Indian J Physiol Pharmacol 2017; 61(3) : 290–294

Original Article

# Visual Evoked Potential in Megaloblastic Anemia : A Cross Sectional Study

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## Abstract

Megaloblastic anemia is the second mostcommon type of anemia after iron deficiencyanemia. Itresults from faulty DNA synthesis attributed to vitamin B12 or folic acid deficiency & may be associated with neuropathy which can lead to substantial morbidity if unrecognized or misdiagnosed.The aim of the study was to evaluate the Visual evoked potential (VEP) in megaloblastic anemia. VEP provide a non-invasive method of assessingneurological function. A delayed VEP supports the diagnosis of optic neuropathy.The study was conducted in 100 subjects- 50 controls and 50 patients of megaloblastic anemia diagnosed by low haemoglobin levels along with increased MCV, low serum vitamin $B_{12}$ or bone marrow changes or both. Patients were tested for visual acuity, field of vision and colour vision. Pattern reversal VEP was carried out. $P_{100}$ latency and amplitude were measured.VEP revealed prolongation of $P_{100}$ latency when compared with control group which was statistically significant.

VEP can be used as an early indicator of optic nerve involvement in patients with asymptomatic megaloblastic anemia.

## Introduction

Megaloblasticanemiaresults from impaired DNA synthesis due to vitamin B12 or folic acid deficiency. The only natural sources of vitamin B12 are of animal origin i.e. meat, dairy products and fish. Therefore the prevalence of megaloblastic anemia is higher in the Indian population, as most of the Indian population is vegetarian, especially Hindus and Jains who exclude animal protein from their diet for religious or social reasons.

Deficiency of vitamin B12 results in asynchrony in the maturation of the nucleus and cytoplasm of rapidly regenerating cells. In the haematopoietic system this asynchrony results in abnormal nuclear maturation with normal cytoplasmic maturation, ineffective erythropoiesis, intramedullary haemolysisand typical morphological abnormalities in the blood and marrow cells leading to the formation of megaloblasts with the development of a macrocytic anaemia (1).

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(Received on March 12, 2017)

In addition to its effect on blood, vitamin B12 deûciency also causes a wide range of gastrointestinal, psychiatric and neurological disorders.In the nervous system, vitamin B12 acts as a coenzyme in the methyl malonyl CoA mutase reaction which is necessary for myelin synthesis. Vitamin B12 deficiency therefore results in defective myelin synthesis leading to diverse central and peripheral nervous system dysfunctions. The neurological syndromes usually presents with subacute combined degeneration involving spinal cord, myelopathy, neuropathy, neuropsychiatric abnormalities and less often optic nerve atrophy, which can lead to substantial morbidity if unrecognized or misdiagnosed.Early diagnosis and treatment may play an important role in the reversibility of neurological deficits. Delayed treatment results in irreversible disabling neurological impairment. Increase in VEP latency may reflect defective retinal transmission, defects in the myelin of the visual pathway from the optic nerve to the occipital cortex, or even synaptic abnormalities in the retina or occipital cortex (2).

A delayed visual evoked potential (VEP) is widely used to support the diagnosis of optic neuropathy (3). The present study was conducted to evaluate the Visual Evoked Potential changes in patients of megaloblastic anemia with apparently normal clinical profile so as to detect neurological impairment, if any.

## Material & Methods

The sample size of study was 100 subjects of age 50 to 75 years, consisting of50 patients and 50 age matched controls. Permission of institutional ethical committee of GrantGovernment Medical College, Mumbai was taken before commencement of the study. Patients with megaloblastic anemia were diagnosed on the basis of low haemoglobin according to WHO criteria, along with increased MCV, low serum vitamin $B_{12}$ (<100 ng/lit)or bone marrow changes.Patients with neurological, ophthalmic & endocrinal diseases were excluded from the study which could affect visual evoked responses.The patients & controls were subjected to a detailed clinical history &examination with emphasis on visual acuity, field of vision& colour vision to rule out any asymptomatic ophthalmic & neurologicdiseases affecting eyes. Then Pattern reversal VEP was carried out.

Patients were explained about the test to ensure full co-operation and were instructed to avoid oil/hair spray after the last hair wash before test was performed. VEPs were performed with the patient's appropriate refractive correction. The patient was seated comfortably on a chair at 100 cm distance from the visual stimulus. To record the VEP, standard silver-silver chloride disc EEG electrodes were fixed to the scalp with conducting paste. The recording (active), reference & ground electrodes were attached on occiput at Oz, forehead at Fpz& the vertex at Cz as per 10-20 international system respectively. The impedance of the scalp-electrode connection was kept below 5 kΩ. Stimulation was provided with black & white checkerboard of size 14×16" at the rate of 1 Hz. Number of epoch analysed were 100 using band pass filter 1-300 Hz. The patients were asked to fix the gaze at the center of the screen. The waveform of the pattern-reversal VEP normally consists of three principal features: an initial negativity with a latency of approximately 70 to 80 msec (N75), a larger positive component with a latency of approximately 90 to 110 msec (P100), and a large negative component with a latency of approximately 130 to 140 msec (N135). Then $P_{100}$ latency and amplitude were measured.

### Statistical analysis

The data is expressed as Mean±SD for each group. Unpaired t test was performed to compare P100 latency and amplitude between the two study groups. The level of significance was at $p<0.05$.

## Results

The P100 latency was delayed in patients of megaloblastic anemia (mean latency 118.7±11.53 ms) when compared to controls (mean latency 101.8±5.73 ms) while amplitude was almost same in both patient (mean amplitude 7.62±0.48 ms) & control (mean amplitude 7.51±0.42 ms) group. There was significant difference in P100 latency between the

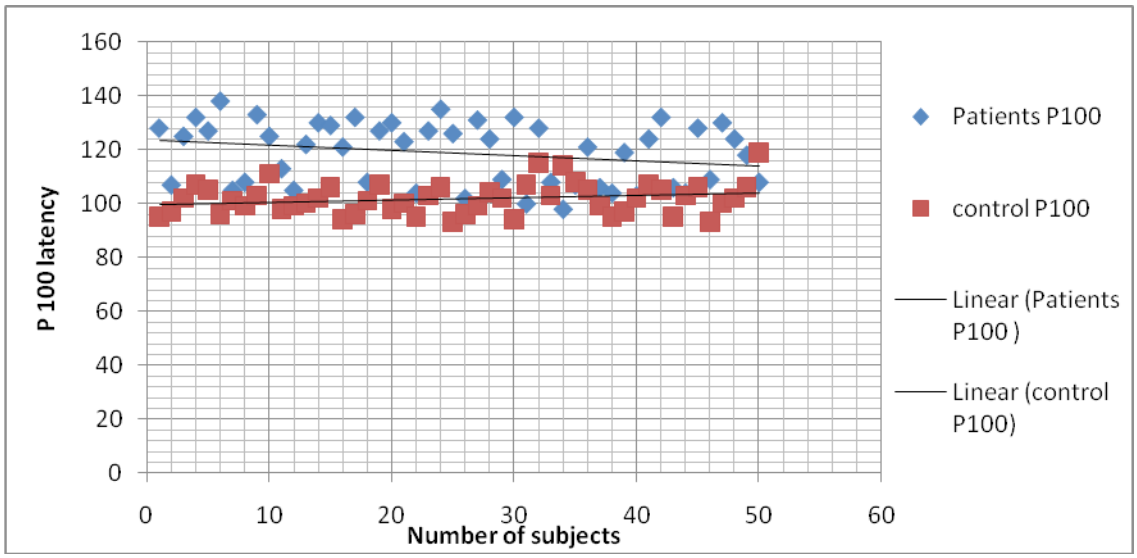


Fig. 1 : P100 latency in patient and control groups. (N=50, Values expressed around Mean±SD).

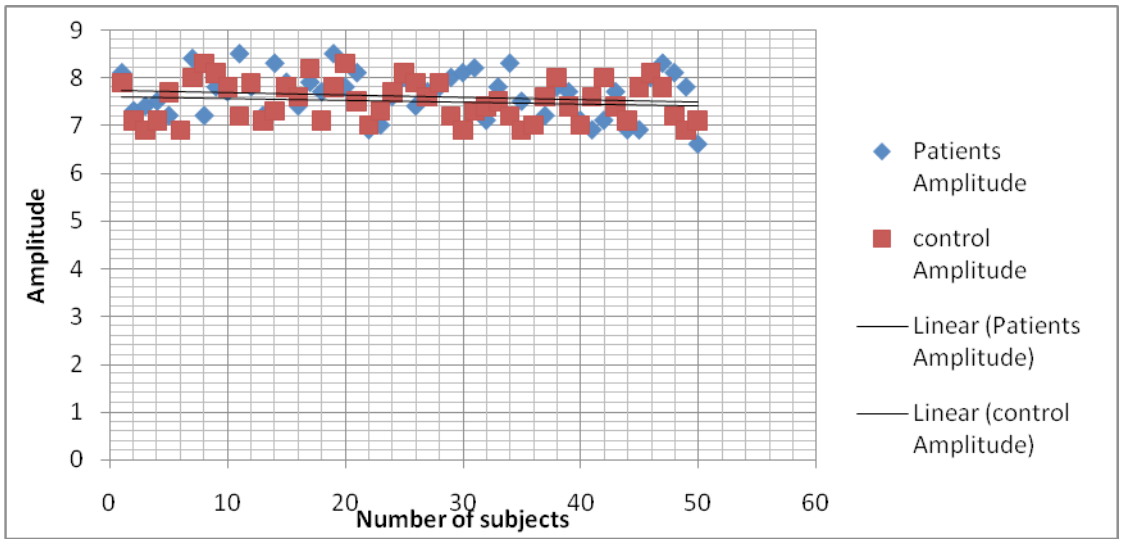


Fig. 2 : P100 amplitude in patient and control groups. (N=30, Values expressed around Mean±SD).

two groups (P<0.001).The P100 latency was delayed in 31 out of 50 (62%) patient's of megaloblastic anemia. The delayed latency in those 31 patients was 126.9±5.35 (Mean latency). Delayed latency was also found in 4 controls with mean 114.75±3.3 ms.

## Discussion

Even though there are no uniform diagnostic criteria for megaloblastic anemia, advanced stages of vitamin B12 deficiency seldom cause diagnostic problems. But early diagnosis is complicated by limitations of the laboratory methods and by the subtle, non-specific symptoms of deficiency (4). The typical haematological changes may be absent or develop late, and neurological and cognitive symptoms are sometimes the first indication of vitamin B12 deficiency (5). However, early recognition is essential, because the damage is progressive and may be reversible if treated early (6). Also in some studies on vitamin B12 deficiency, the neurological deficits were shown to be inversely related to the haematocrit and haemoglobin level (7, 8). Therefore,

screening for asymptomatic people or subjects with possible risk factors for Megaloblastic anemia has been suggested (9).

The visual evoked potential (VEP), also known as the visual evoked response (VER) or the visual evoked cortical potential (VECP), is an electrophysiological signal that can be recorded from the human scalp and is generated by neurons in the brain in response to visual stimulation. The visual evoked potential (VEP) provides a non invasive means of evaluating the central neurophysiology of vision. Visual pathways are vulnerable to vitamin $B_{12}$ & folate deficiency but there is paucity of studies evaluating VEP changes following megaloblastic anemia. Increases in VEP latency may reflect defective retinal transmission, defects in the myelin of the visual pathway from the optic nerve to the occipital cortex, or even synaptic abnormalities in the retina or occipital cortex (6).

VEP amplitude is a measure of the size of the response, whereas VEP latency reflects transmission and processing time in the retina-to-occipital cortex pathway after the onset of stimulation. As delayed VEP supports the diagnosis of optic neuropathy (10), the aim of the study was to find out effect of megaloblastic anemia on visual evoked potential (VEP) in clinically asymptomatic patients.

In the current study,visual evoked responses of patients when compared with control subjects showed that 62% of patients of megaloblastic anemia had delayed P100 latency but amplitudes were not significantly changed.Our study co-relates with the previous study done by U K Misra, J Kalita, who demonstrated prolongation of P100 latency in 63.6% of patients with vitamin B12 deficiency (11).

In another study carried out by Misra et al. (12) a VEP test was carried out in 13 patients with neurological findings due to vitamin $B_{12}$ deficiency. The VEP latencies of 7 patients were determined to be prolonged, and these changes were attributed to the focal demyelination of white matter in the optical nerve and spinal cord due to vitamin $B_{12}$ deficiency. In this study, 16 out of 30 patients were determined as having abnormal VEPs. Studies have demonstrated that the rate of VEP abnormality ranges between 25% and 100% in patients with vitamin $B_{12}$ deficiency (13, 14).

In another study done by A K sood et al. (15), Pattern reversed visual evoked potential in thirty cases of megaloblasticanemia revealed increased latency of P100 wavein 21 cases (70%) and it was significantly prolonged as compared to controls (P<0.00l). This was in line with our study as P100 wave amplitude in megaloblastic anemia casesdid not show any significant difference from thecontrols. Troncoso et al (16) and Fine et (14) had also reported markedly prolonged P100 latencies with normal amplitude in megaloblasticanemia cases.

Deficiency of vitamin $B_{12}$ & folic acid is known to interfere with myelin synthesis. The prolongation of P100 latency could therefore be attributed to demyelination in visual pathways. In the study done by Demir et al, Visual evoked potentials (VEPs) and brainstem auditory evoked potentials (BAEPs)were found to be prolonged in 16 (53.3%) and 15 (50%) patients, respectively (17).

Studies have shown that early treatment of deficiency can reverse the neuropathy changes with significant improvement in P100 & thus early detection becomes important (17, 18, 19).

**Conclusion**

In the absence of single gold standard laboratory method for detection of early subclinical vitamin $B_{12}$ & folic acid deficiency, there is a need to adopt methods which can detect neuropathy at early stage when it is possible to reverse the changes. VEP is a simple, non-invasive, accurate & easily reproducible method. Our study shows significant delay in VEP latencies in asymptomatic patients of megaloblastic anemia. Thus VEP holds a good scope in early identification of subtle neuropathy in visual pathway in clinically normal patients of Megaloblastic anemia.

The present study did not co-related VEP changes in patients of megaloblastic anemia with clinical neurological presentation. Also we did not do the follow up study to check for the improvement in latency of VEP withtreatmentfor megaloblastic anemia.

## Acknowledgements

Authors have gratitude to Dr. S.D. Kaundinya, Ex-Professor and Head of the Department of Physiology for her positive support for conducting this study using VEP unit installed in Department of Physiology. Authors also acknowledge the subjects from Department of Medicine, Grant Government College & Sir JJ Group of Hospital who participated in the study.

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