

## Cerebrospinal fluid syndromes in HIV-positive patients with acute consciousness compromise

Síndromes líquóricas em pacientes HIV positivos com  
comprometimento agudo da consciência

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**Abstract** We reviewed the cerebrospinal fluid (CSF) syndromes of 100 consecutive HIV-positive patients presenting acute consciousness compromise in emergency rooms, and correlated them with clinical data. The most frequent CSF syndromes were: absolute protein-cytological dissociation (21), viral (19), neurocryptococcosis (7), relative protein-cytological dissociation (6) and septic (4), moderate hypoglycorrachia (4), severe hypoglycorrachia (4) and hydroelectrolytic disturbance (3). One fifth of the patients had CSF syndromes considered sufficient for diagnosis or an immediate clinical decision. The most common clinical data were infective and neurological. There was little correlation between the clinical data and the CSF syndromes. We conclude that in HIV-positive individuals presenting acute consciousness disturbances there are frequently non-specific results in the CSF analysis that must be weighed against a detailed history and thorough physical examination. Taking this into account, in about one fifth of cases the CSF analysis can offer useful information for treatment.

**Key-words:** Cerebrospinal fluid. Delirium. Somnolence. AIDS. HIV.

**Resumo** Revisamos as síndromes líquóricas de 100 pacientes HIV-positivos apresentando comprometimento agudo da consciência em pronto-socorro, as correlacionando com dados clínicos. As síndromes mais frequentes foram: dissociação proteino-citológica absoluta (21), viral (19), neurocriptococose (7), dissociação proteino-citológica relativa (6) e séptica (4), hipoglicorraquia moderada (4%), hipoglicorraquia severa (4%), distúrbio hidroeletrolítico (3%). Um quinto dos pacientes apresentou síndromes líquóricas consideradas suficientes para um diagnóstico ou uma conduta imediata. Os dados clínicos mais comuns foram infecciosos e neurológicos. Houve pouca correlação entre os dados clínicos e as síndromes líquóricas. Comparado a dados de literatura, HIV-positivos tem menor chance de resultados decisivos no exame de líquido. Nós concluímos que, em pacientes HIV-positivos, que se apresentam com alterações agudas da consciência, frequentemente há resultados inespecíficos no líquido, o que deve ser julgado em função de uma história clínica e exame físicos detalhados.

**Palavras-chaves:** Líquor. Delírium. Sonolência. AIDS. HIV.

HIV-positive patients admitted to emergency rooms commonly present acute alterations of consciousness. Due to their subjacent disease, these patients are susceptible to a wide range of etiological possibilities, such as opportunistic infections and neoplasias, besides the HIV infection proper. A detailed history, including mode of installation, previous diseases, associated

symptoms and drug exposure, is fundamental but not always obtainable. Diagnosis often defies clinicians, being based more on laboratory tests such as neuroradiological methods and a CSF analysis.

There exist some reports about the interaction of HIV and the CSF of asymptomatic and symptomatic patients<sup>3,4,5,6,13</sup>. The study of the CSF

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Commonly, HIV-positive patients present to emergency rooms with acute alterations of consciousness. Due to their subjacent disease, these patients are susceptible to wide range of etiological possibilities, like opportunistic infections and neoplasias, besides the own HIV infection. A detailed history, concerning mode of installation, previous diseases, associated symptoms and drug exposure is fundamental, but not ever obtainable. Frequently, the diagnosis defies clinicians and becomes much based upon laboratorial tests, like neuroradiological methods and a CSF analysis.

There are some reports about the interaction of HIV and the CSF of asymptomatic and

symptomatic patients<sup>3 4 5 6 13</sup>. The study of the CSF of symptomatic patients is much more difficult because is often impossible to differentiate between the alterations induced by the own viruses and by acute and chronic opportunistic infections or neoplasias. The objective of this paper is to comment on six years results of CSF analysis performed to evaluate symptomatic HIV-positive patients, presenting to emergency rooms with acute alterations of consciousness. We do not intend to describe physiopathological interactions between HIV and hosts. Instead, we verify at what extent the CSF analysis has contributed to evaluation of acute consciousness compromise in HIV-positive patients.

## MATERIAL AND METHODS

We reviewed consecutive laboratory file-cards of the cerebrospinal fluid laboratory of the Federal University of São Paulo/Escola Paulista de Medicina. The inclusion criteria were HIV positivity and acute consciousness compromise: because this is a retrospective study, we didn't classify patients in those presenting in acute confusional state, or *delirium*, and those presenting somnolence or coma. It were not included pediatric, surgical or trauma patients. To be sure that HIV-positivity was present, we included only patients already followed in our AIDS ambulatory. We covered the period from January, 1990 to April, 1996, to find one hundred file-cards that met our selection criteria. Among the patients selected, we also randomly reviewed 30 hospital file-cards to check these criteria. The clinical data were the ones written in the laboratory-card (all the CSF punctions are performed by neurology CSF team, after checking the clinical data). All patients were first seen at the neurological or medical emergency rooms of

the same institution. Only the results of the first CSF analysis were included. We divided the abnormal results into two groups: 1) sufficient for a diagnosis (not necessarily being the final or the only one) or a clinical decision; 2) unespecific, in which the CSF showed inespecific alterations of a pathologic process not necessarily present in the central nervous system (CNS). The groups were composed of: 1) **sufficient**: septic, hemorrhage, hydroeletrolitic disturbances, neurocryptococosis, severe hypoglycorrachia (< 25mg%) and neuro-syphilis; 2) **inespecific**: *viral*, absolute and relative protein-cytologic dissociation, compatible with neuro-tuberculosis (but without visible BAAR); moderate hypoglycorrachia (> 25 and < 35mg%), moderate hyperglycorrachia (> 60 and < 100mg%), isolated qualitative alterations of proteins, and isolated xantochromia. The four age groups were 12 to 25, 26 to 45, 46 to 65 and more than 66 year old. The CSF results were correlated to clinical data using Epi-info, version 5.01 b.

## RESULTS

All 100 patients were HIV-positive and had acute alterations of consciousness, confirming our selection criteria. The mean age was 32.8. There were 20 patients between 14 and 25 years old, 68 between 26 and 45 and 12 patients between 46 and 65. There were 82 men and 18 women. The mean time of consciousness compromise and the CSF examination was 3 days. The CSF puncture was lumbar in 76 patients and cisternal in 24. The commonest clinical data were: headache (14%), focal signs (14%), fever (13%), seizures (11%), meningeal signs (8) and vomiting

(6%). The CSF analysis showed abnormal results in 77 patients, as is shown in Table 1. The results considered sufficient summed 20% and the unespecific ones, 57%.

We found little association between clinical data and CSF syndromes. Only two clinical data (headache and presence of associated pathologies) correlated to a CSF data (positivity of CSF reaction to toxoplasmosis-hematoxo) ( $p < 0.05$ ).

The globulin's reactions (Pandy, Nonne and Weichbrodt) were frequently positive: at least one of them was positive in 84% of patients. The positivity

Table 1 - Frequency of the CSF syndromes.

CSF syndromes	Frequency
Absolute PCD	21
<i>Viral</i>	19
Neurocryptococcosis	7
Relative PCD	6
Septic	4
Moderate hypoglycorrachia	4
Severe hypoglycorrachia	4
Hydro-eletrolyte disturbance	3
Isolated QPA	3
Suggestive of neurotuberculosis	2
Neurosyphilis	1
Hemorrhagic	1
Moderate hyperglycorrachia	1
Isolated xantochromia	1

PCD = protein-cytologic dissociation; QPA = qualitative alteration of proteins.

of the Weichbrodt reaction was 45%, of the Pandy reaction was 69% and of the Nonne reaction was 78%. The correlation between these reactions and other CSF results is in Table 2.

There was association between some CSF syndromes and CSF characteristics:

neurocryptococcosis and hypoglycorrachia and CSF opalescence ( $p < 0.01$ ); septic and opalescence ( $p < 0.01$ ); *viral* and positivity of hematoxo ( $p < 0.01$ ). The group of *sufficient CSF syndromes* was associated to *altered aspect of CSF* ( $p < 0.01$ ).

Table 2 - Relation between CSF data and the globulins reactions.

	Pandy	Nonne	Weichbrodt
Lumbar CSF	.	.	ns
Hematoxo +	.	.	.
Pleocytosis	.	ns	.
CSF lymphocytosis	.	ns	.

Hematoxo = CSF antibodies for toxoplasma (IgG and IgM)

.  $p < 0.01$ ; ns = not significant

## DISCUSSION

The acquired immunodeficiency syndrome (AIDS) is caused by, at least, two retrovirus: HIV-1 and HIV-2. The retrovirus are highly neurotropic, being present in the CNS early in the infection. Neurologic manifestations may herald HIV infection and are present in 90% of the patients with advanced disease. The HIV-1 and HIV-2 virus lead to neurological manifestations by two ways: 1) directly, in the central and peripheral nervous system and in muscle; 2) turning the host susceptible to opportunistic infections and neoplasms.

Acute consciousness compromise in a HIV-positive patient has many possible etiologies.

Chronic infections, use of multiple and toxic medications, nutritional deficits, dehydration, etc. make the clinical picture of these patients very complex. The contribution of the CSF analysis in the evaluation of these patients must be considered in the setting of an acute presentation of a chronic patient. It is interesting to note that abnormal CSF specimens are obtained in 60-90% of asymptomatic HIV-infected patients, without opportunistic infections or tumors<sup>13</sup>.

The majority of our patients was young adults and half was less than 30 years old, with a clear predominance of males. This is in agreement with the epidemiological distribution of AIDS at the time

of the study. The predominance of neurological and infectious signs and symptoms reflect our inclusion criteria.

Among the clinical data, only headache and the presence of an associated pathology was correlated to a CSF data, the positivity of hematoxo. We have published a study of 200 CSF analysis indicated to evaluate non HIV-positive patients presenting acute consciousness compromise<sup>1</sup>. With a similar methodology, we found 36.9% of syndromes considered sufficient for a diagnosis or a clinical decision and correlation of CSF syndromes with various clinical data, such as headache, fever, meningeal signs, seizures, vomiting, male sex, the presence of more than 2 clinical data. Besides, Neves, found that the CSF analysis confirmed a clinical hypothesis in 17.2% of cases, in non HIV-positive patients<sup>7</sup>.

Our results in HIV-positive patients are very different, indicating that they may have less specific manifestations. This finding must be taken into account when thinking of performing a CSF analysis in HIV-positive individuals. Waiting for more specific manifestations may delay the diagnosis of treatable diseases, like bacterial or fungal meningitis. On the other hand, we may obtain less definitive diagnosis with the CSF analysis.

The *viral* syndrome was also correlated to positivity of hematoxo. Being the granulomatous form of toxoplasmosis the one predominantly seen in HIV-positive patients, these associations becomes interesting. The presence of associated pathologies indicate an advanced stage of the HIV infection, in which we usually find cases of toxoplasmosis. The correlation between positivity of hematoxo and the *viral* syndrome reflect that, not infrequently, lymphocytic pleocytosis is found in toxoplasmosis. Given the high frequency of antibodies against *Toxoplasma gondii* in asymptomatic HIV-positive patients, this might be interpreted with caution<sup>9</sup>.

The correlation of an altered macroscopic aspect of the CSF and neurocryptococcosis, of septic syndrome and a diagnosis of a syndrome considered sufficient is interesting. However, it is not an useful information for the physician to decide to perform or not an CSF analysis, because it appears only after this decision.

Qualitative alterations of CSF proteins, reflected in the positivity of the Pandy, Nonne and Weichbrodt, are classically described in chronic infections of the CNS, like syphilis, and in inflammatory or demyelinating diseases, like

multiple sclerosis<sup>10</sup>. However, it has been described in HIV-positive patients, since early in the infection. Chalmers, Aprill and Shephard found oligoclonal bands in 6 of 23 HIV-positive, asymptomatic patients<sup>4</sup>. Five of these also had pleocytosis. In our patients, qualitative alterations of proteins was seen in 85% of the patients and, as an isolated abnormality, only in three. We also found correlation with pleocytosis and lymphocytosis (Table 2). These results might be explained by the advanced stage of the disease and concomitance of other infections.

The correlation of the Pandy, Nonne and Weichbrodt reactions with the positivity of hematoxo might be due to the presence of the antibodies against toxoplasma. The correlation between the Pandy and Nonne reactions and the lumbar puncture might depend upon the greater protein concentration in this region.

Almost half of asymptomatic HIV-positive patients may show pleocytosis in the CSF. Much probably, this indicate alterations induced by the own HIV, since no patient had history of other CNS infection. Besides, HIV is demonstrated in the CNS in early phases of the disease, in asymptomatic patients<sup>6</sup>. In this situation, use of AZT may diminish the pleocytosis and the protein alterations, confirming that the alterations were induced by the own viruses<sup>5</sup>. The *viral* syndrome may reflect a non-specific reaction not only to virus, but also to fungi, protozoan, mycobacteria or treponemas. In our casuistic, we believe that the *viral* syndrome may partly be caused by the own HIV infection. However, in AIDS patients, the *viral* syndrome may reflect a variety of infections commonly found in HIV-positive patients, mainly toxoplasmosis, as is shown in the correlation of the *viral* syndrome and the positivity of Hematoxo.

Acute alterations of consciousness indicate acute insults to CNS. These insults may result in a breakdown of the blood-brain-barrier (BBB), cerebral edema and extravasation of seric proteins in the CNS<sup>8</sup>. The predominance of the protein-cytologic dissociation syndromes, absolute and relative, reflect the situation we studied, indicating an expected breakdown of the BBB.

Neurocryptococcosis (NCC) was relatively uncommon. We included only the first CSF of our patients; so, those that had a previous diagnosis of NCC in our laboratory were excluded from this series. The correlation to hypoglicorrachia shows consumption of glucose by the criptococcus, indicating an active state of the infection. In a

series, 4 of 7 patients with neurocryptococcosis had alterations of consciousness<sup>3</sup>. Our results suggest that neurocryptococcosis may run a more aggressive course, agreeing with Sanchez-Portocarrero<sup>11</sup>.

The finding of 4% of acute meningitis, reminds us that HIV-positive patients are also susceptible to usual bacterial infections of the CNS. One case of subarachnoid hemorrhage shows that, naturally, it also happens in HIV-positive individuals. Moderate and severe hypoglycorrachia, like electrolytic disturbances, as isolate findings, must reflect the state of general consumption and dehydration frequently found in these patients. Moderate hyperglycorrachia, found in one case, may reflect hyperglycemia. Isolated xanthochromia, with no erythrocytes nor hyperproteinorrachia, present in one case, may reflect seric elevation of bilirubins.

Alterations of consciousness are common in patients with tuberculous meningo-encephalitis (TME), regardless of HIV-positivity<sup>2</sup>. It was found a relatively low frequency of this diagnosis probably because of the usually sub-acute or chronic rather than acute presentation of TME. Similarly, acute consciousness disturbances are not usually found in neurosyphilis (NS). Except for acute syphilitic meningitis, all other forms of NS tend to follow a chronic course. The clinical presentation of NS seems not to change in HIV-

positive patients<sup>12</sup>. VDRL has a variable sensitivity, between 10 and 89%<sup>14</sup>. In our laboratory, the Wasserman and indirect hemagglutination reactions are also performed in all CSF specimens. The relative rarity of this diagnosis was not a surprise, since we included only cases with acute presentation.

The majority of our CSF analysis in HIV-positive patients presenting acute consciousness disturbances resulted abnormal. But, while four patients (4/5) of the patients had an abnormal CSF, only 1/5 had a result that we judged sufficient for a diagnosis or a clinical decision. There was little correlation between CSF syndromes and clinical data. The CSF alterations may reflect CNS insults by the own HIV, opportunist infections and neoplastic and systemic disturbances.

Compared to non HIV-positive patients, HIV-positive may show less specific clinical manifestations and a lower proportion of CSF syndromes considered sufficient for a diagnosis or a clinical decision. However, waiting for more specific clinical manifestations may delay the diagnosis of treatable diseases, such as bacterial or fungal meningitis. We suggest that a CSF analysis, besides being obviously indicated in the suspicion of meningitis, also be considered if, after an initial clinical and laboratorial evaluation, there is no evident explanation for acute consciousness compromise in HIV-positive patients.

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