

## Potenciais evocados auditivos de média e longa latências em adultos com AIDS\*\*\*\*

### Middle and late latency auditory evoked potentials in adults with AIDS

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#### Abstract

Background: middle and late latency auditory evoked potentials. Aim: to verify the occurrence of middle and late latency auditory evoked potentials disorders in adults with Acquired Immunodeficiency Syndrome (AIDS). Method: middle and late latency auditory evoked potentials of 8 individuals with AIDS, with ages ranging from 10 to 51 years, with normal hearing, or with sensoryneural hearing losses up to moderate, and normal results in the Auditory Brainstem Response, comparing the results with the responses obtained for a control group which was composed by 25 individuals, with ages ranging from 19 to 24 years, with no hearing complaints and with normal hearing and normal results in the Auditory Brainstem Response. Results: the Pa wave latency and amplitude averages in the C3/A2 and C4/A1 modalities, and the average of the P300 wave were analyzed. No significant differences were observed in the Pa wave amplitude and latency averages between the groups, although a non-statistically significant increase was observed in the latency and a decrease in the amplitude of such wave for the research group in the C3/A2 modality. The latency of the P300 wave was significantly longer to the left for the research group. It was also observed a longer latency to the right, although this was not statistically significant. Conclusion: adult individuals with AIDS do not present alterations in the middle latency auditory evoked potential and do present alterations in the cognitive potential, indicating a disorder in the cortical regions of the auditory pathway and a deficit in the cognitive processing of auditory information for this population. Such findings stress the importance of a careful investigation of the auditory function of individuals with AIDS, thus favoring the therapeutic planning.

**Key Words:** Auditory Evoked Potentials; P300 Event-Related Potentials; Acquired Immunodeficiency Syndrome.

#### Resumo

Tema: potenciais evocados auditivos de média e longa latências. Objetivo: verificar a ocorrência de alterações nos potenciais evocados auditivos de média e longa latências em indivíduos adultos portadores da síndrome da imunodeficiência adquirida (AIDS). Método: foram obtidos os potenciais evocados auditivos de média e longa latências em oito indivíduos com AIDS, de 10 a 51 anos de idade, que apresentavam audição normal ou até perda auditiva neurosensorial de grau moderado e resultados normais na Audiometria de Tronco Encefálico, comparando os resultados com os obtidos no grupo controle constituído por 25 indivíduos, de 19 a 24 anos de idade, sem queixas auditivas e com audição dentro da normalidade, bem como com resultados normais na Audiometria de Tronco Encefálico. Resultados: foram analisadas as médias das latências e amplitudes da onda Pa, nas modalidades contralaterais C3/A2 e C4/A1, e da latência da onda P300. Não foram observadas diferenças estatisticamente significantes com relação às médias da amplitude e latência da onda Pa entre os grupos, embora tenha sido observado um aumento da latência e diminuição da amplitude de tal onda, ainda que não estatisticamente significante, para o grupo estudo na modalidade C3/A2. A latência da onda P300 mostrou-se significativamente aumentada para o lado esquerdo no grupo estudo, sendo também possível observar um aumento da latência, embora não estatisticamente significante, para o lado direito. Conclusão: indivíduos adultos com AIDS não apresentam alterações no potencial evocado auditivo de média latência e apresentam alterações no potencial cognitivo sugerindo, desta forma, comprometimento da via auditiva em regiões corticais e déficit no processamento cognitivo das informações auditivas nesta população. Tais achados reforçam a importância de uma investigação minuciosa da função auditiva em indivíduos com AIDS auxiliando, desta forma, no delineamento da conduta terapêutica junto a estes pacientes.

**Palavras-Chave:** Potenciais Evocados Auditivos; Potencial Evocado P300; Síndrome da Imunodeficiência Adquirida.

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## Introduction

In the Acquired Immunodeficiency Syndrome (AIDS) caused by the human immunodeficiency virus (HIV), a progressive compromise of the immune response of the individual occurs making him/her susceptible to a number of opportunistic infections. With the development of the disease, a progressive impairment of the central nervous system (CNS) may occur including the central auditory system, either due to the direct action of the virus on the CNS affecting the maturational process, or due to opportunistic infections (Chow et al., 2005).

From the clinical point of view, the infection caused by the HIV and AIDS are distinct entities. Many individuals infected by the HIV also present a normal amount of immunologic cells, remaining asymptomatic for long periods of time. Despite being affected by the HIV, those individuals don't match the clinical definition of AIDS.

In order to be clinically defined as having AIDS the HIV-positive individuals must present low amount of immunologic cells ( $CD4 < 350$ ) or develop at least one clinical condition that defines AIDS.

According to the American National Health Institute about 75% of adults with AIDS present some kind of auditory dysfunction due to opportunistic infections or to ototoxic effect treatments.

The incidence of hearing disorders in patients with HIV/AIDS varies approximately from 20 to 40% (Chandrasekhar et al., 2000; Mata Castro et al., 2000; Khoza & Ross, 2002), and the hearing loss may be due to external, middle or inner ear disorders.

Within the innumerable infections that individuals with AIDS might have, there are the otitis that may cause a temporary peripheral hearing loss and should be identified as early as possible in order for the adequate medical treatment to be established.

Individuals with HIV/AIDS may also present an inner ear impairment due to the direct action of the virus (Chandrasekhar et al., 2000; Mata Castro et al., 2000; Khoza & Ross, 2002), as well as to the use of anti-retroviral drugs or ototoxic medicine (Sindom et al., 2000; Williams, 2001; Rey et al., 2002), causing a sensorineural hearing loss.

Due to these impairments we may find abnormalities in the tests that evaluate the central auditory processing reflecting difficulties in the attention, discrimination, recognition and comprehension of auditory information (Roland Jr. et al., 2003).

Besides the behavioral hearing tests failures, there are abnormalities in middle and late auditory evoked potentials following the progress of the disease.

Nowadays, the auditory evoked potentials are of great use in the audiological practice; when associated to the behavioral hearing evaluation they make the diagnosis of central or cognitive auditory disorders more precise (Junqueira & Frizzo, 2002).

The fact that they are obtained objectively and non-invasively allows the use of such potentials to evaluate auditory processing disorders (APD). Such responses don't depend on the subject's linguistic skills and, except from the late potentials, they don't demand a cognitive processing of the sound stimulus (Schochat, 2003).

The middle latency auditory response (MLR) is a synchronic auditory evoked potential that occurs in a time space of approximately 100 milliseconds (ms) after the auditory stimulation composed by a series of positive and negative waves. The first MLR wave is the Na (occurring at around 18 ms) followed by the Pa (30 ms), Nb (40 ms), Pb (50 ms) and sometimes, Nc and Pc; the Pa wave has the greatest amplitude, and is more consistent and more frequently used (Musiek & Lee, 2001).

The MLR has multiple generators reflecting primary and non-primary areas, such as the reticular formation, the thalamus divisions; with a greater contribution of the thalamo-cortical pathways and with a lesser contribution of the inferior colliculi (mesencephalus) and auditory cortex (Budinger & Scheich, 2000).

The late latency potentials are less affected by the physical properties of the stimulus and are more affected by the functional use that the individual makes of the stimulus, being less determined by the frequency or intensity, and more by the attention to the sound stimulus. Such potentials are originated in the primary and secondary areas of the auditory cortex being useful in the cognitive and attention functions study.

The P300, also called cognitive potential, is a positive late latency auditory evoked potential generated by a series of stimuli (frequent) and by the occasional occurrence of a less frequent stimulus (rare) that appears randomly. The rare stimulus occurs from 15 to 20% of the total stimuli, and the subject should identify it counting mentally or pressing a button every time it occurs. At each screening, two waves are recorded; one for the frequent stimulus and one for the rare stimulus.

The auditory system habituates to hearing the frequent stimulus and, therefore less neurons answer to this stimulus. Concerning the rare stimulus, as it is heard less times, the system answers to this stimulus with more neurons generating a wave with greater amplitude. The P300 is obtained subtracting the rare stimulus from the frequent one (Schochat, 2003).

The P300 wave is the greatest positive wave after the complex N1-P2 occurring between 240 and 700 ms (Junqueira & Colafêmina, 2002).

A latency increase or an amplitude decrease indicate clinical and sub-clinical problems. According to Picton (1992) if the P300 is small or late, there will probably be a deficit in the cognitive processing. The latency is a more reliable indicator than the amplitude, once the amplitude is difficult to be altered as a function of the attention.

It is known that individuals with AIDS may present a progressive compromise of the central nervous system, including the central auditory system, by the direct action of the virus on the system's structures leading to the presence of electrophysiological abnormalities in the brainstem auditory evoked potentials, middle and late latencies evoked potentials, including the P300 (Reyes et al., 2002). According to Bankaitis et al. (1998), these abnormalities go along with the disease progression.

The findings of Matas et al. (2000) and Matas et al. (2002) reported a greater incidence of hearing disorders suggestive of central auditory impairment in HIV positive children.

Several studies have documented disorders in the auditory evoked potentials of patients with AIDS (Martin et al., 2001; Polich & Basho, 2002; Chao et al., 2004; Tartar et al., 2004).

As AIDS has been spreading in the past few years and the otorhinolaryngologic manifestations have been more documented, several studies in the literature emphasize the importance of the audiological evaluation of these patients, not only for a more effective diagnosis, but also aiming at a rehabilitation process.

The present study aimed to verify the occurrence of middle and late latency auditory evoked potentials disorders in adult individuals with the acquired immunodeficiency syndrome (AIDS).

## Method

The study had its start after the approval of the Ethics Committee for Research Projects Analysis - CAPPesq from the Clinical Board of the Hospital das Clínicas and from the Medical School of University

of São Paulo (FMUSP), protocol number 1026/04. The participants signed the Informed Consent Term in which all procedures were described.

All individuals were referred by the Audiology Service to the Speech and Hearing Laboratory in Auditory Evoked Potentials of the FMUSP. The audiological evaluation as well as the brainstem auditory evoked potentials were previously carried out.

Thirty three subjects from 10 to 51 years of age took part in the study. In the control group, 25 normal individuals were evaluated, being 5 male and 20 female ranging in age from 19 to 24 years.

The study group was composed by 8 subjects with AIDS, 4 male and 4 female, presenting normal hearing or even a moderate sensorineural hearing loss including the frequencies from 3 to 6 kHz, and normal brainstem auditory evoked potentials results.

Initially, the individuals underwent an anamnesis gathering information related to the virus infection, to the presence of risk factors for hearing loss, to otitis complaints, among other disorders related to the external and middle ears.

Next, the inspection of the external acoustic meatus was performed using an otoscope to verify the conditions for the electrophysiological examination.

The electrophysiological evaluation was done with the portable system Bio-Logic Traveler Express.

In order to get the middle latency auditory evoked potential (MLR), the subject's skin was cleaned with an abrasive paste and the electrodes were placed through an electrolytic paste and a seller tape (micropore) on pre-determined positions: A1, A2, C3, C4 and Cz, according to the IES 10-20 (International Electrode System).

The impedance values of the electrodes were verified and they should be below 5 kOhms. The acoustic stimulus was presented through a pair of earphones eliciting the responses.

The stimulus used was the click presented monaurally at 70 dB HL in a presentation rate of 10 clicks per second, totalizing 1000 clicks.

The MLR results were analyzed concerning the Pa wave latency and amplitude obtained in the contralateral modalities (C3/A2 and C4/A1), once according to the specialized literature the contralateral modality is the most indicated one to analyze the variables that will be studied (Hall, 1992).

In order to obtain the P300, the electrodes were placed on the skin in the positions A1, A2, Cz and Fz also according to the IES 10-20 (International Electrode System).

The tone burst sound stimuli were presented at 75 dB HL. The rare stimulus (1500Hz) occurred from

15 to 20% of the total of 300 stimuli and was presented randomly by the computer.

## Results

The average and the standard deviation of the Pa wave latency were calculated for the contralateral modalities (C3/A2 and C4/A1) in the control and study groups.

Then, the averages of the Pa wave latencies were compared between the control and the study group using the Student's t-test adjusted by the Levene's test for equality of variance, with a significance level of 0,05 (5%) (Table 1).

No significant statistical differences were found regarding the averages of the Pa wave latency between the control and the study groups, either for the modality C3/A2 as for the C4/A1.

The average and standard deviation of the Pa wave amplitudes were also calculated for the contralateral modalities (C3/A2 and C4/A1) in the control and the study groups.

Then, the averages of the Pa wave amplitudes were compared between the control and the study group using the Student's t-test adjusted by the Levene's test for equality of variance, with a significance level of 0,05 (5%) (Table 2).

No significant statistical differences were found regarding the averages of the Pa wave amplitude between the control and the study groups, either for the modality C3/A2 as for the C4/A1.

For the P300 analysis, the average and the standard deviation of this wave latency, whenever present in the right and left ears, were calculated.

The averages of the P300 wave latency were compared between the control and the study group using the Student's t-test adjusted by the Levene's test for equality of variance, with a significance level of 0,05 (5%) (Table 3).

Significant statistical differences were found regarding the P300 wave latency between the control and the study groups for the left side.

Table 1 - Comparison of the averages and Standard deviation of the Pa wave latency between the control and the study groups.

Variable	GROUP	n	Average	Standard deviation	Significance (p)
PA_C4A1	Study	8	32,74	4,90	0,205
	Control	25	32,85	3,84	
PA_C3A2	Study	8	34,76	6,86	0,272
	Control	25	31,00	4,14	

Table 2 - Comparison of the averages and Standard deviation of the Pa wave amplitude between the control and the study groups.

Variable	GROUP	n	Average	Standard deviation	Significance (p)
Amplitude_C4/A1	Study	8	0,83	0,54	0,257
	Control	25	1,40	1,17	
Amplitude_C3/A2	Study	8	1,00	0,99	0,885
	Control	25	1,42	1,61	

Table 3 - Comparison of the averages and standard deviation of the P300 wave latency between the control and the study groups.

Variable	GROUP	n	Average	Standard deviation	Significance (p)
P300_RE	Study	8	355,25	52,86	0,109
	Control	25	309,88	27,30	
P300_LE	Study	7	368,00	52,40	< 0,001
	Control	25	308,84	20,82	

## Discussion

Several studies in the literature emphasize the importance of the auditory evoked potentials for population at risk for central auditory disorders including individuals with AIDS. According to Picton (1992), latency increases or amplitude decreases of auditory evoked potentials are evidences of clinical and sub-clinical problems.

In the middle latency auditory evoked potential (MLR), the averages of the Pa wave latencies for the contralateral modalities C3/A2 and C4/A1, when compared between the control and the study groups, did not reveal significant statistical differences. The Pa wave latency occurred around 32 ms either for the control group as for the study group in the modality C4/A1. For the modality C3/A2, while in the control group the Pa wave latency was at 31 ms, in the study group it was possible to observe a slight increase of this wave latency when compared to the control group, being present

around 34 ms. This finding agrees with the study of Schmitt et al. (1992), who reported an increase of the Pa wave of subjects with AIDS.

The comparison of the Pa wave amplitudes in the contralateral modalities (C3/A2 and C4/A1) revealed no significant statistical difference between the groups. In the control group, the Pa wave presented mean amplitude of 1,4 V in the modalities C3/A2 and C4/A1. It was possible to observe a tendency in the study group, although not statistically significant, to decrease the Pa wave amplitude, once this amplitude was 0,8 V in the modality C4/A1 and 1,0 V in the modality C3/A2.

The results obtained in this research through the statistical analysis performed, despite not being the most frequently observed in the specialized literature that reports an increase of the MLR waves latencies in individuals with AIDS (Bankaitis et al., 1998), could be justified by the small sample (N=8) and also by the great variability of the MLR waves latencies inter-subject.

Such fact demonstrates that further researches should be carried out in this field.

In the late latency auditory evoked potential, the averages of the P300 wave latencies in the right ear did not show significant statistical difference when compared between the groups; this finding could also be justified by the great variability of the mean time of the P300 wave intra-subject. Despite not being statistically significant, it was possible to observe a slight increase of this wave latency when compared to the control group, being present at around 355 ms in the group of individuals with AIDS, and around 309 ms in the control group for the right ear.

The results analysis revealed a significant statistical difference in the P300 wave latencies for the left ear. In the control group, this wave appeared around 308 ms, while in the study group it was found at around 368 ms.

According to Picton (1992), the P300 latency is a more reliable indicator than the P300 amplitude, since this last one is difficult to be altered as a function of the attention; this is the reason why only the P300 wave latency was studied in this research.

Several authors also reported alterations in the P300 in individuals with HIV/AIDS.

In Tartar et al. (2004) study with symptomatic and asymptomatic HIV positive individuals and HIV negative individuals, alterations of the P300 wave were described in both groups with HIV, being more evident in the symptomatic individuals, that is the individuals with AIDS, following their cognitive decline. The authors concluded that the P300 is a complementary exam that is useful to mark the cognitive decline in the diagnostic and treatment of AIDS.

Significant differences in the P300 latency in HIV positive patients were also reported by Fein et al. (1996) and Polich et al. (2000). In the first study, it was observed a 12 ms delay of the P300 component in subjects with AIDS and the delay magnitude was directly related to the severity of the cognitive compromise of such subjects. For the authors, the P300 latency delay is associated to the disease progression once the cognitive capacity decline is considered one of the symptoms that could be present in patients with AIDS, being directly proportional to the individual viral rate.

Corroborating the findings of this research, Reyes et al. (2002) also found significant statistical differences in the auditory evoked potentials of individuals with AIDS, therefore being possible to assume that HIV may compromise the auditory nervous system, which could be detected through auditory evoked potentials.

## Conclusion

From the data obtained in this study it is possible to conclude that adult individuals with AIDS don't present middle latency auditory evoked potential alteration and do present cognitive potential alteration, suggesting thus a compromise in the cortical regions of the auditory pathway and a deficit in the cognitive processing of auditory information in this population.

Such findings emphasize the importance of a detailed investigation of the auditory function of individuals with AIDS aiming at the identification of possible alterations that could be associated with this pathology, as well as the characterization of the type of damage and its possible causes (compromising the peripheral auditory system - external, middle or inner ears, and/or central auditory system) helping thus, the establishment of the therapeutic follow up with these patients.

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