

Research Article

Could anemia be the reason for dysfunctional cognition???

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ABSTRACT

Background: Studies claim that anemia at any time in life can hamper the metabolic processes and subsequently affect the cognitive and behavioral domain of an individual. Late-adolescent girls are one of the most vulnerable groups due to commencement of menstrual cycles, hormonal changes, nutritional deficits etc. It is also the time period where adolescents enter their professional careers in our country where cognition forms the basis of all the learning. This study was focused on seeing whether anemia affects the P300 wave which is a cognitive evoked potential.

Methods: 74 girls of first and second year MBBS were chosen for this study. They were divided into two groups on basis of hemoglobin estimation by cyanmethemoglobin method. A comparative study was done of P300 latency and P300 amplitude between the two groups.

Results: Comparison between the anemic group to the control group revealed: Latency of P300 was significantly delayed in the anemic group and amplitude was significantly higher in the control group.

Conclusion: The results suggested a better cognitive performance of those having normal hemoglobin levels.

Keywords: Anemia, Late-adolescent, P300 latency, P300 amplitude

INTRODUCTION

P300 is an endogenous Event Related Potential (ERP) that can be recorded on external response or event. These potential changes occur after the initial sensory processing of the stimuli when the subject selectively pays attention to a stimulus and is usually elicited in a situation where the subject is required to distinguish one stimulus from the other. The P300 wave in particular is a positive wave recorded from the parieto-central region. The two parameters which are usually measured from the P300 wave are Latency and Amplitude.¹ Amplitude is defined as the difference between the mean pre-stimulus baseline and the largest positive going peak in the time frame of 250-500 ms. Latency is the time period from stimulus onset to the point of maximum positive amplitude.² "P300" wave is named so, because when a young adult subject makes a simple sensory discrimination the peak latency of the wave is 300 ms.³ It

is also called P3 wave because it is the third major positive peak in the late sensory evoked potential.⁴

The generation of P300 can be explained on the basis of the context updating theory in which absence of novelty in the stimulus, leads to appearance of only sensory potentials on the record. However, on detection of a stimulus which is different in characteristic from the previous, "updating" of the neural stimulus is charted in the working memory. P300 amplitude reflects the strength of memory that was formed during the initial encoding of the stimulus.² Latency on the other hand is determined by processes involved in stimulus evaluation and categorization.⁵

Various factors have been researched by scientists that affect the P300 wave in order to explore the functional capacity of P300 wave in diagnostic studies. Of all the physiological factors that can affect the P300 wave,

Anemia - which is the most common condition prevalent in the community, remains relatively unexplored to some extent. A few studies have been carried in the past in similar light, Burden MJ et al. studied the effect of iron deficiency on ERP's of infants and concluded that iron deficiency severely affects the attention and recognition memory task.⁶ Singh NP et al. evaluated the effect of improvement in anemia on P300 wave in chronic kidney disease patients and found a significant improvement in the P300 on administration of erythropoietin.⁷

Anemia, which can affect all the age groups, remains obscured in adolescents.⁸ The causes for its occurrence in late adolescent group especially 15-19 year girls are as follows:

1. General neglect on the part of the family and parents as the are considered young adults.
2. Onset of menstruation not compensated due to dietary lack.
3. Irregularities of menstrual cycles which are common among teenage girls.
4. A need for higher education forcing young adolescents to move away from their homes and leading them to eat outside food which lacks significantly in nutrition.
5. Consumption of contaminated water leading to various worm infestations.
6. Nutritional education in India is not much prevalent even in the families with good educational background, where quantity of food still gains preference over quality.

Therefore, this study was undertaken to study the effects of anemia on endogenous evoked potential of late - adolescent group of girls.

METHODS

The study was carried out on 74 girls between the age group of 18-19 years studying in the 1st and 2nd year MBBS. It was carried out in the hematology and clinical physiology lab of Dr. V.M. Government Medical College, Solapur.

The following steps were undertaken before undergoing the actual cognitive test.

1. A prior written consent was obtained from the subjects before undergoing the procedure.
2. A detailed history of the subject was obtained which included: General history, past history, any significant present history, surgical or medical history if any, menstrual history, diet history, socio-

economic status and educational qualifications of the parents were also obtained.

3. Subjects with chronic disease or any major medical ailment were excluded from the study.

Likewise subjects with hearing defects, subjects on any medications, subjects with any neurological or psychiatric disorders were excluded. Similarly, physical exercise is said to affect cognition positively, therefore such subjects who performed regular physical exercise of any kind were also excluded from the study.

Selecting the girls with the help of inclusion and exclusion criteria, 74 girls who were age matched, qualification matched were taken under consideration and tests were conducted when they were in the same phase of the menstrual cycle (Early follicular was preferred).^[9]

Hb estimation method^{10,11}

Hemoglobin was tested by the cyanmethemoglobin Method with the help of a standardized kit.

Procedure:

1. Drabkin's reagent was used from Yucca Diagnostics, Kolhapur. 5 ml of which was poured in the test-tube.
2. Under all aseptic precautions capillary blood was taken in the Sahli's pipette upto mark 20 µl.
3. This blood from the pipette was then poured into the test-tube and kept aside to stand for 20 minutes.
4. The colorimeter was adjusted to 545 nanometers (HANS-161colorimeter) (ideal arrangement: 520-560 nanometres) and it was set at zero with the help of distilled water.
5. The standard for Drabkin's reagent, having concentration of 60 mg/dl was provided by the Yucca Diagnostics. It's absorbance was measured on the colorimeter for 545 nm.
6. The colorimeter was again set to zero and the absorbance for test sample was measured.

The calculations were done using the following formula:

$$\text{Haemoglobin (gm/dl)} = \frac{\text{Value of test}}{\text{Value of std.}} \times \frac{60}{1000} \times 251$$

Where,

- (a) 60 = Concentration of standard in mg/dl
- (b) 1000 = Conversion factor of std. in mg/dl to gm/dl
- (c) 251 = Dilution factor

Measuring cognitive evoked potential (P300)

The P300 was measured using an odd ball paradigm. The machine that was used to measure this evoked potential was RMSEMG EP II. The room was shielded acoustically. The stimulus that was given in order to evoke an endogenous potential was auditory in nature. In a dimly lit room the subject was asked to sit on a chair, comfortably with closed eyes and emphasis was laid to remain awake and alert. The subject was instructed prior to restrict the eyeball movement in order to avoid any electro-ocular artifacts or contamination in the ERP recording. The subject was asked to keep a mental count of the numbers of target stimuli by raising the finger.¹²

The settings were done as follows¹³

The gain setting was set at 2µ V/D. The filters are usually used for routine rhythm monitoring. The low filter was set at 2 Hz and the high filter was set at 100 Hz. The sweep speed was adjusted at 50 ms/Div. The stimulus rate was set at 0.9 Hz frequency with stimulus given to both the ears through the headphones. The stimulus intensity throughout the procedure was 70 dBnHL. The probability of an occurrence of a rare stimulus in this experimental design was adjusted at 20%.

Electrode placement (Figure 1)

Electrodes were fixed on the scalp and the forehead with the help of a conductive paste provided along with the apparatus by the company. Surface electrodes were placed with reference to the bony landmarks in the following positions:

- 1) The reference electrodes were placed on the mastoid bones - right and left respectively.
- 2) The active electrodes were placed on the forehead (Fz) and Vertex (Cz) respectively.
- 3) The ground electrode was placed in between the eyebrows. (Fpz).¹⁴

Before starting the procedure the electrode impedance was checked to be less than 5 kΩ. After the impedance testing the headphones were placed on subject's ears.¹² Two tones were used as stimulus, a frequent low pitched tone normally 750Hz and a rare relatively high pitched tone of 2 KHz.¹³

Subject was asked to attentively count the number of rare stimuli and ignore the frequent stimuli. As soon as a novelty stimulus i.e. a rare stimuli was attended by the subject, it resulted in recording of an Evoked Potential. Approximately two traces were taken per recording. N1 and P1 was recorded in response to the frequent stimulus, while P3 or P300 was a large positive deflection of wave captured on attending the rare stimuli.¹ (Figure 2). Responses were averaged until minimum 25 stimuli were given and 100 frequent stimuli were given.

The co-ordinates were adjusted well to get an accurate value of the latency and amplitude. The amplitude was measured from the baseline voltage present before the stimulus to the largest positive peak that was present in the time window of approximately 250- 500 milliseconds. Latency was measured by placing the co-ordinate at the peak of the P300 wave.

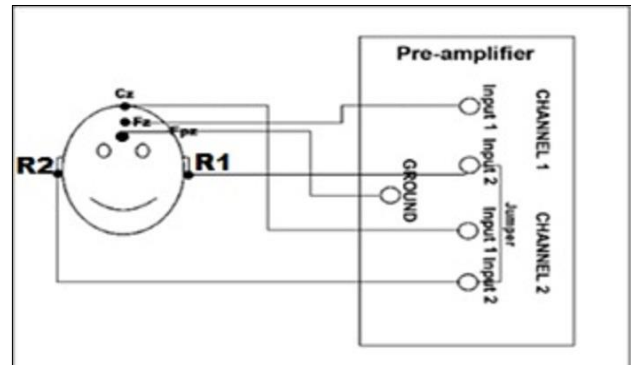


Figure 1: Showing the placement of electrodes.

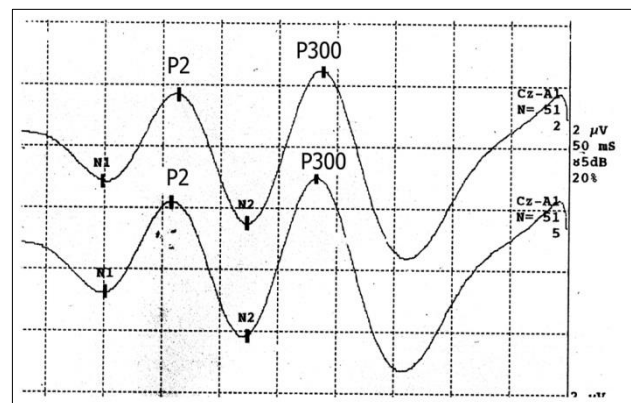


Figure 2: Showing how the P300 wave normally appears.

Analysis of data

The data received was tabulated on Microsoft excel. The components of P300 taken into consideration while tabulation were latency (milliseconds) and amplitude (µV). Mean of each variable and standard deviation of each variable were calculated. The data was analysed using unpaired T-test using openepi.com.

RESULTS

Adolescent girls in the anemic group had significantly delayed P300 latencies (332.45 ± 42.61 milliseconds) as compared to the control group (290.62 ± 34.35 milliseconds) with ($P = 0.00003$) The P300 amplitudes were significantly larger in the girls in the control group ($11.74 \pm 5.3 \mu\text{V}$) as compared to the anemic group ($9.06 \pm 3.64 \mu\text{V}$) with ($P = 0.012$).

Table 1: Showing 74 girls were grouped in two, according to their estimated hemoglobin values as anemic group and control group. As per the WHO definition <12 gm/dl of hemoglobin for females was considered anemia.

Groups	Hb value	Total number
Anemic	<12 gm/dl	32
Control	≥12 gm/dl	42

Therefore, Group 1: Anemic group = 32 girls Group 2: Control group = 42 girls

Table 2: Showing mean values and standard deviation (SD) of ERP latency (msec) for anemic group and control group.

Groups	Mean ± SD	t test	P value
Anemic	332.45 ± 42.61	4.54	0.00003***
Control	290.62 ± 34.35		

P <0.001 = Highly significant and is denoted by***

Table 3: Showing mean values and standard deviation (SD) of ERP amplitude (µV) in anemic group and control group.

Groups	Mean ± SD	t test	P value
Anemic	9.06 ± 3.64	2.58	0.012**
Control	11.74 ± 5.3		

P <0.05 - Significant and is denoted by**

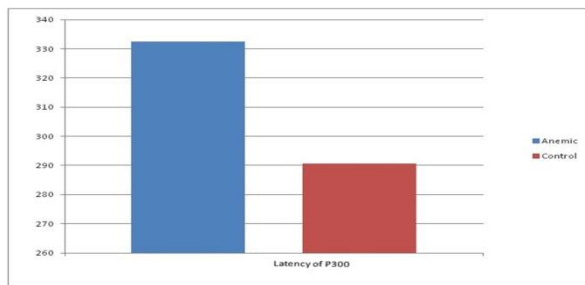


Figure 3: Showing ERP latency in msec for Anemic group and Control group.

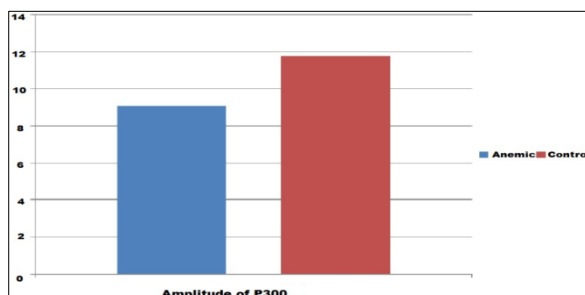


Figure 4: Showing ERP amplitude in µV for Anemic group and control group.

DISCUSSION

The domain of cognition has intrigued man since ages. Cognition is a broad concept which includes: Perception, attention, working memory, reasoning, problem solving, language skills and decision making.¹⁵ In the present study we have concentrated on Perception, attention, working memory and quick decision making aspect represented by the P300 wave which is an endogenous evoked potential.

The P300 wave has 2 parameters of vital importance: 1) Latency 2) Amplitude. Latency of the P300 wave usually represents the neural conduction time.¹⁶ Neural Conduction time largely depends on myelination and synaptic wiring. An efficient myelination and a good strength of synaptic wiring results in decreased latency. Amplitude however reflects subjects attention during the task and the amount of brain energy added during the analysis of the information that was provided.¹⁶ The proposed neural generators of the P300 wave constitute the limbic system especially hippocampus,¹⁷ temporo-parietal junction which includes supramarginal gyrus and caudal parts of Superior temporal gyrus.¹⁸ A very important contribution from inferior parietal lobe.¹⁹ A widely accepted concept is that ERP's [e.g.: P300] are a result of intracortical currents induced by excitatory and inhibitory post-synaptic potentials (EPSP'S, IPSP's) which are triggered by the release of neurotransmitters. Therefore, an indirect reflection of postsynaptic effects of neurotransmitters like glutamate, GABA and neuromodulators like acetylcholine, nor-adrenaline, dopamine and serotonin can be studied by studying them.²⁰

The results in Table 2 and Figure 3: shows that P300 latency was significantly delayed in the anemic group as compared to the control group (P = 0.00003) (P <0.001 = highly significant). While Table 3 and Figure 4: shows the amplitude of P300 for the control group was significantly larger as compared to the anemic group (P = 0.012) (P <0.05 = Significant). Our findings are similar to H. Kecesi who studied quantitative EEG and Evoked potentials in anemia,²¹ Burden MJ et al. who studied ERP's in infants with Iron deficiency⁶ and Otero GA et al. who studied effect of iron supplementation on p300 wave and found significant improvement after the same.²²

The cause for delayed latency in anemic group could be explained as below: Though, our study could not point out for sure as for the exact causes of anemia. But history revealed, 53.12% of the girls in the anemic group significantly lacked intake of green leafy vegetables and vitamin C sources. 6.25% of the girls had been strictly vegetarian since birth. 28.12% of the girls in the anemic group gave history of bleeding problems which included:

- 1) On and off episodes of bleeding piles.
- 2) Irregular menses lasting for >7 days, Dysmenorrhea associated with passage of heavy clots. 3.13% girls

gave a history of being successfully treated for heavy worm infestation in past 3 months.

3) 12.5% girls had mixed causes.

In India, the most common cause for microcytic anemia is Iron deficiency. Iron is an important co-factor for Tyrosine hydroxylase and Tryptophan hydroxylase.²³ These are important in synthesis of dopamine, catecholamines and 5-HT respectively.²⁴ Also, iron has a role in myelination, a study has proposed early iron deficiency causes specific changes in myelin composition which includes a lower relative content of cholesterol, proteolipid protein (PLP), and Myelin Basic Protein 21 (MBP21), thus affecting oligodendrocyte development and function. Thus iron deficiency anemia will lead to increased latency of P300.²⁵

Vitamin B6 deficiency though rare to occur singularly, could also lead to microcytic type of anemia.²⁶ Since it is a co-enzyme for δ -aminolevulinic synthase, it catalyzes the first step of heme synthesis.²⁷ Vitamin B6 is also an important co-factor for production of dopamine. Animal studies have revealed: The time course for release of dopamine and decay of the released dopamine is prolonged by vitamin B-6 deficiency.²⁸

Although careful history was taken in prior to rule out thalassemia in our samples but nevertheless thalassemia trait could go undiagnosed for a longer period of time presenting with only anemic symptoms like fatigue, headache etc. Studies have shown P300 latencies to be delayed and amplitude to be shortened in thalassemia minor patients. They have cited chronic hypoxia and oxidative stress in hemoglobinopathies to be the reason for the cognitive dysfunction.²⁹ Similarly, we would like to rule out chronic disease to be a cause for anemia,²⁶ since we already excluded those who suffered from one (e.g.: asthma patients, juvenile diabetes mellitus, tuberculosis). In addition, the subjects in our study were adolescents where the prevalence of chronic disease is limited.

Vitamin B12 is the most common cause of macrocytic anemia especially among long term vegetarians. It plays an important role as a cofactor in conversion of methylmalonyl Coenzyme A (CoA) to succinyl-CoA. Disruption in the above pathways could lead to increased levels of methylmalonic acid (MMA) which causes abnormal fatty acid synthesis affecting the neuronal membrane.³⁰ Such lipids are found in myelin sheaths and their damage can be in part responsible for the neurologic complications of Vitamin B12 deficiency.^{31,32}

Folic acid could be another potential cause for macrocytic anemia leading to cognitive impairment. The probable causes for cognitive impairment could be:

Folate plays a very important role in biosynthesis of neurotransmitters like dopamine and nor-epinephrine which are proposed to be related with P3 generation.³³

The causes for smaller P300 amplitudes in anemic group as compared to control group could be explained as follows:

Both iron and B6 are important for synthesis of dopamine as discussed above. Dopamine could be related to cortical processing of information through the basal ganglia. It is also considered a key neuroregulator which contributes to the anticipatory process which is required for preparing voluntary action subsequent to intent.³⁴ (e.g.: raising a finger on listening to a rare stimuli). Therefore, decreased dopamine levels could lead to less cortical processing leading to smaller amplitudes. Also iron plays an important role in Nor-epinephrine synthesis, therefore a decrease in Norepinephrine level will affect the amplitude as locus ceruleus-norepinephrine system is also proposed to have been contributory in P3 generation.¹⁸

Also, Vitamin B12 plays an important role as a cofactor in conversion of homocysteine to methionine. Disruption in this pathway could lead to increased levels of homocysteine which displays its neurotoxicity through overstimulation of the N-Methyl-D-Aspartate (NMDA) receptors.³⁰ Also, evidence has suggested decreased folate levels to be associated with high homocysteine levels.²⁷

Although, we could not delineate the cause for anemia in each, results showed a significant effect of lowered hemoglobin levels on the cognition of the adolescent girls. The following tests would have strengthened the study and would have helped us narrow down the exact causes: Serum Iron, ferritin levels, TIBC levels, serum B12 levels, homocysteine levels in blood or urine, electrophoresis to rule out thalassemia.

CONCLUSION

The present study concluded that the late adolescent group of girls who had anemia are more vulnerable to inattentiveness, delayed analysing of information, late decision making and slow processing of working memory as compared to the control group. These were drawn on the basis of statistical analysis which showed significant delay in latencies of P300 and smaller amplitudes in anemic group as compared to the control group. The above factors form the basis of a sound learning of any subject of interest or execution of any task. We would suggest a routine blood check up to be made mandatory in schools and colleges at regular intervals along with serum iron, TIBC, ferritin levels, and homocystine levels whenever required as some studies have shown reversal of cognitive impairment after giving supplements.

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