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BACKGROUND AND PAROXYSTIC ACTIVITIES ON AIDS PATIENTS' EEG

RELATION WITH UREA AND CREATININE SERIC CONCENTRATION

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ABSTRACT - The HIV is responsible for important metabolic and structural alterations of the brain. This affected brain must react to continuous systemic metabolic fluctuations. We search for possibly resulting cerebral electric disturbance that could be found by EEG exploration. Sixty-three AIDS patients ranked as CDC group IV had their EEG background rhythm measured, and were appointed to mutually exclusiding groups delimited by medians' values of urea (24 mg/dl) and creatinine (0.9 mg/dl) seric concentrations. These groups were independently formed for each of the parameters utilized, and each data pair generated therefrom were compared between themselves to verify whether there were differences in background rhythm and the occurrence of paroxysmal activity. Background rhythm and paroxysmal activities have not statistically differed between the group whose creatinine values were lower than 0.9 mg/dl and the group whose creatinine values were equal or higher than 0.9 mg/dl. Background rhythm has not statistically differed between the group whose ures values were <24 mg/dl and the group whose urea values were =24 mg/dl; contrariwise, the occurrence of paroxysmal activities in these groups has significatively differed, being higher in the patient group whose otherwise normal urea values exceeded 24 mg/dl (p=0.02).

KEY WORDS: paroxystic activity, background activity, EEG, HIV, urea, creatinine, AIDS.

Ritmo de base e atividade paroxística no EEG de pacientes com AIDS: relação com as concentrações séricas de uréia e creatinina

RESUMO - Sendo o HIV responsável por alterações estruturais e metabólicas do encéfalo, procuramos verificar se pequenas alterações metabólicas sistêmicas poderiam determinar alterações encefálicas detectáveis através do EEG. Medimos o ritmo de base no EEG de 63 pacientes aidéticos no grupo IV da classificação do CDC e, utilizando os valores das medianas das taxas de uréia e creatinina séricas, constituímos dois grupos para cada um dos referidos parâmetros. Verificamos se os EEGs dos pacientes com uréia abaixo do valor mediano (24 mg/dl), diferiam em relação ao ritmo de base e presença de atividade paroxística, daqueles com uréia = 24 mg/dl. Procedemos da mesma forma para estudar o ritmo de base e atividade paroxística em relação à mediana das concentrações de creatinina (0,9 mg/dl). O ritmo de base e a ocorrência de atividade paroxística não foram diferentes em relação à concentração de creatinina. O mesmo ocorreu em relação ao ritmo de base e concentração de uréia. Observamos, entretanto, maior número de EEGs de pacientes com uréia normal acima de 24 mg/dl com atividade paroxística (p=0,02).

PALAVRAS-CHAVE: atividade paroxística, atividade de base, EEG, HIV, uréia, creatinina, AIDS, SIDA.

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The human immunodeficiency virus (HIV) infects CD4+ cells (lymphocytes, macrophages, monocytes, and microglia), whose malfunction leads to a great number of complicating situations ranging from opportunistic infections to cancers and AIDS related dementia complex, the most frequent disorder of the central nervous system (CNS) seen in these patients[1,2]. Patients present with protean clinical pictures that vary from complete absence of symptoms and signals to focal disorders or severe dementia. During the initial disease's stages, HIV can provoke, like any other virus, an acute encephalitis that may cause coma or patient's death[3]. The AIDS virus keeps on asymptomatically acting on the CNS as well as on the whole organism during a variable time period. At a right time that coincides with immunity worsening, neurologic alterations begin to show up: tremors, weakness, amyotrophy, paraparesis, paresis, and the above mentioned AIDS dementia complex characterized by motor, cognitive, and behavioral disorders[4]. In spite of being neurologically asymptomatic, these patients already exhibit electroencephalographic (EEG) alterations, such as slow background rhythm, that become clearer during the initial phases of AIDS dementia complex. Since the recogniton of neurologic disorders in AIDS patients, it was observed that systemic derangements induce worsening of neurologic symptoms, mostly the demential ones. These patients may begin to show signs and symptoms that were not evident earlier. It is possible that the nervous system already responds abnormally in the subclinical plane, therefore justifying the search for methods that allow detection of early alterations. The EEG has been so utilized and proved to be very sensitive and detective of frequent alterations such as slow background rhythm, and unspecific paroxysmal activities that project diffusely but predominate in the anterior regions of the brain, specially the temporal ones.

The EEG alterations observed in the uremic patient are well known and range from background rhythm alterations (slowing of) to slow waves bursts, some of them with triphasic features[5]. All these are dependent on the increased urea levels, or on the rapidity with which the renal insufficiency ensues and leads to alterations of water, electrolytes and toxic catabolites accumulation.

We have searched for differences in the EEG findings of CDC (Center for Disease Control) group IV AIDS patients who were exposed to varying plasmatic urea concentrations, bearing in mind that a brain compromised by a virus that progressively lessen the neuronal populations, probably works in unusual homeostatic situations.

METHOD

We studied EEG recordings of sixty-three CDC group IV AIDS patients as for the background rhythm and the occurrence of paroxysmal activities. Background rhythms values were visually (as opposed to computer mensurarion) determined, using a millimetric rule, in the posterior regions, and the higher achieved value was adopted, in case of variations, in a single EEG. The patients were also clinically evaluated, classified in relation to the presence or not of encephalic signs and symptoms, and twenty-four individuals showed clinical evidence of CNS involvement. All sixty-three patients had their seric concentrations of urea and creatinine determined. Urea concentrations varied from 10 mg/dl to 270 mg/dl, mean = 39.5±47.3 mg/dl, median = 24 mg/dl, and those ones of creatinine varied from 0.4 mg/dl to 10.2 mg/dl, mean = 1.25±1.66 mg/dl, median = 0.9 mg/dl.

We utilized the urea concentrations' median value in order to divide our sample into two groups: one whose component values were smaller than the median's (31 patients) and another one whose values were higher (32 patients). These groups were then compared as for the distribution of background rhythm. The paroxysmal activities study was done in a subset that resulted from the exclusion of patients whose EEG tracings showed focal paroxysms and those whose urea concentrations were abnormal, that is, higher than 40 mg/dl in the analysis method utilized (automated enzymatic determination in an Abbot-ABA 100 device). This subset was composed of fifty patients who were then divided in the way described above. The same procedures were repeated in the study of the background rhythm and paroxysmal activities in relation to creatinine concentrations.

In this approach, we stated as paroxysmal activity every theta, and/or delta wave burst whose distribution was diffuse and not related to normal neurophysiologic conditions.

We have used Mann-Whitney and Chi-square (χ^2) tests for the statistical analysis. The null hypothesis rejection was set adopting an $\alpha = 0.05$.

RESULTS

The background rhythm's means of the groups with urea concentration below and above 24 mg/dl was 9.42 Hz and 9.09 Hz, respectively. This difference (0.33Hz) was devoid of statistical significance (Table 1). The patient group whose urea concentration was higher or equal to 24 mg/dl showed a rate of 70.83% of EEGs with paroxysmal activities as opposed to the rate of 34.66% of the group whose urea concentrations were below 24 mg/dl, and this disparity was statistically significant (p=0.02) (Table 2).

The background rhythm's means of the groups with creatinine concentration below and above 0.9 mg/dl was 9.09 Hz and 9.35 Hz, respectively. This difference (0.26Hz) was devoid of statistical significance ($z_{calculated}$ = 0.12 and $z_{critical}$ = 1.96). The patient group whose creatinine concentration was higher or equal to 0.9 mg/dl showed a rate of 60% of EEG with paroxysmal activities as opposed to the rate of 52% of the group whose creatinine concentrations were below 0.9 mg/dl, and this difference was not statistically significant ($\chi^2_{calculated}$ = 0.35 e $\chi^2_{critical}$ = 3.84).

Table 1. Distribution of the background rhythm's values (Hz), according to the groups formed based on the urea concentration's median (24 mg/dl) of 73 patients.

<24 mg% group			=24 mg% group		
Background activity in Hz			Background activity in Hz		
9	9	10	2	14	9
14	10	3,5	14	10,5	9
12	14	9	14	7	10
8	8	7,5	8	8	3
8	8	12	11	6	10
6	10	10	7,5	12	14
14	10	9	8	3	9
12	8	11	5	2	10
9	11	2	7	14	14
9	12	10	8	8	11
		7	14	9	
M	32.97			31.06	
X	9.42			9.09	

M, ranks mean; X, values mean (Hz).
$Z_{critical}$ = 1.96. $Z_{calculated}$ = 0.41.
The groups do not significantly differ.

DISCUSSION

The study of the free distribution of the background rhythm, according to the two groups (of a total of sixty-three patients) delimited by the median of urea concentration, showed no significant differences between the rhythm frequencies in the group of patients whose urea was lower than 24 mg/dl and those ones in the group whose concentrations were equal or higher than 24 mg/dl (Mann-Whitney test with closing in on the normal curve: $Z_{calculated}$ = 0.41 and $Z_{critical}$ = 1.96). The mean of the

Table 2. Occurrence of paroxysmal activities, according to the groups formed based on the urea concentration's median (24 mg/dl) of 50 patients, excluding that ones with urea values higher than 40 mg/dl.

PAROXYSMAL ACTIVITY				
Urea	Presence	Absence	Total	% Pres.
<24	9	17	26	34.62
= 24	17	7	24	70.83
Total	26	24	50	52.00

$\chi^2_{calculated}$ = 5.19*, $\chi^2_{citical}$ = 3.84. p = 0.02.
% Pres., percentage of presence.
Paroxysmal activities are observed in 70.83% of EEG's patients group with urea normal concentration above 24 mg/dl.

background rhythm's values was 9.42 Hz and 9.09 Hz respectively, with a difference of 0.33Hz between the groups (Table1). There were only seven patients whose urea concentration levels were twice above the normal values; these patients remained in the background rhythm's study.

The frequency of paroxysmal activity were respectively 70.83% and 34.62% in the group whose urea values were equal to or exceeded 24 mg/dl and the one whose values were below this level. The Chi-square test revealed a significant association between the presence of paroxysmal activity and urea concentration levels that were equal to or exceeded 24 mg/dl ($\chi^2_{calculated} = 5.19^*$ e $\chi^2_{critical} = 3.84$; p=0.02). Put in other words: patients whose otherwise normal urea concentration values exceeded 24 mg/dl have a higher proportion of EEGs exhibiting paroxysmal activity. It is worth to remind that we excluded from this analysis those cases that presented with focal paroxysmal activity for this fact puts forward the possibility of a localized pathologic process.

It is possible at this point to conjecture that the patients who show urea levels above 24 mg/dl are the ones with brains already in jeopardy, but only eight patients (among twenty-four with urea concentrations equal or above 24 mg/dl) exhibited clinically detectable signs in their neurologic examination. By the other way, sixteen patients (among twenty-six with urea concentrations below 24 mg/dl) were classified as presenting signs of brain involvement. As a matter of fact, the inverse phenomenon has occurred: the lower the urea concentration levels, the more compromised were the patients.

Should there be some relationship among low urea concentrations, brain involvement and paroxysmal activity, we do not know how to explain it, nor have we found any bibliographic reference upon which we could make an appreciation. However, one would expect to find the worst EEG alterations exactly in the group whose clinical examination suggested encephalic involvement, but paradoxically that has not happened.

Our opinion and that of Navia et al. is that metabolic alterations, though small ones, have a bigger impact on the brain of an AIDS patient. In the detailed description of the AIDS dementia complex[4,6], it was noted that systemic complications accelerated it and added to its intensity. We believe that is necessary a more accurate study, where various factors will be taken into account during their matching, as well as a bigger sample, in order to clarify this point.

Paroxysmal activity (theta, sometimes delta, waves bursts, mostly in the temporal regions) and background rhythm slowing are frequently found in acute renal insufficiency. The EEG findings vary much according to the consciousness level and are commonly expressed by spikes, sharp waves or spike wave complexes, and seizures.

The EEG abnormalities may get better with the clinical improvement, however, it is slower, in spite of biological disorders betterment[4,7]. These EEG alterations may correlate with the concentration levels of blood urea, chiefly in chronic renal insufficiency. However, this correlation becomes more unspecific in acute renal insufficiency, where hydroelectrolitic and acid-base equilibria are more sensitive and important correlators[4].

We sampled only two patients with chronic renal insufficiency (undergoing dialytic treatment) and two with acute insufficiency (whose renal compromise was low or moderate) who did not need to dialyse. The remainder showed small elevations of urea and creatinine concentrations due to major diarrhea and ensuing volemic contraction.

The behavioral and EEG alterations (slowing) correlate with the degree of renal insufficiency (evaluated by the creatinine concentration) in chronic patients undergoing conservative treatment, and there is a poorer cognitive performance as the renal insufficiency gets worse[8]. Thus, we reiterate once more that it is probable that renal disorders (most of time hardly separable from hydroelectrolytic disorders), not very expressive in our sample, may contribute in an important way for the genesis of EEG alterations in the AIDS patient. We also believe that there must be a synergistic action between

the HIV actions (direct and indirect) on the CNS and urea concentration levels. We insist then that HIV positive patients must be more sensitive to urea concentration levels, since even those with normal urea values that exceeded 24 mg/dl had a higher proportion of EEGs showing paroxysmal activity.

No EEG criteria studied by us correlated with creatinine concentrations. It is appropriate to say that creatinine alone is not toxic to the CNS, reflecting only a renal functional condition. Differently however, urea and its accompanying substances determines neurologic and EEG alterations. This study has not measured creatinine clearance and thus we could not arrange groups according to it, making correlations with clinical pictures and EEG findings.

The high creatinine concentrations and mostly its clearance lowering reflect the build-up of toxic metabolites, chiefly products derived from protein metabolism, with concurrent elevation in the concentrations of urea, urates, organic and inorganic acids and PTH, this one of prime role in the uremic encephalopathy pathophysiology, inasmuch as it functions as a modulator of cerebral neurotransmission. Worth to say that PTH is the only here cited substance that mimic the EEG pattern of uremia when infused in dogs and that it relates as well to the elevated concentrations of intraneuronal calcium observed in uremic patients[9-11].

Even though calcium is also involved in cell death mechanisms in HIV positive patients, we could not glimpse any relationship between the occurrence of paroxysmal activity and normal urea concentrations above 24 mg/dl [12,13].

All the metabolic alterations observed in the nervous tissue intimacy of HIV infected patients probably justify the already described EEG and neurologic disorders in these patients[14-16]. Summing up to the virus direct effects those indirect ones due to its actions on the organism as a whole (mostly the complications due to immunologic deficit), it would not be surprising to find a higher number of alterations under these circumstances.

The alpha rhythm becomes alterated in a major portion of AIDS patients, earlier or later during the disease's evolution, being more evidently alterated when the patient exhibits signs and symptoms of dementia[17-20]. We have observed that the background rhythm's mean of our study groups varied between 9 Hz and 9.5 Hz, a value under what would be the expected normal mean for the matched age healthy population[15]. It seems that the paroxysmal activities begin to be detected when the nervous system already has some degree of lesion (expressed by the lowering of the background rhythm frequency), getting disproportionately worse by the slightest metabolic alterations, even in patients without clinically detectable encephalic involvement[21]. This is the reason why we assume that diffuse theta or delta wave bursts with a temporal and anterior predominance must be considered clues of a greater gravity of neurologic compromise[22,23], pointing out a abnormal neurophysiologic response to homeostatic variations that usually would not lead to abnormal phenomena.

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