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ARTICLE

Auditory P300 event-related potentials in children with Sydenham's chorea

Potenciais auditivos evento-relacionados à P300 em crianças com coreia de Sydenham

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ABSTRACT

P300 event-related potentials (ERPs), objective measures related to cognitive processing, have not been studied in Sydenham's chorea (SC) patients. **Purpose:** To assess cognitive impairment with P300 ERPs. **Method:** Seventeen patients with SC and 20 unaffected healthy children were included. Stanford–Binet test was used for psychometric assessment, and odd-ball paradigm was used for auditory ERPs. **Results:** There was no significant difference in P300 latencies between the SC-pretreatment group, SC-posttreatment group and control group ($p>0.05$). Mean interpeak latencies in SC-pretreatment group and SC-posttreatment group showed significant prolongation compared with the control group ($p<0.05$). Mean interpeak latencies in SC-posttreatment group were significantly decreased compared with SC-pretreatment group ($p<0.05$). Compared to controls, patients did not show significant difference in Stanford-Binet intelligence examination. **Conclusion:** This report suggests that interpeak latencies and amplitudes of P300 ERPs could be useful for detecting and monitoring cognitive impairment in SC patients.

Keywords: Sydenham's chorea, cognitive function, event-related potentials.

RESUMO

Os potenciais evento-relacionados à P300 (ERPs), medidas objetivas relacionadas ao processamento cognitivo, não foram ainda estudados em pacientes com Coreia de Sydenham (CS). **Objetivo:** avaliar o comprometimento cognitivo através dos ERPs P300. **Método:** foram incluídos 17 pacientes com CS e 20 crianças saudáveis. A avaliação psicométrica foi feita utilizando o teste de Stanford–Binet e, para os ERPs auditivos, foi usado o paradigma *odd-ball*. **Resultados:** Não houve diferença significativa nas latências P300 entre os grupos CS pré-tratamento, CS pós-tratamento e grupo controle. ($p>0,05$). A média das latências interpicos no grupo CS pré-tratamento e CS pós-tratamento apresentava aumento significativo em comparação aos pacientes do grupo controle ($p<0,05$). A média das latências interpicos no grupo CS pós-tratamento apresentava decréscimo significativo quando comparada àquela do grupo CS pré-tratamento ($p<0,05$). Comparados aos controles, os pacientes com CS não mostravam diferença significativa em relação aos controles ao teste de Stanford-Binet. **Conclusão:** Este estudo sugere que as latências interpicos e as amplitudes dos ERPs P300 podem ser úteis para detectar e monitorar a ocorrência de comprometimento cognitivo em pacientes com CS.

Palavras-chave: Coreia de Sydenham, função cognitiva, potenciais evento-relacionados.

Sydenham's chorea (SC) is characterized by chorea and other movement disorders as well as behavioural changes such as attention deficit hyperactivity disorder, emotional lability, irritability, and obsessive-compulsive symptoms. Cognitive function in SC patients has not been well studied[1]. Some authors have described impairment of learning capacity, lower intellectual level, changes in response inhibition, divided attention, and planning ability tasks[2,3]. In most studies it is suggested that, there is an evidence of basal ganglia dysfunction which can be showed by morphologic and functional neuroimaging techniques[4]. Basal ganglia dysfunction can also present with cognitive impairment, characterized mainly by executive dysfunction[5]. So, it may be considered that degeneration of frontostriatal loops could lead not only to motor and behavioural changes but also to cognitive abnormalities in SC[6].

The P300 event related potential is a reflection of cognitive processing. P300 latency is related to stimulus evaluation processes such as encoding and classification. P300 amplitude reflects the effort of attention allocation and correlates

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with the volume of gray matter contributing to wave generation[7]. Children with acute rheumatic fever who develop movement disorder are more likely to have poor scores in cognitive tests. This finding cannot be explained only with clinical presentation, because of the presence of many confounding variables that may affect cognitive functions. Cognitive functions were only assessed using neuropsychological tests in SC studies[1]. It is not clear whether the different results of the various studies are a consequence of differences of tests or some other factor. Objective measures like P300 ERPs may be more appropriate than subjective measures for studies involving the cognitive performance assessments in these patients. P300 generally reflects the higher-order cognitive operations related to selective attention and resource allocation rather than differences in stimulus characteristics per se. However, P300 is not completely independent from stimulus parameters[8,9]. No study was found in the literature regarding P300 ERPs in a group of patients diagnosed with SC. The aim of this study is to assess cognitive performance with P300 ERPs in SC patients.

METHOD

Seventeen school children with SC and 20 unaffected healthy school children as the control group, who have same educational status were included the study. The 1992 update of the Jones criteria was used to diagnose SC. For the patients with SC diagnosis, other possible causes of chorea in childhood, such as juvenile Huntington's chorea, benign hereditary chorea, drug induced chorea, and chorea due to autoimmune disorders were excluded. Inclusion criteria were age (7-17 years), SC diagnosis, absence of other neurological and psychiatric disorder, absence of psychoactive and illicit drugs, and absence of hearing loss. Cardiac evaluation of each case was made by a paediatric cardiologist.

All patients are followed in Neurologic Disorders Unit and performed an evaluation with the *Universidade Federal de Minas Gerais* (UFMG) Sydenham's chorea Rating Scale (USCRS)[10]. This scale assesses behaviour, functionality as reflected by ability to perform activities of daily living, and motor function. All participants underwent assessment by the Turkish version of the Stanford–Binet test (4th edition), a standardized and well-validated psychometric testing used to assess memory, attention, language, and concentration. This test is characterized by its relevance to daily living activities in a population of children. The Stanford–Binet test consists of vocabulary, comprehension, verbal relations test, abstract visual reasoning test, quantitative reasoning test, memory for sentences test, bead memory test, and intelligent quotient. The evaluation was performed by a clinical child psychologist, within a time frame +10 days apart from the event related potentials study.

Auditory P300 event-related potentials

The P300 ERPs were recorded with Ag/AgCI electrodes with impedance 5 k Ohm or less by the same physician who was unaware of the subjects' clinical data. An active electrode was placed at the Cz (vertex) and was referenced to the linked earlobe Al according to the international 10-20 system. The P300 evoked potentials were generated following a binaurally presented tone discrimination paradigm through a headphone. The "odd-ball" paradigm was used in which subjects were asked to silently count rate tones differing from others in pitch (2000 Hz; probability ¼ 0.2), and occurring randomly among non-target events (1000 Hz; probability ¼ 0.8). Thirty potentials were averaged following target and non-target stimuli. The latencies (ms) of the P300 peak and the amplitudes (μV) of the N2P3 (potential difference between the N200 and P300 peaks) were recorded. P1, N1, P2, N2, and P3 peaks were determined. P1, first positive deflection that occurs after artefact of stimulus; N1, the first negative deflection that occurs after P1; P2, the first positive deflection after N1; N2, the negative deflection that occurs after P2; P3 the next highest amplitude was determined as a positive deflection after N2. Interpeak latencies were measured between the peaks of the consecutive waves. Auditory P300 ERPs were recorded at Fz, Cz, and Pz. The wave forms, amplitudes, latencies and interpeak latencies were evaluated from Cz. Before any treatment began, the pretreatment P300 ERPs were examined in all patients within two days of the time the diagnostic consensus was confirmed, the posttreatment examinations were made after 12 months of treatment and in control subjects. This study was approved by the local ethics committee. Parental consents were obtained for all patients.

Statistics

The Statistical Package for the Social Sciences (SPSS 12.0, Chicago, IL, USA) was used for analysis. Normal distributions were tested with the Kolmogorov-Smirnov test with Lilliefors correction. Mann-Whitney U test was used for inter-group comparisons. Repeated measurements were analysed with Wilcoxon signed-rank tests. Correlation analyses were made using the Pearson's product moment test. A two tailed p value <0.05 was considered statistically significant.

RESULTS

Seventeen SC patients comprised 14 girls and 3 boys, with a mean age of 12±1.1 years (range: 9-17 years). The control group comprised 13 girls and 7 boys, with a mean age of 13.1±1 years (range: 9-17 years). Demographic and clinic features of SC patients are presented in Table 1.

Compared to controls, patients reported lower scores in vocabulary, comprehension, verbal relations test, abstract visual reasoning test, quantitative reasoning test, memory for

Table 1. Demographic and clinic features of patients.

Patients	Gender	Age	USCRS score pretreatment	Medication	Active carditis	USCRS score 12 months after treatment
1	F	15	61	HAL	-	1
2	F	16	54	HAL	-	2
3	F	12	59	HAL	-	1
4	F	13	57	VPA	-	1
5	F	9	62	HAL	-	0
6	F	12	58	HAL, CS	+	0
7	M	9	96	HAL, VPA	-	2
8	F	13	59	HAL	-	1
9	F	14	61	HAL	-	2
10	F	17	63	HAL	-	1
11	F	15	62	HAL	-	1
12	F	13	59	VPA	-	1
13	F	13	62	HAL	-	0
14	M	10	57	HAL, CS	+	1
15	F	16	54	HAL	-	1
16	M	13	61	HAL, VPA	-	2
17	F	10	57	HAL	-	0

HAL; haloperidol, VPA; valproic acid, CS; corticosteroid.

sentences test, bead memory test, total short-term memory, and intelligent quotient were detected among controls and patients. However, the differences did not reach a significant level (Table 2). There was no significant correlation between individual intelligence test scores and P300 ERPs parameters.

There was no significant difference in P300 latencies between the SC-pretreatment group (317.3±6.8), SC-posttreatment group (313.6±6.8) and control group (318.2±5.5) ($p>0.05$ for all).

Mean interpeak latencies in SC-pretreatment group (240±7.4) and SC-posttreatment group (237.3±7.7) showed significant prolongation compared with the control group (198.4±10) ($p<0.05$). Mean interpeak latencies in SC-posttreatment group were significantly decreased compared with SC-pretreatment group ($p<0.05$) (Figure 1).

Mean P300 amplitudes in SC-pretreatment group (2.32±0.22) and SC-posttreatment group (2.28±0.18) were significantly decreased compared with the control group (3.62±0.58) ($p<0.05$). There was no significant difference in the mean P300 amplitudes between SC-pretreatment group and SC-posttreatment group ($p>0.05$) (Figure 2).

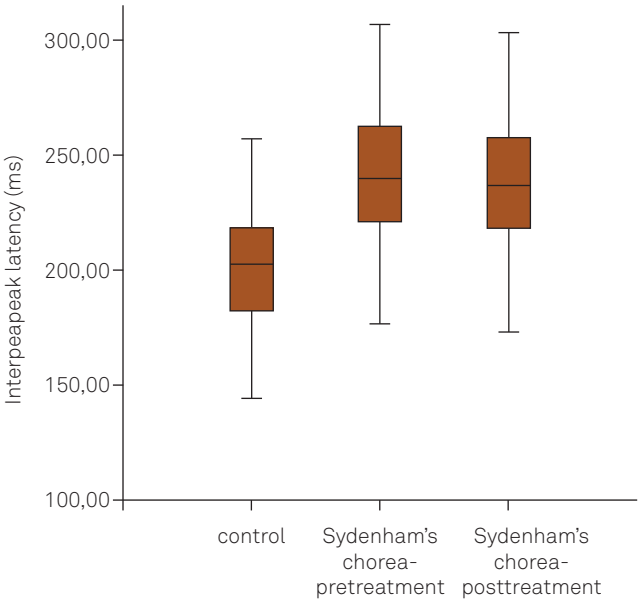

Figure 1. Box plots graph shows the median levels and the range of the interpeak latencies.

Table 2. Syndenham's Chorea (SC) patients and controls in relation to various cognitive functions.

Cognitive functions	Control group (n=20)	SC patients (n=17)	p value
Vocabulary	45.31±5.75	42.40±9.70	.320
Comprehension	49.18±4.57	46.85±8.34	.138
Verbal relations test	91.87±15.54	88.92±19.36	.175
Abstract visual reasoning test	94.21±16.45	92.47±21.32	.43
Quantitative reasoning test	97.48±10.75	95.12±19.74	.237
Memory for sentences test	46.68±8.46	45.12±13.25	.278
Bead memory test	47.86±8.54	46.65±11.18	.480
Total short-term memory	97.65±16.54	92.08±23.87	.316
Intelligent quotient	95.89±11.54	93.45±21.75	.452

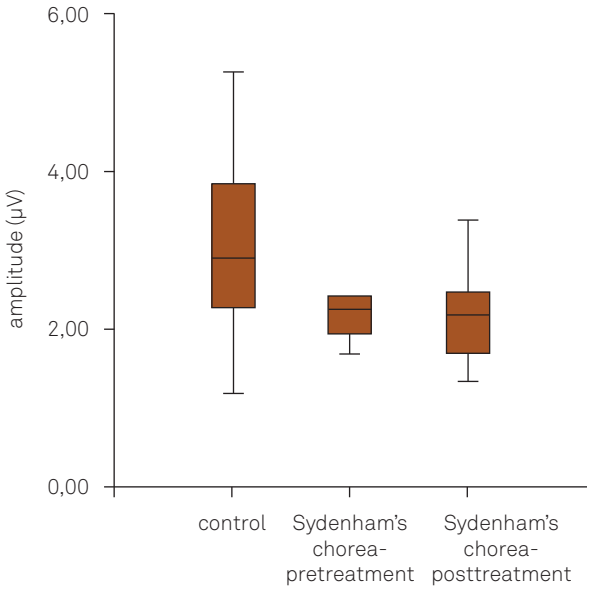

Figure 2. Box plots graph shows the median levels and the range of the amplitudes.

DISCUSSION

This is the first study evaluating P300 ERPs in patients with SC. In our sample, SC patients showed evidence of cognitive dysfunction. However, no significant difference in Stanford-Binet intelligence examination is to be noted between patients and controls. Improvement in cognitive dysfunction was seen after 12 months of treatment. In some studies it has been suggested that there was no change in cognitive performance in SC patients[1,11,12]. However, the scales for rating the clinical features of SC included items for cognitive functions[10]. Additionally, in most studies it has been described that there is an impairment of cognitive function[13,14]. Moreover, some studies suggested that patients who had SC during childhood can exhibit cognitive dysfunction[15]. The first striking finding in the present investigation was the absence of a significant difference in P300 latencies between the SC group and control group. However, there was significant prolongation of the interpeak latencies between the SC groups (pretreatment and posttreatment) and control group. Slow cortical potentials reflect changes in cortical polarization lasting from 300 ms up to several seconds. Functionally, slow cortical potentials represent a threshold regulation mechanism for local excitatory cortical mobilization. If active structure is deeper and farther to the surface, this action potential is recorded larger on the surface[16]. Parameters of these potentials measures adaptive processes of the brain against unexpected events. P300 occurs when subjects attend and discriminate stimulus events that differ from one another on some dimension. P300 latency is considered to reflect the speed of neural events underlying perception and discrimination; matching that particular information against stimulus categories in memory, and making an appropriate decision[17,18]. So, it requires attention and short term memory. Indeed, P300 latency has been reported to be associated with cognitive processing, especially attention and short time memory. However, prolongation of interpeak latencies suggests that adaptive processes are interrupted in one or more steps. In other words, a corrupted form of the wave suggests presence of processing disturbance, but level of this disturbance not high enough to cause prolongation of P300 latencies. Compared with the healthy controls, reduced P300 amplitudes in SC patients (pretreatment and posttreatment) closely agrees with the above mentioned previous studies that suggested a relationship between cognitive dysfunction and SC. Decreased P300 amplitude is often observed in attention deficits[19,20]. It is expected that treatment led to the increase in the amplitudes, but amplitudes did not differ significantly between pretreatment and posttreatment measurements. This result may indicate a negative-side effect of antipsychotic or anticonvulsant medication that is used as treatment for those who have chorea, or there may be still have another unclear pathophysiology cause of decreased amplitude. Nearly all of our patients were received haloperidol (HAL). Some studies suggest that the relevant regulatory circuits of SC include prefrontal cortex and basal ganglia, which are modulated by dopaminergic innervations. Haloperidol acts as a potent, partially selective dopamine D_2 receptor antagonist, which is often used to treat hyperkinetic movement disorders. Haloperidol affects spontaneous EEG activity, increasing slow waves and decreasing alpha and beta activity in healthy humans[21,22]. It is suggested that HAL decreases the transient 40 Hz response elicited by selectively attended tones[23], on the other hand it is shown that droperidol an antidopaminergic drug has also antiadrenergic properties affecting cognitive functioning[21,24,25]; whereas, HAL is relatively devoid of them[26]. However, HAL is known to bind with high affinity to sigma receptors[27]. Therefore, it is possible that some of the observed effects in D2-poor areas reflect direct binding at nondopaminergic sites. In additionally, a meta-analysis showed that cognitive performance improves while on HAL, and provided data that suggests the effects of HAL on cognitive functions might be dose related[28]. In this study mean duration of HAL treatment was 4 months (range; 1-11 months). Most side-effects usually disappear rapidly after HAL is discontinued or the dosage reduced. Furthermore, including possible effects on P300 ERPs are less likely to be apparent, since HAL treatment was given meanly 4 months. Patients showed significant decrease in their P300 interpeak latencies after 12 months treatment compared to before treatment. It seems reasonable to suggest that these changes at interpeak latencies may be due to improving in circuits of executive dysfunction with treatment. These results indicate that treatments for chorea in SC patients may be as effective for cognitive impairment.

We demonstrated a good relationship between some parameters of P300 ERPs and cognitive performance. Our study did not closely agree with the above mentioned previous studies, since our results did not reveal significant differences in neuropsychological assessment between patients and controls. However, the interpeak latencies appear sensitive enough to identify improvement in cognitive performance after treatment. Moreover, treatments could be aimed not only at normalizing P300 latencies but also at decreasing prolongation of the interpeak latencies so partially improvement of adaptive processes. In one study, the cognitive status of one patient was reported to be reversible. Whereas our results show that the shapes of waveforms had been corrupted during the follow up period. Some studies suggest that symptoms of SC persist throughout life and that as adults these individuals have significant problems in executive functions as well as psychopathologies[15].

Therefore, SC treatment is becoming more important for these children for their academic attainment, social behaviour and cognitions as well as later life. Our study has some limitations. First, serum growth hormone measurement was not performed. There are some studies indicate the prolongation of P300 latencies in patients with severe GH deficiency[29]. However, our findings indicate no significant difference in P300 latencies between the SC patients and controls. Second, the study lacked a positive control group, and it is unclear if the P300 interpeak latencies undergo natural changes over time. Compared with a positive control group would be beneficial for validating the current findings.

Patients who had SC during childhood can exhibit lower performance in tasks that evaluate attention, speeded information processing, executive functions, and working memory in adult life. Therefore, there may be an indirect evidence of the persistence of dysfunction in cerebral circuits involved with the basal ganglia[15]. Our results showed impaired cognitive performance, which was mainly expressed by the longer interpeak latencies and lower amplitudes in patients with SC. In this study, USCRS scores decreased markedly in all patients following multidisciplinary treatment at 12 months. The poor correlation between P300 latencies and clinical motor score indicated that P300 delay was due to a mechanism that was different from that responsible for motor disability. Thus, this type of analysis can help in obtaining more precise results in the assessment of the cognitive performance by means of electrophysiological procedures. P300 is one of the most extensively studied ERP components for evaluating the neural underpinnings of cognition. We have assessed the participants with ERPs P300 and Stanford-Binet test together. This study represents the first effort to address the ERPs P300 -an electrophysiological test- using concurrent Stanford-Binet test in SC patients and a number of methodological issues should be taken into consideration. First, our results are based on single trial ERP information. Future studies are required to investigate the influence of different approaches to single-trial ERP information. Second, our analyses focused specifically on P300 parameters but interpeak latency has also demonstrated sensitivity to cognition and would also warrant investigation in future studies in SC patients.

In conclusion evaluation of P300 ERPs has an advantage of being free of possible exaggeration and response biases, but does not give detailed information on cognitive performance such as verbal fluency, verbal knowledge or free recall.

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