

IMMUNOLOGIC PARAMETERS OF CEREBROSPINAL FLUID IN HTLV-I ASSOCIATED MYELOPATHY (Abstract)*. Thesis. Göttingen, 1994.

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Objectives: - 1. To report the importance of the cerebrospinal fluid (CSF) analysis for the diagnosis of HTLV-I associated myelopathy / tropical spastic paraparesis (HAM/TSP) and to correlate the neurological manifestations of HAM/TSP with these findings. - 2. To analyse the intrathecal synthesis of specific antibodies (measles, rubella, HSV, VZV, HTLV-I) in patients with HAM/TSP. - 3. To examine whether a soluble tumor necrosis factor receptor (sTNF-R) can be detected in CSF and if it is elevated in patients with HAM/TSP. The findings were correlated to clinical status, cell count, blood-CSF barrier function and intrathecal HTLV-I antibodies synthesis. - 4. To study on the detection and characterization of the HTLV-I proviruses.

Patients: Paired CSF and serum samples were collected from 18 patients with HAM/TSP (WHO criteria, 1989) and from 16 HTLV-I seronegative patients with other neurological diseases: six cases with spinal form of multiple sclerosis (MS), three with other myelopathies of unknown etiology, and seven cases with idiopathic epilepsy. These patients were seen at the Neurologic Clinic of the Federal University of Rio de Janeiro, Brazil.

Methods: Antibodies to HTLV-I were detected by ELISA (du Pont) and confirmed by radioimmunoprecipitation (RIPA). Albumin and immunoglobulins in serum and CSF were determined by nephelometry in all patients. In addition, isoelectric focusing was performed. Levels of antibodies against measles, rubella, HSV, VZV and HTLV-I in serum and CSF were evaluated by ELISA (Behring, Marburg) according to Reiber and Lange (1991). The soluble form of the TNF-R (60 KDa) was measured in serum and CSF using a commercial enzyme immunoassay kit (Bender, Vienna). The characterization of the HTLV-I proviruses was determined by polymerase chain reaction (PCR) using different sets of primers and by sequencing some portions of few isolates of these patients. This work was done in Pasteur Institut, Paris, under the guidance of Dr A. Gessain.

Results: Frequent CSF findings were intrathecal immunoglobulin synthesis (IgG 5/18; IgA 2/18; IgM 1/18) and restricted oligoclonal bands in CSF (all patients). An increased antibody-index (intrathecal specific antibody responses) was detected in some of the 17 HAM/TSP patients: HTLV-I (14/17), HSV (0/17), measles and rubella (1/17), and VZV (1/17). In total only 1/17 cases showed a polyspecific pattern against viruses. In MS, specific antibodies against measles and rubella and/or VZV, HSV were detected in all patients (6/6) but not in the control with idiopathic epilepsy (0/6) or with myelopathy of unknown etiology (0/2). Higher levels of sTNF-R were found in CSF of patients with HAM/TSP and MS than in non-inflammatory CNS diseases. Interestingly high levels of intrathecal sTNF-R were also detected in the patients with non-inflammatory diseases.

Conclusion: According to our findings there is evidence for a chronic inflammatory disease of the CNS in all HAM/TSP patients tested. Our data suggest that, although CSF analysis is important for the diagnosis of HAM/TSP no association could be shown between the progression of disease and CSF findings.

A polyspecific antibody synthesis against neurotropic viruses has been observed in several chronic diseases including MS. It is considered a sensible parameter of inflammation. In this study, it was observed that the most of HAM/TSP patients had a monospecific immune response in contrast to that observed in MS patients.

We found sTNF-R intrathecal synthesis in all of our patients. Our data suggest that sTNF-R could be produced by the central nervous system (CNS) cells and implies a physiological function in the homeostasis of the CNS protein content, which can be raised in CNS inflammatory disease. The concentration of this receptor in CSF suggested a CNS synthesis above 99%. The high values of sTNF-R found in patients with MS and HAM/TSP show that this soluble receptor could be a new parameter of inflammation and a sensible indicator of activity.

KEY WORDS: HTLV-I, HTLV-I associated myelopathy/ tropical spastic paraparesis, multiple sclerosis, cerebrospinal fluid, soluble tumor necrosis factor receptor.

*Immunologische Liquorparameter bei HTLV-I assoziierte Myelopathie (Zusammenfassung) [Parâmetros imunológicos do líquido cefalorraquidiano na mielopatia associada ao HTLV-I (Resumo)]. Dissertação inaugural para o Grau de Doutor, Georg August- Universität zu Göttingen, Deutschland (Abteilung Neurologie im Zentrum Neurologische Medizin des Fachbereichs Medizin der Universität Göttingen). Orientadores: K. Felgenhauer, P. Rieckmann.

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