Brief Report

P300 Latency and Neurocognitive Functioning in Recently Diagnosed Human Immunodeficiency Virus Patients

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ABSTRACT

Aim: To assess the P300 latency and amplitude in recently diagnosed human immunodeficiency virus (HIV)-positive patients and compare the same with a healthy control group. Further an attempt was made to study the correlation between P300 amplitude and latency (in milliseconds) with neurocognitive functions. **Materials and Methods:** Thirty newly diagnosed HIV-positive patients who on self report did not have any cognitive dysfunction were recruited. The patients were evaluated for P300 evoked response using the odd-ball paradigm, MMSE and a comprehensive neuropsychological battery. The P300 latencies were compared with 30 normal control subjects. **Results:** The mean P300 latency (in milliseconds) of the HIV-positive subjects was significantly more than the healthy control group. The mean amplitude of HIV group was significantly less than the normal control group. On MMSE, 7 HIV-positive subjects had mild cognitive impairment (MMSE total score 20-23), six patients had minimal cognitive impairment (MMSE total score 24-27) and 17 patients had no cognitive impairment (MMSE total score >27). On neuropsychological test battery only three (10%) of HIV-positive subjects had cognitive dysfunction. There was negative correlation between P300 latency (in milliseconds) and MMSE total score and performance on Koh's Block subtest. **Conclusion:** P300 may be a reliable indicator of cognitive impairments in HIV patients.

Key words: *Cognitive functions, evoked potential, human immunodeficiency virus*

INTRODUCTION

The epidemic of human immunodeficiency virus (HIV) continues to grow. India has the third largest number of people living with HIV/AIDS. NACO reported 22.7 lakh people living with HIV/AIDS in India.[1]

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The major neurological complication of human immunodeficiency virus type 1 (HIV-1) infection is cognitive impairment, which can range in severity from a mild subclinical cognitive inefficiency to a severe dementing illness. The prevalence and severity of cognitive impairment associated with HIV-1 infection increases as the disease progresses. The cognitive dysfunction associated with HIV infection has been well described and it effects domains such as verbal and visual memory, executive functioning, working memory, information processing speed and psychomotor skills.[2]

Event-related potentials (ERPs) are time locked cortical excitation in direct response to sensory stimulation, termed sensory-evoked potentials (SEPs), or the higher order processing of an external event, often termed

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endogenous event related potentials. The use of ERP appears to be a sensitive technique to detect subclinical manifestation for cognitive deficits in asymptomatic subjects, and therefore can help to identify subjects at higher risk for developing cognitive impairment. It is suggested that the electrophysiological abnormalities on the brainstem auditory-evoked potentials (BAEP) and on the cognitive potentials (P300) may be detected,[3-8] prior to the clinical signs and symptoms.[9,10]

The long latency auditory-evoked potentials are observed between 80 and 700 milliseconds (ms) after the presentation of an acoustic stimulus[11] and their components are N1 (N100), P2 (P200), N2 (N200) and P3 (P300). These are further subdivided as exogenous potentials (N1, P2, N2), which are strongly influenced by the physical characteristics of the stimuli (intensity and frequency, among others); and endogenous potentials (P300) mainly influenced by internal events related to the cognitive abilities.

Some of the previous studies have evaluated the long latency auditory-evoked potentials and have shown that compared to healthy control group HIV patients have significantly higher P300 latency and lower P300 amplitude.[10,12-14] With regards to N1 wave but not for P2 wave, HIV patients have significantly higher latency compared to control group.[12,15] Studies have also shown that P300 latency is primarily associated with the progression of HIV-associated cognitive impairment, with a secondary and additive association with severity of HIV-associated medical illness.[13] Studies have also shown a correlation between the P300 amplitude and emotional deficit in HIV patients.[15] Some authors have also suggested that ERP is a sensitive technique to detect subclinical manifestations in asymptomatic HIV subjects and also helpful in identifying subjects at higher risk for developing cognitive impairments.[14,15] In this background, the aim of the present study was to assess the P300 latency and amplitude in recently diagnosed HIV-positive patients and compare the same with a healthy control group. Further an attempt was made to study the correlation between P300 amplitude and latency with neurocognitive functions as assessed by using mini-mental status examination (MMSE) and a comprehensive neuropsychological battery.

MATERIALS AND METHODS

The study was approved by the Institute Ethics Committee and all the patients were recruited after obtaining written informed consent.

Thirty HIV-positive patients who on self report did not have any cognitive dysfunction and were aged between 20 and 60 years were recruited from the patient pool attending the Internal Medicine Outpatient Clinic of PGIMER, Chandigarh, were enrolled by purposive sampling. The diagnosis of HIV was based on the triple test conducted at our surveillance center.

Instruments

P300

It was done on the Nicolet Viking IV evoked response equipment using the odd-ball paradigm methodology.[13] Patients were given auditory stimulus at regular intervals and intermittently subjected to a stimulus of different pitch/intensity. They were required to discriminate and count the rare stimuli. Responses were recorded from F_z, C_z and P_z electrodes according to the standard 10-20 international system on the scalp, referenced to mastoid or ear lobule. Averaged responses after 400 stimuli were taken with marking and noting the P300 latency (in milliseconds). A mean of three such recordings of the P300 latencies were considered as the test value of the patient. The P300 latencies (in milliseconds) were compared with 30 normal control subjects. When a patient had scores of more than 1 or less than 1 standard deviation of mean obtained for the normal control group, and the P300 latency was taken as increased latency.

Neuropsychological assessment

PGI Battery of Brain Dysfunction[16] was used for neuropsychological assessment. It is a standardized battery developed at PGI for screening cognitive dysfunction. It assesses cognitive functions in the domains of intelligence, memory and perceptuomotor functions.

Mini-mental status examination

It is an instrument used for assessment of an array of cognitive functions including orientation, attention, memory, concentration and language.[17] It is one of the most commonly used instruments for screening for dementia and monitoring the progress of dementia over time. The maximum score which a subject can obtain is 30 and a score of 20-24 is considered to indicate mild cognitive impairment, 11-19 indicates moderate cognitive impairment and score of 10 or less indicates severe cognitive impairment.[17] Since the patients in the present study were asymptomatic for cognitive complaints, a modified grouping was done on basis of MMSE score to identify patients with minimal cognitive dysfunction. Accordingly patients with M MSE score of more than 27 were considered to have normal cognitive functioning, those with a score of 24-27 were considered to have minimal cognitive disturbance and those with score of 20-23 were considered to have mild cognitive dysfunction.

Intelligence

Intelligence was assessed by Hindi adaptation of Verbal

Adult Intelligence Scale (VAIS)[18] and performance intelligence was assessed on Bhatia's Short Battery of Performance Tests of Intelligence.[19] Verbal Adult Intelligence Scale has four subtests, i.e., information, digit span, arithmetic and comprehension. Standardized norms are available with regards to age, sex and education. In the present study three subtests i.e., information, digit span and arithmetic were taken into consideration and the Verbal Quotient (VQ) was calculated by taking a mean of the three subtests. Bhatia's Short Battery of Performance Tests of Intelligence (BSB-R) consists of Koh's block and pass-a long test and this was used to assess performance intelligence (PQ). Standardized norms are available. Intelligent Quotient (IQ) was obtained as mean of VIQ and PQ.

PGI Memory Test[20] has 10 subtests which use verbal and nonverbal material and measures remote, recent, immediate, short-term, very short-term, intermediate-term and long-term memories. It is a standardized test with norms for general population. Scores of 10 subtests were used to calculate percentile ratio as more than 40 and less than equal to 40.

Nahar and Benson Test[21] was used for assessment of perceptuomotor ability. It consists of eight cards, five of which contain a design and three have the instructions which are to be followed. Number of designs and drawings performed wrongly is counted as 'error score'.

In the present study, a patient was considered to have cognitive dysfunction when the patient had dysfunction on two out of three tests.

The data was analysed using SPSS-14. Frequency and percentage values were calculated for nominal and ordinal variables. Mean and standard deviation was calculated fro continuous variables. Comparisons were made using't' test and Chi-square test. The relationship between MMSE scores, P300 latency and P300 amplitude and neuropsychological functioning were studied by Pearson product moment correlation and Spearman rank correlations. All the tests were 2 tailed and in view of multiple correlations a $P<0.01$ was taken as significant.

RESULTS

The study included 16 males and 14 females. Mean age of the sample was 33.4 (SD-8.8; range 20-60 years).

The mean P300 latency of the study group was 320 (SD-37.61; 244-375) whereas the mean P300 latency of the control group was 301.58 (SD-25.20) and the difference between the two groups was statistically significant ('t' value- 2.22; $P<0.05$). The mean amplitude of HIV group was 5.8 (SD-3.46; 0.71-13) and that of control group was 8.35 (SD-4.48) and the difference between the two groups was statistically significant ('t' value- 2.46; $P=0.01$).

As per the study design, P300 latency (in milliseconds) and amplitude were considered to be abnormal, if the patient group scored 1 standard deviation above or below the normal health control values (Latency: mean 301.58±25.20 milliseconds; Amplitude: 8.35±4.48). Accordingly the value of P300 latency more than 327 milliseconds was considered to be abnormal (i.e., increased latency) and that of amplitude less than 3.87 was considered to be abnormal (i.e., decreased amplitude). According to the above cutoffs 13 (43.33%) patients had increased P300 latency and 11 (36.66%) patients had decreased P300 amplitude.

The mean MMSE score of the sample was 26.87 (SD-8.8; range 20-30). On MMSE, 7 patients had mild cognitive impairment (MMSE total score 20-23), six patients had minimal cognitive impairment (MMSE total score 24-27) and 17 patients had no cognitive impairment (MMSE total score >27).

As shown in Table 1, on neuropsychological assessment, seven patients had IQ <90 (Normal IQ ranges from 90 to 110) and rest of them had an IQ of more than equal to 90. On PGI memory scale, 12 patients had memory below the 40th percentile. On Nahar and Benson test (perceptuomotor function) only one patient scored in the range of moderate dysfunction. Three out of the 30 patients had cognitive dysfunction (had dysfunction on two out of three tests included in the PGI Brain battery).

Table 1: Neurocognitive functioning of the patients

Variables	Mean (SD)/Frequency (%)
Mean MMSE score	26.87 (SD-8.8)
Cognitive dysfunction as per MMSE	
Mild cognitive impairment (MMSE score 20-23)	7 (23.32)
Minimal cognitive impairment (MMSE score 24-27)	6 (20)
No cognitive impairment (MMSE score > 27)	17 (56.66)
Intelligence quotient	
IQ <90	7 (23.3)
IQ ≥90	23 (76.66)
PGI memory scale	
Memory below the 40th percentile	12 (40)
Memory above the 40th percentile	18 (60)
Nahar and Benson test (perceptuomotor function)	
Moderate dysfunction	1 (3.32)
No dysfunction	29 (96.66)

Correlations

There was negative correlation between P300 latency (in milliseconds) and MMSE total score (Pearson's Product moment correlation coefficient −0.723; $P<0.001$) [Figure 1]. There was negative correlation between P300 latency (in milliseconds) and performance on Koh's Block subtest (Pearson's Product moment correlation coefficient −0.445; $P=0.01$). Negative correlation was seen between perceptuomotor function error score and MMSE (Pearson's Product moment correlation coefficient −0.561; $P<0.001$).

Comparison between patients with normal and abnormal P300 latency

Although, those with longer P300 latency (in milliseconds) performed poorly on various cognitive tests but there was no significant difference between those with normal and abnormal P300 latency (in milliseconds) on various cognitive function tests except for total MMSE score. Those will longer P300 latency (in milliseconds) had significantly lower MMSE scores compared to those with normal P300 latency (in milliseconds) (24.07±2.81 versus 29.35±1.11; t value =5.27; $P<0.001$).

Similarly those with lower P300 amplitude performed poorly on various cognitive tests but there was no significant difference between those with normal and abnormal P300 amplitude on various cognitive function tests.

DISCUSSION

Evaluating P300 latency and amplitude can help in detecting cognitive deficits in asymptomatic phase, which are often not picked by routine MMSE examination. Although previous studies from India have evaluated cognitive dysfunction in patients with HIV, none of the previous studies from India evaluated the P300 latency and amplitude in recently diagnosed HIV patients. Findings of the present study suggest that P300 latency is increased and P300 amplitude is reduced in recently diagnosed HIV patients. The finding of increased latency is similar to the previous studies from other parts of the globe.[12-14,22-26] Similarly the finding of decreased amplitude is also supported by the literature.[12,27]

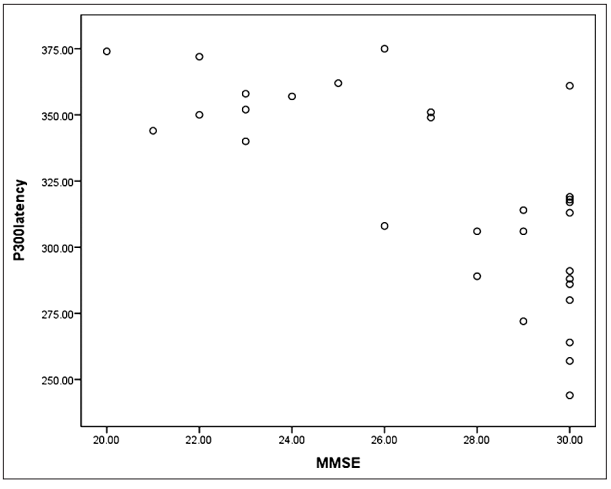

Figure 1: Scatter plot showing relationship between MMSE and P300 latency

Findings of the present study suggest that most of the recently diagnosed HIV patients do not have cognitive deficits and when present these are minimal or mild. Further, the cognitive deficits as assessed by MMSE have negative correlation with P300 latency (in milliseconds), indicating that as the P300 latency increases the cognitive deficits increase. Hence, findings of the present suggest that P300 may be a reliable indicator of cognitive impairments in HIV patients. Hence, increase in P300 latency can be taken as a neurophysiological marker of the cognitive deficits in HIV. So, patients with increase in P300 latency (in milliseconds) must be targeted for prevention and treatment to reduce the brain damage and neurocognitive deficit in HIV patients.

Our study was limited by small sample size and cross-sectional assessment. Future studies should study larger sample size and follow-up the patients longitudinally to further understand the relationship of P300 latency and amplitude with neurocognitive deficits.

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