

## BRAINSTEM AUDITORY EVOKED POTENTIAL RESPONSES IN IRON-DEFICIENT ANEMIC CHILDREN

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**Abstract :** Iron deficiency is a major health problem in developing countries manifesting not only as overt anemia but also involving the CNS resulting in cognitive and behavioral deficits. Iron is an important nutrient and essential element involved in myelin formation and neurotransmitter synthesis and thus contributes to normal neurological activity. Hypomyelination has been reported in iron deficient states with possible neural conduction defects. The brainstem auditory evoked potential response is used extensively to identify lesions associated with various demyelinating diseases and hence has been used in the present study to observe the effect of iron deficiency on sensory brain function. A trend of increased absolute and interpeak latencies and reduced amplitudes of the waves leading to a definite linear correlation between the severity of anemia and the degree of neurophysiological deficit suggests a subclinical involvement of the auditory pathway in the brainstem of iron deficient children.

**Key words :** iron deficiency      brainstem auditory evoked potentials  
mean corpuscular volume      absolute peak latencies  
neurophysiological deficit

### INTRODUCTION

Iron deficiency (ID) is the most common single nutrient deficiency in the world. It has been described as a major health problem in developing countries including India (1). Several reviews of ID (2, 3) have noted that the documentation of prevalence by virtue of measurement of anemia dramatically underestimates the prevalence of tissue ID. As in other tissues, iron is an essential element and an important nutrient of the

brain. Specific to neurological activity, iron has a major role in myelin formation (4) besides its involvement in the synthesis and function of various neurotransmitters namely dopamine, serotonin, catecholamines and possibly GABA (5, 6). There are data that indicate that iron uptake into the brain is maximal during the period of rapid brain growth (7) which coincides with the peak of myelinogenesis (8) and that perinatal iron deficiency significantly alters myelination of the spinal cord and white matter of

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cerebellar folds (9). However, iron uptake into the brain continues throughout life (10). In general, the existing data strongly suggest that the majority of iron, in the normal brain, is related to oligodendrocytes where it is directly involved in myelin production as a required co-factor for cholesterol and lipid biosynthesis and indirectly because of its requirement for oxidative metabolism (11). Oligodendrocytes participate in iron homeostasis through the synthesis and secretion of transferrin which is essential for their maturation and function (12). Conditions such as ID may reduce iron acquisition by oligodendrocytes and in this regard the observation that ID rats are hypomyelinated is highly relevant (13). Since myelination is concerned with the conduction in nerve fibers and brainstem auditory evoked potential (BAEP) recordings have been used extensively to identify subclinical lesions associated with various demyelinating diseases (14) we undertook the present study to see if there was any effect of ID in the BAEP recordings of anemic children.

## METHODS

*Subjects:* 36 children, of both sexes, from a low socioeconomic group, were selected for the study after a thorough clinical assessment to exclude any other pathological disorder besides anemia. On the basis of their hemoglobin content they were divided into a control group (Group I, n = 17, Hb > 12 g/dl) and an anemic group (Group II, n = 19, Hb < 12 g/dl). The mean age of the control group was  $8.65 \pm 3.28$  y while that of the anemic group was  $7.53 \pm 4.29$  y. The parents were informed about the nature of the study and following their written

consent all the investigations were performed in their presence.

### *Recording of hematological parameters:*

A number of hemotological parameters were investigated to evaluate the iron-deficient anemic (IDA) status of the subjects. Hb, MCV and MCHC were detected by electrical impedance method using Coulter Hematological Particle Counter Model T-890, Coulter Electronics, UK. Serum iron (SI) and total iron binding capacity (TIBC) were measured by spectrophotometry.

*Recording of BAEPs:* The subjects were briefed about the test procedure. They were seated comfortably in a chair in a standard audiometric, sound proof and air-conditioned room. The recording was done using the Neuropack II Evoked Potential Recorder MEB-5200, Nihon Kohden (Japan). The BAEPs were obtained from scalp electrodes (Ag/AgCl disc electrodes) anchored on the vertex with collodian. The active electrode was placed at CZ with reference electrodes on the mastoid at M1 & M2 and the ground electrode at FZ. Both ears were tested individually using shielded headphones. The stimulus consisted of 0.1 ms square waves of an intensity of 70 dB nHL. On an average 2048 of such stimuli were given. Recordings consisted of the absolute peak latencies (ms) of waves I, II, III, IV and V together with interpeak latencies (ms) of I-III, III-V & I-V and the amplitudes ( $\mu$ v) of wave I and V. The methods used are similar to those reported in earlier studies (15).

*Statistical analysis:* Unpaired Student "t" test was done to find out the statistical significance of changes in the BAEP waves in the anemic children as compared to the

controls. ANOVA test was performed to find the correlation between different parameters. Regression studies were also done between the various BAEP recordings and the hematological parameters.

**RESULTS**

1. *Mean age of both groups*: Statistical analysis showed no significant difference between the mean ages of the anemics and controls (Table I).

2. *Comparison of the hematological and BAEP values of both groups*:

(a) *Hematological values*: There were significantly lower values of Hb, MCV, MCHC and SI in the anemic group as compared to the control group thus corroborating their IDA status. The TIBC of the anemic group was found to be more than that of the controls though this difference was not statistically significant (Table I).

TABLE I: Age and hematological parameters of control (Group I) and anemic (Group II) children.

Parameter	Group I (n = 17) mean ± SD	Group II (n = 19) mean ± SD
Age (y)	8.65±3.28	7.53±4.29
Hb (g/dL)	12.88±0.67	9.39±2.63**
MCV (fL)	84.84±7.46	72.51±11.09**
MCHC (g/dL)	34.62±1.76	30.22±3.17*
SI (mg/L)	0.80±0.35	0.51±0.23*
TIBC (mg/L)	3.50±0.59	3.77±0.83

Significance: \*\*P<0.001, \*P<0.01

TABLE II: BAEP parameters (average value both ears) of control (Group I) and anemic (Group II) children.

Parameter	Group I (n = 17) mean ± SD	Group II (n = 19) mean ± SD
<b>Peak latencies (ms)</b>		
I	1.63±0.23	1.71±0.24
II	2.61±0.23	2.66±0.24
III	3.70±0.25	3.81±0.27
IV	4.77±0.25	4.96±0.27*
V	5.56±0.23	5.67±0.30
<b>Interpeak latencies (ms)</b>		
I-V	3.94±0.16	3.98±0.22
III-V	1.86±0.15	1.90±0.20
I-III	2.08±0.13	2.09±0.15
<b>Amplitude (µV)</b>		
I	0.38±0.21	0.36±0.14
V	0.39±0.22	0.37±0.11

Significance: \*P<0.05

(b) BAEP values: The absolute peak latencies of all the waves (I to V) were more in the case of anemic children though the value was significantly different from the controls only in the case of wave IV. The interpeak latencies of the waves as well as their amplitudes were not significantly different between the two groups even though the anemic group showed increased latencies and lower amplitudes as compared to the controls (Table II).

(c) Correlation between hematological parameters and the BAEP recordings in the anemic group by Regression studies: A significant correlation was found between MCV values and the waves III to V with

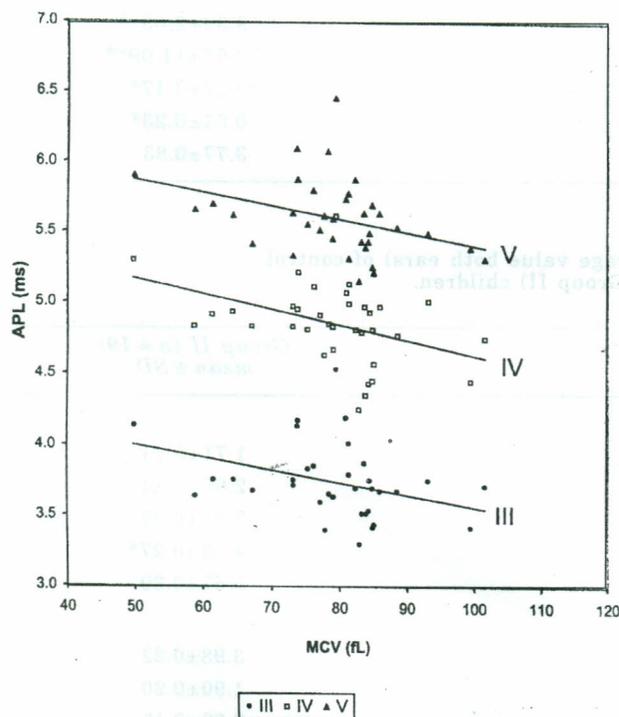


Fig. 1: Scatter diagram showing a significant correlation between MCV values (fL) and the absolute peak latencies (APL ms) of BAEP waves III, IV and V. (The  $r$  values for waves III, IV and V are 0.372, 0.432 and 0.382 respectively).

lower values of MCV corresponding with longer absolute peak latencies of the waves (Fig. 1). The significance was maximally seen with wave IV. The other hematological values though correlating with the latencies of the BAEP waves did not show statistically significant results.

## DISCUSSION

The brainstem auditory evoked potentials have been found to be a useful tool in investigating neurologic disorders that may involve the brainstem auditory pathway (14). On the basis of several studies it appears that waves I, III and V primarily represent volume-conducted electrical activity from the acoustic nerve, superior olivary and inferior olivary nuclei while II and IV represent the activity from cochlear nucleus and lateral laminae respectively. The interpeak latencies between the waves indirectly reflect neural conduction in the corresponding segments of the central auditory pathway. Another basic BAEP parameter of central auditory conduction is based on the relative amplitudes of the wave (16). BAEP has been used extensively to identify subclinical lesions associated with various pathological disorders including demyelinating diseases (17, 18). The latencies have been shown to increase in these disorders as has been seen in our study. Several studies have shown the disruption of iron homeostasis in demyelinating diseases (13, 14) and in sensorimotor deficit seen in ID children (19).

This study reveals that a correlation exists between the hematological parameters and the BAEP recordings of IDA children

suggesting a subclinical involvement of auditory pathway in the brainstem as indicated by the increased absolute and interpeak latencies of the waves. These findings suggest that the functional integrity of this pathway is perhaps dependent upon the normal hematological profile of the individual and that the unfavorable environment of ID could lead to structural or functional damage of the pathway resulting in the BAEP abnormalities. A definite correlation is also seen between the severity of anemia and the degree of neuro-physiological deficits. A Chinese study also showed a direct relationship between the severity of IDA and the degree of abnormality of the auditory brainstem responses in infants (20).

The mechanisms for this alteration in the conductive process may be multifactorial involving a number of biochemical pathways in which iron is essential. These include mitochondrial enzymes, various neurotransmitters and laying down of myelin sheath. The altered levels of these may explain decreased conduction and some of the behavioral and developmental changes that occur. Moore et al (21) have shown that myelination accounts for the onset of acoustimotor reflexes and BAEPs, processes which depend on rapid synchronized conduction of auditory impulses in the cochlear nerve and brainstem. Animal models of nutritional ID have demonstrated a reduction of the brain nonheme iron (22, 23) with a most significant and selective diminution of central dopaminergic neurotransmission resulting from decreased number of the

dopamine D<sub>2</sub> receptors in various regions of CNS including frontal cortex (24, 25). The consequences of diminished dopaminergic neurotransmission is modification of the dopamine dependent sensory and cognitive mechanisms of behavior and biochemical reactions, the most important of which is the learning process (26). Erikson et al (27) showed a heterogenous decrease in regional brain iron due to ID in rats, with significant amounts of iron lost from the hippocampus and the cortex as compared to other regions of the brain.

The ability to detect ID has improved vastly over the past several decades (28). A measure of the hemoglobin concentration is often preferred over hematocrit or the number of red cells to establish the presence of anemia. In children anemia is defined as hemoglobin values less than 12 g/dl (29). Functional iron exists mainly as hemoglobin in circulating red cells and in lesser amounts in myoglobin and various tissue enzymes. Laboratory measurements of IDA have been taken as Hb < 12 g/dl, MCHC < 34 g/dl, MCV < 80 fL, ferritin < 12 µg/L and transferrin saturation < 16% (30). In case of populations with high prevalence of IDA, red cell measure and serum iron measures (serum iron and transferrin saturation) are more preferable for diagnosis (31). Serum transferrin or total iron binding capacity (TIBC) is inversely related to serum ferritin in otherwise normal subjects and hence it also provides an indirect measure of storage iron (32). In the present study the various hematological parameters measured were indicative of ID in the anemic children.

Regression studies revealed a relationship between the various hematological parameters in the anemic children and the defects in the BAEP waves which was significant between MCV and the absolute peak latencies of waves III, IV and V. The severity of the defect correlated with the abnormal hematological finding in that

increasing microcytosis produced longer latencies of the waves. Thus the findings are indicative of a neurological involvement consequent to IDA though, perhaps, the significance could not be revealed in all the groups because the children showed only mild anemia and may be larger numbers have to be studied.

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that while studies are available with reference to the blood pressure in children in India. The present results indicate a systematic indication of low systolic blood pressure and weight for the children in the study. The present study was conducted in the town of Aligarh district in North India.

METHODS

The study was conducted in Aligarh city of Uttar Pradesh in North Indian State. The demography and characteristics of the district are fairly typical of that prevailing in other parts of the state. The school children and girls were purposively chosen from the different mohallas (colonies). A total of 100 children between ages 8 to 12 years. The age was determined from the school register book.

INTRODUCTION

It is well established that hypertension is a major public health burden. A number of correlative studies on the various etiological factors like sex, weight, build, socio-economic status, psychological factors have so far been inconclusive (1). There is evidence to suggest that genetic factors predispose their siblings of hypertensive persons to higher blood pressure levels at younger ages (2). Today, most researchers appear to accept the multifactorial environmental background for blood pressure and entertain mostly polygenic or mixed models (3-5).

In Indian population, few hospital based studies have been carried out to investigate the racial-ethnic differences in blood pressure levels (6, 7) and also in school children (8). However, hardly any

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