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EFFECTS OF IRON THERAPY ON COGNITION IN ANEMIC SCHOOL GOING BOYS

R. BANDHU*, N. SHANKAR, O. P. TANDON AND N. MADAN

Department of Physiology,
University College of Medical Sciences & Guru Teg Bahadur Hospital,
Dilshad Garden, Delhi – 110 095

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Abstract : The present study was conducted on 18 anemic and 34 control subjects (mean age 9.26 ± 0.26 years) to observe the effect of anemia on cognition and to see effect of 3 months of iron therapy on it. Anemia was defined on the basis of hematological values and peripheral smear examinations. Cognitive data consisted of the recording of the P_{300} wave of Auditory Event Related Potentials (AERP), Ravens Progressive Matrices Test (RPMT), and Digit Span Attention Test (DSAT) under standard test conditions. RPMT scores were then converted to the intelligence quotient (IQ) scores for comparison. Both anemic and control boys were dewormed after recording pretreatment values and then anemic boys were given iron therapy for 3 months, after which the recordings were taken again. Pretreatment, anemic boys showed significantly lower hematological values, delayed P_{300} latency, and lower RPMT scores as compared to controls. Post therapy the hematological profile of anemic boys though significantly improved as compared to the pretreatment values, was still significantly lower than that of control boys. The P_{300} latency values of anemic boys showed improvement but were still significantly delayed than the control group. RPMT values and derived IQ scores of anemic boys were similar to control boys after therapy suggesting that though the 3 months iron therapy regime resulted in improvement in psychometric cognitive tests in anemic boys, the basic P_{300} defects persisted. This suggests that the P_{300} component of AERP in anemic children is relatively refractory to 3 months of iron therapy.

Key words : anemia, iron deficiency, auditory event related potentials, P_{300}, cognition

INTRODUCTION

A significant correlation has been found between anemia particularly that due to iron deficiency (ID) and cognition (1, 2, 3). Cognition represents higher mental functions pertaining to thought and includes consciousness, orientation, concentration, attention, memory and intelligence (4). It is an extremely vital function and the effects

*Corresponding Author : Fax : 91-11-2290495, E-mail : dbmi@ucms.ernet.in

of iron deficiency anemia (IDA) on cognition are of utmost concern. Worldwide 1.3 billion people are anemic with nearly half of them having IDA (5), the problem being more acute in developing countries where it is a major health problem (6). Iron deficient infants and children have alteration in attention span, lower intelligence scores and some degree of perceptual disturbance together with delayed psychomotor development (7). An increase in intelligence quotient (IQ) scores and development quotient (DQ) scores have been observed with an increase in hemoglobin concentration (3) and ID associated cognitive defects have been shown to be reversible with iron therapy (8). Studies in Indian children have also shown lower levels of attention and concentration (9) in IDA and iron supplementation resulted in significant improvement in tests measuring cognition (10). In these subjects iron status, IQ and school language achievement tests showed improved scores and could be correlated (11), with improved hematological status (12). Even in adolescent girls iron supplementation has been shown to improve verbal learning and memory (1). However, some studies have suggested that cognitive deficits associated with IDA persist despite intensive long term therapy (13). Neurophysiological deficits have been found in IDA (14) and in our own laboratory, Shankar et al (15) have shown that brainstem auditory evoked potentials are significantly affected in IDA children. Event Related Potentials (ERPs) are linked with cognition and information processing, and are used as a measure of recognition memory (16). The generator sites for ERP component of P_{300} have been reported to be in the frontal lobe, hippocampus and parietal cortex (17) and the involvement of dopaminergic system at these sites in generation of P_{300}, is well documented (18). This system is maximally affected in IDA (19). A more objective assessment about the IDA and its effects on cognition together with its potential reversibility with iron therapy needs to be studied. This study was therefore undertaken to see the effect of IDA on cognition before and after oral iron therapy.

METHODS

Fifty-two boys of 8–10 years age (mean age 9.26 ± 0.26 years), with similar lower socioeconomic status, were selected for the study after obtaining detailed history and a thorough physical examination. School children with any chronic/acute disease or infection, hearing and neurological abnormality, hematological disorder, genetic disorders, jaundice, long term drug therapy, h/o hospitalization and h/o hematinic therapy were not included in the study. Parents were informed about the nature of the study following which a written consent was obtained for conducting the investigation and conducting the neurological tests. Malnutrition was ruled out using specific anthropometric criteria of Body Mass Index (BMI) and ratio of midarm circumference to the head circumference.

INVESTIGATION

Hematological investigations

Complete blood counts (CBC) were carried out using the automated hematology cell counter (Coulter T 890). For measuring serum iron (SI) and total iron binding

capacity (TIBC), the ICSH method (20) and Ressler & Zak method (21) were used respectively. Wright's stained peripheral blood smears were examined for RBC morphology.

Investigation for measurement of cognitive function

Auditory event related potentials : P_{300} recording (22):

For P_{300} component of auditory events related potentials (AERP), the standard procedure for recording the auditory response to 'odd ball paradigm' being used in our lab was performed. The children were briefed about the test procedure. They were made to sit on a comfortable chair in a soundproof air-conditioned room. SMP 4100 auditory/visual stimulator and MEB 5200 Neuropack II evoked potential recorder, Nihon Kohden, Japan, were used for AERP recordings. In odd ball paradigm the subjects are binaurally presented, a sequence of two distinguishable sound click stimuli with different characteristics. One occurred frequently (non target stimulus) and the other infrequently (target stimulus). The children were asked to respond by pressing a button using their preferred hands whenever the target stimulus was presented. The cerebral response obtained was recorded on the screen of the evoked potential recorder.

The electrode recording sites on the scalp were cleaned with spirit, skin pure electrolyte paste was applied and Ag/AgCl disc electrodes were subsequently anchored as per 10–20 international system of electrode placement as follows

Active electrode (–ve) : Vertex (Cz), Midline

Reference Electrodes (+ve) : Both ears connected (A1+A2)

Grounding electrode : Forehead (FP_2) FP_Z

The input impedance was kept below 5 kilo-ohms. Shielded headphones were used for recording. Target stimulus (infrequent stimulus) was presented in the form of alternating tone bursts with a starting condensation phase of 10 ms rise/fall time, 100 ms duration (plateau time), intensity 70 dB NHL and rate 1 every 2 seconds. Eighty percent of total 160 tones were 1 KHz (frequent) and 20% were 2 KHz (rare). Stimulus sequence was random. The MEB 5200 settings were appropriately selected and evoked responses to frequent and rare stimuli were filtered with a band pass 5–30 Hz and averaged simultaneously for 32 responses. Data obtained was stored, analyzed and averaged by the computer. The latency and amplitude of P_{300} for target stimuli were calculated. During the recording session the subject was asked to fix his eyes on a particular spot on the ceiling in order to avoid electro-oculographic artifacts due to eye movements and improve his concentration and attention to the stimulus presented.

Psychometric tests

(a) Ravens progressive matrices test (RPMT) (23):

This measures a person's capacity to apprehend meaningless figures presented for his observation, see the relationship between them, conceive nature of the figure completing each

system of relation presented, and by so doing, develop a systematic method of reasoning. The scale consisted of 60 problems divided into 5 sets of 12 problems each. The first problem of each set is nearly self evident and the problems which follow become progressively more difficult. The order or the tests provided the standard training in the method of working. The 5 sets provided 5 opportunities for grasping the method and 5 progressive assessments of the person's capacity for intellectual activity. An attempt was made to convert the percentile score into Weschler's equivalent score (IQ) which was an added advantage of using this test.

(b) Digit span attention test (DSAT) (24):

The test measures immediate auditory recall. Even more basically it measures attention, short term memory and freedom from distractibility due to external environmental stimuli. A high score based upon grouping the numbers suggest a quick adaptation to the demands of the stimulus from which might be inferred a flexibility in adaptation. The test comprises of 2 sections: In the first part the subject repeats a series of digits enunciated by the examiner and in the second section the subject repeats the digits in reverse order. The test begins with the subjects being asked to repeat 3 digits. In subsequent presentation the number of digit is increased. Norms have been provided on Indian population with a provision to convert raw scores into transformed quotient (TQ).

Treatment modality

The subjects were divided into control groups (C) and anemic groups (A) on the basis of hemoglobin concentration (Hb).

The control group comprised of 34 male children with Hb $\geq$ 12 g/dL and the anemic group of 18 children with Hb < 12 g/dL. The treatment consisted of deworming of both groups of children using a single dose of albendazole (400 mg) and given vitamin C therapy (100 mg) OD for 90 days. Children of the anemic group were given oral iron therapy in the form of ferrous iron (Fe^{+2}) 3–4 mg/kg bw in two divided doses daily. Pre (I) and Post (II) treatment hematological investigations, ERPs and psychometric test recordings were carried out and analysed.

Statistical analysis

Data were analyzed using unpaired 't-test' for comparison of the control and anemic groups of boys studied (comparison between control and anemic group for pre and post treatment results). The paired 't-test' was used for the comparison among the same group between pre-treatment (I) and post-treatment visit (II).

RESULTS

The results were tabulated wherein A stands for anemic boys and C for control boys, I and II for pre and post-therapy recordings respectively.

The four tables are as follows :

I. C I vs A I

II. C I vs C II

III. A I vs A II

IV. C II vs A II

The mean age for the control boys was 9.23 ± 0.25 years and for the anemic boys it was 9.31 ± 0.29 years. Inter group comparisons were done before starting the intervention and after the intervention had been completed. Post intervention recording of the same group was also compared with the preintervention observations. The hematological parameters of the control boys were significantly better than the anemic boys before the therapy was started. The mean Hb of the control boys was 13.1 ± 0.67 g/dL as compared to 10.9 ± 1.72 g/dL in the anemic boys (P<0.001) (Table I). In control boys the hematocrit (Hct) was 0.39 ± 0.02 L/L and in the anemic boys the value was 0.34 ± 0.04 L/L, MCV was 87.7 ± 6.55 fL and 78.5 ± 11.44 fL, MCH was 30.2 ± 2.58 pg and 26.4 ± 4.79 pg (P<0.05) and SI was 79.8 ± 31.90 µg/dL and 61.1 ± 22.40 µg/dL (P<0.05) while the TIBC was 366.1 ± 74.20 µg/dL and 320.3 ± 44.50 µg/dL (P<0.05) and % transferrin saturation (TS%) was 22.9 ± 10.10% and 19.6 ± 5.14% respectively. The P_{300} latency was significantly longer in the anemic boys being 372.8 ± 25.49 ms compared to 345.5 ± 25.20 ms in the control boys (P<0.05). The psychometric tests showed better scores in the control boys as compared to the anemic boys with RPMT gross scores (Y_1) being 52.8 ± 22.28 and 39.1 ± 17.0 (P<0.05) and the

TABLE I: Pre treatment hematological and cognitive functions in control (C-I) and anemic (A-I) school children.

Variable	*C-I (n = 34)*		*A-I (n = 18)*		*P value*
	Mean	*SD*	*Mean*	*SD*	
Hematological					
Hb (g/dL)	13.1	0.67	10.9	1.72	0.00**
Hct (L/L)	0.39	0.02	0.34	0.04	0.121
MCV (fL)	87.7	6.55	78.5	11.44	0.001*
MCH (pg)	30.2	2.58	26.4	4.97	0.007*
SI (µg/dL)	79.8	31.90	61.1	22.40	0.033*
TIBC (µg/dL)	366.1	74.20	320.3	44.50	0.009*
TS%	22.9	10.11	19.6	5.14	0.133
P_{300}					
Latency (ms)	345.5	25.20	372.8	25.49	0.001*
Amplitude (µV)	9.4	3.57	9.3	5.83	0.97
Psychometric#					
Y1	29.7	7.84	25.2	6.37	0.045*
Y2	52.8	22.28	39.1	17.0	0.027*
Y3	101.2	9.53	95.7	6.93	0.033*
Y4	9.6	2.23	9.1	1.92	0.422
Y5	97.3	15.71	93.6	13.54	0.397

#Y1: Ravens test gross score, Y2: Ravens test percentile rank, Y3: derived IQ, Y4: Digits Span Attention Test (DSAT) Gross Score, Y5: DSAT: Thet Quotient (TQ)

*P<0.05 **P<0.001

derived intelligence quotient (Y_3) being 101.2 ± 9.53 and 95.7 ± 6.93 respectively (P<0.05).

After the therapy, the Hb of the control boys did not increase significantly (Table II). The MCV and MCH values also showed insignificant increase. However, an increase in Hct value from 0.38 ± 0.02 L/L to 0.40 ± 0.03 L/L (P<0.05) and SI value from 77.0 ± 32.0 µg/dL to 99.1 ± 30.50 µg/dL (P<0.05) was seen consequent to deworming and low dose ascorbic acid therapy. No improvement in the P_{300} latency and amplitude values was seen in the control boys. The RPMT gross scores (Y_1) showed improvement from 29.9 ± 8.41 to 31.2 ± 8.02 (P<0.001) and DSAT gross scores (Y_4) also showed improvement from 9.6 ± 2.29 to 9.9 ± 2.12 (P<0.001) while the DSAT derived scores (Y_5) improved from 97.3 ± 16.12 to 99.7 ± 15.46 (P<0.001). Post therapy, the anemic boys showed increase in Hb from 10.8 ± 1.85 g/dL to 12.3 ± 0.94 g/dL (P<0.05), Hct from 0.34 ± 0.03 to 0.39 ± 0.03 L/L (P<0.05) and MCV from 79.1 ± 12.23 fL to 85.1 ± 12.86 fL (P<0.05) (Table III). The RPMT also showed significant improvement in gross scores (Y_1) from 25.3 ± 7.07 to 28.6 ± 6.88 (P<0.001), in percentile (Y_2) rank from 39.4 ± 18.93 to 48.6 ± 19.55 (P<0.001) and derived intelligence quotient scores (Y_3) from 95.8 ± 7.74 to 99.4 ± 8.23 (P<0.001). The DSAT gross scores (Y_4) improved from 9.1 ± 2.02 to 9.6 ± 1.91 (P<0.05) and DSAT derived scores (Y_5) improved from 93.7 ± 14.25 to 97.5 ± 13.77 (P<0.05). No improvement in the P_{300} latency and amplitude values was seen. When comparison was done between post therapy observations of the control and anemic boys, the significant differences persisted for hematological parameters. The

TABLE II: Hematological parameters and cognitive functions in control boys in first (C-I) and second (C-II) visits.

Variable	*C-I (n = 23)*		*C-II (n = 23)*		*P value*
	Mean	*SD*	*Mean*	*SD*	
Hematological					
Hb (g/dL)	13.1	0.68	13.2	0.83	0.721
Hct (L/L)	0.38	0.02	0.40	0.03	0.021*
MCV (fL)	87.4	6.57	90.6	5.88	0.120
MCH (pg)	29.8	2.61	29.8	2.66	0.996
SI (µg/dL)	77.0	32.40	99.1	30.50	0.011*
TIBC (µg/dL)	360.3	78.80	378.5	33.40	0.351
TS%	21.9	9.48	25.9	7.74	0.082
P_{300}					
Latency (ms)	341.1	23.17	340.5	25.96	0.931
Amplitude (µV)	9.1	3.76	10.3	2.97	0.242
Psychometric#					
Y1	29.9	8.41	31.2	8.02	0.00**
Y2	54.1	23.77	56.6	23.01	0.055
Y3	101.8	10.18	102.8	9.96	0.064
Y4	9.6	2.29	9.9	2.12	0.00**
Y5	97.3	16.12	99.7	15.46	0.00**

#Y1: Ravens test gross score, Y2: Ravens test percentile rank, Y3: derived IQ, Y4: Digits Span Attention Test (DSAT) Gross Score, Y5: DSAT: Thet Quotient (TQ)
*P<0.05 **P<0.001

TABLE III: Hematological parameters and cognitive functions in anemic boys before (A-I) and after (A-II) treatment with oral iron.

Variable	*A-I (n = 14)*		*A-II (n = 14)*		*P value*
	Mean	*SD*	*Mean*	*SD*	
Hematological					
Hb (g/dL)	10.8	1.85	12.3	0.94	0.003*
Hct (L/L)	0.34	0.03	0.39	0.03	0.002*
MCV (fL)	79.1	12.23	85.1	12.86	0.004
MCH (pg)	26.4	5.53	26.8	4.43	0.731
SI (µg/dL)	67.6	24.70	82.9	27.20	0.165
TIBC (µg/dL)	327.8	42.40	339.1	34.20	0.436
TS%	20.7	5.89	24.3	7.09	0.194
P_{300}					
Latency (ms)	369.7	23.18	361.1	30.81	0.294
Amplitude (µV)	8.8	5.87	10.4	3.98	0.431
Psychometric#					
Y1	25.3	7.07	28.6	6.88	0.00**
Y2	39.4	18.93	48.6	19.55	0.00**
Y3	95.8	7.74	99.4	8.23	0.00**
Y4	9.1	2.02	9.6	1.91	0.006*
Y5	93.7	14.25	97.5	13.77	0.008*

#Y1: Ravens test gross score, Y2: Ravens test percentile rank, Y3: derived IQ, Y4: Digits Span Attention Test (DSAT) Gross Score, Y5: DSAT: Thet Quotient (TQ)
*P<0.05 **P<0.001

TABLE IV: Post treatment hematological parameters and cognitive functions in control (C-II) and anemic school (A-II) children.

Variable	*C-II (n = 23)*		*A-II (n = 15)*		*P value*
	Mean	*SD*	*Mean*	*SD*	
Hematological					
Hb (g/dL)	13.2	0.83	12.3	0.94	0.004*
Hct (L/L)	0.40	0.03	0.39	0.03	0.255
MCV (fL)	90.6	5.88	85.1	12.86	0.182
MCH (pg)	29.8	2.66	26.8	4.43	0.02*
SI (µg/dL)	99.1	30.50	82.9	27.20	0.134
TIBC (µg/dL)	378.5	33.40	339.1	34.20	0.003*
TS%	25.9	7.74	24.3	7.10	0.554
P_{300}					
Latency (ms)	340.6	25.96	361.1	30.81	0.033*
Amplitude (µV)	10.3	2.97	10.3	3.98	0.971
Psychometric#					
Y1	31.2	8.02	28.6	6.88	0.311
Y2	56.6	23.01	48.6	19.55	0.272
Y3	102.8	9.96	99.4	8.23	0.285
Y4	9.9	2.12	9.6	1.91	0.669
Y5	99.7	15.46	97.5	13.77	0.665

#Y1: Ravens test gross score, Y2: Ravens test percentile rank, Y3: derived IQ, Y4: Digits Span Attention Test (DSAT) Gross Score, Y5: DSAT: Thet Quotient (TQ)
*P<0.05 **P<0.001

values of Hb for controls was 13.2 ± 0.83 g/dL and for anemics it was 12.3 ± 0.94 g/dL ($P<0.05$). Controls showed MCH values of 29.8 ± 2.66 pg and anemics had MCH of 26.8 ± 4.43 pg ($P<0.05$). TIBC values were 378.5 ± 33.40 µg/dL for control boys and 339.1 ± 34.20 µg/dL for anemic boys ($P<0.05$) whereas P_{300} latency values were 340.6 ± 25.96 ms for control boys and 361.1 ± 30.81 ms for anemic boys ($P<0.05$) (Table IV). No significant differences were found in the psychometric test scores. Thus, the hematological parameters and psychometric test scores of the anemic boys showed relative improvement when compared to the control boys. The P_{300} latency values of the anemic group remained persistently longer than the control group inspite of the therapy.

DISCUSSION

In this study it was observed that anemic children showed longer P_{300} latencies as compared to their age matched controls. Following therapy there was significant improvement in the hematological profile of the anemic group as well as a decrease in their P_{300} latency indicating improved cognitive functions. In a recent study by Tandon et al (25) a significant correlation between the degree of anemia and P_{300} latency has been observed in pregnant women. Temple et al (16) have also recorded the P_{300} wave and reported that cognitive functions and memory improve after anemia correction. Use of ERPs has been repeatedly emphasized for assessing recognition memory (26) and for investigation of the memory acquisition process (27) as well as for diagnosis of disorders of recent memory (28) and primary degenerative dementia (29). A significant relationship between speech recognition and P_{300} latencies also exist (30). EEG power spectrum and ERP studies have shown that the iron status of an individual correlates significantly with cognitive performances and EEG asymmetries (31).

Anemic children in the present study were also found to have lower scores for both RPMT and DSAT as compared to controls. Following iron therapy, the scores improved significantly in the anemic boys from the pretreatment values and were almost similar to the control group of boys. Thus, our study indicates the association of lower cognitive functions and anemic states, with improvement following iron therapy. Several studies have reported significant differences in the scores of anemic children as compared to the controls when assessed for memory, attention, visual motor coordination, visual perception and discrimination, intelligence and mental development index scores, alertness, responsiveness and school achievement test scores (8, 9, 10), with significant improvement seen after iron therapy (3, 10, 11, 12).

Although the improvement in P_{300} latency was observed in both anemic and control group of boys, the statistically significant pretreatment differences observed between the 2 groups persisted post-treatment. This suggests that certain underlying neural deficits remain despite deworming and the 3 months of intensive oral iron therapy in the anemic boys. These findings corroborate with the other neurophysiological research done on Auditory Brainstem Responses in infants before and after iron therapy, which showed persistence

of differences (14). This indicates that either the 3 months therapy is insufficient for correction of the underlying neural deficit or the changes induced by ID are irreversible. The improvement observed in the psychometric tests may be attributed to increased attentiveness and concentration of the children caused by the oral iron therapy but the persistance of deficits in ERPs indicate that the anemic children are still not completely normalized by the therapy. More extensive psychometric analysis may perhaps be required to analyze cognitive variables that will show deficits in ID children and will correspond better with the neurophysiological variable being studied.

ID has been shown to affect the brain and body monoamine metabolism, GABA metabolism and dopamine-opiate system, which can be reversed by iron therapy (32). Alteration in urinary nor-epinephrine excretion (33) and pituitary-adrenal responsiveness to stress (34) along with other neuroendocrine imbalances (32, 35) has been suggested in ID. The correction in the neurotransmitter metabolism and neuroendocrine imbalances might explain the increased attentiveness, concentration and decrease in behavioral abnormalities observed when therapy was given to ID children. ID has also been associated with defects in myelinogenesis and alteration in oligodendrocyte physiology during the growth periods (36, 37), which may be responsible for certain behavioral and developmental factors that have been shown to be irreversibly altered with ID and show no improvement even with very long term iron therapy (13). Thus, prevention of ID is the best strategy, even though, iron therapy does benefit the anemics to a certain extent. Long term iron therapy with consequent neurophysiological follow up can give more conclusive evidence about the potential reversibility of the cognitive deficits induced by the ID/IDA.

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