Auditory and Visual P300 Responses in Early Cognitive Assessment of Children and Adolescents with Epilepsy

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Background: The event-related potential P300 has been suggested to be valuable in the assessment of cognitive dysfunctions. Not a great deal of neurophysiological assessment has been performed at early stages in patients with epilepsy involving visual and auditory P300 measures. Aims and Objectives: This study aimed to assess the cognitive status in patients with epilepsy earlier by visual and auditory P300 and to find their correlation with various risk factors. Materials and Methods: P300 was recorded in 60 children with epilepsy in the age-group of 5–18 years and 60 age- and sex-matched controls by a rare-frequent (oddball) paradigm. Mean auditory and visual P300 latencies and amplitudes were compared among patients with epilepsy and controls and among patients with generalized and focal epilepsy by unpaired t-test. Pearson's correlation coefficient test was computed for studying the correlation between risk factors and P300 responses. A value of $P < 0.05$ was considered statistically significant. Results: Statistically significant delay in P300 latencies and reduction in amplitudes (both visual and auditory) was found in patients with epilepsy as compared to controls and also among patients with generalized and focal epilepsy. In generalized epilepsy, both visual and auditory P300 revealed significant delay, whereas only auditory P300 delay was found in focal form. No significant correlation was obtained with risk factors. No significant difference was found in P300 responses among patients with and without antiepileptic treatment. Conclusion: Visual and auditory P300 latencies have an important role in the evaluation of early cognitive dysfunctions in children with epilepsy. P300 potentials are not influenced by antiepileptic treatment, whereas the type of epilepsy alters them.

Keywords: Auditory, cognitive, epilepsy, P300, visual
with a stable latency among the normal individuals. It is an event-related long-latency component, generated during decision-making and in stimulus evaluation and categorization. Oddball paradigm is used to record the wave, which involves random and less-frequent presentation of the target stimuli mixed with frequent repetition of the nontarget stimuli. In the auditory version of this test (auditory evoked event-related potentials [ERPs]), two different tones are repeated where the targeted stimulus (tone) appears fewer times than the nontargeted stimulus (tone). Visual event-related P300 potentials are recorded by presentation of target and nontarget visual stimuli in the similar rare-frequent (oddball) paradigm. Visual modality however has barely been studied for the cognitive evaluation. Cognitive potential P300 is known to be present in children from 5 to 7 years of age and hence can be a useful tool to test their cognitive development especially in those diagnosed with epilepsy. There still exists a scarcity of data reporting such evaluations of cognitive abilities at early stages involving the study group as children and adolescents.

This study aimed with the research questions to find the role of ERPs in evaluating the cognitive status at earlier stages in children and adolescents with epilepsy and to find, if any, association with various risk factors (age of onset, frequency of epileptic episodes, and duration of illness) with P300 ERPs and the effect of antiepileptic drugs (AEDs) on P300 responses. The study also aimed at evaluating both the modalities visual and auditory, to record P300 ERPs in the assessment of cognitive dysfunction in children with epilepsy.

**MATERIALS AND METHODS**

The study was conducted on a total of 120 subjects (60 children and adolescents with epilepsy as compared with 60 age- and sex-matched healthy controls) in the Neurophysiology Laboratory, Department of Physiology, All India Institute of Medical Sciences (AIIMS), Patna. The study was approved by institutional ethics committee. It was a case-control study in which auditory and visual P300 potentials were recorded and analyzed in patients with epilepsy in the age group of 5–18 years, diagnosed with epilepsy (clinical and Electroencephalography findings) and compared with age- and sex-matched normal subjects. Sample size calculation was performed by computing the effect size (difference in the means) in the previous similar study (with power of 80% and the level of statistical significance as 1.96). Informed consent was obtained before undertaking the tests with minor assent forms appropriately filled by the participants.

The inclusion criteria for the study group were the patients with epilepsy in the age group of 5–18 years with normal neuro-otological and neuro-ophthalmological examination. The exclusion criteria for the study group were the subjects less than 5 years, those with external/middle/inner ear pathology, and those with evidence of optic atrophy. Laterality was considered as an exclusion criterion for visual P300 records. The Edinburgh Inventory was used to assess laterality and exclude left-handed individuals from the experiment. Classification of epilepsy was performed according to 2017 ILAE (International League Against Epilepsy) for classification of seizures, as generalized and focal groups. Patients were also classified on the basis of those receiving and not receiving antiepileptic treatment.

**RECORDING OF VISUAL AND AUDITORY EVOKED P300 POTENTIALS**

P300 was recorded on Neuro-MEPO electromyography and EP Digital Neurophysiological System software (M/S Neurosoft Ltd, Ivanovo, Russia) in Neurophysiology Laboratory, AIIMS, Patna by a single channel recording performed in a quiet environment [Figure 1]. The international 10–20 system was used for electrode placement. Ground at forehead (Fpz), Active
at Vertex (Cz), and Reference were placed at right Mastoid (M2). Patients were trained and instructed to discriminate the two types (target and nontarget) stimuli before starting the test (both for visual and auditory P300 recordings) to ensure the validity of the responses.

For recording auditory P300, patients were instructed to detect (rare) (meaningful) stimuli within a series of (frequent)(nonmeaningful) stimuli (2000/1000 Hz). Stimuli were condensation clicks delivered via headphones binaurally with 85-dB sound pressure level intensity. Patients were instructed to keep their eyes open and to avoid eye movement. Electrical signals were filtered with 35-Hz high-pass and 0.5-Hz low-pass filters. A 700-ms time window was used.

For visual P300 potentials, the rare-frequent odd ball paradigm comprised blue–white and black–white checkerboards patterns (112 min, check size) (reversal rate: 1 Hz) on a video monitor with a screen size of 26 cm × 33 cm. Two records of 200 trials each for visual and auditory P300 were recorded and analyzed.

**Statistical Analysis**

The data were expressed as mean ± standard error of mean (SEM). Mean P300 latencies and amplitudes in the groups (patients with epilepsy and controls and among patients with generalized and focal epilepsy) were compared by unpaired *t*-test. Pearson’s correlation coefficient test was computed for studying the correlation between age of onset, duration of illness, and the frequency of the episodes with the P300 latencies. The effect of antiepileptic treatment on the P300 responses was compared among those with and without treatment by unpaired *t*-test. A value of *P* < 0.05 was considered as the criterion of statistically significant differences.

**Results**

P300 was recorded in 60 children with epilepsy (mean age: 11.25 ± 3.2 years) and 60 age- and sex-matched healthy children (mean age: 12.1 ± 2.8 years) (*P* < 0.05) (no significant difference was found in the mean ages in the two groups). Gender was also comparable in the groups (32 men and 28 women in epileptic group, whereas 30 men and 30 women were studied in the control group).

Mean auditory and visual P300 latencies and N200-P300 amplitudes were measured and compared with those in controls. Mean auditory and visual P300 latencies (mean ± SEM) were 322.56 ± 5.6 ms and 310.78 ± 5.16 ms, respectively, in the controls, whereas N200-P300 amplitudes were 10.56 ± 0.34 µv and 4.78 ± 0.19 µv, respectively [Table 1]. P300 recorded by both the modalities were delayed among the patients with epilepsy (mean auditory P300 latency: 431.48 ± 7.26 ms, mean visual P300: 332.98 ± 5.06 ms) with statistical significance (*P* < 0.01 for visual P300 and *P* < 0.0001 for auditory P300 [Table 1] Figures 2 and 3). Similar statistical significance was observed for N200-P300 amplitude differences (*P* < 0.0001 for auditory and visual P300) [Table 1].

A comparison of the P300 latencies between the two forms (generalized and focal epilepsy) was also studied, which reveals statistically significant difference (*P* < 0.05) for both auditory (452.09 ± 9.84 vs. 410.87 ± 10.6) and visual P300 variations (344.3 ± 6.43 vs. 321.65 ± 7.09) with increased mean values in the generalized form by both the modalities [Figure 4A and B].

| Table 1: Auditory and visual P300 among children with epilepsy and controls |
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| **Auditory P300** | **Visual P300** |
| (mean ± SEM) | (mean ± SEM) |
| Latency (ms) | Amplitude (N200-P300 (µv)) | Latency (ms) | Amplitude (N200-P300 (µv)) |
| Controls (*n* = 60) | 322.56 ± 5.6 | 10.56 ± 0.34 | 310.78 ± 5.16 | 4.78 ± 0.19 |
| Epileptics (*n* = 60) | 431.48 ± 7.26** | 6.34 ± 0.36** | 332.98 ± 5.06* | 1.3 ± 0.13** |

ms = milliseconds, µv = microvolts, *n* = number, SEM = standard error of mean

* *P* < 0.01 for the difference in mean latency of visual P300 between controls and patients with epilepsy

** **P* < 0.0001 for the difference in mean latency and mean amplitude of auditory P300 between controls and patients with epilepsy (unpaired *t*-test)
To study auditory P300 in the two forms of epilepsy, a comparison of auditory P300 latencies was carried out with the controls in generalized and focal groups separately. The mean values (452.09 ± 19.68 ms) in generalized as well as in focal forms (410.87 ± 10.62 ms) were significantly greater than those in controls (322.56 ± 5.6 ms) [Table 2].

Similar comparison for visual P300 variations with controls also provides increased mean values (344.3 ± 6.42 ms) of visual P300 in generalized patients with epilepsy. However, the increase in values in patients with focal epilepsy (321.65 ± 7.09 ms) as compared with the controls (310.78 ± 5.16 ms) did not reveal statistical significance (P > 0.05) [Table 3].

No significant correlation was obtained with risk factors studied (Pearson's correlation coefficient test). No significant difference was found in P300 responses among patients with and without antiepileptic treatment (P > 0.05) (unpaired t-test).

**DISCUSSION**

A significant delay in P300 latencies and the reduction in the amplitudes in the children with epilepsy obtained in this study evince the state of cognitive dysfunction. P300, which is thought to be generated in response to the processing of sensory stimuli into behavioral responses, has fairly been successful in assessing the disturbances in the cognitive functions supporting the present findings. Significant alterations in this long-latency component of ERPs have been attributed to damage to the hippocampus in patients with epilepsy because of its suggested involvement in ERP generation. Involvement of mesencephalic reticular formation and the sum of the activities of different areas including cortical and subcortical structures are thought to be involved in its generation. This study has obtained the influence of the type of epilepsy on P300 responses. Generalized epilepsy provides the greater delay, which can be explained on the basis of the extent of the damage by the epileptic foci. Significant P300 latency variations among different forms of epilepsy have been reported previously too.

Auditory P300 was significantly delayed in both generalized and focal forms of epilepsy, whereas visual P300 was found to be delayed only in generalized group in our study. This indicates the possibility of different visual and auditory processing systems in the brain and...
that the auditory P300 is more susceptible. The greater vulnerability of auditory processing system has been suggested in a previous study too. The study that reports ERP analysis and information processing deficits in closed head injury patients raises the possibility of differences in ERP generation by the two modalities. Another study that included the patients with absence seizures and those with complex partial seizures also reports the differences in the susceptibility of the two ERPs.

Association of P300 responses with the risk factors could not be obtained in our study. It is consistent with many previous reports. Lack of such significant association has not been an infrequent finding in many researches. The conflicting results regarding the association of the risk factors with the P300 responses hence suggest a questionable role of P300 potentials in predicting the prognosis of the cognitive status of the patients with epilepsy. Further studies are necessitated in the future that can provide an insight into such correlation. Antiepileptic treatment also did not influence the responses of P300 potentials in this study. Similar lack of correlation is reported before too. One such study assessed the association of the type of the AED, AED serum level, and the seizure control with the P300 responses with no significant influence on P300 potentials.

### CONCLUSION

The use of visual and auditory P300 component in patients with epilepsy is beneficial in the early identification of their cognitive status and hence can be a clinically useful indicator of the cognitive functions. P300 potentials are not influenced by antiepileptic drugs, whereas the type of epilepsy alters them. Both modalities, visual and auditory ERPs, show P300 prolongations in patients with epilepsy but auditory P300 is more vulnerable, hence more sensitive to the cognitive decline in children with epilepsy.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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