# [Journal of Medicine in Scientific Research](https://jmisr.researchcommons.org/home)

[Volume 1](https://jmisr.researchcommons.org/home/vol1) | [Issue 4](https://jmisr.researchcommons.org/home/vol1/iss4) Article 5

Subject Area:

# Effects of iron-deficiency anemia on auditory function in schoolaged children

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## Recommended Citation

Abd El-Gaffar, Eman Soliman; S. Abd El-Salam, Gehan M.; and Abd El-Samad, Hala M. (2018) "Effects of iron-deficiency anemia on auditory function in school-aged children," Journal of Medicine in Scientific Research: Vol. 1: Iss. 4, Article 5.

DOI: [https://doi.org/10.4103/JMISR.JMISR\\_71\\_18](https://doi.org/10.4103/JMISR.JMISR_71_18)

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# **Effects of iron‑deficiency anemia on auditory function in school‑aged children**

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# **Abstract**

#### **Introduction**

Iron is important for proper myelination of spinal cord and white matter of cerebellar folds in brain and is a cofactor for a number of enzymes involved in neurotransmitter synthesis. Auditory brainstem evoked response (ABR) represents the progressive activation of different levels of the auditory pathway from the acoustic nerve (wave I) to the lateral lemniscuses(wave V). Otoacoustic emissions(OAEs) are sounds measured in the external ear canal that reflect movement of the outer hair cells in the cochlea.

#### **Patients and methods**

A total of 40 children, of both sexes, with age ranging from 6–12 years old, were selected for this study after a thorough clinical assessment to exclude any other pathological disorder other than anemia. They are compared with a control group that consisted of 20 normal children of the same age. After laboratory investigations, all children were examined by ABR and transient-evoked OAEs. The study group children were classified according to ABR results into study group 1, comprising anemic children with abnormal ABR results and study group 2, comprising anemic children with normal ABR results.

#### **Results**

ABR showed that absolute peak latencies of waves I, III, and V and interpeak latencies were prolonged; moreover, ABR waves I and V showed reduced amplitude in study group 1 than control group, and the difference is statistically significant. In contrast, there was no statistically significant difference between study group 2 and control group regarding ABR results. Transient‑evoked OAEs results showed no statistically significant difference between anemic children and control group.

#### **Conclusion**

This study added to the evidences that iron-deficiency anemia is a risk factor for auditory function impairment. Further studies for the effect of timing, duration, and severity of iron deficiency on auditory functions are needed. Well‑designed large‑scale studies are needed to address the iron-deficiency anemia in health planning programs to put plans for control and prevention especially in developing countries.

**Keywords:** Auditory brainstem evoked response, iron, otoacoustic emissions, inter-peak latencies

# **Introduction**

Iron deficiency is the most common type of nutritional deficiency in both developing and developed countries [1]. It is estimated that roughly 25% of the world population are anemic [2]. It has been suggested that nearly one half of anemic individuals have iron‑deficiency anemia (IDA). Iron is an essential component of brain growth and is essential not only for cell differentiation but also protein production, hormone synthesis, and detrimental aspects of cellular energy functioning and metabolism [1]. Iron deficiency causes varying



degrees of impairment in cognitive performance [3], lowered work capacity, increase infections owing to lower immunity [4], poor learning capacity, and impaired psychomotor skills [5]. Iron is important for proper myelination of spinal cord and white matter of cerebellar folds in brain and is a cofactor for a number of enzymes involved in neurotransmitter synthesis. There is considerable evidence that iron is also

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**How to cite this article:** El‑Salam GM, El-Gaffar ES, El‑Samadc HM. Effects of iron-deficiency anemia on auditory function in school-aged children. J Med Sci Res 2018;1:239-44.

important for neurological development and functioning. The biological basis of the behavioral, neurological, and cognitive developmental delays observed in iron‑deficient children is not completely understood, but possibly include (i) abnormalities in neurotransmitters metabolism and (ii) alteration in brain energy metabolism [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 myelin genesis and that perinatal iron deficiency significantly alters myelination of the spinal cord and white matter of cerebellar folds [8]. However, iron uptake into the brain continues throughout life [9]. It was reported that iron plays an important role in proper axonal maturation and reveals a new pathology caused by iron deficiency in the absence of anemia [10]. To identify iron deficiency in children, age‑specific reference ranges must be employed. A serum ferritin level of less than 12 g/l and hemoglobin (Hb) level of less than 10 g/dl is indicative of iron deficiency in children [11].

Auditory brainstem evoked response (ABR) provides a noninvasive means of examining the auditory aspect of central nervous system functions. ABR consists of a succession of five or seven waves recorded at the scalp within the first 10 ms of stimulation. ABR represents the progressive activation of different levels of the auditory pathway from the acoustic nerve (wave I) to the lateral lemniscuses (wave V). The central conduction time [wave I–V interpeak latency (IPL)] 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 IPLs and decreases in amplitude of the waves suggest axonal dysmyelination or a synchronization at the axonal or synaptic levels [12]. Otoacoustic emissions (OAEs) are sounds measured in the external ear canal that reflect movement of the outer hair cells in the cochlea. Energy produced by outer hair cell motility serves as an amplifier within the cochlea, contributing to better hearing. OAEs are produced by the energy from outer hair cell motility that passes from the cochlea through the middle ear to the external ear canal by vibrating the tympanic membrane. Although the sound energy produced by outer hair cell movement within the cochlea may be as high as 50 dB, residual energy reaching the ear canal is normally in the range of 0–15 dB. Transient‑evoked otoacoustic emissions (TEOAEs) are elicited with transient sounds, such as clicks or tone bursts, presented at an intensity level of 80 dB SPL [13]. This study aimed to investigate the effect of iron deficiency on auditory functions in iron-deficient school children by using brainstem auditory‑evoked potentials and TEOAEs.

## **Patients and methods**

#### **Patients**

The parents were informed about the nature of the study, and following their written consent, all the investigations were performed in their presence. Study group consists of 40 children, of both sexes, their age range 6-12 years old were selected for this study after a thorough clinical assessment to exclude any other pathological disorder other than anemia. Their hemoglobin level is less than 11.5 gm/dl. The parents were informed about the nature of the study and following their written consent all the investigations were performed in their presence. This study was carried out in Audiology and Laboratory Units of Hearing and Speech Institute Giza, Egypt. The control group consists of 20 children; they were toddlers of some employers of Hearing and Speech Institute who responded to announcement of the authors. The authors clearly informed them that their children will be safely involved in research in the Audiology Unit and they will indirectly benefit from this study by evaluation of their children's hearing function and hematologic state.

#### **Equipment**

- (1) A two‑channelaudiometer (Interacoustics, model AC40, Denmark) withair and bone conductionfacilities.
- (2) Sound‑treated room (I.A.C model 1602, North Aurora, USA).
- (3) Middle ear analyzer (Impedance Audiometer Interacoustic AZ26, Denmark).
- (4) ABR was evaluated using Interacoustic Eclipse 25.
- (5) TEOAEs was evaluated using Interacoustic Eclipse 25.

#### **Methods**

All participants in this study were subjected to the following:

- (1) Full history taking regarding any hearing complaints.
- (2) Otological examination.
- (3) Basic audiological evaluation in the form of the following:
	- (a) Pure tone audiometry:
		- (i) Air conduction thresholds were tested at the following frequencies: 0.25, 0.5, 1, 2, 4, and 8 kHz.
		- (ii) Bone conduction thresholds at the following frequencies:  $0.5$ ,  $1$ ,  $2$ , and  $4$  kHz.
	- (b) Acoustic immittancemetry testing: it included tympanometry and acoustic reflex threshold measurements.
- (4) ABR response to a rarefaction acoustic clicks was used as the acoustic stimulus; at rate of 21.4 clicks/s were delivered through monaural insertion earphones at an intensity of 90 dBnHL, totaling 1000 stimuli. The active electrode was placed at CZ with reference electrodes on the mastoid at M1 and M2 and the ground electrode at check. Stimuli were manipulated in 10 dB steps until reaching threshold. Latencies were calculated in traces of 90 dBnHL intensity level. Absolute latencies for waves I, III, and V and IPLs I–III, III–V, and I–V and value of wave I and V were recorded for each participant and compared for both groups.
- (5) TEOAEs were obtained by using Interacoustic Eclipse 25. Children were resting in a sound-treated room. A probe fitted to the tested ear delivered acoustic stimuli at an average of 85 dB SPL, and responses (echo levels) were recorded at five frequency bands over a range of 1–4.0 kHz responses. The results of TEOAEs were interpreted into one of three categories: (i) Pass: response was 3 dB or

above in all test frequency bands;(ii) Partial pass; response was present in at least one of the test frequency bands; but not in all frequency bands, and (iii) Fail; no response is present in any of the test frequency bands.

- (6) Laboratory Investigations: venous blood samples of 5 ml were collected from each patient and divided as follows: 2ml was collected into a tube containing EDTA for complete blood count. The remaining volume of the blood was collected in a plain tube [for serum iron, ferritin, and total iron‑binding capacity (TIBC)], allowed to clot for 30min and then centrifuged at 3000 rpm. The serum from each patient was collected individually and stored at −20°C as aliquots until use. All samples were subjected to the following:
	- (a) Complete blood count estimation by fully automated blood cells counter (Sysmex K‑800; Sysmex Europe GmbH, Norderstedt, Germany). Hb, mean corpuscular volume (MCV), and mean corpuscular Hb were recorded.
	- (b) Quantitative determination of serum ferritin by enzyme‑linked immunosorbent assay technique. Kit was provided by Leinco Technologies (Nanterre, France). The absorbance values were read using ELISA reader (TC96, tecodiagnostics, Austin, Texas, USA). The concentration was calculated using computer software capable of generating a four parameters algorithm.
	- (c) Quantitative determination of serum iron and TIBC by colorimetric method using spectrophotometer at 510 nm (Chem‑7; ERBA, Mannheim, Germany). The kit was provided by Pointe Scientific Inc. (Canton, Michigan, USA). Iron transferrin saturation was calculated by division of serum iron by TIBC.

Depending on the Hb levels, children were divided into anemic children (study group) with Hb levels below 11.5 g/dl and nonanemic children (control group) who had Hb levels equal to or more than 11.5 g/dl. The transferrin saturation levels were used to diagnose anemia to be iron deficiency in nature. The study group patients were classified according to ABR results into study group 1, having anemic children with abnormal ABR results, and study group 2, and having anemic children with normal ABR results.

#### **Statistical methods**

IBM SPSS statistics(v. 23.0; IBM Corp., Armonk, New York, USA) was used for data analysis. Data were expressed as  $mean \pm SD$  for quantitative measures. Comparison between two patient groups was done using Student's *t*‑test. The probability of error (*P*) was considered as follows: *P* value more than 0.05 is nonsignificant, *P* value less than 0.05 is significant, and *P* value less than 0.01 is highly significant. A nonsignificant difference between right and left ear ABR and TEOAEs indices was found, accordingly adding both ears measures were used in the statistical procedures.

## **Results**

The mean age of the control group was  $8.65 \pm 2.28$  years, whereas that of the study group was  $8.53 \pm 2.19$  years ( $P > 0.05$ ). Mean pure tone average value was 19.71 dB in the control group and was 20.53 dB in the study group ( $P > 0.05$ ). Regarding hematological values, there were statistically significant lower values for all parameters in study group except MCV. MCV showed reduced values in anemic children compared with normal children, but the difference was nonsignificant as shown in Table 1 and Fig. 1. According to ABR results, children with anemia were divided to two groups. Study group 1 consists of 20 anemic children with abnormal ABR results, and study group 2 consists of 20 anemic children with normal ABR results. ABR results showed that absolute peak latencies of waves I, III, and V and IPLs were prolonged in study group 1 than control group, and this prolongation was highly statistically significant. Moreover, there was decreased wave I and V amplitude in study group 1 in comparison with control group, and this decrease was



**Table 2: Comparison between absolute, interpeak latencies, and value of auditory brainstem evoked response waves in anemic children with abnormal auditory brainstem evoked response (study group 1) and control group**



IPL, interpeak latency; PL, peak latency. *P*>0.05, NS. \*\*\**P*<0.01, highly significant.



**Figure 1:** Comparison between hematological results in anemic children and normal children. Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume.

highly statistically significant, as shown in Table 2 and Fig. 2. In contrast, there was no statistically significant difference between study group 2 and control group regarding ABR results as shown in Table 3 and Fig. 3. TEOAEs results showed no statistically significant difference between anemic children and control group as shown in Table 4 and Fig. 4. Table 5 showed negative correlation between Hb level and hearing loss. As Hb level decreases, peak latencies increase.

# **Discussion**

Iron deficiency is the most common form of nutrient deficiency worldwide. It is highly prevalent owing to limited availability of high‑quality food in developing countries and poor dietary habits in industrial countries. According to WHO, it affects nearly two billion people [14]. It was found that nearly one half of anemic individuals have IDA. ABR provides a noninvasive means of examining the auditory aspect of the central nervous system functions. In this study, 40 children, of both sexes, with age ranging from 6–12 years old, were selected after a thorough clinical assessment to exclude any other pathological disorder other than anemia. They were compared with 20 healthy children of the same age regarding hematological and auditory functions. Hematological results from both groups showed a highly statistically difference between both groups (Table 1). The study group is further divided into two subgroups according to ABR results, and each subgroup is compared with the control group. Results of ABR from both study group 1 and control group (Table 2) showed that absolute peak latencies of wave I, III, and V and interpeak and wave values were prolonged in study group 1 than control group, and this prolongation was highly statistically significant. This may be owing to a subclinical involvement in the auditory pathway in the brainstem, as its functional integrity is dependent upon the normal hematological profile and iron deficiency could lead to functional changes in the auditory pathways. Similar results





**Table 3: Comparison between absolute, interpeak latencies, and value of auditory brainstem evoked response waves in anemic children with normal auditory brainstem evoked response (study group 2) and control group**



IPL, interpeak latency; PL, peak latency. *P*>0.05=NS.





were obtained by Shanker *et al.* [15] and Kamel *et al.* [16]; they attributed that to alteration in the conductive process by changes in mitochondrial enzymes, various neurotransmitters, and myelin development. They reported that myelination accounts for the onset of acoustimotor reflexes and brainstem auditory‑evoked potentials processes, which depend on rapid synchronized conduction of auditory impulses in the cochlear nerve and brainstem. Khalifa *et al.* [17] also reported that ABR latencies and IPLs were significantly prolonged, and the amplitude was significantly lower in preschool iron‑deficiency children group compared with control group. They attributed that to the generalized affection of the ascending auditory pathways located in the brainstem owing to ischemic and thrombotic events associated with iron deficiency as iron deficiency causes thrombocytosis, hypercoagulable state, and tissue hypoxia. Moreover, Li *et al.* [18] showed a direct relationship between the severity of IDA and the degree of abnormality of auditory brainstem responses in infants. In contrast, the results of ABR from both study group 2 and control group (Table 3) showed that absolute peak latencies of wave I, III and V and interpeak and wave values were prolonged in study group 2 than control group, but this prolongation was not statistically significant. This may be attributed to a recent onset of IDA in this group as myelination is completed and no time for neurotransmitters changes to be reflected on ABR results to reach abnormality degree. Similar results were obtained by Algarin *et al.* [19] and Ramadan *et al.* [20]; they reported that the nature of ABR components as short distal neural potentials might make them less vulnerable to the nutritional insults. Moreover, Berglund *et al.* [21] reported that infants with IDA did not have impaired ABR latencies early in life, suggesting that ABR is not a sensitive measure of impaired neurological development. The debate between anemic children in our study may be related to onset of acquiring iron deficiency. One subgroup acquired IDA early in life during brain growth, whereas the other acquired IDA during childhood period. This is supported by Roncagliolo *et al.* [22] who reported that infants who had IDA at the age



**Figure 4:** Comparison between transient-evoked otoacoustic emissions results in anemic children and normal children.



# **Table 4: Comparison between transient‑evoked otoacoustic emissions results in anemic children and normal children**

*P*>0.05=NS.

## **Table 5: Statistical correlations between auditory brainstem evoked response thresholds and hemoglobin level in anemic children**



ABL, auditory brainstem evoked response; PL, peak latency. \*\**P*<0.05, significant. \*\*\**P*<0.01, highly significant.

of 6 months had less mature ABRs, particularly evidenced by longer absolute and IPL values than in control infants, and these differences remained as the infants got older, despite effective iron therapy. They attributed that to the long-lasting effects of IDA on the central nervous system during brain growth. Moreover, Berglund *et al.*[21] concluded that iron supplements did not improve ABR latencies. Regarding TEOAEs, Table 4 showed no statistically significant difference between normal children and anemic children. This was expected as the outer hair cell which is the origin of OAE is not affected by iron deficiency. Similar results were obtained by Kamel *et al*. [16] For the study group, negative correlation was found between Hb level and ABR parameters: the lower the Hb level, the higher the absolute latencies (Table 5).

# **Conclusion**

This study added to the evidences that IDA is a risk factor for auditory function impairment. Further studies for the effect of timing, duration, and severity of iron deficiency on auditory functions, testing the effect of iron deficiency alone, without anemia, are needed. Well‑designed large scale studies are needed

to address the IDA in health planning programs to put outlines for control and prevention especially in developing countries.

#### **Financial support and sponsorship**

Nil.

#### **Conflicts of interest**

There are no conflicts of interest.

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