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Human immunodeficiency virus dementia: Evidence of a subcortical process from studies of fine finger movements

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HIV-1 associated dementia is the major manifestation of HIV-1 within the central nervous system and a devastating disease which is characterized by cognitive, motor, and emotional deficits. HIV-1 associated minor motor deficits can manifest as psychomotor slowing and predict the later development of HIV-1 associated dementia, AIDS, and death. These minor motor deficits can be described, e.g., by electrophysiological assessment of basal ganglia motor function (frequency of most rapid alternating finger movements, reaction and contraction times of most rapid index finger extensions). Minor motor deficits quantified by contraction times can be subdivided into a more incipient and a more sustained type of deficit. Parallel examination of motor function and positron emission tomography, magnetic resonance spectroscopy of the basal ganglia, or SPECT helps to point to the basal ganglia as a pivotal point of HIV-1 associated CNS pathology. *Journal of NeuroVirology* (2002) **8(suppl. 2),** 27–32.

Keywords: basal ganglia; electrophysiological motor testing; HIV-1 associated dementia; HIV-1 associated minor motor deficits; subcortical dementia

Introduction

In 1983, Snider *et al* (Snider *et al*, 1983) published for the first time neurological complications in acquired immunodeficiency syndrome (AIDS) patients. They described so-called opportunistic brain infections (i.e., toxoplasma encephalitis, cryptococcal meningoencephalitis, cytomegalovirus encephalitis, progressive multifocal leukoencephalopathy, and many others). Furthermore, they found immunodeficiency virus (at that time named human T-cell lymphotropic virus [HTLV] III)-associated diseases, polyneuropathy, myelitis, and a form of dementia, to be characterized mainly by subcortical deficits. Snider *et al*, as well as other authors (McArthur and McArthur, 1986; Navia *et al*, 1986a and b), described during the following years the most striking cerebral AIDS manifestation—finally called human immunodeficiency virus (HIV)-1–associated dementia or AIDS dementia complex (ADC)—in more detail. They found psychomotor slowing, apathy, bradykinesia, altered posture and gait, cognitive deficits, and emotional disturbances such as depression to be characteristics of this disease, often presenting as the first AIDS manifestation during the pretreatment era, i.e., before antiretroviral substances could be applied to the infected individuals. In most of the early publications describing HIV-associated dementia, common clinical features ressembled those of patients with Parkinson's disease, i.e., bradykinesia, impaired manual dexterity, gait abnormalities (Navia *et al*, 1986b), postural instability (McArthur and McArthur, 1986; Navia *et al*, 1986b; Arendt *et al*, 1994b), ocular motility abnormalities, as well as rigidity, hypomimia, hypophonia, poorly articulated speech, and seborrhoic dermatitis. During the following years, i.e, from 1987 to 1994, several groups tried to establish test batteries for early diagnosis of the devastating dementia of all the young infected people (McArthur, 1987; Arendt *et al*, 1990, 1993, 1994; Brew *et al*, 1990; Bornstein *et al*, 1992,

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1993; McAllister *et al*, 1992; Baldeweg *et al*, 1993a and b; Berger *et al*, 1994) and found psychomotor slowing to be predictive for developing dementive symptoms and patients' death (McArthur *et al*, 1993; Arendt *et al*, 1994; Sacktor *et al*, 1996). Because psychomotor slowing is one of the parkinsonian symptoms characteristic of HIV-1–associated dementia, some groups (Nath and Jankovic, 1989; Arendt *et al*, 1993; Berger *et al*, 1994; Berger and Nath, 1997; Berger and Arendt, 2000) specialized in examining basal ganglia deficits in HIV-1–positive and AIDS patients by electrophysiological procedures (Arendt *et al*, 1990, 1993) and cerebrospinal fluid analysis (Berger *et al*, 1994; Berger and Arendt, 2000). This paper focuses on electrophysiological methods.

Results

In parallel to the motor test results revealing basal ganglia dysfunction in HIV-1–associated dementia (Nath and Jankovic, 1989; Arendt *et al*, 1990, 1993, 1994a), positron emission tomography (PET) studies showed contradictory results, some studies demonstrating hypometabolism (Rottenberg *et al*, 1987, 1996) in the basal ganglia as well as publications showing hypermetabolism (van Gorp *et al*, 1992; Turjanski *et al*, 1994). von Giesen *et al* (2000a) concluded from these differing results and from their own studies on a multiphasic course of HIV-1–related brain disease: a first phase of normal metabolic and electrophysiological function; a second phase of primary hypermetabolism with on-going normal electrophysiological function, followed by a metabolic "pseudonormalization" in parallel to first functional deficits; and, finally, by a secondary hypometabolism with marked electrophysiological deficits, resulting in the HIV-1–associated cognitive/motor complex and later on in HIV-1–associated dementia. Magnetic resonance (MR) spectroscopy results (von Giesen *et al*, 2001) reveal an elevation of glial cell markers in HIV-1–positive patients with minor motor deficits as a hint for an inflammatory process in the basal ganglia during early virus-associated brain disease, whereas neuronal cell markers are normal. Figure 1 shows an example of an HIV-1–positive patient without any form of functional cerebral deficit in comparison with a patient with a so-called "sustained minor motor deficit," which is motor dysfunction without response to highly active antiretroviral therapy (HAART). The elevated glial and the normal neuronal cell markers in the basal ganglia are evident.

The question is whether the virus provokes basal ganglia dysfunction by irritation of the active dopamine transporters or by disturbing D-receptor function. Single photon emission computer tomography (SPECT) studies try to clarify this issue. Figure 2 shows FPCIT = [^{123}I]N-ω -(fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([^{123}I]FP-CIT, Ioflupane [^{123}I]) (FPCIT)-SPECT results of an HIV-1–positive patient in comparison to a patient with idiopathic Parkinson's disease. In the HIV-1–positive patient, the active dopamine transport remains normal.

Figure 2 is taken from a small pilot study and the results must be verified in more patients. However, correlation of functional imaging and

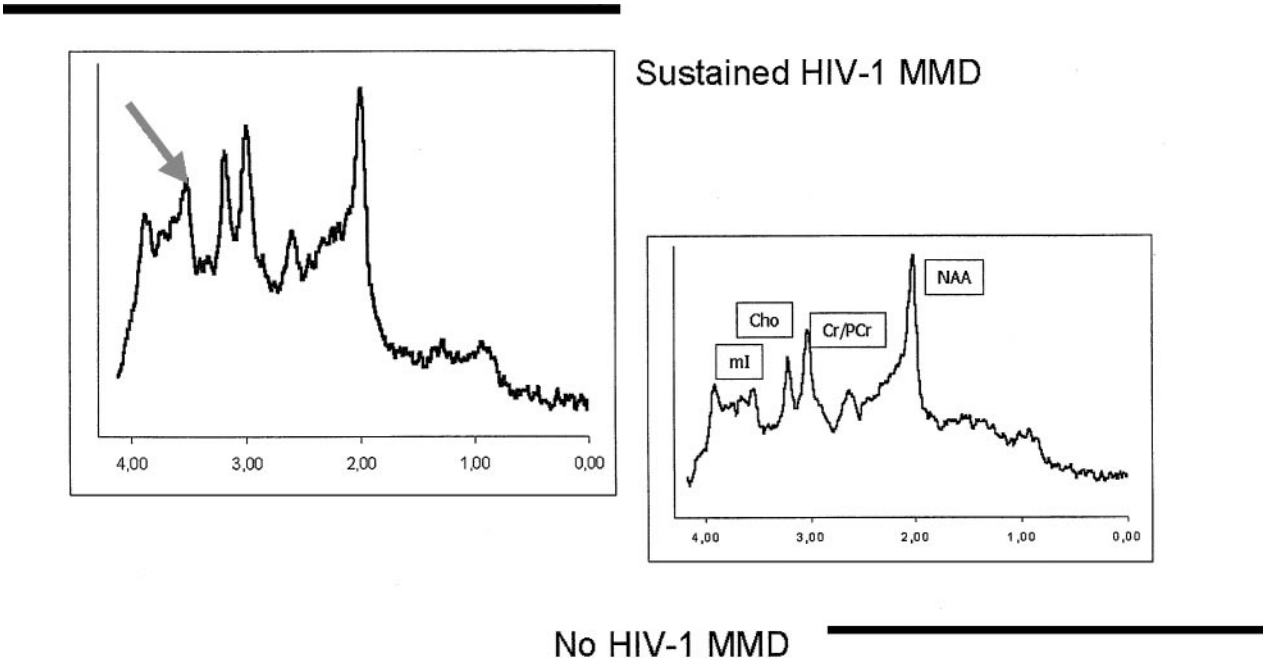

Figure 1 MR spectra of the basal ganglia region in a patient with sustained HIV-1–associated minor motor deficits (MMDs) (*left*) and an asymptomatic patient (*right*), demonstrating the increase in *myo*-inositol in MMD.

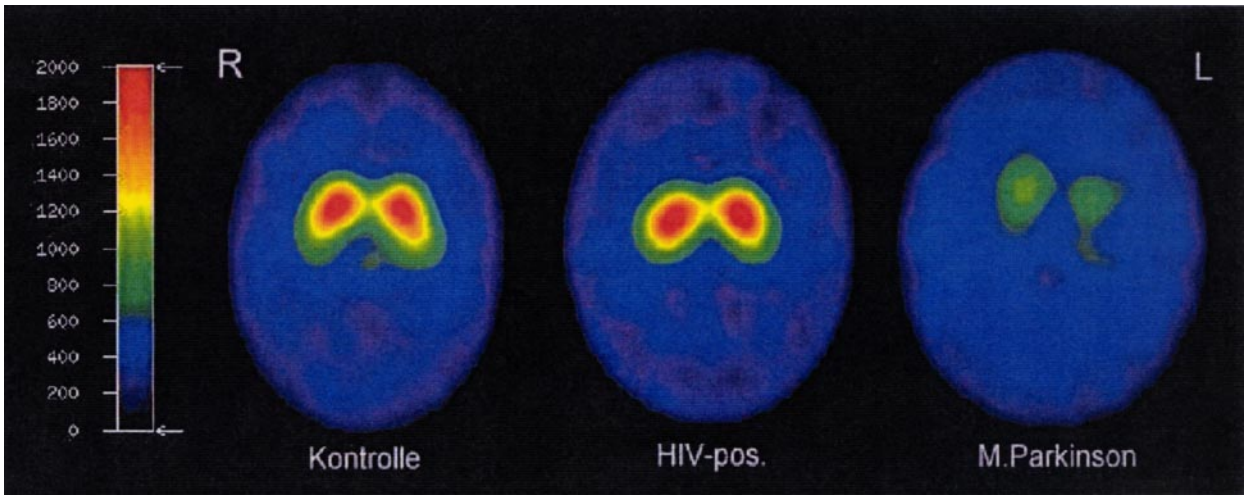

Figure 2 SPECT scan with I-123-FP-CIT visualizing the dopamine transporter in the basal ganglia of a healthy control (*left*), an HIV-1–positive patient (*middle*), and a patient suffering from Parkinson's disease (*right*).

electrophysiological studies underline the theory of basal ganglia dysregulation in HIV-1–related brain disease.

Neuropathological data show reactive cell changes, multinucleated giant cells, as well as glial-microglial collections and HIV-1–positive macrophages in subcortical gray matter (Navia *et al*, 1986a; Neuen-Jacob *et al*, 1993; Brew *et al*, 1995), presence of gp41 in basal ganglia (Kure *et al*, 1990), and decline of neuronal cell bodies (Reyes *et al*, 1991).

Discussion

Clinical and radiological changes in HIV-1–related brain disease have been shown to decline in the era of antiretroviral therapy. This development results from improved treatment options with respect to HAART. Schmitt *et al* (1988) demonstrated very early the positive effect of zidovudine—at that time the only treatment option—on subclinical and clinical virus-associated brain disease. Further studies (Arendt *et al*, 1992; Sidtis *et al*, 1993) underlined and extended these first results. After the introduction of HAART in 1996, studies (Sacktor *et al*, 1999; von Giesen *et al*, 2000b, 2002; Arendt *et al*, 2001; Sacktor *et al*, 2001) demonstrated a positive therapeutic and prophylactic effect of antiretroviral combination therapy on minor motor deficits and manifest dementia. Epidemiological studies (Janssen *et al*, 1989; Portegies *et al*, 1989; Day *et al*, 1992; McArthur *et al*, 1993; Sacktor *et al*, 1999; von Giesen *et al*, 2000b) show a constant decline of HIV-1–associated dementia under HAART. But it has become quite clear that the incidence has not gone down to zero. The Düsseldorf group has subclassified the minor motor deficits in incipient, transient, and sustained abnormalities; transient are those improving under HAART, and sustained are motor deficits not reacting positively to antiretroviral therapy. In conclusion, for those patients without response to HAART, other forms of therapy have to be evaluated, e.g., *N*-methyl-D-aspartate (NMDA) receptor antagonists and dopamine agonists have to be tested for potential efficacy. Furthermore, the complex neuropathogenesis of the AIDS dementia complex has to be further clarified, i.e., the inflammatory and potential neurodegenerative mechanisms, the role of certain viral proteins (tat, nef), characterization of neurotropic viral strains and their resistance profile with respect to antiretroviral drugs, and the analysis of receptor and coreceptor function in the brain altered by the HIV. These are urgent issues to be further clarified during the next decade.

Methods

Basal ganglia disease provokes a lack of control in movement planning, a lack of control in movement performance, and a lack of force development. The disturbance of the time structure of a movement destroys coordinated muscle interaction and a loss of movement control results. Additional problems result from unpredictable changes of movement intensity and/or amplitude and a disturbed selection of muscles taking part in a voluntary movement. Movement initiation and termination are the variables tested with the motor test battery of Arendt *et al* (1990, 1993, 1994), once developed for testing motor performance in patients with defined basal ganglia disease such as Parkinson's, Wilson's, or Huntington's disease. The most important parameters tested are impairment of most rapid alternating

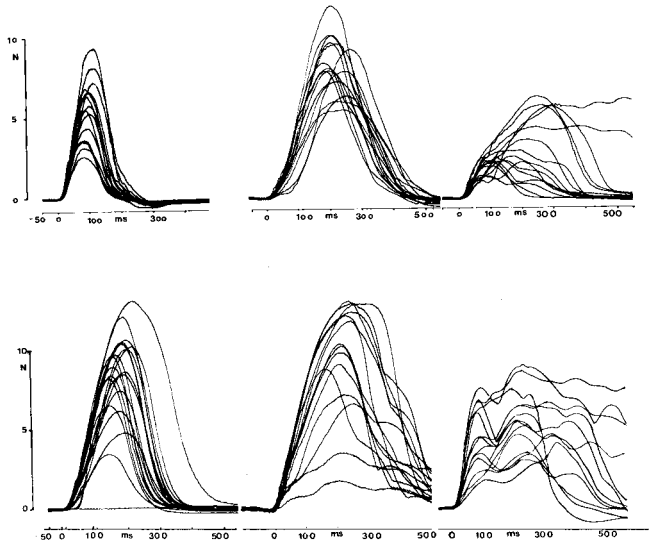

Figure 3 Registration curves of contraction times (CT) of a normal control (*upper row, left*) and HIV-1–positive patients (*upper row, middle*: clinically asymptomatic; *upper row*; *right* slightly demented), compared with the results of patients with defined basal ganglia diseases (*lower row, left to right*: patients with Huntington's, Wilson's, and Parkinson's diseases). Contraction time (ms) is the time the movement starts until it reaches its maximum.

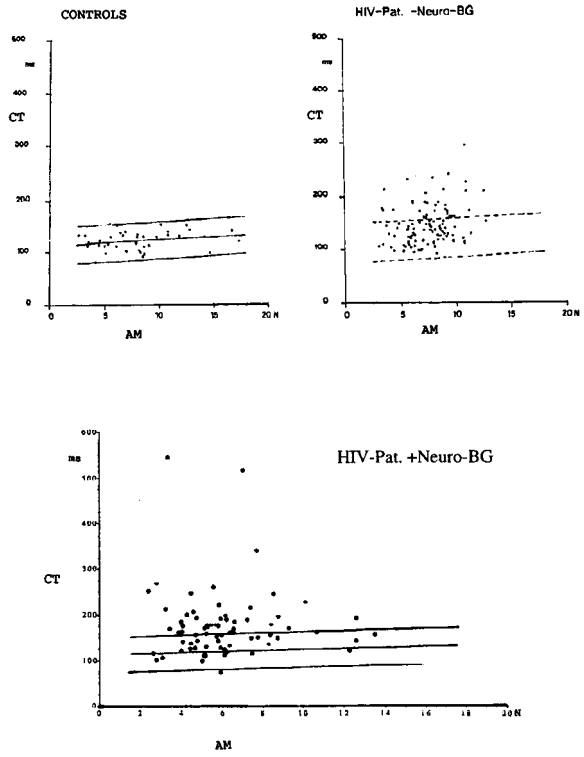

Figure 4 Relation between contraction times (CT) (ms) and the amplitude in different groups of HIV-1–positive patients (see Arendt, 1994).

index finger movements (MRAM) and prolongation of the most rapid index finger extensions (MRC) with the mathematically extracted parameter named contraction time (CT, ms).

Other groups (Dunlop *et al*, 1992; Karlsen *et al*, 1992) measured simple reaction times and found them prolonged in clinically asymptomatic HIV-1–positive patients, but this parameter did not turn out to be predictive for cerebral disease progression. Assessing postural imbalance—as in parkinsonian patients—is a method to detect pathology in beginning HIV-1–associated dementia (Beckley *et al*, 1998). The most sensitive parameter of the Düsseldorf test battery is contraction time. Figure 3 gives an example in comparing contraction times (CT) of clinically symptomatic and asymptomatic HIV-1–positive patients with the results of patients with defined basal ganglia diseases, i.e., of patients with Huntington's, Wilson's, and Parkinson's disease. Contraction time is the time the movement starts until it reaches its maximum.

In 1990, the Düsseldorf group defined in a prospective study normal CT ranges in HIV-1–seronegative patients, asymptomatic HIV-1–positive patients, and demented patients. Results of the demented individuals obviously lie outside the normal two standard deviation range (Figure 4).

Other groups used alternative methods to detect HIV-1–positive patients with impending cerebral affection, e.g., topographical electroencephalography (EEG) and evoked potential mapping (Baldeweg *et al*, 1993a, 1993b). But evoked potential and EEG examinations again did not turn out to be predictive disease markers.

Neuroradiological methods gave further hints for the special involvement of basal ganglia in HIV-1–associated dementia. Volumetric studies (Aylward *et al*, 1993, 1994) revealed a reduced basal ganglia volume; also, conventional MR imaging procedures show caudate atrophy (Dal Pan *et al*, 1992) and basal ganglia signal hyperintensity (Filippi *et al*, 1998). Metabolic studies revealed basal ganglia hypermetabolism (FDG-PET) (Rottenberg *et al*, 1987; van Gorp *et al*, 1992; von Giesen *et al*, 2000a), a decreased N-Acetyl Aspartat/choline (NAA/Cho) ratio in the basal ganglia (MRS) (Meyerhoff *et al*, 1993, 1999), a decreased NAA/creatin/creatinin (Cr) ratios in children with clinically manifest HIV-1–related dementia (Lu *et al*, 1996), elevated myo-inositol (mI) and Cho and decreased NAA levels in clinically overt HIV-1–associated dementia (Chang *et al*, 1999), and elevated mI/Cr ratios in patients with subclinical basal ganglia disease.

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