

The Effect of Iron Supplementation on Visual-evoked Potentials in Infants with Iron-deficiency Anemia

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Summary

Flash visual-evoked potentials were studied in 20 infants with iron-deficiency anemia to determine the effect of iron deficiency on visual function by using visual-evoked potentials in this type of anemia. After iron therapy for 12 weeks, visual-evoked potentials were retested in these otherwise healthy infants. All infants showed an excellent hematological response to iron therapy. Post-treatment visual-evoked potential N₂ latencies (negative deflections) decreased significantly compared to the pre-treatment values ($p < 0.05$). These results suggest that iron-deficiency anemia causes subclinical visual impairment, and visual-evoked potentials may be a useful non-invasive means of detecting subtle effects of nutritional deficiencies and monitoring the nutritional status of infants.

Introduction

Iron deficiency (ID) is a more frequently encountered problem in children than in adults, and it affects approximately 20 per cent of the world population.¹ In addition to iron-deficiency anemia (IDA), ID has many more systemic effects; e.g. physical capacity, growth, and immunity may be affected negatively in children, and behavioral changes and decreases in developmental test scores may be observed in infants.²⁻⁶ This negative effect on the mental and motor development of infants could also be related to the visual system.

The effect of ID on cerebral functions has recently been investigated in studies using evoked potentials, which is a non-invasive electrophysiological method. To our knowledge, however, there has been no reported clinical neurophysiologic study investigating any probable effects of ID on visual functions.

Visual-evoked potentials (VEP) can be defined as a stimulus-synchronized electroencephalography (EEG) for a defined time after a visual stimulus. VEP reflects the end-result of a long neural information cascade that starts at the photoreceptors and passes through synapses in the retina, the lateral geniculate body in the thalamus, and the primary visual cortex. In clinical practice, repeated stimuli are presented and the resulting traces are averaged to produce a final waveform. Latency and amplitude of the components of this waveform are analysed. VEP

is a triphasic response, the major component of which is a positive deflection appearing 100 ms after the visual stimulus. This deflection, termed P100, is followed by less robust negative deflections (N₁ and N₂). Delayed responses in these components of the VEP waveform, in the absence of abnormal findings of fundus examination, are considered to be an indication of subclinical visual pathology beyond the retina.⁷ In this study, we aimed to investigate the effect of ID on visual functions by using VEP.

Materials and Methods

This study was performed at the Departments of Pediatrics at the Gülhane Military Medical Academy and the Ankara University School of Medicine. Twenty infants with IDA, who were otherwise healthy and who had no pathology in physical examination, were enrolled in the study. Infants with any history of perinatal asphyxia, neonatal hyperbilirubinemia or respiratory disease, central nervous system infection, and past or current familial visual disturbance were not included in the study. The clinical ophthalmologic and neurologic examinations performed were normal in all of the patients, and the growth parameters of the patients were within normal limits for their ages. Of the 20 patients studied, 12 were male and eight were female with a median age of 14 (range 7–24) months.

Hematological parameters related with IDA were recorded in each patient, and all the infants met the laboratory criteria required for the diagnosis of IDA. All the cases were given a daily oral dose of 4 mg/kg iron sulphate for 12 weeks.

In each case flash VEPs with a LED goggle

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stimulator were performed before and after iron supplementation at the pediatric neurology and electrophysiology laboratory with a Nihon Kohden Neuropack 4 MEB-5304 K04 (Japan). To obtain VEPs, every subject was put to sleep with hydroxyzine (1 mg/kg peroral) and taken to a special room which is sound and light-proof. The VEPs were recorded over both hemispheres, areas 01 and 02, which were referenced to electrodes applied to both ears (places 10–20, according to international system of electrode placement). Each eye was tested separately using a frequency of 1 Hz for 300 ms duration and 100–200 responses were averaged during the trial. Normal VEP values for the age group of 6 months to 3 years were determined before in our laboratory and were found to be 104 ± 4 ms.

Informed consent was obtained from the parents of all subjects, and the study was approved by the local ethics committee.

Paired *t*-test was used to compare the pre- and post-treatment results in the statistical analysis of the data.

Results

After iron therapy for 12 weeks, anemia resolved and hemoglobin levels rose to normal in all subjects. There were significant differences between the pre- and post-treatment hematologic parameters, and the post-treatment VEP N₂ negative deflections were significantly shorter than the pre-treatment ones (Table 1, Fig. 1).

Discussion

Although it is not entirely known how ID affects cerebral function, several theories have been put forward. Iron deficiency may have an impact on several metabolic and neural functions, such as the synthesis, uptake and utility of neurotransmitters, mitochondrial functions, cerebral iron content and distribution, synthesis of proteins, oxidation–reduction, and electron transport. The decrease in cerebral iron content may diminish the activity of several

TABLE 1
The pre- and post-treatment hematologic parameters and VEP results of the study group

	Before treatment	After treatment	<i>p</i> value
Hemoglobin (g/dl)	8.8 ± 1.2	11.9 ± 0.6	< 0.0001
Hematocrit (%)	27.9 ± 2.9	35.4 ± 1.8	< 0.0001
MCV (fl)	60.5 ± 3.4	74.6 ± 3.4	< 0.0001
Red cell distribution width (%)	20.6 ± 2.0	16.8 ± 1.3	< 0.0001
VEP N ₂ (ms)	113.7 ± 16.1	106.6 ± 12.4	< 0.05

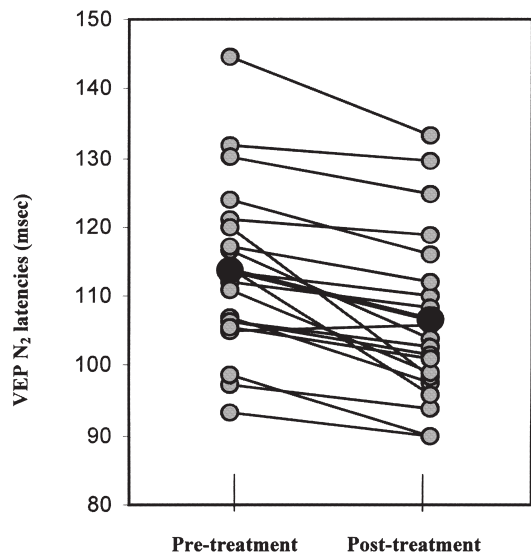


FIG. 1. Comparison of the pre- and post-treatment VEP N₂ latencies of the study group (●—●, indicate mean values).

neurotransmitters, such as dopamine, serotonin, and noradrenaline, by interfering with the iron-dependent enzymes which are important in the synthesis of these particular neurotransmitters. It has been speculated that there may be a relationship between behavioral abnormalities and monoamine oxidase deficiency. A decrease in the activity of aldehyde oxidase, an important enzyme for the utilization of serotonin, may cause a decrease in cognitive functions.^{8–12} The abnormalities in the visual system may also contribute to these alterations in the cognitive processes. Our study, therefore, focused on the effect of ID on visual functions.

In this study, patients showed a good response to iron therapy. At the end of iron supplementation for 12 weeks, we observed a significant decrease in VEP N₂ latencies. This decrease means improvement in visual function. Before iron supplementation, there were no visual symptoms in our cases, and they had normal ophthalmologic examinations. It has been suggested that VEPs can detect subclinical involvement on visual pathways in patients who have normal ophthalmologic examination and who do not have any visual symptoms.^{13,14} The longer N₂ latencies before treatment in our study may, therefore, be explained by the possible subclinical effects of IDA on the visual system, even in the absence of clinical stigmata of visual impairment. Thus, shortening of N₂ latencies after treatment in our study must be due to the iron supplementation or to the correction of anemia.

In a study performed on thalassemic patients who received desferoxamine (DFO), an iron-chelating

agent, it was reported that the great percentage of these transfusion-dependent patients had VEP abnormalities.¹⁵ It was concluded that these abnormalities might be due either to DFO, or to iron overload. In another study patients who had received high-dose DFO had increased latencies in their VEPs, and these cases had lower serum ferritin levels.¹⁶ In most of these patients VEPs improved after drug withdrawal.

A similar study in thalassemic patients demonstrated the improvement of abnormal VEPs after the withdrawal of DFO, and furthermore, recurrence of VEPs abnormalities after reinstitution of DFO was documented.¹⁷ Marciani, *et al.*¹⁸ reported that high-dose DFO caused a further delay in P100 latencies in patients receiving DFO therapy at standard doses, who had already delayed P100 latency. Deferiprone, a recently introduced orally-active iron chelator, also has similar toxic effects.¹⁹

Although the studies referred to above cannot clarify the exact etiological and pathological mechanisms, they strongly suggest that there are significant relations between iron metabolism and visual function. The possible relationship between anemia and brain functions was also investigated in various studies. In a study performed on stable continuous ambulatory peritoneal dialysis patients with adequate body iron stores, it was reported that the correction of renal anemia by using recombinant human erythropoietin induced a decrease in latency of P100 VEP. The authors suggested that increased hematocrit levels provided enhanced brain oxygen delivery, directly improving brain metabolism.²⁰ Studies in patients with chronic renal failure demonstrated the recovery of brain dysfunction after treatment of anemia, and it was claimed that this recovery was due to the decreased delivery of uremic toxins to the brain resulting from a decrease in cerebral blood flow following increased hematocrit levels.^{21–25}

In a study performed on iron-deficient adolescent girls, it has been reported that iron supplementation improves some cognitive functions, even in the absence of anemia.²⁶ In some studies it has been reported that cognitive and behavioral disturbances may be independent from hemoglobin concentrations in iron-deficient patients.^{27–29} The studies performed on rats and adults to elucidate the relationship between ID and hearing functions have shown that hearing disorders might be produced by the iron deficiency but not by the anemia. It has been suggested that the negative effect of ID on the auditory system is more responsible for the hearing impairment than the anemic anoxia resulting from ID.^{30,31}

In our study, the subjects were iron deficient, anemic but otherwise healthy infants. The fact that a decrease in VEP N₂ latencies may also be induced by rapid development of organ functions of infants in this period of life may raise a question about whether

the subclinical visual disturbance observed in this study was due to ID or to maturation of visual functions. However, as the maturation of visual functions lasts until up to 5–6 years of age, it is very difficult to explain the pre-and post-treatment differences of VEP N₂ latencies by rapid maturation in such a short period of 12 weeks. To our knowledge this is the first study showing that iron supplementation induced a decrease in VEP N₂ latencies in infants with IDA. This result suggests that these infants had subclinical visual impairment before treatment. Since no other etiologic factors were identified in these infants, it is likely that this impairment in visual function may be due either to ID or to anemia.

Further large-scale experimental and clinical studies including healthy, matched controls are necessary to elucidate the relation between IDA and visual functions. If this relation can be confirmed, recording VEPs, which are a quantitative measure of visual system function, may be a useful non-invasive means in detecting subtle effects of nutritional deficiencies and monitoring the nutritional status of infants.

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