Cerebrospinal fluid (CSF) analyses in HIV-1 primary neurological disease

Nogales-Gaete J. */, Syndulko K.**, Tourtellotte W.W.****

* *Unidad de Neurologia, Depto de Medicina Division Occidente, Facultad Medicina Universidad de Chile, Santiago de Chile*

** *Department of Neurology, UCLA School of Medicine, Neurology Service, W 127A VAMC Wasworth, Los Angeles, CA 90073, USA*

This paper will focus on CSF findings in HIV-1 Neurological Disease (ND). Why use CSF as exploration window of the HIV-CNS involvement? Traditionally, CSF analysis has been an effective diagnostic method as well as a means of monitoring treatment in several infectious and immune pathologies of the CNS. Consequently there is an abundance of mature background information [113, 145, 147] particularly in terms of detecting infectious agents, using IgG findings as immunological indexes, and utilizing CSF findings to map the evolution of ND. We will explore the papers that utilize CSF variables as dependent measures to explore the effects of HIV disease, particularly HIV ND, cited in Index Medicus and MEDLINE data base, and published in Spanish, Italian and English, betwen 1985 to 1991. We will restrict out review to those studies that exclude HIV cases with CNS opportunistic infections or neoplasms, and thus focus on what the CSF can tell us about the primary effects of HIV on the brain as defined above. The primary long-term goal is to find some elements of the CSF that would lead to an understanding of the etiopathogenesis of HIV ND. However, an almost equally important aim is to determine which CSF variables may be clinically predictive of HIV ND occurrence and progression. The latter variables can also be expected to provide the best measures of HIV ND treatment efficacy. This is particularly important since it is our contention that treatment of HIV ND will eventually be initiated and monitored on the basis of laboratory markers of HIV ND, most likely from the CSF.

Finally, this summarized information would be useful in drafting a CSF profile in order to have a reference pattern for cases with complications. The data of this review will be broken down, when the information permits, according to clinical stage and presence or absence of clinical manifestations of ND.

Key Words: Cerebrospinal fluid — HIV-1 infection — neuroimmunology — immunoglobulins — viral diseases

This investigation was supported by the Fogarty International Center, National Institutes of Health, Fogarty International AIDS Research Program at UCLA, TW-00003.

Received 9 April 1992 - Accepted 30 May 1992

Introduction

There is general agreement that central nervous system (CNS) involvement in HIV-1 infection is frequent in the course of HIV disease, but the estimation of exactly how often it occurs varies depending on two considerations:
A) Which of two types of involvement are considered: (1) primary or related to direct effects of HIV-1 on cells in the nervous system; or the indirect damage to CNS cells by toxic by-products of the immune system's response to HIV-1; (2) secondary, the result of CNS opportunistic infections or tumors that are related to the progressive immune system deterioration characteristic of HIV disease. In some patients or in some stages of HIV-1 disease, both types of involvement may be present. B) The evaluation methodology used to determine this involvement. There are a variety of laboratory and clinical procedures to measure or indicate whether, where and why HIV-1 affects the nervous system. Each method provides a proverbial window onto CNS changes related to HIV-1, and each has intrinsic advantages or limitations. The most commonly considered methodologies include: 1. — Neurological evaluations to detect and classify clinical changes seen in HIV disease, and perhaps to help localize the site of CNS damage [7, 43, 83, 93, 101]; 2. — Neuropsychological and neuroperformance testing to quantify with maximum sensitivity the type and severity of neurobehavioral changes [52, 77, 138, 151-153]; 3. — Direct spatial imaging of brain structures in situ, and their neurochemical and neurometabolic changes [6, 27, 30, 76, 84, 97, 104, 123]; 4. — Neurophysiological evaluations using conventional clinical electroencephalography, event-related potentials, or computerized scalp mapping techniques [8, 28, 106, 107, 139, 142]; 5. — Pathological studies of tissues by biopsy or necropsy [13, 14, 53, 63, 103, 111, 155]; and 6. — Laboratory studies of blood and cerebrospinal fluid. The various methodologies provide complementary views of CNS function and damage, but the vastly different time scales and levels of analyses provided (behavioural to molecular biological) can make discerning relationships among the measurement domains difficult at best.

General CSF profile in HIV

Although CSF studies are diverse and may be quite sophisticated, there is a standard minimal protocol that is followed. This includes blood cell count, and protein and glucose levels.

Cells
The frequency of alteration found in the white blood cell count (WBC) in the CSF from HIV-1 infected patients in non-AIDS stages is high [149]. The frequency of alteration of CSF WBC when the value of abnormality is >5 cells is between 15-100% (see Table I).
Pleocytosis in CSF in present in HIV-1 very early in the subacute aseptic meningitis as part of seroconversion [67]. Leukocytes are increased in about 18-32% of asymptomatic seropositive patients [20, 91, 94, 149]; but, with the progression of the disease the cellularity of the CSF declines [91, 149]. Subsequently, in AIDS, the CSF WBC has often been found to be normal [31, 85], even in cases with cryptococcal meningitis [129].
When HIV patients are grouped with or without clinical neurological abnormalities, there is no correlation with the neurological status and the CSF-WBC [149]. The CSF-WBC is found normal or low in patients with ADC [46, 73, 95].
The proportion of CD4-CD8 cell subtypes in CSF of HIV infected patients is highly correlated with that of peripheral blood [88, 95]. When the monocyte cell subtypes are analyzed in the CSF, T helper/inducer (CD4) ratio is reduced and T suppressor/cytotoxic ratio is increased [95].
There is a progressive decrease in CD4 lymphocytes in CSF and peripheral blood when HIV seropositive groups, a) with no symptoms, and with non-specific neuropsychological abnormalities, and b) with dementia, are compared [95].

Total Protein
CSF total protein mean level was found elevated in HIV patient groups at all stages of the infection in comparisons with controls [31]. In most of the HIV infected patients (12/14, 86%) with AIDS and neurological symptoms, total protein level is elevated >45 mg/dl [82]. In HIV seropositive patients without AIDS, the total protein level is also found elevated (>60 mg/dl) but only in 8-11.4% of the patients [5, 20].
Slightly elevated total protein levels were found in the CSF from HIV infected patients with ADC [73] and neurological complications such as cryptococcal meningitis, CNS lymphomas and CNS toxoplasmosis [73].

Albumin
CSF albumin levels in HIV-1 patients do not differ from controls [31].
The CSF/serum albumin ratio index of the integrity of the brain blood barrier (BBB) of HIV patients as a group also does not differ from controls. When, however, HIV patients are further divided into subgroups, the ratio is slightly ele-

TABLE I. *Abnormalities in the white cell count of CSF.*

Author	P. in general	Patients (P) grouped by clinical stage of the infection						P. grouped by neurological status CNM*c	
		ASP *a	ARC *a	AIDS *a	WR1-2 *b	WR3-5 *b	WR6 *b	(+)	(−)
Appleman (5)	36/114 31.6%								
Bukasa (15)	8/15 53.3%	1/2 50%		7/13 53.8%					
Chiodi (24)	7/22 31.8%	2/9 22.2%	5/13*d 38.5%						
Goudsmit (51)	10/10 100%	10/10 100%							
Lloyd (85)	5/33*e 15.2%	0/8 0%	5/14 35.7%	0/11 0%					
Luer (86)	5/14 37.5%	5/14 35.7%							
Margolick (88)	14/60 23.3%	4/12 33.3%						10/48 20.8%	4/12 33.3%
Marshall (91)	194/611 31.7%				169/513 32.9%	24/81 29.6%	1/17 5.8%		
Ortona (105)	0/15 0%			0/15 0%					
Tourtellotte (149)	23/143 16.1%	12/57 21.0%	10/56 17.8%	1/7 14.3%				12/56 21.4%	9/61 14.7
Tourtellotte (149)		XXXX						9/47*f 19.1%	2/11*f 18.2%
Tourtellotte (149)			XXXX					9/38*f 23.6%	0/14*f 0%
Summary	302/1037 29%	34/112 30%	15/70 21%	8/46 17%	169/513 33%	24/81 30%	1/17 6%	40/189 21%	15/98 15%

Abnormality criterion >de 5 cells/ml.
x/y = x = Number of samples with abnormalities, y = Total number of patients
*a = CDC's criterion (REF)
*b = Walter Reed Center's criterion (REF)
*c = Clinical Neurological Manifestations
*d = ARC and AIDS (not included in the summary)
*e = The author's criterion of abnormality is different, but it is possible to use the data
*f = The neurological condition is related only with the marked (XXXX) clinical stage.

vated in HIV patients with neurological problems such as ADC, ocular motility disorder and polyneuropathy, in comparison to asymptomatic HIV patients or controls [31].

As an additional and more proven approach to measuring the integrity of the BBB by the albumin in CSF, our group uses a formula to quantify trans-BBB albumin leakage rate in mg/day that is incorporated in the Tourtellote's I-BBB IgG synthesis rate formula [144, 150].

The normal range for trans-BBB albumin leakage is less than 75 mg/day.

Abnormal findings of this parameter were shown in 25% of HIV positive asymptomatic patients and 44% of the AIDS group, the difference between the groups is not statistically significant. Similarly, when a population of HIV positive patients with and without signs and symptoms of ND was tested, the differences in the trans-BBB albumin leakage abnormalities were not statistically significant [149].

Glucose

Glucose levels in the CSF of HIV infected patients are usually within normal limits [62, 73, 82, 105].

Although the glucose mean value remains within the normal range, there is a trend for a decline between WR1 and WR6 stages (Walter Reed Classification [118], independently of the serum glucose [91].

HIV detection

Viral detection is undoubtedly one of the areas in which considerable advances have been achieved. In the search for more sensitive and specific diagnostic procedures, methods such as virus isolation, antibody detection and antigen detection have been improved. Recently, extra sensitive methods of nucleic acid detection have been developed (for review see [56]).

The isolation methods have been valuable because they have permitted definition of the HIV disease as a specific entity. However, there are several problems inherent in this complex technique. In addition, the technique is time critical from time of fluid withdrawal, has a high cost and a low yield, all of which have reduced or limited its use.

Antibody detection has represented a great advance not only because it has a higher sensitivity, but also because it can be automated, resulting in less risk for the operators, greater speed and lower cost. However, it also has some limitations. It measures the host's response to the virus, but not actual viral activity. There are two blind periods at the beginning as well as at the end of the infection when antibody detection is of little use. At onset of HIV infection there is an inherent delay for antigenic stimulation. In the last stages of HIV infection, there is little or no antigenic stimulus because the immune system is effectively destroyed.

The detection of antigens has constituted another advance. This technique has the advantages of being an indicator of direct viral activity, has higher sensitivity, and less delay than virus isolation. Antigen present before than antibody can be detected after seroconversion. Quantitative measurement of antigen may be an effective monitor of antiviral treatment. Its biggest limitation is relatively low sensitivity.

The polymerase chain reaction (PCR) is a new technique that permits measurement of RNA or DNA directly [108]. PCR has been proposed as

TABLE II. *VIH-1 isolation from CSF.*

Author	P. in general	Patients (P) grouped by clinical stage of infection			P. grouped by neurological status CNM	
		ASP	ARC	AIDS	(+)	(−)
Chiodi (24)	11/25 44%	3/9 33.3%	3/9 33.3%	5/7 71.4%	9/18 50%	4/11 36.4%
Chiodi (21)	25/63 39.7%	10/22 45.5%	10/27*a 37%		*b 48%	*b 32%
Ho (67)	23/37 62.2%		23/37*a 62.2%		23/25 92.0%	0/12 0%
Hollander (68)	30/48 62.5%	11/16*c 68.7%		19/32 59.4%	7/10 70%	17/27 62.9%
Levy (82)	13/14 92.8%					
Resnick (120)	8/48 16.6%					
Resnick (120)	*d	3/8 37.5%	1/7 14.3%	1/8 12.5%		XXX
Resnick (120)	*d		3/13 23.0%	0/12 0%	XXX	
Sonnerborg (135)	44/71 62%	4/11 36.4%	19/28 67.9%	12/19 63.2%	15/23 65.2%	29/48 60.4%
Sonnerborg (133)	35/67 52.2	3/12 25%	24/38 63.1%	8/17 47%		
Tourtellotte (149)	20/109 18.3%	4/55 7.2%	14/47 29.8%	2/7 28.6%	9-46 19.6%	9/57 15.8%
Summary	209/482 43%	27/117 23%	64/142 45%	47/102 46%	66/147 45%	61/170 36%

x/y = x = Number of CSF samples with VIH-1 isolation y = Total number of patients
*a = ARC and AIDS
*b = The authors mentioned only the percentage
*c = ASP and ARC
*d = The information is related only with the marked (XXX) neurological status.

potentially the most sensitive and specific method, not only to detect the presence of the virus, but also to provide quantitative data of HIV and other viral load [116].

Virus demonstration by direct means

— Isolation

There is agreement that HIV-1 isolation from CSF is possible in all the clinical stages of infection [21, 22, 24, 25, 68, 120, 135, 149], but there is some controversy regarding which stage of infection shows the highest rate of recovery (see Table II). Some have found a lower frequency in asymptomatic and immunologically normal HIV patients [133]. Others found a higher frequency of HIV-1 recovery in the non-AIDS groups, and a lower one when AIDS is present [120]. However, others have reported no correlation between frequency of HIV isolation and clinical stages of infection (using Walter Reed [118] and CDC [19] classifications) [21, 25, 135, 149]. One explanation for this difference may be the difference in classification of patients with and without neurological involvement. Some authors do not include the patients with AIDS Dementia Complex (ADC) who have no other systemic manifestations in the AIDS group [149] in contrast to the formal CDC criteria [19].

There is no correlation between frequency of HIV-1 isolation and clinical neurological status [21, 62, 120, 135, 149] or including comparisons of severity of ADC [25].

There is no correlation between frequency of HIV-1 isolation and duration of the infection [135]. It is possible to isolate HIV-1 from the CSF at seroconversion [21], and in the aseptic meningitis associated with the HIV seroconversion [67].

The possibility of finding free viruses vs viruses in the cells seems to increase with the progression of the disease. In the earlier stages of infection free viruses are, in general infrequently present in CSF and could be isolated from cells. In the later stages of infection free viruses can readily be isolated in the CSF [135].

There appears to be a significant correlation between the duration of the lag between the lumbar puncture to culture and the rate of virus recovery. Highest recovery occurs within five hour lumbar puncture [135]. Most of the studies have not reported this time lag.

HIV recovery has been reported from CSF and absent from plasma in a patient with existing matched samples. However, this finding is rare [68]. Usually when a culture is positive for HIV in CSF, the blood sample is also positive [133].

— HIV-1 Antigen (Ag) detection

Ag is a molecule that can be recognized by an antibody; the HIV molecules as gag: p17, p24, p55, pol: p31, p55, p66; and env: gp41, gp120, gp160 have antigenic characteristic.

HIV-1 p24 Ag is a gag core Ag, at present the meaning of finding p24 Ag in serum of HIV-positive patients is considered mainly a marker of active viral replication and systemic disease progression [2, 78, 87]. HIV-1 p24 Ag can be mainly detected in CSF in the most advanced stages of HIV-1 infection [17, 25, 131, 149] (also see Table III).

Detection of HIV-1 p24 Ag seems to be correlated with neurological status [149]. HIV-Ag was rarely found in CSF of HIV-1 infected individuals who were neurologically normal [35, 114] and it seems to be associated with the most severe stages of ADC [25, 149]. Persistence of HIV Ag in CSF is strongly correlated with progressive encephalopathy [50]. However, since the presence of p24 Ag is only occasionally detectable before neurological deterioration, p24 Ag is not a useful predictive marker of CNS involvement [114].

There is no strict correlation between CSF and serum levels of p24 Ag [17]. When matched samples of serum and CSF from the same HIV infected patients are studied, it is possible to find HIV-1 Ag only in the serum, only in the CSF, or in both samples at the same time [105].

The decrease of HIV-1 p24 Ag levels in CSF by antiviral treatment is not necessarily associated with clinical neurological improvement [26].

— Viral Nucleid Acid detection

It is possible to study HIV proviral sequences in nucleated cells from the CSF of HIV seropositive patients by PCR. In a study that included asymptomatic, ARC and AIDS patients, there was a correlation between neurological clinical abnormalities and detection of provirus. There was no correlation between general clinical stages and detection of provirus [128].

Virus demonstration by indirect means

IgG Immunoglobulins.

Evidence from our group [143-145] suggests that the CNS-CSF compartment, surrounded by its blood-brain-barrier (BBB) to protein, can perform as an immunological unit and can synthesize IgG independently of the systemic immune system. Accordingly, the intra-BBB IgG synthesis can be considered the expression of a local CNS immunological abnormality.

High levels of IgG in CSF from HIV-1 infected patients (in general >6 mg) have been reported by various authors [5, 24, 31, 90, 91, 128].

The CSF levels of IgG tend to increase according to the time of infection [90, 154]. This observation seems to be particularly valid in the earliest and middle stages of the illness, because in the

TABLE III. *HIV p24 antigen detection from CSF.*

Author	P. in general	Patients (P) grouped by clinical stage of infection						P. grouped by neurologic. status CNM	
		ASP	ARC	AIDS	WR1-2	WR3-5	WR6	(+)	(−)
Epstein (35)	8/27 29.6%	1/2 50%	1/15 6.7%	6/10 60%				8/20 40.0%	0/7 0%
Gallo (44)	3/22 13.6%				0/7 0	1/4 25%	3/11 27.2%	4/11 36.4%	0/12 0%
Ortona (105)	6/14 42.9%			6/14 42.9%					
Portegies (114)	20/85*a 23.5%			20/85 23.5%			12/24 50%	8/61 13.1%	
Tourtellotte (149)	33/120 27.5%	11/56 19.6%	19/56 33.9%	3/8 37.5%				22/52 42.3%	11/58 19.0%
Summary	70/268 26%	15/58 22%	20/71 28%	35/117 30%	0/7 0	1/4 25%	3/11 27%	46/107 43%	19/138 14%

x/y = x = Number of samples with Ag p24 (+), y = Total number of Patients
*a: Data related only to the adult population.

later stages, the levels of IgG return to starting values [33, 91, 149]. This final change with decreasing levels of IgG does not mean a return to normality, but rather a severe compromise of the immune system.

It is important to mention that only one part of the synthesized IgG is actually anti HIV-specific and the remainder is not accounted for [91, 120]. As all or almost all the patients with Ab against HIV-1 in their serum have Ab in CSF [24, 70], it is crucial to determine the origin of the increased CSF IgG. There are various methods of determining whether the detected IgG is of intrathecal origin, such as: A) Synthesis rate by Tourtellotte formula [143, 144, 150], B) IgG index of Tibbling [141], C) IgG index of Lefvert [81], D) Synthesis rate by Reiber and Felgenhauer formula [36, 38, 119], E) Values by Schuller & Sagar formula [125] and F) Oligoclonal bands [146].

In general, the criteria used to demonstrate intra-BBB IgG synthesis establish some absolute or proportional relationship to establish that a higher level or a particular type of antibodies in CSF is of intrathecal origin and differs from the one found in the autologous serum. The validity of these methods in defining intra-BBB IgG synthesis was established in studies of multiple sclerosis [81, 143, 145], and there is no reason to expect dissimilar behavior in HIV infection.

It is important to point out that intra-BBB IgG synthesis is not pathognomonic of any disease or disorder and can occur even in normal individuals [149].

The following methods have been used to detect the presence of antibodies against HIV-Ag: fixed-cell immunofluorescence assay, ELISA, immunoblots, immunoprecipitation and immunofixation.

The first evidence of intra-BBB IgG synthesis in patients with HIV infection was reported in ARC and AIDS clinical stages [121] and later in all the clinical stages including asymptomatic patients [35, 51, 120].

The appearance of antibodies in CSF that occurs right from the earliest stages of the infection [31, 120] can precede the appearance of specific antibodies in the blood [122].

The occurrence of intra-BBB IgG synthesis in HIV infected patients is generally high, however, the actual percentage varies depending on the technique and the criteria used as follows:

A. — IgG synthesis rate according to Tourtellotte formula.

Increased rates (>3.3 mg/day) were found in 22 to 93% of the patients at all the HIV infection clinical stages [4, 5, 9, 62, 90, 120, 130]. The frequency of intra-BBB IgG synthesis found in non-AIDS seropositives HIV-1 patients (88%) was significantly higher ($p<.009$) than in the AIDS group (55%). Further, when patients were grouped only according to the presence or absence of neurological manifestations, no significant difference was found in the rates of IgG synthesis [120]. In comparing the means of theses rates, however, our group reported a significantly higher ($p<.01$) mean of IgG synthesis rate in HIV infected individuals with neurological dysfunction [148].

B. — The IgG Index, according to Tibbling, is considered abnormal over 0.7. It is found elevated in 35-80% of patients [4, 15, 18, 23, 31, 46,

58, 62, 90, 91, 134] including all stages of the infection [23] and in patients with or without neurological compromise [18, 44, 46], although in one report the highest antibody index has been observed in the most advanced stages of ADC [134]. A study that included HIV infected patients in various stages of infection shows a strong relationship between the recovery of HIV-1 from CSF and intra-BBB IgG synthesis, stressing the importance of a persistent HIV-1 antigenic stimulation in the genesis of the intra-BBB IgG synthesis [134].

C. — IgG Index, according to Lefvert, was found abnormal (>3) in 29/41 (71%) in a group of patients that included all stages of the infection. There was a progressive tendency of the index to increase with the progression of the infection, but a decrease in the AIDS stage. In a comparison of patients grouped as AIDS or non-AIDS, no significant difference was found [85].

D. — IgG synthesis rate according to Reibner formula and Felgenhauer formula and diagram. A study that included Reibner formula did not find significant differences from the data obtained according to the Tourtellotte formula in the same study [9]. Felgenhauer diagram method has been proposed for use in HIV infected patients [37, 156]. By this method intra-BBB IgG synthesis was detected in 47-84% of HIV infected patients in various stages of the disease [1, 34, 86]. Only one of these studies shows a difference in the frequency of intra-BBB IgG synthesis related to the stage of the infection, with increased frequency in AIDS [86].

E. — IgG intra-BBB IgG synthesis according to Schuller formula.
In a study that included patients in diverse stages of the disease the values were found raised to 33/37 (89%) [117].

F. — Unique oligoclonal IgG bands are defined as an intra-BBB IgG synthesis indicator when they are found exclusively or more intensely in the CSF compared to autologous serum. They are detected by agarose isoelectric focusing electrophoresis [44, 120], IgG specific immunofixation and silver nitrate staining [72, 120, 121, 149] and affinity-mediated immunoblot (AMI) [29, 72]. The percentages of detection of oligoclonal bands vary according to the techniques used [15].
When reviewing this indicator of intra-BBB IgG synthesis, it is important to consider two elements: 1) in HIV infection the synthesis of IgG antibodies is fundamentally polyclonal [15, 23, 121], 2) not all the oligoclonal immunoglobulins are necessarily specific anti-HIV antibodies [15, 23, 44, 60, 121]. Oligoclonal bands have been reported at several stages of HIV infection [4, 5, 15, 18, 23, 29, 45, 46, 51, 58, 62, 72, 85, 120, 132]. There do not appear to be differences in their presentation in the various stages of the illness [44, 85, 148]. However, a higher incidence of oligoclonal bands has been reported in asymptomatic and ARC stages than in AIDS [149]. Oligoclonal bands have been reported in patients both with and without neurological symptoms [18, 46, 58, 94, 120, 134].

Non-IgG immunoglobulins
The intra-BBB synthesis of other immunoglobulins was reported in two studies. Intra-BBB synthesis of IgA, was found in 42% of 37 patients at different stages of HIV infection, but this IgA was not HIV-1 specific. In the same series of patients intra-BBB synthesis of IgM was found in 37% [117]. Another study that included 59 patients in all the stages of the infection found neither IgA nor IgM intra-BBB synthesis. However, they comment that they have data on existing IgG and IgM intra-BBB synthesis in HIV patients with opportunistics infections of the CNS [86].

Pathogenesis of the CNS involvement by HIV and its markers

There are several hypotheses of the pathogenesis of CNS dysfunction caused by HIV (for review see [13, 14, 43, 49, 66, 71, 116, 159]). In this section we summarize some of these hypotheses and give a general picture of the CSF findings associated with them. Additionally, although no study has confirmed a formal and definitive marker for HIV-1 ND, we comment here on "CSF markers".

A. — The hypotheses
1. — The CNS dysfunction is part of the general immunological dysfunction [115]. Accordingly, the laboratory markers for general immunological dysfunction, would also be important in terms of monitoring for HIV-1 ND. The following markers are found in serum: decreased in T4 cell count, elevated levels of Ag-p24, loss or decrease of anti-viral antibodies and a higher recovery of HIV. In CSF elevated levels of Ag-p24, loss or decrease of anti-viral antibodies and a higher recovery of HIV, are also markers.
2. — The CNS dysfunction is associated with the activation of T cells, macrophages and B-cells [3]. This is an extension of the first hypothesis since laboratory markers for this activation are also considered markers of systemic progression of the disease. Elevated levels of B2M, neopterin, sIL-

2R and other lymphokines could support this hypothesis.
3. — HIV-1, either via one of its viral proteins or via the induction of cellular products produced as part of the immune response, alters neurohormone and/or neurotransmitter synthesis, uptake, release and/or metabolism in a specific CNS pathway, resulting in the unique constellation of signs and symptoms of ADC.
Related hypotheses postulate that the gp120 part of the viral envelope may compete with a putative neurotransmitter, a vasoactive intestinal peptide, which has a sequence structurally homologous [109]: or gp120 may interfere with the uptake of trophic factor as neuroleukin [61]. There is evidence of several neurochemical abnormalities in HIV-positive patients, such as decreased choline acetyltransferase [100], abnormal concentrations of 5HIAA, a serotonin metabolite [11], HVA, a dopamine metabolite [11], kynurenine, a tryptophan metabolite [42, 158] and cortisol [149]. We want to point out another related hypothesis concordant with the last findings. A defect in tryptophan (Trp) metabolism in AIDS has been reported with significantly decreased levels of Trp and elevated levels of kynurenine, a product of Trp degradatation [158]. It has been demonstrated that gamma interferon (GINF), a product of activated T cells and macrophages, induces degradation of Trp via the kynurenine pathway [16, 158]. One metabolic product of this pathway is quinolinic acid (QUIN), an endogenous excitatory neurotoxin [39, 137], found in small amounts in brain/CSF of normals [99, 161], and which has been reported to be elevated in CSF of HIV-1 seropositives and to correlate with deterioration in some neuropsychologic test [64, 92]. QUIN has an affinity for the N-methyl-D-aspartate (NMDA) [40] receptor found in high concentrations in the basal ganglia [98] and has been used to create an experimental animal model of Huntington Disease (HD) [40, 126]. HD is a subcortical dementia associated with motor disorders and psychiatric symptoms that has been found psychometrically to share many of the characteristics of ADC [12]. The appearance of neopterin has also been associated with GINF induced Trp degradation in cell culture [157]. Our group hypothesizes that HIV-1 activates brain macrophages to produce GINF, which induces an increase in Trp degradation via the kynurenine pathways to QUIN, and concurrent decrease in metabolic conversion to serotonin and 5HIAA. This hypothesis could account for some behavioral changes in HIV-1, and explains elevated CSF neopterin and QUIN. QUIN affixes to the NMDA receptor in basal ganglia causing neuronal dysfunction, death and/or gliosis, and resulting in lower levels of Dopamine (DA), and HVA, motor slowing, movement disorders, and other features of "subcortical dementia".
4. — The CNS dysfunction is precipitated by infectious cofactors. For example, CMV and HIV-1 can co-infect brain cells [102], and a percentage of the total intra-BBB IgG synthesis in AIDS is specific for CMV, HZV and HSV [86].

B. — Substances studied in CSF of HIV seropositive patients as potential indexes of the local CNS immunological status.

1. — Cytokines. They are in general substances produced by activated lymphocytes and macrophages that show a broad spectrum of regulatory effects on immunological, hematopoietic, and inflammatory processes.
— Interleukin-2 (IL-2). — This is a T-cell derived factor. It was not detected in CSF of HIV seropositive patients [46, 47].
— Soluble interleukin-2 receptor (sIL-2R). — The elevation of sIL-2R in CSF can be an indicator of T-cell activation in the CNS [74]. There is no agreement in the findings of sIL-2R levels in CSF. They were detected at very high levels in CSF form patients with AIDS [127], in HIV infection with neurological complications [46], and in opportunistic infection of the CNS [46, 47]. CSF levels of sIL-2R were found to be similar or marginally lower in HIV seropositive patients than in individuals with non-HIV associated neurological diseases [54]. CSF levels of sIL-2R were elevated compared to asymptomatic patients only during the earliest acute stage of infection associated with meningitis and inflammatory demyelinating polyneuropathy [54].
— Interleukin-1β (IL-1β). — This cytokine's role in the CSF is not well known yet. It was found in 58% of the HIV patients, both with and without neurological complications, but the highest values of IL-1β were found in patients lacking neurological symptoms [46, 47].
— Interleukin-6 (IL-6). — The function of IL-6 induces the terminal differentiation of B cells into immunoglobulin-producing cells and it has co-stimulator effects on T cell proliferation. Therefore, IL-6 in CSF in HIV infection may contribute to the production of anti-HIV Ab as well as IgG intra-BBB synthesis in general [46]. IL-6 was found in 40-42% [46, 47] in HIV patients with and without neurological complications [46]. However, the highest titers of IL-6 were found in patients with cryptococcal meningitis [47].
— M-CSF (macrophage-colony stimulating factor). — It was found in CSF from 21 to 37% of HIV infected patients, including asymptomatic patients as well as those with ADC or with opportunistic infections [47, 48].
— Alpha-TNF (tumor necrosis factor). — Alpha-

TNF is a T cell stimulating factor. It was not detected in the CSF from HIV infected patients by some investigators [46, 47], while it was found detectable in 54% of the patients and associated with ADC or CNS opportunistic infection by others [57, 59].

2. — Interferons. They are, in general, proteins and glycoproteins that affect a variety of cellular functions, including normal and neoplastic cell growth, immune reactivity, and host-parasite interactions [80].

— Alpha-interferon. — It is a leukocyte-derived protein capable of inducing neutralizing antibodies [80]. It was found elevated in CSF from 14/20 (70%) HIV infected patients [117].

3. — Complement components. The decrease of these general immunological parameters suggests complement activation as a feature of the immune response.

— C3-complement. — The decrease of C3 complement in the CSF from HIV infected patients is prominent [117].

C. — Substances studied in CSF of HIV seropositive patients as possible markers of ND progression.

— Neopterin. — This is a pteridin compound whose phosphorylated form is a precursor of biopterin a cofactor of the tissue hydroxylases leading to the synthesis of catecholamines and serotonin [69]. It is produced by macrophages after stimulation with gamma-interferon during activation of the cell-mediated immune response [136]. It is considered a marker of specific monocyte/macrophage activation [75] and also has been considered a potential marker of systemic progression in HIV infection [78]. It has also been suggested that increased synthesis of neopterin may induce enhanced degradation of tryptophan, a precursor of serotonin with concomitant disturbances of brain serotonin metabolism [136].

Neopterin, was found in CSF from HIV infected patients at higher concentrations than in controls [41, 55, 69, 136]. On the other hand, patients with HIV related meningitis and with opportunistic CNS infections had higher serum and CSF neopterin levels than seropositive asymptomatic patients [55]. In patients with ADC, CSF neopterin concentrations correlated with the severity of disease [10].

— Beta 2 microglobulin (B_2M). — This is a low molecular weight protein. The main source of B_2M in biological fluids seems to be the increased turnover of cell membranes. Its function has not been assessed but it is probably involved in lymphocyte activation [69]. Elevated levels are considered to reflect an activation of the cellular immune system or an increased cell membrane turnover [136]. CSF from HIV infected patients shows B_2M at higher concentrations [32, 69, 136] and levels than controls [32]. This seems to be more frequent in neurologically symptomatic patients [32, 78].

A recent study of our laboratory show some correlations between serum and CSF neopterin and B2-M levels in HIV infected patients. A normal serum neopterin level predicts normal levels of serum B2-M, CSF neopterin or CSF B2-M in 90%, 100% and 100% respectively, of the patients. On the other hand, an elevated serum neopterin level predicts an elevated level of serum B2-M or CSF neopterin in 81% and 62%, respectively of the patients [110].

— Myelin basic protein (MBP). — It has been used as specific index of acute demyelination. No HIV infected patients had elevated CSF levels (>8 mg/ml) [89, 112].

D. — Neurotransmitters, a new key for neuropathogenesis.

As we commented in the pathogenesis section of this article, some neurotransmitters have been said to have an important potential role in brain damage in ADC. For this reason the monitoring of this substance in CSF has attracted the interest of researchers.

— Tryptophan. — CSF from HIV seropositives patients had significantly decreased tryptophan levels than controls [79].

— 5-hydroxyindoleacetic Acid (5-HIAA). — No significant difference was detected in the mean of 5-HIAA CSF concentration between HIV seropositive patients and controls [79, 96]. Other researchers, however, report a marked reduction of 5-HIAA in the CSF of HIV infected patients [11].

— Homovanillic acid (HVA). — The CSF level of HVA was found moderately reduced [11] or normal [96].

— Quinolinic Acid. — The CSF concentration of Quinolinic Acid in HIV seropositive patients was found increased threefold over controls [64], and correlated well to the severity of the neuropsychological deficits [65].

CSF in treatment and in the monitoring of treatment

Information on intrathecal antiviral HIV-1 treatment is scanty and limited to the use of Zidovudine (AZT). There is a report of 3 patients who have become AZT intolerant because of hematological toxicity. When AZT was administered intrathecally, the patient's mental status improved in all three cases within 2-3 weeks, but the follow-up was done for only 3-5 months [124].

Information on changes in the CSF profile as a result of antiviral HIV-1 treatments in scanty too. There is one report of a decline in HIV Ag in six AIDS or ARC-AIDS patients undergoing AZT treatment. This modification of the CSF levels of Ag was not associated with neurological improvement [26]. Another study shows that CSF neopterin concentration decreased in conjunction with clinical improvement following treatment with AZT [10]. In another study of patients treated with AZT it was observed that some CSF abnormalities in the dopamine and cortisol concentrations tended to return to normal after treatment [160]. Finally, in one study no correlation was found between the clinical improvement of the neurological alterations as a result of the treatment with AZT and some parameters of the CSF such as AZT concentration and HIV isolation from CSF [140].
However, since there is so little available information in this direction, it will be very useful in future studies to consider the markers discussed above as a method of monitoring treatment.

Indications and controindications of CSF examination in HIV infection

Indications. — CSF examinations are an important source of diagnostic information and may be of predictive markers of primary affections, although they are most important in diagnosing or excluding secondary involvement, especially infections. It is important to keep in mind that the serology in CSF can be positive for HIV even earlier than in the blood [122].
All the classic controindications to the puncture of the cerebrospinal fluid space (for review see [147]), must be considered in HIV patients, paying special attention to excluding coagulation defects and intracranial space-occuping lesions because of their higher frequency of presentation in HIV-1 infected patients.

Conclusions

As it is apparent, the published material on CSF examination as a means of exploring the specific involvement of the CNS in HIV-1 infection is abundant and valuable. The knowledge that these studies have contributed has been fundamental in establishing the early and high-frequency involvement of the CNS in HIV-1 infection as well as in contributing vital elements to the analysis of pathogenesis in neurological involvement. And the study of CSF has been important not only in research, but also as a fundamental clinical tool in the differential diagnosis of CNS complications.

In this section we will comment on findings of some of the studies carried out on the CSF of patients with primary neurological HIV involvement. We also intend to address some of the most frequently asked clinical questions on this subject.
How early is the CNS compromised in the HIV infection? CSF analyses to determine the direct presence of HIV such as isolation and antigen detection require a heavy viral load to be positive and are therefore not useful in establishing early viral presence. Analyses which examine the expression of the host reaction against HIV presence such as the intra-BBB IgG synthesis permit us to establish that the inflammatory and immunological local response is very early, practically from the period of seroconversion which means that the virus must be present even earlier. Techniques which combine specificity and sensitivity such as the PCR will be ones to provide more definitive information on this issue.
What does the demonstration of HIV in the CSF mean? It is important to remember here that CSF permits us to evaluate only the extracellular compartment of the CNS, that is, a compartment very close to the nervous tissue but not completely homologous to it. However, from the point of view of disease management we think that, in the same way as in neurosyphillis, the determination of the direct presence of HIV in the CSF must be considered diagnostic proof of the viral presence in the CNS.
What does the presence of HIV in the CNS mean? Although neuropathological studies show that the infected cells in the CNS are fundamentally macrophages and endothelial cells, it may be supposed that the direct viral presence in the nervous tissue is relevant to the triggering, facilitation or determination of the neuropathological process, even though it also depends on systemic factors such as the general immune response expressed in the activation of the T cells and macrophages. For this reason, the viral presence in CSF must at least be considered an index of higher risk of neurological damage. On the other hand, the existence of the virus in a compartment such as the intra-BBB, which has a different permeability for drugs from the systemic compartment, may mean a potential viral reserve out of the reach of therapeutic anti-HIV drugs.
Should the demonstration of the viral presence in the CSF dictate treatment, then? Nowadays the prevailing criteria for beginning anti HIV treatment are clinical systemic or neurological involvement. Only those patients with T cell count under 500 cells or the neurologically symptomatic are treated. However, in a system with a big functional reserve such as the CNS, waiting for clinical expression of damage could mean waiting

too long. Why wait for the symptomatic stage and not treat the HIV CNS presence as a potential element of neurological damage, then? As we will comment, HIV is present very early in the infection and there is the tendency to restrict the use of antiviral treatments in very early stages, on the one hand because of the general toxicity of the available drugs, and on the other hand because of the possibility of generating a higher risk of viral resistance to the drug.

For this reason an eclectic position would be to presume that the presence of HIV in CSF is due to the expression of the virus in the nervous tissue; so a more strict vigilance of both the clinical and laboratory signs of neurological involvement would be prudent. Ideally, the identification of some laboratory marker predictive of the neurological clinical involvement would allow a more objective identification of the best opportunity to start antiviral treatment for neurological reasons.

Are there markers of this kind available? The CSF elements studied for this purpose have been varied and included general elements of the CSF cytochemical analysis such as cell count, protein, IgG levels to specific viral test such as HIV antibodies and antigens. Although there is absence of significant correlation of the elements mentioned, the search in the other fields such as cytokines, B2-M, neopterin, and quinolinic acid, albeit more promising, have not turned out to be of predictive value in neurological compromise either.

Is it then possible to reject definitely the CSF analyses mentioned as predictive markers? We do not think so. When attempting to utilize the available information in the search for predictive markers of the CNS HIV-1 involvement, however, some general weaknesses in the analyzed studies are detected which impede the achievement of the conclusions that this method of exploration could potentially provide. Some limitations are partially owing to the nature of the illness, such as the difficulty of obtaining an adequate and proportional number of patients with a long follow-up in the various stages of the infection; other limitations lie in the lack of specific background on the studied variables, and still others in the type of study.

In general, the studies published between 1985-1989 are only observational studies of the retrospective type, most without explicit criteria of patient inclusion. In these studies the fundamental objective was the reporting of some finding, or the measurement of some variable and its results, which not always have or allow a statistical analysis for the purpose of identifying the prognostic markers.

Of the few recent prospective studies that have appeared, some have not always well defined groups or, if they are defined, there is no standard method of reporting the results. There is frequently no correlation between the number of patients and the number of samples. This weaknes the conclusion in terms of establishing a group norm in a particular stage of infection. The problem is including more than one sample from a patient with acutely atypical findings, which unduly influences the typing of the group in question.

What new directions could be taken in the search of predictive markers of the HIV primary neurological involvement?

Perhaps the answer is in the development of some techniques for the quantification of viral load (eg. as PCR), determination of viral presence and quantification of viral samples with special neurological affinity and determination of the conditions of the intrinsic biological activity of the virus with knowledge of the balance between activators and inhibitory factors.

Is there some evaluation of the CSF that is diagnostic of some type of primary specific involvement? In general, CSF alterations are unspecific and do not constitute diagnosis of some specific type of HIV primary involvement.

Is CSF analysis useful in monitoring antiviral treatment? Although at present there seems to be no strict correlation between the modifications of the CSF alterations and the clinical alterations there is not enough information to be definite on this point.

Finally, we believe that continuous advances in our knowledge of the illness are bound to necessitate a permanent review of the significance of the available findings, since there are several variables which in spite of having been measured in great quantities are still of uncertain meaning.

Sommario

Questo lavoro si incentra nei reperti liquorali che si verificano nella patologia neurologica (ND) da HIV-1. Perché usare il liquor come spia della compromissione snc da HIV-1? Perché l'esame liquorale viene da tempo considerato sia come efficace indagine diagnostica sia come mezzo di monitoraggio della terapia in varie malattie infettive ed immunologiche del snc. Di conseguenza, esiste già un'abbondanza di dati di riferimento assodati [113, 145, 147], specialmente nel campo dell'individuazione di agenti infettivi, dell'utilizzo di reperti IgG come indici immunologici e dell'utilizzo di reperti liquorali per mappare l'evoluzione della ND.

Noi esamineremo i lavori che utilizzino come variabili dipendenti i dati liquorali per indagare gli effetti della malattia HIV, ed in particolare la ND da HIV, citati nell'Index Medicus e nella database MEDLINE, pubblicati dal 1985 al 1991 in lingua spagnola, italiana e inglese. Nella nostra revisione ci limiteremo a quegli studi che escludino i casi di HIV con infezioni opportunistiche o tumori, per poter puntare sugli effetti dell'HIV sul cervello come definiti sopra. Lo scopo primario a lungo termine è quello di individuare alcuni elementi liquorali capaci di portare ad una migliore comprensione dell'eziopatogenesi della ND. Tuttavia, un altro scopo quasi ugualmente importante è di determinare quali variabili liquorali potrebbero essere ritenute predittive della comparsa e della progressione della ND da HIV. Da queste si potrebbe pensare di ricavare le misure migliori dell'efficacia delle terapie della ND da HIV. Questo risultato è particolarmente importante in quanto siamo convinti che a lungo andare il trattamento della ND da HIV prenderà le mosse e verrà monitorato dagli esiti di laboratorio marcatori della ND da HIV, molto probabilmente liquorali.
Infine, questa compilazione riassuntiva di informazioni sarebbe utile anche per la redazione di un profilo liquorale come quadro di riferimento per i casi con complicazioni. I dati di questo ragguaglio saranno suddivisi, ove possibile, secondo lo stadio clinico e la presenza/assenza di manifestazioni cliniche di ND.

Address reprint requests to:
Jorge Nogales-Gaete, M.D.
Dr. P.L. Ferrer 2803-E Nunoa
Santiago - Chile

References

[1] ACKERMANN R., NECKIC M., JURGENS R.: *Locally synthesized antibodies in cerebrospinal fluid of patients with AIDS.* J. Neurol. 233:140-141, 1986.
[2] ALLAIN J.P., LAURIAN Y., PAUL D.: *Long term evaluation of HIV antigen and antibodies to p24 and gp41 in patients with hemophilia.* N. Engl. J. Med. 317:1114-1121, 1987.
[3] ANDERSSON M., BERGSTRÖM T., BLOMSTRAND C. et al.: *Cerebrospinal fluid changes in HIV-1 infection.* Ann. NY Acad. Sci. 540:624-627, 1988.
[4] ANDERSSON M., BERGSTRÖM T., BLOMSTRAND C. et al.: *Increasing intrathecal lymphocytosis and immunoglobulin G production in neurologically asymptomatic HIV-1 infection.* J. Neuroimmunol. 19:291-304, 1988.
[5] APPLEMAN M.E., MARSHALL D.W., BREY R.L. et al.: *Cerebrospinal fluid abnormalities in patients without AIDS who are seropositive for the human immunodeficiency virus.* J. Inf. Dis. 138:193-199, 1988.
[6] BALAKRISHNAN J., BECKER P.S., KUMAR A.J. et al.: *Acquired immunodeficiency syndrome: correlation of radiologic and pathologic findings in the brain.* Radiographics 10(2):201-15, 1990.
[7] BERGER J.: *Neurologic complications of human immunodeficiency virus infection.* Postgraduate Med. 81:72-79, 1987.
[8] BERNARD P.G.: *The neurological and electroencelophalographic changes in AIDS.* Clin. Electroencephalogr. 22:65-70, 1991.
[9] BINIEK R., BARTHOLOME M., SCHULTZ M. et al.: *Intrathecal production of HIV antibodies in suspected AIDS encephalopathy.* J. Neurol. 235:131-135, 1988b.
[10] BREW B.J., BHALLA R.B., PAUL M. et al.: *Cerebrospinal fluid neopterin in human immunodeficiency virus type 1 infection.* Ann. Neurol. 28:556-560, 1990.
[11] BRITTON C.B., COTE L., ALTSTEIL L.: *Cerebrospinal fluid biogenic amine metabolites in patients with AIDS.* Neurology 39 (Suppl. 1):380, 1989.
[12] BROUWERS P., MOHR E., HENDRICKS M., BARON I.: *The use of discriminant analysis to differentiate the neuropsychological profile of HIV patients.* J. Clin. Exp. Neuropsychol. 11(1):35, 1989.
[13] BUDKA H.: *Human immunodeficiency virus (HIV) induced disease of the central nervous system: pathology and implications for pathogenesis.* Acta Neuropathol. (Berl.) 77:225-236, 1989.
[14] BUDKA H., COSTANZI G., CRISTINA S. et al.: *Brain pathology induced by infection with human immunodeficiency virus HIV. A: histological, immunocytochemical and electron microscopical study of 100 autopsy cases.* Acta Neuropathol. (Berl.) 75:185-198, 1987.
[15] BUKASA K.S., SINDIC C.J., BODEUS M. et al.: *Anti-HIV antibodies in the CSF of AIDS patients: a serological and immunoblotting study.* J. Neurol. Neurosurg. Psychiatry 51(8):1063-1068, 1988.
[16] BYRNE G.I., LEHMANN L.K., KIRSCHBAUM J.G. et al.: *Induction of tryptophan degradation in vitro and in vivo: A g-interferon-stimulated activity.* J. Interferon. Res., 6:389-396, 1986.
[17] CARBONARA S., ANGARANO G., ZIMATORE G.B. et al.: *Clinical value of HIV p24 Ag in cerebrospinal fluid of symptomatic or asymptomatic HIV-*

infected patients. Acta Neurologica 12(1):44-48, 1990.

[18] CARRIERI P.B., PERRELLA O., IZZO E. et al.: *Immunopathology of cerebrospinal fluid in the HIV infection*. Acta Neurologica 12(1):40-41, 1990.

[19] Centers for Disease Control: *Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome*. MMWR 36 (Suppl.):1s-15s, 1987.

[20] CHALMERS A.C., APRILL B.S., SHEPHARD H.: *Cerebrospinal fluid and human immunodeficiency virus*. Arch. Intern. Med. 150:1538-1540, 1990.

[21] CHIODI F., ALBERT J., OLAUSSON E. et al.: *Isolation frequency of HIV from CSF and blood of patients with varying severity of HIV infection*. AIDS Res. Human. Retroviruses 4:351-358, 1988.

[22] CHIODI F., ASJO B., FENYO E.M. et al.: *Isolation of human immunodeficiency virus from cerebrospinal of antibody positive virus carrier without neurologic symptoms*. Lancet 2:1276-1277, 1986.

[23] CHIODI F., NORKRANS G., HAGBERG L. et al.: *Human immunodeficiency virus infection of the brain. II: Detection of intrathecally synthesized antibodies by enzyme linked immunosorbent assay and imprint immunofixation*. J. Neurol. Sci. 87:37-48, 1988.

[24] CHIODI F., SÖNNERBORG A., ALBERT J. et al.: *Human immunodeficiency virus infection of the brain. I: Virus isolation and detection of HIV specific antibodies in the cerebrospinal fluid of patients with varying clinical conditions*. J. Neurol. Sci. 85:245-257, 1988.

[25] D'AGARO P., ANDRIAN P., ROSCIOLI B. et al.: *HIV-1 isolation and p24 antigen detection in cerebrospinal fluid of subjects with neurological abnormalities related to AIDS*. Acta Neurologica 12(1):49-52, 1990.

[26] DE GANS J., LANGE J.M.A., DERIX M.M.A. et al.: *Decline of HIV antigen levels in cerebrospinal fluid during treatment with low-dose zidovudine*. AIDS 2(1):37-40, 1988.

[27] DE LA PAZ R., ENZEMANN D.: *Neuroradiology of acquired immunodeficiency syndrome, in AIDS and the Nervous System*, M.L. Rosemblum, R.M. Levy and D.E. Bredesen, Eds. Raven Press: New York, p. 121-153, 1988.

[28] DELA CRUZ C.R., VERMA N.P.: *Periodic lateralized epileptiform discharges in acquired immunodeficiency syndrome*. Clin. Electroencephalogr. 20(1):35-8, 1989.

[29] DORRIES R., KAISER R., MEULEN V.T.: *Human immunodeficiency virus infection: affinity-mediated immunoblot detects intrathecal synthesis of oligoclonal IgG specific for individual viral protein*. AIDS Res. Hum. Retroviruses 5:303-310, 1989.

[30] EKHOLM S., SIMON J.H.: *Magnetic resonance imaging and the acquired immunodeficiency syndrome dementia complex*. Acta Radiol. 29(2):227-30, 1988.

[31] ELOVAARA I., IIVANAINEN M., VALLE S. et al.: *CSF protein and cellular profiles in various stages of HIV infection related to neurological manifestations*. J. Neurol. Sci. 78:331-342, 1987.

[32] ELOVAARA I., LIVANAINEN M., POUTIAINEN E. et al.: *CSF and serum β-2 microglobulin in HIV infection related to neurological dysfunction*. Acta Neurol. Scand. 79:81-87, 1989.

[33] ELOVAARA I., SEPPALA I., POUTIAINEN E.: *Intrathecal humoral immunologic response in neurologically symptomatic and asymptomatic patients with human immunodeficiency virus infection*. Neurology 38:1451-1456, 1988.

[34] EMSKOETTER T., LAER D., VEISMANN S., ERMER M.: *Human immunodeficiency virus (HIV)-specific antibodies, neutralizing activity and antibody-dependent cellular cytotoxicity (ADCC) in the cerebrospinal fluid of HIV infected patients*. J. Neuroimmunol. 24:61-66, 1989.

[35] EPSTEIN L., GOUDSMIT J., PAUL D. et al.: *Expression of human immunodeficiency virus in cerebrospinal fluid of children with progressive encephalopathy*. Ann. Neurol. 21:397-401, 1987.

[36] FELGENHAUER K.: *Differentiation of the humoral immune response in inflammatory diseases of central nervous system*. J. Neurol. 228:223-237, 1982.

[37] FELGENHAUER K., LUER W., POSER P.: *Chronic HIV encephalitis*. J. Neuroimmunol. 20:141-144, 1988.

[38] FELGENHAUER K., SCHADLICH J.-H., NECKIC M., ACKERMANN R.: *Cerebrospinal fluid virus antibodies: a diagnostic indicator for multiple sclerosis?* J. Neurol. Sci. 71:291-299, 1985.

[39] FOSTER A.C., COLLINS J.F., SCHWARCZ R.: *On the excitotoxic properties of quinolinic acid, 2,3-piperidine dicarboxylic acids and structurally related compounds*. Neuropharmacology 22:1331-1342, 1983.

[40] FREESE A., SWARTZ K.J., DURING M.J., MARTIN J.B.: *Kynurenine metabolites of tryptophan: implications for neurologic diseases*. Neurology 40:691-695, 1990.

[41] FUCHS D., CHIODI F., ALBERT J. et al.: *Neopterin concentrations in cerebrospinal fluid and serum of individuals infected with HIV-1*. AIDS 3(5):285-288, 1989.

[42] FUCHS D., MOLLER A.A., REIBNEGGER G. et al.: *Decreased serum tryptophan in patients with HIV-1 infection correlates with increased serum neopterin and with neurologic/psychiatric symptoms*. J. Acquir. Immune Defic. Syndr. 3(9):873-6, 1990.

[43] GABUZDA D.H., HIRSCH M.S.: *Neurologic manifestation of infection with human immunodeficiency virus*. Ann. Intern. Med. 107:383-391, 1987.

[44] GALLO P., DE ROSSI A., AMADORI A.: *Central nervous system involvement in HIV infection*. AIDS Res. Hum. Retroviruses 4:211-221, 1988.

[45] GALLO P., DE ROSSI A., CADROBBI P. et al.: *Intrathecal synthesis of anti-HIV oligoclonal IgG in HIV-seropositive patients having no signs of HIV-induced neurological diseases*. Ann. NY Acad. Sci. 540:615-618, 1988.

[46] GALLO P., FREI K., RORDORF C. et al.: *Human immunodeficiency virus type 1 (HIV-1) infection of the central nervous system: an evaluation of cytokines in cerebrospinal fluid*. J. Neuroimmunol. 23:109-116, 1989.

[47] GALLO P., LAVERDA A.M., DE ROSSI A. et al.: *Macrophage-derived cytokines in cerebrospinal fluid of HIV-1 infected patients*. Acta Neurologica 12(1):62-65, 1990.

[48] GALLO P., PAGNI S., GIOMETTO B. et al.: *Macrophage-colony stimulating factor (M-CSF) in cerebrospinal fluid.* J. Neuroimmunol. 29:105-112, 1990.

[49] GENDELMAN H.E., ORENSTEIN J.M., BACA L.M. et al.: *The macrophage in the persistence and pathogenesis of HIV infection.* AIDS 475-495, 1989.

[50] GOUDSMIT J., EPSTEIN L.G., PAUL D.A. et al.: *Intra-blood-brain barrier synthesis of humans and chimpanzees.* Proc. Natl. Acad. Sci. USA 84:3876-3880, 1987.

[51] GOUDSMIT J., WOLTERS E.C., BAKKER M. et al.: *Intrathecal synthesis of antibodies to HTLV-III in patients without AIDS or AIDS related complex.* Br. Med. J. 292:1231-1234, 1986.

[52] GRANT I., ATKINSON J.H., HESSELINK J.R. et al.: *Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections. Studies with neuropsychologic testing and magnetic resonance imaging.* Ann. Intern. Med. 107(6):828-36, 1987.

[53] GRAY F., GHERARDI R., SCARAVELLI F.: *The neuropathology of the acquired immunodeficiency syndrome (AIDS).* Brain 111:245-266, 1988.

[54] GRIFFIN D.E., MC ARTHUR J.C., CORNBLATH D.R.: *Soluble interleukin-2 receptor and soluble CD8 in serum and cerebrospinal fluid during human immunodeficiency virus-associated neurologic disease.* J. Neuroimmunol. 28:97-109, 1990.

[55] GRIFFIN D.E., MCARTHUR J.C., CORNBLATH D.R.: *Neopterin and interferon-gamma in serum and cerebrospinal fluid of patients with HIV-associated neurologic disease.* Neurology 41:69-74, 1991.

[56] GRIFFITH B.P.: *Principles of laboratory isolation and identification of the human immunodeficiency virus (HIV).* Yale J. Biol. Med. 60:575-587, 1987.

[57] GRIMALDI L., MARTINO G., FRACIOTTA D. et al.: *Elevated δ-TNF CSF level in HIV-1 encephalopathy.* J. Neurol. 237 (suppl. 1):S7, 1990.

[58] GRIMALDI L.M.E., CASTAGNA A., LAZZARIN A. et al.: *Oligoclonal IgG bands in cerebrospinal fluid and serum during asymptomatic immunodeficiency virus infection.* Ann. Neurol. (8):277-279, 1988.

[59] GRIMALDI L.M.E., MARTINO G.V., FRANCIOTTA D.M. et al.: *Elevated alpha-tumor necrosis factor levels in spinal fluid from HIV-1-infected patients with central nervous system involvement.* Ann. Neurol. 29:21-25, 1991.

[60] GRIMALDI L.M.E., ROOS R.P., LAZZARIN A. et al.: *Human immunodeficiency virus gp120 and p24 oligoclonal antibody in acquired immunodeficiency syndrome cerebrospinal fluid and sera.* Ann. NY Acad. Sci. 540:611-614, 1988.

[61] GURNEY M.E., APATOFF B.R., SPEAR G.T. et al.: *Neuroleukin: A lymphokine product of lectin stimulated T cells.* Science 234:574-581, 1986.

[62] HAGBERG L., FORSMAN A., NORKRANS G.: *Cytological and immunoglobulin findings in cerebrospinal fluid of symptomatic and asymptomatic human immunodeficiency virus (HIV) seropositive patients.* Infection 16:13-18, 1988.

[63] HENIN D., HAUW J.-J.: *The neuropathology of AIDS, in Handbook of Clinical Neurology*, P. Vinken, G. Bruyn and R.R. McKendall, Eds. Elsevier Science Publishers B.V.: Amsterdam, p. 507-524, 1989.

[64] HEYES M., RUBINOW D., LANE C., MARKEY S.: *Cerebrospinal fluid quinolinic acid are increased in acquired immune deficiency syndrome.* Ann. Neurol. 26:275-277, 1989.

[65] HEYES M.P., BREW B.J., MARTIN A. et al.: *Quinolinic acid in cerebrospinal fluid and serum in HIV-1 infection: relationship to clinical and neurological status.* Ann. Neurol. 29:202-209, 1991.

[66] HO D.D., POMERANTZ R.J., KAPLAN J.C.: *Pathogenesis of infection with human immunodeficiency virus.* N. Engl. J. Med. 317:278-286, 1987.

[67] HO D.D., SARNGADHARAN M.G., RESNICK L. et al.: *Primary human T-lymphotrophic virus type III infection.* Ann. Intern. Med. 103:880-883, 1985.

[68] HOLLANDER H., LEVY J.A.: *Neurologic abnormalities and recovery of human immunodeficiency virus from cerebrospinal fluid.* Ann. Intern. Med. 106:692-695, 1987.

[69] MBERCIADORI G., PIERSANTELLI N., BO A. et al.: *Study of beta-2 microglobulin and neopterin in serum and cerebrospinal fluid of HIV-infected patients.* Acta Neurologica 12(1):58-61, 1990.

[70] JOHNSON J., ZOLLA-PAZNER S.: *Detection of HTLV-III antibody in cerebrospinal fluid from patients with AIDS and pre-AIDS with the use of a commercial test system.* Am. J. Clin. Pathol. 88:351-353, 1987.

[71] JOHNSON R., MCARTHUR J., NARAYAN O.: *The neurobiology of human immunodeficiency virus infections.* FASEB J. 2:p. 2970-2981, 1988.

[72] KAISER R., DÖRRIES R., LUER W. et al.: *Analysis of oligoclonal antibody bands against individual HIV structural proteins in the CSF of patients infected with HIV.* J. Neurol. 236:157-160, 1989.

[73] KATZ R., ALAPPATIU C., GLASS J.P., BRUNER J.M.: *Cerebrospinal fluid manifestations of neurologic complications of Human Immunodeficiency Virus infection.* Acta Cytol. 23(2):233-244, 1989.

[74] KITTUR S.D., KITTUR D.S., SONCRANT T.S. et al.: *Soluble interleukine-2 receptor in cerebrospinal fluid from individuals with various neurological disorders.* Ann. Neurol. 28:168-173, 1990.

[75] KRAMER A., WIKTOR S.Z., FUCHS D. et al.: *Neopterin: a predictive marker of acquired immune deficiency syndrome in human immunodeficiency virus infection.* J. Acquir. Immune Defic. Syndr. 2:291-296, 1989.

[76] KRAMER E.L., SANGER J.J.: *Brain imaging in acquired immunodeficiency syndrome dementia complex.* Semminars Nuclear Med. XX(4):353-363, 1990.

[77] KRIKORIAN R., WROBEL A.J., MEINECKE C. et al.: *Cognitive deficits associated with human immunodeficiency virus encephalopathy.* J. Neuropsychiatry Clin. Neurosc. 2:256-260, 1990.

[78] LANGE M.A., DE WOLF F., GOUDSMIT J.: *Markers for progressions in HIV infection.* AIDS 3(suppl.):s153-s160, 1989.

[79] LARSSON M., HAGBERG L., NORKRANS G., FORSMAN A.: *Indole amine deficiency in blood and cerebrospinal fluid from patients with human im-*

munodeficiency virus infection. J. Neuroscience Res. 23:441-446, 1989.

[80] LAURENCE J.: *Immunology of HIV infection, I: biology of the interferons.* AIDS Res. Hum. Retroviruses 10:p. 1149-1156, 1990.

[81] LEFVERT A.K., LINK H.: *IgG production within the central nervous system: a critical review of proposed formulae.* Ann. Neurol. 17:13-20, 1985.

[82] LEVY J.A., SHIMABUKURO J., HOLLANDER H. et al.: *Isolation of AIDS-associated retrovirus from CSF and brain of patients with neurological symptoms.* Lancet 2:586-588, 1985.

[83] LEVY R.M., BREDESEN D.E.: *Central nervous system dysfunction in acquired immunodeficiency syndrome,* in AIDS and the Nervous System, M.L. Rosenblum, R.M. Levy and D.E. Bredesen, Eds. Raven Press: New York p. 29-63, 1988.

[84] LEVY R.M., MILLS C.M., POSIN J.P. et al.: *The efficacy and clinical impact of brain imaging in neurologically symptomatic AIDS patients: A prospective CT/MRI study.* J. Acquir. Immune Defic. Syndr. 3:461-471, 1990.

[85] LLOYD A., WAKEFIELD D., ROBERTSON P., DWYER J.M.: *Antibodies to HIV are produced within the central nervous system of all subjects with all categories of HIV infection.* Aust. N.Z.J. Med. 18:854-860, 1988.

[86] LUER W., POSER S., WEBER T. et al.: *Chronic HIV Encephalitis I. Cerebrospinal fluid diagnosis.* Klin. Wochenschr. 66:21-25, 1988.

[87] MACDONELL K.B., CHMIEL J.S., POGGENSEE L., WU S.: *Predicting progression to AIDS: combined usefulness of CD4 lymphocyte counts and p24 antigenemia.* Am. J. Med. 89:706-712, 1990.

[88] MARGOLICK J.B., MCARTHUR J.C., SCOTT E.R. et al.: *Flow cytometric quantitation of cell phenotypes in cerebrospinal fluid and peripheral blood of homosexual men with and without antibodies to human immunodeficiency virus type I.* J. Neuroimmunol. 20:73-81, 1988.

[89] MARSHALL D.W., BREY R.L., BUTZIN C.A.: *Lack of cerebrospinal fluyid myelin basic protein in HIV infected asymptomatic individuals with intrathecal synthesis of IgG.* Neurology 39:1127-1129, 1989.

[90] MARSHALL D.W., BREY R.L., BUTZIN C.A. et al.: *CSF changes in a longitudinal study of 124 neurologically normal HIV-1 infected U.S. Air Force personnel.* J. Acquir. Immune Defic. Syndr. 4:777-781, 1991.

[91] MARSHALL D.W., BREY R.L., CAHILL W.T. et al.: *Spectrum of cerebrospinal fluid findings in various stages of HIV infection.* Arch. Neurol. 45:945-958, 1988.

[92] MARTIN A., SALAZAR A., WILLIAMS J. et al.: *The Walter Reed study on the neurobehavioral consequences of HIV infection. In Workshop on the diagnosis and prognosis of retrovirus infections. 1989. Walter Reed Army Institute of Research,* Washington, D.C., March 27, 1989.

[93] MCARTHUR J.: *Neurologic manifestation of AIDS.* Medicine 66:407-437, 1987.

[94] MCARTHUR J.C., COHEN B.A., FARZEDEGAN H. et al.: *Cerebrospinal fluid abnormalities in homosexual men with and without neuropsychiatric findings.* Ann. Neurol. 23 (Suppl.):s34-s37, 1988.

[95] MCARTHUR J.C., SIPOS E., CORNBLATH D.R. et al.: *Identification of mononuclear cells in CSF of patients with HIV infection.* Neurology 39:66-70, 1989.

[96] MOELLER A.A., PIRKE K.M.: *Metabolites of serotonin and catecholamines in the cerebrospinal fluid of patients in advanced stages of HIV-1 infection.* J. Neurol. 237:124, 1990.

[97] MOLLER A.A., BACKMUND H.: *CT findings in different stages of HIV infection: a prospective study.* J. Neurol. 237:94-97, 1990.

[98] MONAGHAN D.T., COTMAN C.W.: *Distribution of N-Methyl-D-aspartate-sensitive L-[3H] glutamate-binding sites in rat brain.* J. Neurosci. 5:2909-2919, 1985.

[99] MORONI F., LOMBARDI G., CARLA V. et al.: *Increase in the content of quinolinic acid in cerebrospinal fluid and frontal cortex of patients with hepatic failure.* J. Neurochem. 47(6):1667-1671, 1986.

[100] NAVIA B.A., HAHN A., PUMAROLA-SUNE T., PRICE R.W.: *Acholine acetyl transferase activity is reduced in AIDS dementia complex.* Ann. Neurol. 20:142, 1986b.

[101] NAVIA B.A., JORDAN B.D., PRICE R.W.: *The AIDS dementia complex: I. Clinical features.* Ann. Neurol. 19:517-524, 1986a.

[102] NELSON J.A., REYNOLDS-KOHLER C.R., OLDSTONE M.B.A., WILEY C.A.: *HIV and CMV coinfect brain cells in patients with AIDS.* Virology 165:286-290, 1988.

[103] NIELSEN S.L., DAVIS R.L.: *Neuropathology of acquired immunodeficiency syndrome, in AIDS and the nervous system,* M.L. Rosemblum, R.M. Levy and D.E. Breseden, Editor. Raven Press: New York, p. 155-181, 1988.

[104] OLSEN W.L., LONGO F.M., MILLS C.M., NORMAN D.: *White matter disease in AIDS: findings at MR imaging.* Radiology 169(2):445-448, 1988.

[105] ORTONA L., TAMBURRINI E., ANTINORI A., VENTURA G.: *Neurological features in AIDS patients: studies on cerebrospinal fluid.* Ital. J. Neurol. Sci. 9:567-572, 1988.

[106] PARISI A., DI PERRI P.G., STROSSELLI M. et al.: *Usefulness of computerized electroencephalography in diagnosing, staging and monitoring AIDS-dementia complex.* AIDS 3(4):209-13, 1989.

[107] PARISI A., STROSSELLI M., DI PERRI G. et al.: *Electroencephalography in the early diagnosis of HIV-related subacute encephalitis: analysis of 185 patients.* Clin. Electroencephalogr. 20(1):1-5, 1989.

[108] PERSING D.H., LANDRY M.L.: *In vitro amplification techniques for the detection of nucleic acids: new tools for the diagnostic laboratory.* Yale J. Biol. Med. 62:159-171, 1989.

[109] PERT C.B., SMITH C.C., RUFF M.R., HILL J.M.: *AIDS and its dementia as a neuropeptide disorder: role of VIP receptor blockade by human immunodeficiency virus envelope.* Ann. Neurol., 1988.

[110] PETER J.B., MCKEOWN K.L., BARKA N.E. et al.: *Neopterin and B2-Microglobulin and the assessment of intra-blood-brain-barrier synthesis of*

HIV-specific and total IgG. JCLA 5: in press, 1991.

[111] PETITO C.K., CHO E.S., LEMANN W. et al.: *Neuropathology of AIDS: An autopsy review.* J. Neuropath. Exp. Neurol. 45:635-646, 1986.

[112] PFISTER H.W., EINHAUPL K.M., WICK M. et al.: *Myelin basic protein in the cerebrospinal fluid of patients infected with HIV.* J. Neurol. 236:288-291, 1989.

[113] PICK P.W., TOURTELLOTTE W.W.: *Neurochemistry of the cerebrospinal fluid.* Current Opinion Neurol. Neurosurg. 2:972-978, 1989.

[114] PORTEGIES P., EPSTEIN L.G., HUNG S.T.A. et al.: *Human immunodeficiency virus type 1 antigen in cerebrospinal fluid. Correlation with clinical neurologic status.* Arch. Neurol. 46(3):261-264, 1989.

[115] PRICE R.W., BREW B.J.: *The AIDS dementia complex.* J. Infect. Dis. 158:1114-1121, 1988.

[116] RATNER L.: *Measurement of human immunodeficiency virus load and its relations to disease progression.* AIDS Res. Hum. Retroviruses 5:115-119, 1989.

[117] REBOUL J., SCHULLER E., PIALOUX G. et al.: *Immunoglobulins and complement components in 37 patients infected by HIV-1: Comparison of general (systemic) and intrathecal immunity.* J. Neurol. Sci. 89:243-252, 1989.

[118] REDFIELD R., WRIGHT D.C., TRAMONT E.C.: *The Walter Reed staging classification for HTLV-III/LAV infection.* N. Engl. J. Med. 314:131-132, 1986.

[119] REIBER H.: *Evaluation of IgG synthesis in the central nervous system,* in *Progress in Multiple Sclerosis Research,* H. Bahuer, S. Poser and G. Ritter, Eds. Springer-Verlag: Berlin, 1980.

[120] RESNICK L., BERGER J.R., SHAPSHAK P., TOURTELLOTTE W.W.: *Early penetration of the blood-brain-barrier by HIV.* Neurology 38:9-14, 1988.

[121] RESNICK L., DIMARZO-VERONESE F., SCHUPBACH J. et al.: *Intra-blood-brain-barrier synthesis of HTLV-III-specific IgG in patients with neurological symptoms associated with AIDS or AIDS-related complex.* New Engl. J. Med. 313:1498-1504, 1985.

[122] ROLFS A., SCHUMAKER H.C.: *Early findings in the cerebrospinal fluid of patients with hiv-1 infection of the central nervous system.* N. Engl. J. Med. 323:418-419, 1990.

[123] ROTTENBERG D.A., MOELLER J.R., STROTHER S.C. et al.: *The metabolic pathology of the AIDS dementia complex.* Ann. Neurol. 22(6):700-6, 1987.

[124] ROUTY J.P., BLANC A.P., RODRIGUEZ E. et al.: *Intrathecal Zidovudine for AIDS.* Lancet 2:248, 1990.

[125] SCHULLER E., SAGAR H.J.: *Local synthesis of CSF immunoglobulins.* J. Neurol. Sci. 51:361-370, 1981.

[126] SCHWARCZ R., WHETSELL W.O.J., MANGANO R.M.: *Quinolinic acid: an endogenous metabolite that produces axon sparing lesions in the rat brain.* Science 219:316-318, 1983.

[127] SETHI K.K., NAHER H.: *Elevated titers of cell-free interleukin-2 receptor in serum and cerebrospinal fluid specimens of patients with acquired immunodeficiency syndrome.* Immunol. Lett. 13:179-184, 1986.

[128] SHAUNAK S., ALBRIGHT R.E., KLOTMAN M.E. et al.: *Amplification of HIV-1 provirus from cerebrospinal fluid and its correlation with neurologic disease.* J. Infect. Dis. 161(6):1068-1072, 1990.

[129] SIGNER E.: *Management of the patient with AIDS dementia complex.* AIDS Medical Report 3:131-136, 1990.

[130] SINGER E., RUANE P., RESNICK L. et al.: *Asymptomatic human immunodeficiency virus-seropositive individuals: Early laboratory markers in cerebrospinal fluid and blood.* Ann. Neurol. 24:166, 1988.

[131] SINGER E.J., RUANE P., SYNDULKO K. et al.: *Search for laboratory markers of CNS disease in HIV-seropositive individuals.* Neurology 39 (Suppl. 1):420, 1989.

[132] SKOTZEK B., SANDER T., ZIMMERMANN J.: *Oligoclonal bands in serum and cerebrospinal fluid of patients with HIV infection.* J. Neuroimmunol. 20:151-152, 1988.

[133] SONNERBORG A., EHRNST A., STRANNEGARD O.: *Relationship between the occurrence of virus in plasma and cerebrospinal fluid of HIV-1 infected individuals.* J. Med. Virol. 27:258-263, 1989.

[134] SONNERBORG A., VON SYDOW M.A.E., FORSGREN M., STRANNEGARD O.O.: *Association between intrathecal anti-HIV-1 immunoglobulin G synthesis and occurrence of HIV-1 in cerebrospinal fluid.* AIDS 3:701-705, 1989.

[135] SONNERBORG A.B., EHRNST A.C., BERGDAHL S.K.M. et al.: *HIV isolation from cerebrospinal fluid in relation to immunological and neurological symptoms.* AIDS 2:89-93, 1988.

[136] SONNERBORG A.B., VON STEDINGK L.V., HANSSON L.O., STRANNEGARD O.O.: *Elevated neopterin and beta-2-microglobulin levels in blood and cerebrospinal fluid occur early in HIV-1 infection.* AIDS 3:277-283, 1989.

[137] STONE T.W., CONICK J.H.: *Quinolinic acid and other kynurenines in the CNS.* Neuroscience 15:597-613, 1985.

[138] SYNDULKO K., SINGER E., RUANE P. et al.: *Neuropsychological and computerized memory testing in HIV seropositive individuals.* J. Clin. Exp. Neuropsychol. 11(1):35, 1989.

[139] SYNDULKO K., SINGER E., RUANE P.: *Electrophysiological evaluation of human immunodeficiency virus-related neurological dysfunction.* Ann. Neurol. 26:155, 1989.

[140] TARTAGLIONE T.A., COLLIER A.C., COOMBS R.W. et al.: *Acquired immunodeficiency syndrome. Cerebrospinal fluid findings in patients before and during long-term oral zidovudine therapy.* Arch. Neurol. 48:695-699, 1991.

[141] TIBBLING G., LINK H., OHMAN S.: *Principles of albumin and IgG analyses in neurological disorders.* Scand. J. Clin. Lab. Invest. 37:385-390, 1977.

[142] TINUPER P., DE CAROLIS P., GALEOTTI M. et al.: *Electroencephalogram and HIV infection: a prospective study in 100 patients.* Clin. Elec-

troencephalogr. 21(3):145-50, 1990.

[143] TOURTELLOTTE W.W.: *Cerebrospinal fluid in multiple sclerosis, in Handbook of Clinical Neurology*, P.J. Vinken and G.W. Bruyn, Eds. North-Holland Publishing Co.: Amsterdam, p. 324-382, 1970a.

[144] TOURTELLOTTE W.W.: *On cerebrospinal fluid immunoglobulin-G(IgG) quotients in multiple sclerosis and other diseases- a review and a new formula to estimate the amount of IgG synthesized per day by the central nervous system*. J. Neurol. Sci. 10:p. 279-304, 1970b.

[145] TOURTELLOTTE W.W.: *The cerebrospinal fluid in multiple sclerosis, in Handbook of Clinical Neurology (rev ser)*, P.J. Vinken, G.W. Bruyn, H.L. Klawans, et al., Eds. Elsevier Science Publishers B.V.: Amsterdam, p. 79-130, 1985.

[146] TOURTELLOTTE W.W., MA B.L.: *Multiple Sclerosis: The blood-brain barrier and the measurement of de novo central nervous system IgG synthesis*. Neurology 28:76-83, 1978.

[147] TOURTELLOTTE W.W., SHORR R.J.: *Cerebrospinal fluid, in Neurological Surgery*, J.R. Youmans, Eds. W.B. Saunders Co.: Philadelphia. p. 335-363, 1990.

[148] TOURTELLOTTE W.W., SINGER E., SYNDULKO K. et al.: *Intra-Blood-Brain-Barrier IgG synthesis in HIV, in Enzymes as Targets for Drug Design*, M. Palfreyman, P.P. McCann, W. Lovenberg, et al., Eds. Academic Press, INC.: San Diego. p. 211-217, 1989a.

[149] TOURTELLOTTE W.W., SYNDULKO K., SINGER E. et al.: *Cerebrospinal fluid and neuro-performance findings in HIV-infected individuals with and without neurological deficits: preliminary findings of a prospective study*. In *Proceedings 1st Satellite conference on Neurological & Neuropsychological Complications of HIV Infection*. Quebec, Canada, 1989.

[150] TOURTELLOTTE, W.W., TAVOLATO B., PARKER J.A. et al.: *Multiple sclerosis: Measurement and validation of central nervous system IgG synthesis rate*. Neurology 30:240-244, 1980.

[151] TROSS S., HOLLAND J., WETZLER S. et al.: *Psychological and neuropsychological functions in AIDS spectrum disorder patients*. In *The First International Conference on AIDS*. Philadelphia, PA: American College of Physicians, 1985.

[152] TROSS S., PRICE R.W., NAVIA B. et al.: *Neuropsychological characterization of the AIDS dementia complex: a preliminary report*. AIDS 2:81-88, 1988.

[153] VAN GORP W.G., SATZ P., HINKIN C. et al.: *The neuropsychological aspects of HIV-1 spectrum disease*. Psychiatr. Med. 7:59-78, 1989.

[154] VAN WIELINK G., MCARTHUR J.C., MOENCH T. et al.: *Intrathecal synthesis of anti HIV IgG correlation with increasing duration of HIV-1 infection*. Neurology 40:816-819, 1990.

[155] VINTERS H.V., ANDERS K.H.: *Neuropathology of AIDS*. Florida: CRC Press Inc., 1990.

[156] WEBER T., BUTNER W., FELGENHAUER: *Evidence for different immune responses to HIV in CSF and Serum?* Klin. Wochenschr. 65:259-263, 1987.

[157] WERNER E.R., BITTERLICH G., FUCHS D. et al.: *Human macrophages degrade tryptophan upon induction by interferon-gamma*. Life Sci. 41(3):273-280, 1987.

[158] WERNER E.R., FUCHS D., HAUSEN A. et al.: *Tryptophan degradation in patients infected by human immunodeficiency virus*. Biol. Chem. Hoppe-Seyler 369:337-340, 1988.

[159] WIGDAHL B., KUNSCH C.: *Role of HIV in human nervous system dysfunction*. AIDS Res. Hum. Retroviruses 5:369-374, 1989.

[160] WILKINS J., SINGER E., MITSUYASU R. et al.: *Cerebrospinal fluid (CSF) biogenic amines and cortisol are altered by zidovidine (AZT) therapy for the AIDS dementia complex (ADC)*. Neurology 40 (suppl. 1):237, 1990.

[161] WOLFENSBERGER M., AMSLER U., CUENOD M. et al.: *Identification of quinolinic acid in rat and human brain tissue*. Neurosci. 41:247-252, 1983.