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EVENT RELATED EVOKED POTENTIALS IN DEMENTIA : ROLE OF VITAMIN E

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Abstract : Dementia is a common cognitive syndrome reflecting a wide spread chronic progressive disease as an extension to normal aging process. Oxidative stress has been implicated in dementia and antioxidants have become attractive therapeutic agents. Among the antioxidants vitamin E is the most potent in the treatment of dementia. Study was conducted in 20 patients suffering from dementia in the age group of 66–74 and in 20 age and sex matched controls. Latency of the P3 component of event related evoked potential (ERP) showed an increase from 338.65 ± 42.22 msec in control group to 348.9 ± 46.38 msec in patients of dementia.

In control group P3 latency decreased from 338.65 ± 42.22 msec to 331.6 ± 38.75 msec after Vitamin E therapy. In patients of dementia latency decreased significantly from 348.9 ± 46.38 msec to 324.62 ± 44.25 msec after vitamin therapy for one month. P3 amplitude in controls and demented was 7.2 ± 3.62 μv and 7.07 ± 3.73 μv respectively. After vitamin E therapy a statistically significant increase in amplitude ($P<0.05$) was observed in controls (9.34 ± 5.04 μv) and in patients of dementia (9.58 ± 5.24 μv). The study suggests that the latency and amplitude of P3 were not significantly different in control and dementia patients, while vitamin E supplementation (oral 800 mg per day for 30 days) decreased the latency and increased the P3 amplitude in both the control and dementia patients. Our study further supports that Vitamin E supplementation, because of its antioxidant property might be decreasing oxidative stress, which may lead to improvement in cognitive pool of generator neurons of P3.

Key words : *dementia* *event related potentials* *oxidative stress* *antioxidants*

INTRODUCTION

Dementia is a neurodegenerative disease characterized by a general decrease in memory, attention and cognitive functions. It is therefore important to develop adequate objective diagnostic tools to differentiate dementia and other neurodegenerative conditions. Application of P3 component of event related evoked

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potential (ERP) for the study of cognitive disorders has begun to provide means of quantifying the level of mental impairment usually assessed by means of other psychometric tests (1, 2).

The auditory ERPs that are evoked by an improbable signal contain a late positive P3 wave. Depth electrode recordings and magnetic field studies suggest that P3 wave originates in hippocampus and associated brain sites, which are the most important neuronal structures concerned with process of learning and memory (3, 4). The P3 component appears to be related to fundamental cognitive activities and may reflect individual differences in normal short-term memory functions (5, 6). Thus any factor which modifies the timing of neural mechanisms underlying perception and cognition may lead to changes in the morphology or latency of P3. Aging produces an increase in P3 latency of about 1.0–1.8 msec/year for ages ranging from 20 to 80 years (7, 8, 9, 10). While the exact origin of this latency change with age is not known, P3 latency has been found to decrease as immediate memory improves with maturational development of brain in children (11). An abnormal delay in P3 latency may therefore be indicative of cognitive slowing which is one of the hallmarks of dementia. Delay in latency suggests that the time required to complete various aspects of cognitive processing are prolonged (12) and this coincides with clinical picture of dementia. Study of demented population has found P3 latency generally exceeding as compared to normative age matched controls (7, 13, 14, 15, 16) although some reports do indicate relatively normal P3 latencies in the patients with clinical impairment (17, 18).

Free radicals are implicated in a number of neurological diseases such as dementia of Alzheimer's type and Parkinson's disease. Significant decrease in levels of antioxidants like Vitamin E and C was observed in the patients of Alzheimer's disease (19). Alpha (α) tocopherol is an integral part of the cell membrane which is believed to be essential for the maintenance of normal structure and function of human nervous system. A prolonged deficiency of α tocopherol leads to a number of degenerative neurological syndromes in humans and experimental animals (20, 21). In order to see the effect of Vitamin E on improvement of cognitive function in dementing illness, P3 was recorded before and after one month of Vitamin E supplementation.

METHODS

The study was carried our on patients suffering from dementia reporting to Psychiatry OPD of GTB Hospital. The patients selected were: both male and female, above the age of 65 years (66–74 years); fulfilling the criteria of dementia as per ICD classification (International classification of diseases and related health problems) with a reliable history, good compliance and regular follow ups. Subjects addicted to alcohol, drug abuse, suffering from any other major psychiatric illness or any other concurrent drug intake were excluded from the study.

P3 recording was done on 20 age and sex matched controls and 20 dementia patients, which was repeated after one month of antioxidant therapy i.e. Vitamin E (800 mg/day).

Recording of P3

Subjects were briefed about the test procedure and consent was taken before. They were asked to lie down and relax in standard audiometric, soundproof air-conditioned room. P3 was measured by using MEB 5200 Evoked Potential Recorder (Nihon Kohden, Japan) from vertex (Cz and Pz) in response to random application of two types of sound stimuli, presented binaurally through headphones applied to the ears of the subject. Odd ball paradigm (22) in which sequence of two distinguishable sound click stimuli (one frequent stimulus non-target and other infrequent target stimulus) were presented. Subject was asked to respond to the target stimulus by pressing a button. Active electrodes were placed at Cz and Pz with reference electrodes at ear lobules (A1+A2) while the ground electrode at Fpz. The input impedance was less than 5 KOhms. Alternating tone bursts with a starting condensation phase of 10 msec rise/fall time. 100 msec duration (plateau time), intensity 70 dB n HL and rate one every 2 secs were used as target stimuli. 80% of total (160) stimulus tones were 1kHz (frequent 128 in number) and 20% were 2kHz (rare 32 in number). Stimulus sequence was random. Signals were in phase in both the ears. Evoked responses were filtered with a band pass 5–30Hz (Filter slope 12dB/octave) and averaged simultaneously for 32 responses. Data for 2 trials were obtained consequently and stored analyzed and averaged by computer. Evoked responses so obtained were recorded on the screen of the on line evoked potential recorder. The latency and amplitude of waves P3 for target stimulus were calculated. The methods used for recording P3 were similar to the ones reported earlier from our laboratory (23). During recording session subject was instructed to fix his eyes on a particular spot on the ceiling to avoid electro-oculographic artifacts due to eye movements and improve his concentration and attention to the stimuli presented. Data were complied and computed by using SPSS/PC + software package for various statistical measures.

RESULTS

Largest positive potential occurring between 300 and 500 msec was designated as P3 component. Amplitude was measured relative to the pre-stimulus baseline. P3 latency values observed were 338.65 ± 42.22 msec in control group and 348.9 ± 46.38 msec in the patients of dementia. Latency prolongation was not statistically significant.

In control group P3 latency decreased from 338.65 ± 42.22 msec to 331.6 ± 38.75 msec after Vitamin E therapy. In dementia patients, the latency decreased significantly from 348.9 ± 46.38 msec to 324.62 ± 44.25 msec after vitamin therapy. P3 amplitude in controls and patients of dementia was 7.2 ± 3.62 μv and 7.07 ±

3.73 μv respectively. After vitamin E therapy increased significantly to 9.34 ± 5.04 μv in controls and to 9.58 ± 5.24 μv in patients of dementia. (Table I, Fig. 1)

TABLE I : P 300 latency and amplitude in controls and dementia before and after Vitamin E therapy.

	Control		*Patients*	
	Pre-treatment	*Post-treatment*	*Pre-treatment*	*Post-treatment*
P300 Latency ms	338.65±42.22	331.6±38.75	348.9±46.38	324.62±44.25*
P300 Amplitude μv	7.2±3.62	9.34±5.04*	7.07±3.73	9.58±5.24*

*P value <0.05

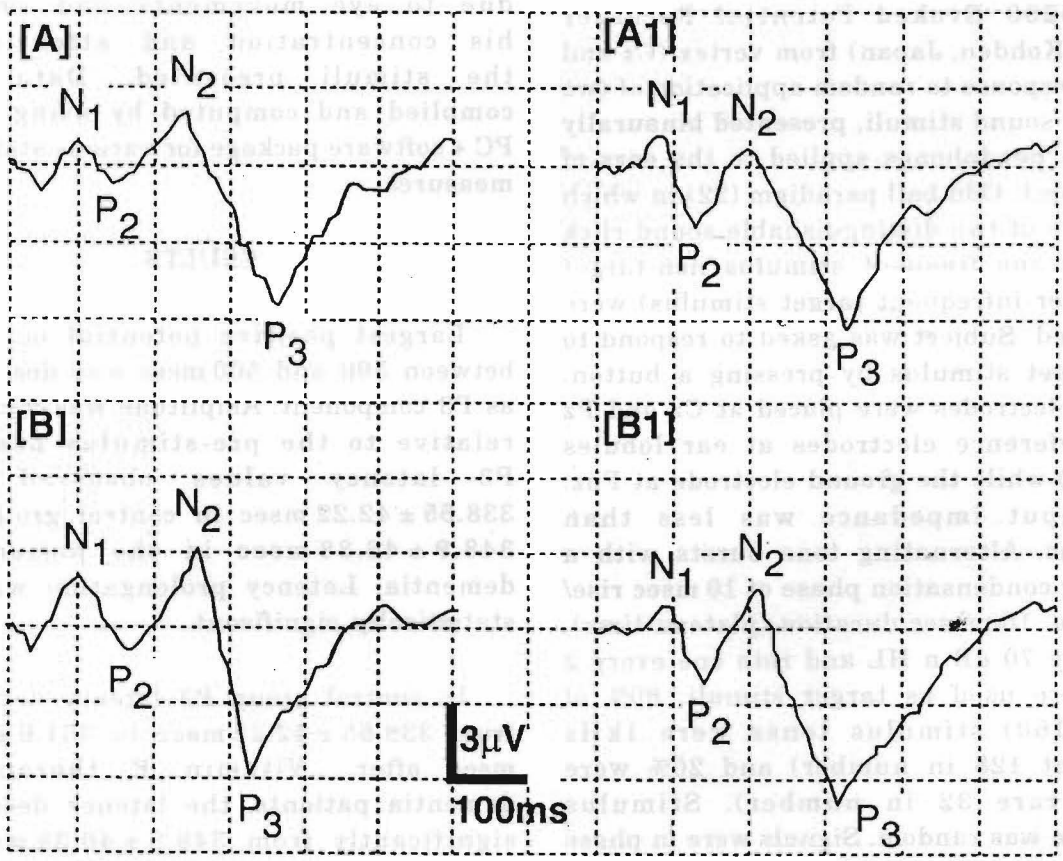

Fig. 1 : Showing effect of vitamin E therapy on P3 in controls and dementia patients
(A) before, (B) after vit. E in controls;
(A1) before, (B1) after vit. E in patient.

DISCUSSION

In recent years there has been different reports of the clinical utility of evoked potential responses in different psychiatric disorders. Goodin et al (13) were the first to suggest that P3 latency delay might provide a sensitive and specific marker for dementia. Normal increase in P3 latency/ cognitive-processing time with age might be due to a decrease in neural conduction velocity caused by as age related decreases in myelination (24). P3 latency becomes longer as cognitive impairment becomes more pronounced for a variety of dementing illness like senile, Alzheimer's, cardiovascular diseases dementia and alcohol abuse dementia. This might be due to the fact that brain sites directly or indirectly associated with P3 production are affected by all types of dementia. No reliable effects on P3 amplitude across cognitive impairment levels were found (25). Our results of P3 latency match with the latency of senile dementia subjects. P3 latency in dementia of Alzheimer's type was much more i.e. 404 msec. Similar results have been obtained by St Clair et al (26) who reported significant longer latency of P3 (391 ± 37.0 msec) and smaller amplitude (3.23 ± 1.6 μv) in dementia patients and 342 ± 43 msec latency and 6.85 ± 2.2 μv amplitude in controls. P3 latency in 12 patients out of 19 was delayed more than two SD from normal latency of their age predicted (15). However Neshige et al (16) found difference in P1, N1 and P2 latencies among three groups normal, Alzheimer's disease and MID (multi infarct dementia) but it was not statistically significant. N2 and P3 latencies in two-dementia group were significantly prolonged compared with normal group. P3 latency was 356.0 ± 26.4 msec in normal and 415.1 ± 42.0 msec in Alzheimer's dementia With regard to amplitude of all groups there were no statistically significant difference between patients and age matched controls. P3 amplitude in controls was 9.5 ± 5.9 μv and in dementia patients was 8.2 ± 4.2 μv.

All these studies support the hypothesis that P3 latency is strongly affected by dementing illness. The proportion of cases with significant delayed P3 latency is 45% by Neshige et al. (16), 50% by Brown et al (14), 80% by Goodin et al (13) and 83% by Syndulko et al (7). The main difference seems to lie in the response task and their subjects kept mental count whereas Pfeferrbaum and Neshige et al (16, 18) & we used a button pressing task which might be easier to perform then the count task. Using similar paradigm Slaets and Fortgens (27) reported P3 latency 337 ± 25 msec in young controls, 347 ± 48 msec in non-dementia and 396 ± 50 msec in dementia patients showing prolongation of P3 latency but no significant difference was found in P3 latency between demented and non-demented patients. Similarly in our study P3 latency in the patients was slightly higher but not statistically significant than the control groups. The findings of a considerable increase in P3 latency in dementia as compared to age matched non-dementia subjects by Syndulko, Goodin, Pfefferbaum (7, 13, 17) have not been replicated in our study.

Some authors have reported different findings. P3 latency is not markedly affected in milder cases of dementia (28). Kraiuhin et al (29) were no more successful in identifying individual cases of Alzheimer's as compared with the P3 latencies of similarly aged normals and also disagred with earlier reports that P3 latency was delayed in patients with dementia. According to Pfefferbaum et al (18) P3 latency prolongation was significant for the group as a whole but would result in too many false negatives if used diagnostically for individuals.

An explanation for these contradictory results might be found in the differences between the population of patients used in these studies.

In our study selection of patients was based mainly on clinical examination due to non-availability of sophisticated diagnostic procedures like Magnetic resonance imaging or Positron emission tomography. Hence we were unable to quantitatively classify our patients, on the basis of the extent of involvement of the brain.

A pronounced decrease in P3 amplitude in dementia by some reporters (13, 15, 18, 30) could not be confirmed in our study. There is no uniform agreement on this. Efforts must be directed towards finding the paradigms, which yield P3 waves that are more consistent and not dependent on the cooperation and motivation from the patients. Several suggestions on this can be found in literature but they need to be applied in larger population sample.

Concept of Reactive oxygen species is an important factor in pathogenesis of dementia and might provide a useful additional tool in the diagnosis of dementia. Oxidative stress is a term that has been used to describe imbalance between oxidative reactions and antioxidant protection which plays a role in pathogenesis of some neurodegenerative disorders of nervous system like Parkinson's, Alzheimer's diseases etc. Hence antioxidants have become attractive therapeutic agents. One of the purposes of this study was to test whether P3 latency might serve as a useful tool to evaluate the effectiveness of specific drugs including antioxidants. Several workers have tried to observe whether prophylactic supplementation with Vitamin E in geriatric population at high risk, would have a beneficial effect on memory or not.

Vitamin E supplementation in higher doses slows the progression of Alzheimer's disease (31). Peskind (32) demonstrated Vitamin E to be marginally superior to placebo for slowing functional deterioration in the patients with moderately advanced Alzheimer's disease. Moreover based on psycho physiological rating tests antioxidant therapies are being promoted to enhance mental functions and delay cognitive losses with aging (33). Studies have shown that decreased levels of Vitamin E were significantly associated with decreased cognitive functions and supplementation with some antioxidants might protect against cognitive impairment in older people (34). Duraney (35) proposed pharmacological approaches which break vicious cycles of

oxidative stress and neurodegeneration like Advanced glycation endproduct inhibitors, anti-inflammatory drugs and antioxidants which might offer new opportunities for Alzheimer's disease treatment. Antioxidants are likely to scavenge intracellular and extracellular superoxide radicals and hydrogen peroxide before these radicals damage cell constituents or activate microglia. Recently it was confirmed that Vitamin E 2000 IU slows functional deterioration (36).

In our study we have also found positive effect of Vitamin E on P3 latency and amplitude in controls as well as demented which also supports the evidence that antioxidants are useful in promoting neural cognitive pool in old age as well as in case of loss of memory.

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