



SEVERE NEUROLOGICAL IMPAIRMENT AS INITIAL MANIFESTATION OF HIV INFECTION - CLINICAL CASES

A. Văță¹, Carmen Manciu¹, Cristina Nicolau², L. Prisăcariu², Gabriela Jugănariu¹, Gh. Dorobăț¹, D. Duiculescu³, Carmen Dorobăț¹

¹ University of Medicine and Pharmacy "Gr T. Popa"

² Infectious Diseases Hospital Iasi

³ Infectious and Tropical Diseases Hospital "Dr. Victor Babes" Bucharest

Abstract. The neuro-cognitive impairment in HIV infected patients may take an extremely wide range of clinical manifestations and can occur early (acute retroviral syndrome) or late in the history of the infection. We present three case reports of patients in whom some complex and atypical neurological manifestations led to the diagnosis of HIV infection after close collaboration of neurologists and infectious diseases specialists from several counties; the outcome and therapeutic approach are discussed. This kind of manifestations could become more frequent now in the newly diagnosed, late presenter, slow progressor patient.

Keywords: HIV encephalopathy, immunodeficiency, myoclonus

Introduction

The neuro-cognitive impairment in HIV infected patients may take an extremely wide range of clinical manifestations. It can be caused either by human immunodeficiency virus itself (by achieving high levels of replication in the central nervous system (CNS) or by associated immunological mechanisms) or by opportunistic infections (toxoplasma, CMV, JC virus, tuberculosis, cryptococcus) or associated tumoral manifestations (lymphoma). [1, 2]

The emergence of these neuropsychiatric events as first manifestation of immunosuppression syndrome associated with HIV infection is possible, either during the acute stage or later, in AIDS patients.

One of the most frequent and enigmatic neurological complications of the HIV infection is the HIV encephalopathy (HIVE) (also called complex AIDS dementia, sub acute encephalitis, HIV dementia, and HIV-1-associated cognitive/motor complex). In the pre-HAART era, some 15–20% of patients devel-

oped HIVE. Since then, the incidence has decreased, but to a lesser extent than the incidence of extracerebral AIDS manifestations. As the life expectancy of HIV-infected individuals in the developed world comes close to that of the general population, the prevalence of HIV-associated neurocognitive impairment has risen to some 20 to 50%. [3]

The symptoms of HIVE can be subdivided into three main categories: cognitive, motor, and behavioral [4]. The main cognitive manifestation is memory loss in association with impaired motor and mental performance. Apathy and social isolation are the earliest behavioral disturbances and are sometimes mistaken as depression. In a minority of cases intense manifestation of some organic psychosis, as acute mania, are the first signs of HIV dementia.[5]

We propose the presentation of 3 patients in which the relatively sudden appearance of neurological distress led to the diagnosis of HIV infection.

Case 1

Patient ADD, female, aged 21 (born in March 1989), from an urban area, college student, gets hospitalized on 30 December 2010, being directed by the County Hospital for motor deficit in the right hemycorpus in association with paraesthesia with the same topography, difficulty standing and

Andrei Văță

4 Fdt. Ursulea, Iasi, Romania

e-mail: andreiandrei@yahoo.com

walking, attention and speech disorders, insomnia.

Among the personal pathological history retains a hospitalization at the age of 9 months for an acute viral hepatitis, appendectomy at the age of 8 years, chicken pox at 13 and a year ago she presented two episodes of intercostal herpes zoster. Both parents and older brother were apparently healthy.

Laboratory examinations previously carried out showed a quasi-normal white blood count, with mild leucopenia, the absence of inflammatory reaction in the CSF; cerebral MRI showed no intracranial expansive processes, only diffuse white matter (demyelization) injuries.

Symptoms started about two weeks prior to admission with the appearance of paresthesia and muscle startles in the right upper limb, mild speech disorder, headache, which were initially ignored by the patient and her entourage. The emergence of motility disorders and their progression to the right leg led to addressing the neurologist. Unfavorable clinical evolution and the emergence of non-systematized fever (up to 38°C) have determined the admission to our clinic with suspected acute viral encephalitis.

On admission she was not febrile, had an influenced general condition, was conscious, cooperative, with motor deficit widened at the right upper limb and partially right leg, bone-tendon polykinetic reflexes at all levels, right Babinski, bilateral Hoffmann, mild speech disorder, unsafe walking, with whitish tongue, mild splenomegaly.

At this time we took into consideration a possible acute viral encephalitis, a poliradiculoneuritis, a possible onset of multiple sclerosis (based on the cerebral imaging examination).

Initial explorations revealed leucopenia (3340/mm³) with normal leukocyte formula, thrombocytopenia (124000/mm³), mild hepatocytolysis syndrome (ALAT-110/mm³), urea, creatinine, glucose, chest X-ray normal, no inflammatory reaction and normal chemistry in the CSF. Abdominal ultrasound showed enlarged spleen with longitudinal diameter of 142 mm.

We started treatment aiming to decrease the cerebral edema, pathogenic treatment with Solumedrol, group B vitamins and other neurotrophics.

The neurological manifestations apparently without explanation, the lingual aspect in combination with leucopenia in a patient born in 1989 with two episodes of zoster herpes in history raised suspicion of a possible HIV infection, sustained by a positive rapid test and then confirmed by two ELISA tests and Western Blot.

Immunological evaluation showed a high degree of immunosuppression with a total of 54 CD4/mm³. The viral load was 3*10⁶ copies/ml. Further explorations showed no co-infection with hepatitis

viruses (HBsAg negative, anti-HCV Ac absent), RPR negative, acute phase antibody absent and IgG present at minimal titers for toxoplasma and CMV. The determination of HIV viral load in CSF or conducting PCR for JC virus was not available.

The patient was staged as C3 AIDS, the suspicion for the neurological impairment being HIV progressive leucoencephalitis.

It was decided to initiate without delay ARV therapy associated with LPV/r + 3TC + ABC + RAL + T20, prophylactic administration of Biseptol, anti-fungal therapy with fluconazole.

The patient's clinical condition progressively worsened, with increasing limb motor deficits, the appearance of cranial nerves paralysis: right eye abduction limitation, pupillary inequality, right facial paresis, absence of velo-palatine reflexes, tongue kinetic and swallowing disorders and later the disappearance of spontaneous verbal communication and occurrence of repetitive myoclonus in the left upper limb.

The patient was transferred after 21 days of hospitalization to the Infectious Diseases Clinic „V. Babes“ Bucharest, where the unfavorable clinical course continues with loss of consciousness, sphincter control and development of respiratory distress for which she was intubated and mechanically ventilated in the ICU unit. The patient dies a week later, despite vigorous supportive care, due to MSOF.

Case 2

Patient BS, male, 21 years old (born 01.1989), from urban area who presented to our clinic (with his mom) in May 2010 for the appearance of neurological phenomena that consisted of myoclonus localized at right hemicorpus and walking disorders (walking with broad base of support) with sudden onset 5 days previously, in apparent health.

Myoclonus was gradually extensive, initially subintractant, diminishes during sleep and rest, were exacerbated by voluntary movements. Topographically it interested the right toe, right leg (causing involuntary movements), right thigh, right abdominal muscles (and left partially), paravertebral muscles (generating chest axial dystonia), right pectoralis major muscle and back muscles of the right shoulder and neck muscles.

From the pathological history of patient we retain repeated respiratory infections, he was hospitalized in the first year of life, adenoidectomy at the age of four, phimosis surgery – age 11, had most of the childhood diseases and was vaccinated according to recommendations.

The patient has a normal mental and intellectual development, he's a student. He has a HIV-negative girlfriend.

Later the mother admitted that the patient was diagnosed as HIV-positive at the age of 8 years (in 1997) but the illness was concealed by his parents for 13 years (1997-2010) (even after the age of majority) and he didn't receive any monitoring or ARV treatment.

Clinical examination at admission shows a good general condition, weight 96Kg, height of 180 cm, generalized micropoliadenopathy, lingual whitish deposits. He presented broad base walking, without disturbance of sensitivity, without affecting the cranial nerves and myoclonus with the characters described above.

Neurological examination states for a complex myoclonic syndrome and imposes that following investigations should be carried out: barium transit - for investigation of esophageal muscle - normal, echocardiography - normal myocardial kinetics, eye exams - slight decrease in visual acuity, with RFM absent, eye bottom examination - visual nerve papilla slightly pale in the right eye, bright reflections at macular level, vessels with normal emergence, size, trajectory.

Laboratory investigations showed a total of 92 CD4 cells/mm³, VL - 136000 cp/ml, AgHBs - negative, HCV antibody - absent, IgM antibodies against CMV and toxoplasma - absents, craniocerebral CT - without significant changes.

The patient was staged as stage B3 HIV seropositive, with Oropharyngeal candidiasis and a progressive multifocal leukoencephalopathy is suspected. ARV treatment is initiated with Raltegravir + LPV/r + ABC+3TC, anti-inflammatory drugs - SoluMedrol in decreasing doses, anticonvulsants as indicated by the neurologist - Clonazepam, Tiapridal, antifungal - Fluconazole, prophylaxis of pneumocystosis - Biseptol.

The therapy is well tolerated, with partial improvement of neurological symptoms myoclonic shock like contractions spacing, but keeping their intensity constant and topographic extension of the lesions. The family insisted for the transfer of the patient to the „Victor Babes” Hospital in Bucharest.

Here we find a slight improvement of viro-immunological status with CD4 - 137 cells/mm³, VL - 617 copies/ml. Lumbar puncture shows clear CSF, with no inflammatory reaction, normal chemistry and a VL in the CSF = 1010 copies/ml, BK, yeasts absent. Serological tests shows no type IgM antibodies anti-measles, but IgG positive = 2.47 (VN = 0-1), anti - HSV, anti CMV - Ig.M antibodies absent. Neurological review shows myoclonus with partial continuous epilepsy aspect, suggesting a subacute myoclonic encephalitis.

MRI scan shows multiple diffuse lesions with symmetrical T1 hiposignal and T2 hipersignal at the thalamus level, lenticular nuclei and occipital,

periventricular deep into the white matter bilaterally, in the frontal cortex bilaterally and left parietal and infratentorial ponto-mid-brain with no mass effect and no outlet contrast.

It is recommended to add T20 and maraviroc to the ARV treatment. The next few months bring in terms of clinical - neurological symptoms a stagnation consistent with a discrete improvement of MRI lesions and ARN-HIV LCR decrease (1010 copies/ml => <40 copies/ml). At present (January 2011) the general condition has improved the convulsive phenomena disappeared, with partial recovery of motor acquisitions, but he maintains difficulties in the voluntary exercise of fine movements. The intellect was not affected and he continues his studies - the second year of college.

Case 3

Patient SSI, male, aged 22 (born in 1988), from a rural area, unemployed, who is hospitalized in our clinic in January 2011 for headache, vomiting, paralysis of multiple cranial nerves (facial (VII), oculomotor (III), IX), reversible seizures and a brief suspension of consciousness associated with sphincter control abnormalities.

Personal pathological history is poor, with two hospitalizations before the age of one year for unspecified respiratory disease, pneumonia and other respiratory viral infections in 2009 for which the patient took frequently antibiotics. Both parents and younger sister are apparently healthy. The patient was a nonsmoker, denied drinking alcohol.

The onset of the disease was insidious, with approximately 2 weeks prior to the admission by the emergence and progressively aggravation of a predominantly occipital headache followed by nausea and vomiting, drowsiness without fever; the symptoms were not responsive to nonsteroidian anti-inflammatory and antibiotic (Augmentin) treatment administered.

The appearance of repeated and reversible crises of suspension of consciousness with retrograde amnesia in association with sphincter incontinence resulted in admission to the neurology department of the local hospital with suspicion of grand mal epilepsy.

During hospitalization at Neurology the patient remains nonfeverish, installs progressive cranial nerve paresis: left facial initially, then bilateral oculomotor, nerves VI, IX, X, the patient showing bilateral eyelid ptosis, dysphagia for liquids and solids, dysphonia, speech disorder (dysarthria), bilateral horizontal nystagmus.

Clinical examination shows that there was no meningeal syndrome, mild hepato-splenomegaly, tongue with abundant white deposits (interpreted as a lingual candidiasis after antibiotic therapy); the

patient is conscious, easily bradilalic, sleepy.

The laboratory examinations showed mild leukopenia (GA - 5900/mm³) and no biological inflammatory syndrome, normal renal and liver function. Brain MRI shows no intracranial expansive processes, only diffuse demyelinating lesions, likely with vascular substrate. The lumbar puncture shows a clear CSF with no inflammatory reaction and a quasi-normal chemistry (mild decrease of clorurorahia).

The aggravation of intracranial hypertension syndrome and motor deficits entail the transfer to Neurosurgery Hospital Iasi, after 4 days of hospitalization with a diagnosis of brainstem syndrome and suspicion of Miller Fisher type poliradiculonevritis.

The neurologist from Iasi faced with the patient with multiple facial nerve pareses require an infectious diseases consult for a suspected botulism.

The patient reaches the clinic in late January 2011 with the intensely influenced general condition, sleepy, conscious but spatial and temporal disoriented, afebrile, presenting a stiff neck and Kernig I sign and multiple cranial nerve paresis previously cited (nerve VI, VII, IX, X), mild hepatosplenomegaly, oropharyngeal candidiasis, urinary probe catheters.

The presence of a subtle meningeal contracture syndrome causes the reiteration of the lumbar puncture showing a clear CSF with 9-elements/mm³, 100% lymphocytes and chemistry within normal limits (AR-0.28 g/l, GR-0.46 g/L, CR-7.35 g/l) highlighting numerous encapsulated yeast, some of them budding.

Identification of fungal meningitis, determines

a HIV test whose result is positive; the diagnosis was subsequently confirmed by Western-Blot. CD4 lymphocyte count was extremely low - 5/mm³ and viral load was 62400 c/ml. Further explorations showed no other organ distress, evidence of renal, hepatic, cardio-pulmonary imaging investigations, abdominal being normal. Serologically, a hepatitis virus infection (VHB, VHC, VHD), syphilis, a recent infection with CMV, toxoplasma are invalidated.

The therapy was started with iv fluconazole, pneumocistosis prophylaxis with Biseptol and ARV treatment with ABC+3TC+LPV/r+T20.

The yeasts from the CSF were identified as *Cryptococcus neoformans* with susceptibility to fluconazole, amphotericin B, Voriconazole, Itraconazole.

Evolution under antifungal and antiretroviral therapy has been slow, with repeated tonico-clonic seizures, cranial nerves paresis persistence for about 10 days and then gradually improvement of the neurological phenomena.

Discussion

The three presented patients had different neurological signs as the primary clinical manifestation of HIV infection. These events did not belong to encephalitis during the acute retroviral syndrome, but occurred in patients with advanced immunosuppression and most likely with a long history of asymptomatic HIV infection. This was confirmed only for patient no. 2, in which HIV was deliberately ignored for 13 years due to concealment of the HIV positive status by the parents, but can be suspected in the other two patients, who belong to the 1989 cohort, most likely being infected perinatally.

	Cazul 1 (ADD)	Cazul 2 (BS)	Cazul 3 (SSI)
Age (years)	21	21	22
Sex	f	m	m
Fever	+	-	-
Motor signs	+++	++	++
Sensitive impairment	+	+/-	-
Cognitive impairment	++++	+	++
Coma	yes	no	no
CD4 /ml	54	92	5
VL (copies/ml)	3*10 ⁶	1.3*10 ⁵	6.2*10 ⁴
Diagnostic	HIVE	HIVE	Cryptococcic meningo-encephalitis
ARV treatment	LPV/r + 3TC + ABC + RAL + T20	RAL + LPV/r + ABC + 3TC+ T20 + maraviroc	ABC+3TC+LPV/r+T20

Table I. Demographic, clinical, laboratory and therapeutical characteristics of the case reports

These patients can be considered as late presenters, with advanced HIV infection based both on the initial low CD4 levels (between 5 and 92/mm³) and on the clinical manifestation which led to an AIDS diagnosis.

We noted that just one patient (ADD) had fever during the acute phase of the neurological illness, which was low grade (below 38°C) and appeared after several days of hospitalisation.

Making an HIVE diagnosis requires a synopsis of clinical information and the results of many laboratory tests. No test result on its own can warrant a diagnosis of HIVE. Rather, the diagnosis requires the exclusion of other conditions.

In the first two patients we couldn't find another cause for the neuro-psychological distress manifested and based on a rather typical clinical picture and brain MRI appearance (multiple lesions of white matter, no space occupying effect, no edema, no contrast enhancement) may be classified as having Progressive multifocal leukoencephalopathy.

Several criteria are employed for the assessment of the severity of HIVE, one of the widely used score is the Memorial Sloan Kettering scale (Price 1988).[6]

Another particularity of the first two cases was the relatively sudden appearance of neurological phenomena and rapid progress towards aggravation of the encephalitis. In the case of ADD patient (case 1) they have been moving from stage 0 to stage 4 in about 2 months and have not been followed by an improvement, even after the imposition of potent antiretroviral therapy. In the case of BC patient (case 2) neuro-psychological phenomena have occurred and have increased gradually over 30 days, moving from stage 0 to stage 2 (moderate distress) and were successfully controlled by the therapeutic intervention on HIV replication and intensive neurotropic treatment.

Cryptococcus neoformans is the third most common etiological agent for severe CNS sufferance in HIV infected patient after viruses (HIV or CMV) and toxoplasma. In some communities cryptococcal meningitis is more common than cerebral toxoplasmosis in these patients.[7]

The third case was the one with the fastest evolution. The development of motor deficits and seizures initially suggested the presence of an intracranial expansive process, but ultimately turned out to be secondary to cryptococcal meningoencephalitis in a severely immunocompromised patient and which (surprisingly) has responded particularly well to antifungal therapy with fluconazole and to potent ARV therapy that has been administered.

The level of HIV replication and the viral subtypes from the CNS are not always correlated with the hemato-lymphatic compartment. According

to the pathogenesis of HIVE, treatment should be aimed on suppressing viral replication in the CNS. Although the CNS is a separate compartment of viral replication, the initiation of HAART leads to a generally rapid decline of viral load in the CSF [8] with clinical improvement of neuro-cognitive performance occurring in 3 to 9 months. [9] The extent of penetration into the CSF and the brain parenchyma is generally assumed to be essential. Achieving a fastest possible effective viral suppression, particularly in the CNS compartment was the motivation for the choice of ART in all cases presented.

All cases had benefited from the good cooperation between doctors: neurologists, radiologists and infectious diseases specialist without which an accurate and early diagnosis and appropriate therapy would not have been possible.

Conclusions

- Severe neurological symptoms can sometimes be (especially in patients born around 1989) reminiscent of a severe immunosuppression due to the HIV infection
- The frequency of these events, especially in the late presenter, slow progressor seems to be increasing lately
- A good cooperation between the neurologist, psychiatrist, radiologist and infectionist is mandatory to resolve favorably this type of pathology

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