficient (either IDA or ID) infants did not provide any extra improvements in BAEP measurements after 12 weeks. Although there was no negative electrophysiological effect of iron deficiency on brainstem auditory functions in the present study, further longer term (late childhood or adult) studies are necessary to elucidate the relationships among anemia (maybe other than IDA), iron deficiency and auditory functions, and clinical implications of hearing loss (if any) should be questioned.

REFERENCES

1. Dallman PR. Manifestation of iron deficiency. Semin Hematol 1982; 19: 19-30.
2. Oski F. The non-hematologic manifestations of iron deficiency. Am J Dis Child 1979; 133: 315-322.
3. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr 2001; 131: 649S-668S.
4. Roncagliolo M, Garrido M, Walter T, Peirano P, Lozoff B. Evidence of altered central nervous system development in infants with iron deficiency anemia at 6 mo: delayed maturation of auditory brainstem responses. Am J Clin Nutr 1998; 68: 683-690.
5. Algarin C, Peirano P, Garrido M, Pizarro F, Lozoff B. Iron deficiency anemia in infancy: long-lasting effects on auditory and visual system functioning. Pediatr Res 2003; 53: 217-223.
6. Sarıcı SÜ, Serdar MA, Dündaröz MR, et al. Brainstem auditory-evoked potentials in iron-deficiency anemia. Pediatr Neurol 2001; 24: 205-208.
7. Li YY, Wang HM, Wang WG. The effect of iron deficiency anemia on the auditory brainstem response in infant (Chinese). Chung-Hua I Hsueh Tsa Chih 1994; 74: 367-369, 392.
8. Shankar N, Tandon OP, Bandhu R, Madan N, Gomber S. Brainstem auditory evoked potential responses in iron-deficient anemic children. Indian J Physiol Pharmacol 2000; 44: 297-303.
9. Zhou B, Sun A, Wang S, Ma Y, Shen J, Wang Q. The effects of iron supplementation on auditory brain-stem response with iron deficiency anemia in rats. Lin Chuang Er Bi Yan Hou Ke Za Zhi 2001; 15: 173-175.
10. Sarıcı SÜ, Okutan V, Dündaröz MR, et al. The effect of iron supplementation on visual-evoked potentials in infants with iron-deficiency anemia. J Trop Pediatr 2001; 47: 132-135.
11. Lozoff B, De Andraca I, Castillo M, Smith JB, Walter T, Pino P. Behavioral and developmental effects of preventing iron-deficiency anemia in healthy full-term infants. Pediatrics 2003; 112: 846-854.

12. Friel JK, Aziz K, Andrews WL, Harding SV, Courage ML, Adams RJ. A double-masked, randomized control trial of iron supplementation in early infancy in healthy term breast-fed infants. J Pediatr 2003; 143: 582-586.
13. Dallman PR, Reeves JD, Driggers DA, Lo EY. Diagnosis of iron deficiency: the limitations of laboratory tests in predicting response to iron treatment in 1-year-old infants. J Pediatr 1981; 98: 376-381.
14. Deinard AS, Schwartz S, Yip R. Developmental changes in serum ferritin and erythrocyte protoporphyrin in normal (nonanemic) children. Am J Clin Nutr 1983; 38: 71-76.
15. Felt BT, Lozoff B. Brain iron and behavior of rats are not normalized by treatment of iron deficiency anemia during early development. J Nutr 1996; 126: 693-701.
16. Connor JR, Menzies SL. Altered cellular distribution of iron in the central nervous system of myelin deficient rats. Neuroscience 1990; 34: 265-271.
17. Connor JR, Benkovic SA. Iron regulation in the brain: histochemical, biochemical, and molecular considerations. Ann Neurol 1992; 32: S51-S61.
18. Connor JR, Menzies SL. Relationship of iron to oligodendrocytes and myelination. GLIA 1996; 17: 83-93.
19. Salamy A, McKean CM. Postnatal development of human brainstem potentials during the first year of life. Electroencephalogr Clin Neurophysiol 1976; 40: 418-426.
20. Hecox K, Burkard R. Developmental dependencies of the human brainstem auditory evoked response. Ann N Y Acad Sci 1982; 388: 538-556.
21. Jiang ZD. Maturation of the auditory brainstem in low risk preterm infants: a comparison with age-matched full term infants up to 6 years. Early Human Dev 1995; 42: 49-65.