Review Article

P300, a tool for cognitive assessment in women with iron deficiency anemia: A systematic review

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Abstract

Iron-deficiency anemia (IDA) is a common nutritional disorder and an important risk factor for the development of mild cognitive impairment that may progress to dementia, if untreated. The anemic status due to iron deficiency (ID) alters the electrogenesis in the central nervous system. P300 is a cognitive evoked potential (CEP) used as an objective tool to assess cognitive function. Mild cognitive impairment is indicated by prolonged P300 wave latency and reduced amplitude. IDA is highly prevalent among women particularly in the reproductive phase and data on cognitive assessment using P300 in them are sparse. This review aims to analyze the evidence from recent literature regarding the effect of IDA on evoked potentials like P300 in women. A systematic literature review was conducted and databases, like PubMed, Medline, Scopus, and Google Scholar, were searched for studies from the last 20 years. We selected research papers that compared P300 between anemic women and controls of the same age, and evaluated the effects of iron supplementation on P300 in anemic women. Based on the inclusion criteria, three studies were found. The studies demonstrated impaired P300 potentials in anemic women that improved following iron supplementation. Promoting screening of anemic women with P300 aids in the early detection of subclinical cognitive decline. Ensuring adequate iron treatment can prevent mild cognitive impairment from progressing to severe forms like dementia and other neuropsychological disorders. Further studies utilizing P300 as a cognitive tool need to be encouraged to establish definite conclusions regarding its efficacy in detecting cognitive dysfunctions in anemia.

Keywords: Adult females, event-related potentials, microcytic hypochromic anemia

Introduction

Anemia is a major health problem present globally affecting 1.8 billion people, which is estimated to be 25% of the population, of which iron deficiency (ID) is a major contributing factor.[1] The World Health Organization (WHO) report estimates that 30% of non-pregnant and 42% of pregnant women suffer from anemia. The prevalence of anemia is higher in women compared to men (12%). Women in developing countries are more susceptible to this deficiency due to low-dietary intake, menstrual blood loss, and increased demand during pregnancy and lactation.[1] National Family Health Survey (NFHS) 5 carried out by the Union Ministry of Health and Family Welfare, India during the year 2019–2020 shows a prevalence of anemia to be 57% in non-pregnant women belonging to the age group of 15–49 years.[2] According to WHO, iron deficiency anemia (IDA) in non-pregnant adult females is blood hemoglobin <12 g/dl and serum ferritin <15 ng/ml.[3]

Low hemoglobin levels in iron deficiency anemia (IDA) diminish the tissue oxygenation. The chronic low-oxygen supply may

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affect the brain energy metabolism, intellectual functioning, and cerebral integrity.[4] Reduced cerebral blood flow due to anemia causes prolonged hypoxia altering the iron channel's excitability and its functional expression. This functional deviation of iron channels is a contributing factor to neurodegeneration.[5] IDA indicates a severe form of ID that leads to reduced erythropoiesis, subsequently causing anemia. IDA has a significant impact on the attention domain of cognition compared to iron-deficient and iron-replete individuals, indicating that IDA is a grievous form of deficiency, which further aggravates the cognitive dysfunction.[6] Evidence from various prospective[7,8] and cross-sectional[9-11] studies shows a significant correlation between hemoglobin levels and cognition. Anemia is therefore a potential risk factor for cognitive decline conceivably due to chronic brain hypo-oxygenation.[4]

Besides iron having a key role in hemoglobin synthesis, it is required for non-hematological functions by various tissues both during developmental and non-developmental phases of life. From various researches, there is strong evidence that iron is essential for neurological development during infancy and childhood. The development of oligodendrocytes, myelination, neurogenesis, synaptogenesis, and neurotransmitter synthesis are all iron dependent. Disruption in these processes due to its deficiency during the developmental stages compromises the motor, sensory, behavioral, language, memory, and cognitive functions.[12,13] In adulthood, iron is essential for the synthesis of brain neurotransmitters and their regulation (e.g., dopamine, norepinephrine [NE], and serotonin) and brain energy metabolism.[14,15] Because of its requirement in the maintenance of these functions, deficiency may lead to impaired electrogenesis and impulse transmission in the brain.[4,16] When electroencephalogram (EEG) signals were correlated with blood hemoglobin and serum ferritin levels, slowed power spectrum in EEG was noted, indicating that systemic iron status affects normal brain functioning.[16-18]

The cortical impulses triggered by neurotransmitter released in response to an external stimulus can be recorded non-invasively using evoked potentials.[19] Evoked potentials are electrophysiological signals produced by the nervous system that are recorded in response to a particular stimulus like light flash (visual) or a pure tone (auditory).[20] The auditory evoked potential like the P300, also known as cognitive evoked potential (CEP) or event-related potential (ERP), is a long latency evoked potential. It non-invasively helps to measure the electrophysiological signals which are generated by neuronal activities in multiple regions in the brain. The auditory ERP is an index to measure the attention and working memory domains of cognition.[19] Daryl Fougnie quotes "The ability to selectively process information (attention) and to retain information in an accessible state (working memory) are critical aspects of cognitive capacities."[21] As cognition is a fundamental factor for maintaining the quality of life, impaired cognitive function is correlated with poor quality of life and poor life outlook.[22]

Anemic individuals are vulnerable to inattentiveness, poor working memory, delayed information analysis, and decision making, eventually impairing their cognitive capacity.[23] A meta-analysis revealed that P300 is a sensitive tool for monitoring cognition and an index in evaluating cognitive deterioration.[24] Researchers have studied the effect of IDA on the different domains of cognition in adults using various cognitive tests, for example, mini-mental state examination (MMSE),[10,11,16] Wechsler Memory Scale-Revised (WMS-R),[16] Detterman's Cognitive Abilities Test,[25] and various computerized tests,[26] and concluded that the severity of IDA inversely correlated with cognitive score and directly correlated with task completion time. P300 is a new technique that is underutilized in neurological and psychiatric disorders. Additionally, it is useful to complement other cognitive tests.[27] As it is an objective method for cognitive assessment, P300 requires minimum subject cooperation, and even detects subtle cognitive changes.[28,29] P300 finds its applicability in clinical practice for assessing the cognitive status and in electrophysiological research to monitor the effects of therapies in clinical trials.[30,31]

A brief overview regarding the origin of P300 and its neural generators is essential to understand the underlying mechanisms by which IDA alters P300. P300 was first reported 50 years ago to measure human neuroelectric signals.[32] It is a component of the auditory ERP, recorded as a large positive wave with a peak latency approximately at 300 ms after the stimulus onset, therefore the term P300.[32] The signal detection tasks, for example, the oddball paradigm are used to elicit P300, which was first employed by Ritter and Vaughan in 1969.[33] The oddball paradigm involves two types of auditory stimuli where the participant is presented with infrequent target stimuli in a background of frequent standard/non-target stimuli [Figure 1]. The participant responds mentally (counts) or physically (presses the button) to the target stimuli and not to the standard stimuli. A response to the target stimulus elicits a large positive potential with a peak latency at approximately 300 ms, i.e, P300. The amplitude (μV) is measured as a difference between the pre-stimulus baseline and the peak of the positive large wave appearing in a time window of 250–500 ms (depending on the stimulus and subject characteristics). Latency (ms) is marked as the time from the stimulus onset to the peak of the positive wave.[32] The scalp distribution of this wave is predominantly parietocentral, occurring when the subject is consciously

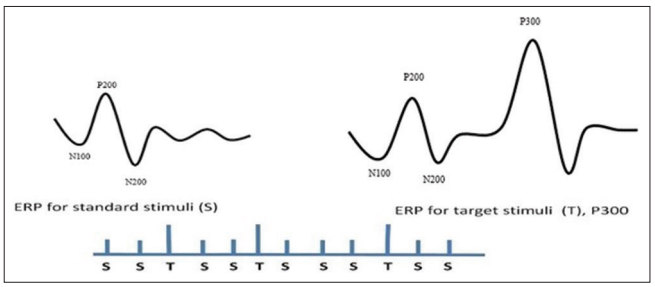

Figure 1: Diagrammatic illustration of the oddball paradigm eliciting ERP wave for the standard (S) and the target (T) stimuli.(Source[35])

involved in signal detection tasks.[34] The amplitude of P300 measures the brain's processing action to the change in the environmental stimulus, therefore it is hypothesized as an index of attentional resources and working memory.[35] An increase in P300 amplitude reflects increased activation of neural circuits and is proportionate to the attention and memory resources allocated, with larger amplitudes indicating higher cognitive capability.[36] P300 latency is related to cognitive efficacy and is proportional to the time required to detect and evaluate the stimulus. It assesses how rapidly the attentional and memory resources are recruited indicating the processing time required before the response is generated. Shorter latencies are related to superior cognitive performance, while cognitive disorders record prolonged latencies.[32] In cognitive disorders such as mild cognitive impairment (MCI),[24,30,37] Alzheimer's,[38] and Parkinsonism,[39] the P300 latency is prolonged and the amplitude is reduced. Population-based cohort and case-control studies reported that anemic people are at the higher risk for developing dementia.[40,41] Furthermore, a case-control study supports an association of low hemoglobin levels with the development of Parkinson's disease in the later part of life.[42] Hence, P300 can be used as a decisive tool in determining subclinical cognitive impairments in the newly diagnosed anemic population.[24]

The generation of the P300 wave is explained by the context updating theory [Figure 2]. After the initial sensory processing, the stimuli presented are compared, if no change is detected the previous "schema" of sensory evoked potentials is recorded as N100, P200, and N200. But if a new stimulus is detected, the attention mechanisms are engaged and the working memory evaluates it with the previous event. This cascade of attention and memory "updating" results in the appearance of the P300 [Figures 1 and 2].[32]

The proposed hypothesis for neural generators of P300 is that during auditory tasks, for example, the oddball paradigm, the discrimination between the target and the standard stimuli initiate activity in the frontal lobe which is involved in the attentional function.[43] This is followed by activation of memory operations in the temporo-parietal regions, requiring intact integrity at this junctional area. This cascade of activation was evident by neuroimaging techniques like functional magnetic resonance imaging (fMRI) with simultaneous ERP recording revealing frontal to temporo-parietal lobe activation.[44,45] According to the dual transmitter P300 hypothesis, the attention domain which is a function of the frontal area is mediated by dopaminergic activity, while the working memory involving the temporo-parietal junction is associated with NE activity.[35] ID and hypoxia in IDA are implicated in impairing the P300 wave due to their possible effect on neurotransmitter and brain energy metabolism.[36,46]

With this brief understanding regarding P300, a systematic literature review was conducted to know the usefulness of P300 for assessing cognition in anemic women and changes associated with iron supplementation.

Objective

Systematically review the literature to determine the impact of IDA on cognitive performance using auditory evoked potentials like P300 in anemic women. And also to observe the changes in P300 after iron supplementation administered to improve the anemic status.

Materials and Methods

Systematic literature search for studies using electronic databases, for example PubMed, Medline, Scopus, and Google Scholar was done from the day of inception to December 2020. With a general scheme including terms related to "IDA", "cognition," and "P300". Boolean operators like AND/OR were applied for the searching process. Mesh terms were: {("Nutritional deficiencies"[Mesh]) OR ("Nutritional anemia"[Mesh]) OR ("Micronutrients"[Mesh]) OR ("Anaemia" [Mesh]) OR ("Iron deficiency" [Mesh]) OR ("Iron deficiency anemia" [Mesh])} AND {(P300 [Mesh]) OR ("event-related potential"[Mesh]) OR ("cognitive evoked potential"[Mesh]) OR ("auditory event-related potential"[Mesh]) OR ("electrophysiological" [Mesh])}.

Activated filters: research in humans, aged: 18–40 years.

Literature search mainly included articles published in the last 20 years (2001-2020). Abstracts of various comparative, cross-sectional, prospective cohort and clinical trials were screened

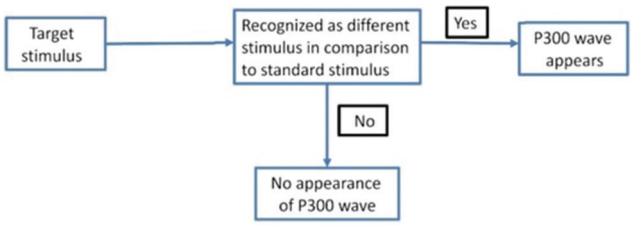

Figure 2: Illustration of the P300 context-updating model. (Source[35])

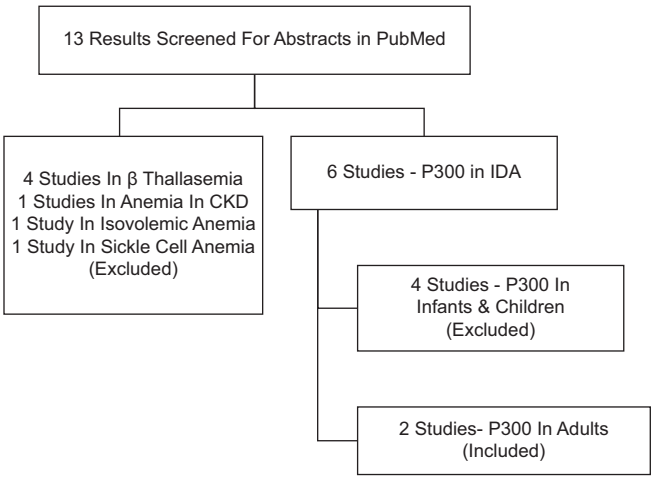

Figure 3: Study selection flow diagram

and studies that included adult females with IDA and assessed cognition using P300 in them were selected [Figure 3].

The exclusion criteria were (1) case reports, (2) populations with pathologies other than IDA (e.g., sickle cell, thalassemia), (3) full text/abstract not available, and (4) languages other than English.

This review is designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results

The search results identified three studies as per the inclusion criteria. Of the three articles extracted, two of them compared P300 values in anemic women before and after iron supplementation. The study characteristics and results of the included studies are mentioned in Table 1.

The studies had reported the blood parameters and P300 values (amplitude and latency) as mean ± standard deviation. Analytical tests for statistical evaluation applied in these studies included Student's "*t*" test and Pearson's correlation coefficient, and the significance was set at *P* value < 0.05.

The study by Kececi and Degirmenci[4] "Quantitative EEG and cognitive evoked potentials in anemia," included a total of 51 subjects with IDA of which 46 were females with a mean age of 30.98 ± 9.15 years. Significant differences were observed in hematological parameters between the pre- and post-iron (Fe) treatment. The pre-treatment P300 latency was significantly longer compared to post-treatment values, suggesting anemia decreases cognitive performance.

The study conducted by Khedr *et al.*;[16] "Iron states and cognitive abilities in young adults: neuropsychological and neurophysiological assessment," included 28 patients with IDA of which 13 were females with a mean age of 25.50 ± 4.10. Though the study included both male and female subjects, no gender differences in ERPs were identified. Compared to controls, the blood hemoglobin, serum iron, and total iron-binding capacity of the cases were significantly lower ($P < 0.001$). P300 latencies of the cases were significantly longer ($P < 0.05$) than that of controls and the P300 amplitudes of the cases were significantly lower ($P < 0.05$) than that of the controls. Among the cases, a significant negative correlation among P300 latency, hemoglobin level (*r*-value − 0.46, *P* value 0.04), and serum iron (*r*-value -0.450, *P* value 0.047) was observed. Also, a significant positive correlation between P300 amplitude and serum iron level (*r*-value 0.750, *P* value 0.001) was noted in the anemic group. The differences in latencies remained unchanged after the iron intervention while a significant increase was observed in P300 amplitudes. In the study by Kharat *et al.*;[23] "Could anemia be the reason for dysfunctional cognition?" P300 was recorded in anemic and compared with healthy controls. The anemic particpants were not investigated for the type of anemia in the study. According to the medical history given by the subjects, most anemic participants had insufficient dietary intake or had suffered blood loss due to either menstrual disorders, bleeding piles, or worm infestation. We assume, the majority of participants could have IDA as per the history. We included this study in our review as IDA is relatively more prevalent in India compared to other forms of anemia and moreover, comparative studies on this topic are also lacking. The study included 32 anemic (Hb <12 g/dl) and 42 healthy females (Hb >12 g/dl) between 18 and 19 years. The study shows that P300 latency was significantly increased in the anemic group when compared to the control group ($P = 0.00003$) and the P300 amplitude in the control group was significantly larger as compared to the anemic group ($P = 0.012$).

Discussion

IDA is identified as a prevalent nutritional disorder affecting all age groups. Several clinical studies have reported its significant effect on various aspects of cognition like perception, attention, memory, evaluation, judgment, and execution. P300 being an objective method is useful in indexing the attention and working memory domains of cognition.[28]

From the above studies, cognitive performance that was assessed by amplitude and latency of P300 wave strongly co-related to hemoglobin levels. The appearance of low

Table 1: Characteristics of included studies

Study by	Country and year	Study type	Sample size	Measures for anemic status	P300 outcome
Kececi and Degirmenci[4] 28 citations	Turkey, 2008	Cohort	46 women with IDA	Hb, Ht, MCV, MCH, MCHC, TIBC, RDW	Latency significantly decreased after Fe supplementation
Khedr *et al.*[16] 72 citations	Egypt, 2008	Clinical trial	13 women with IDA, 13 controls	Hb, TIBC, Serum Iron	Significantly reduced amplitude in anemics before Fe treatment compared to controls, amplitudes increased post-Fe therapy. Prolonged latency compared to controls, unchanged post-Fe therapy. Negative correlation between Hb and latency, positive correlation between S. Fe and amplitude.
Kharat *et al.*[23]	India, 2015	Case-control	32 anemic women, 42 controls	Hemoglobin	Significantly prolonged latency and reduced amplitude compared to controls

Hb: hemoglobin; Ht: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular-hemoglobin concentration; TIBC: total iron-binding concentration; RDW: red cell division width; Fe-iron

amplitude and longer latency P300 waves in anemic females when compared to non-anemic females indicates that low-hemoglobin levels result in the poor functioning of the central nervous system (CNS).[16,23] Similar studies in infants, children, and adolescents also reported a positive correlation between hemoglobin levels and cognitive performance using P300.[28,47-49] Iron supplements to improve hemoglobin levels resulted in augmented P300 waveforms in them.[28,50,51] Kececi[4] and Eman *et al*.[16] studied the effect of improvement in blood hemoglobin levels by iron supplementation on P300 in adults with IDA. Post supplementation improvement in hematological parameters was associated with relative latency reduction[4] and amplitude enhancement,[16] indicating that inadequate central oxygenation had resulted in delayed P300 latency.[46] P300 documented in patients with chronic kidney disorders (CKD) after administration of erythropoietin to increase the hematocrit revealed shortened latencies and amplified the P300 wave, suggesting that anemia correction improves the ERP and hence neurocognitive functions.[52,53] The significant positive correlation between serum iron levels and P300 amplitude suggests the role of iron in the generation of ERP. It is known that ID in its severe form leads to reduced hemoglobin synthesis and erythropoiesis. Besides causing anemia, poor iron status interferes with brain neurotransmitters and energy metabolism.[14,15] Iron is a vital component of cytochrome oxidase, its deficiency causes mitochondrial damage and hampers brain energy metabolism. It is also an essential cofactor for tyrosine hydroxylase participating in dopamine and NE synthesis.[36,54] The dual transmitter hypothesis proposes a predominant involvement of these neurotransmitters in the generation of P300 in the frontal (dopamine) and temporo-parietal regions (NE). ERP's like P300 measures the cortical activity due to excitatory and inhibitory postsynaptic potentials which are a resultant of neurotransmitter release.[55,56] Alterations in dopamine transporter and receptors along with monoamine and non-monoamine neurotransmitters were evident in rodent models with induced dietary ID.[57,58] The importance of an intact dopaminergic system for attention and learning was demonstrated by pharmacological manipulations. Use of drugs lowering dopaminergic activity reversibly impaired P300 in healthy subjects.[59] Hence, a possible deviation in neurotransmitter activity due to ID may adversely affect cognition.[60] However, these evidences are predominantly reported in developmental ages, for example, infancy and childhood, highlighting the need to prevent IDA in the younger age group to curb its adverse effects on cognitive development. IDA has an impact on cognitive performance in adults too, particularly in women belonging to reproductive age due to its high prevalence in them. Small sample size, unaddressed underlying etiology of IDA, and post-Fe therapy changes not compared to controls[4] were a few limitations of the above studies. We propose that the number of such research studies in a larger anemic women population using P300 must be encouraged to come to an absolute conclusion.

Data, on the consequences of IDA on cognition using electrophysiological tools like P300, are just beginning to emerge. Such studies mainly involve developing brains with the impression that IDA has deleterious effects on cognition and behavior by affecting myelinogenesis and neurogenesis. The effect of iron status on cognition is not only limited to the early age groups but also includes all age groups. Only four prospective cohort studies conducted addressed the potential association between anemia and risk of developing dementia in adults.[61] Women with IDA revealed prolonged P300 latency and reduced amplitude indicating cognitive impairment in comparison to healthy subjects. Mild cognitive impairment is asymptomatic with a possibility to progress to dementia and Alzheimer's disease. Improving the hemoglobin level with timely treatment has a beneficial effect in reducing the risk of progression to overall cognitive impairment.[62] Similar studies reporting utilization of P300 for the diagnosis of cognitive impairment associated with IDA in women must be encouraged to prevent its complications. Further research in a small population and at the community level for screening cognitive dysfunction using P300 and reporting whether correction of anemia restores it is required to support the present findings. It is important to detect IDA, its causes, and consequences in females of reproductive age group as they may extend beyond the individual, to her family especially to her offspring. India's prevalence of anemia among women in the age group of 15-49 years has increased from 53%(NFHS- 4) to 57% (NFHS-5). This increase in prevalence can be addressed by further enhancing the effectiveness of the current policy responses to anemia prevention and control. Some of the ways that it can be done is by (i) addressing the gaps in the knowledge about anemia, (ii) accurately diagnosing the multifactorial etiology of anemia, (iii) prioritizing infection control intensively, (iv) fortifying food with iron [17, 63], (v) early identification of changes in physiological functions due to iron deficiency anemia, (vi) monitoring side effects of iron supplementation to encourage and ensure compliance to treatment.

P300 can be useful in the early detection of subclinical impaired cognition and prevent progression to cognitive decline and dementia. Hence, it is important to create awareness regarding the usefulness and reliability of P300 as a tool for screening, diagnostic and prognostic purposes in cognitive dysfunction associated with IDA, especially in women and improve the quality of life. Finally, this review recognized the need for studies intended to explicitly explore cognitive status utilizing P300 in adult females with IDA.

Relevance to practice:

Anemia caused by iron deficiency is a common health problem among Indian women.

It is a risk factor for the development of cognitive dysfunctions and dementia.

Screening women using electrophysiological tools like P300 for detection of subclinical cognitive impairment.

To prevent cognitive disorders associated with iron deficiency, early intervention is the key.

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Conflicts of Interest

There are no conflicts of interest.

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