MAJOR HIV – ASSOCIATED NEUROLOGICAL DISORDERS IN YOUNG PATIENTS

Summary:
Introduction: Disorders of both the central nervous system (CNS) and peripheral nervous system (PNS) can complicate HIV infection from the period after initial infection through the end stages of the severe immunosuppression.

Material and methods: We received 13 patients hospitalized on emergency between March 2009 – March 2011 (only self-casuistry). Demographic (sex, age), clinical, imaging (cerebral MRI, abdominal MRI), paraclinical (CSF, PCR), extensive laboratory workup data (Western blot test, CD4 + T-lymphocytes, Viral load, antibodies for CMV, Ebstein-Barr, Toxoplasma, Toxocara, hepatic markers, tumoral markers, VDRL), ECG, Ecocardiography, as well as risk factors, treatment, evolution and neurologic recovery were all considered. All patients had firstly a clinic neurological examination.

Results: The study group consisted of 13 patients, 9 male and 4 female; aged between 19 and 56 years (mean age = 31 years). The number of hospitalization days ranged between 3-44, with an average of 22 days (3 hospitalization days were reported in the case of one single death). Clinical spectrum of neuro-HIV disease: diffuse disorders of the meninges (CMV, Meningococcus meningitis- 2 cases); focal CNS disorders (cerebral toxoplasmosis and toxocara infection-1 case, PML-1 case, stroke-4 cases, cerebral tuberculomas-1 case, HSV encephalitis-2 case); VZV myelitis (1 case), brachial plexopathy (1 case), Zidovudine myopathy and stroke (1 case). The symptomatology was various related both to the disease etiology as well as to neuroanatomical localization.

Conclusions: Causes of ischemic stroke include coinfection with Toxoplasma, Toxocara and VZV which determines local vasculitis. Another cause of ischemic stroke at one patient with HIV-infection was non-bacterial thrombotic endocarditis and procoagulant states. In young patients with HIV - infection and symmetrical lesions predominantly located in the parieto–occipital white matter at the junction of gray and white matter, without mass effect, we should think at PML. Cerebral tuberculomas may develop in patients with HIV–infection. Major HIV–associated neurological disorders may occur at any time from infancy to old age, but most reported cases have been in young patients.

Keywords:
HIV–associated neurological disorders, cerebral MRI, Western blot, viral load, echocardiography
INTRODUCTION

The neurological complications of HIV (Human Immunodeficiency Virus) infection occur in all stages of the HIV disease. Disorders of both the central nervous system (CNS) and peripheral nervous system (PNS) can complicate HIV infection from the period after initial infection through the end stages of the severe immunosuppression (1).

We used a classification based on the underlying pathophysiology and HIV disease stage for the CNS disorders; for HIV – associated neuromuscular disorders we present classification based on neuroanatomical localization.

Clinicians must be aware that more than one site of neural axis can be involved in the same HIV – infected patient at the same time.

We study diffuse disorders of the meninges like: aseptic HIV meningitis; cryptococcal meningitis, syphilitic meningitis.

Predominantly nonfocal brain disorders associated with HIV infection described in our study are: toxoplastic encephalitis, cytomegalovirus (CMV), encephalitis, herpes virus encephalitis and, more important are predominantly focal disorders: progressive multifocal leukoencephalopathy (PML), stroke, tuberculomas, cerebral toxoplasmosis and toxocara. At the spinal cord level we have VZV (Varicella – Zoster Virus) myelitis. Peripheral neuropathies associated with HIV infection, in the early stages (immune dysregulation) include vasculitic neuropathy, brachial plexopathy.

Myopathic symptoms in HIV infected individuals can arise from toxic (zidovudine) or dysimmune causes(2). 

AIM OF STUDY

Experience in large HIV clinics indicated that the diagnosis of the neurological complications of the HIV infection and AIDS is far from being an academic exercise (1). Precise diagnosis is critical but we want to establish a new standard to approach of this disease, considering that it becomes more frequent. This paper is an ongoing study about major HIV associated neurological disorders, the first reports being done in 2010.

MATERIAL AND METHODS

Patients

We received 13 patients hospitalized on emergency between March 2009 – March 2011 (only self - casuistry). Demographic (sex, age), clinical, imagistic (cerebral magnetic resonance imaging- cerebral MRI), paraclinic (Cerebrospinal fluid - CSF), extensive laboratory workup data, as well as risk factors, treatment, evolution and neurologic recovery were all

Rezumat:
Infectia cu HIV afecteaza sistemul nervos central si periferic pe tot parcursul evolutiei bolii, din stadiul initial pana in stadiul terminal caracterizat prin imunosupresie severa.

Material si metoda: Au fost evaluati 13 pacienti spitalizati prin urgenta intre martie 2009 si martie 2011 (numai cazistica proprie). Au fost studiate datele demografice (sex, varsta), examenul clinic neurologic si cardiologic, date imagistice (RMN cerebral si abdominal, Echocardiografie), paraclini(LCR, PCR), precum si analizele de laborator specifice bolii (Western blot, CD4+ limfocite T, viral load, anticorpii pentru CMV, Ebstein-Barr, Toxoplasma, Toxocara, markerii hepatitici si tumorali, VDRL), factorii de risc, tratament, evolutie si recuperare neurologica. R

rezultate: In studiu au intrat 13 pacienti, 9 barbati si 4 femei, cu varste cuprinse intre 19 si 56 de ani (varsta medie 31 ani). Numarul zilelor de spitalizare a fost cuprins intre 3-44, cu o medie de 22 zile (3 zile raportate numai pentru singurul caz de deces). Spectrul clinic al manifestarilor neurologice in infectia cu HIV este: boli difuze care afecteaza meningele (meningite cu CMV si meningococ-2 cazuri); boli focale ale SNC (toxoplasma si toxocara cerebral-1 caz; PML-1 caz; AVC ischemic-4 cazuri); tuberculoma cerebral-1 caz; encefalita cu virus herpetic-2 cazuri); mielita cu VZV-1 caz; plexopatie brahiala cu VZV; miopatie la Zidovudina. Simptomatologia a variat in functie de etiologia bolii precum si de localizarea neuroanatomica a leziunilor.

Concluzii: Cauza accidentelor vasculare cerebrale (AVC) ischemic in infectia cu HIV include suprainfectarea cu Toxoplasma, Toxocara si VZV care pot determina vasculite locale. Alte cauze implicate in AVC ischemic la tineri au fost endocardita trombotica non-bacteriala si statusul procoagulant. La pacientii tineri infectati cu HIV cu leziuni cerebrale simetrice localizate parieto-occipital la jonctiunea dintre substanta alba si cenuzie, fara efect de masa, trebuie sa ne gandim la PML. Tuberculomele cerebrale pot aparea la pacientii tineri infectati cu HIV. Bolile neurologice majore asociate infectiei cu HIV pot aparea oricand, din copilarie la varste inaintate, dar cele mai multe cazuri au fost raportate la pacientii tineri.

Cuvinte cheie: manifestari neurologice, RMN cerebral, Western blot, viral load, Echocardiografie
considered. All patients had firstly a clinic neurological examination.

Investigations

Cerebral MRI – the optimal method of diagnosis for HIV related focal CNS disorders (cerebral toxoplasmosis, progressive multifocal leukoencephalopathy, primary CNS lymphoma and stroke). Cerebral MRI T2- weighted and Flair used minimum two plans (axial, coronal and/or sagittal) find multiple lesions in multiple locations.

Abdominal MRI shows hydatic hepatic and splenic cysts (2 cases).

Other tests:

- Lumbar puncture with CSF analyses may be normal but over 50% of patients have increased concentration of protein associated with a normal concentration of glucose (4). Most of this protein is IgG antibody to HIV and it is present in a much higher titer than in serum, suggesting that the antibody is being synthesized within the CNS (5). A mild lymphocytic pleocytosis is present at a few patients.
- PCR (polymerase chain reaction) was made for progressive multifocal leukoencephalopathy, CMV encephalitis and for Ebstein-Barr infection.
- Laboratory:
  - The most commonly used tests to detect HIV antibody utilize enzyme immunoassay and Western blot analysis. Western blot detects antibodies to different HIV - 1 or HIV - 2 proteins and is more sensitive for some viral proteins than for others. However, both the sensitivity and the specificity of this test are high, with a false – negative rate of approx. 1 in 250.000, and a false - positive rate of about 1 in 20.000 (6).
  - CD4 + T - lymphocytes – accurate measures of CD4 + T - lymphocytes are essential to the assessment of the immune system of HIV - infected persons. The CD4 + T-lymphocytes level is a prognostic indicator in patients with HIV infection.
  - Viral load assays directly measure HIV RNA copy numbers in plasma
  - Antibodies for CMV, Ebstein –Barr, Toxoplasma, Toxocara, Echinococcus (IgG, IgM)
  - Hepatic markers
  - Tumoral markers (ACE and CA 19/9)
  - VDRL
  - Chest X-ray
  - ECG, Echocardiography – patients were evaluated by the cardiologist.

RESULTS

The study group consisted of 13 patients, 9 male and 4 female; aged between 19 and 56 years (mean age = 31 years).

The number of hospitalization day ranged between 3 - 44, with an average of 22 days (3 hospitalization days were reported in the case of one single death).

Clinical spectrum of neuro – HIV disease:

- Diffuse disorders of the meninges:
  - CMV meningitis (1 case - male)
  - Meningococcus meningitis (1 case - female)
- Focal CNS disorders:
  - Cerebral toxoplasmosis and toxocara infection (1 case-male)
  - Progressive Multifocal Leukoencephalopathy (1 case - male)
    - Stroke (4 cases - males)
    - Mycobacterium tuberculosis abscess (tuberculomas) with chronic lymphadenitis TBC (1 case - male)
    - Herpes simplex virus encephalitis (2 case - females)
- At the spinal cord: - VZV myelitis at the thoracal level (T6-T10) - (1 case - female)
- Peripheral neuropathies associated with HIV - infection in the early stages and VZV infection – brachial plexopathy - (1 case-male)
- Zidovudine myopathy and stroke - (1 case-male)

We mention that the patients with CMV meningitis, cerebral toxoplasmosis and toxocara infection, Zidovudin myopathy and ischemic stroke were diagnosed for the first time at the Hospital “M. Bals” – Bucharest. We received these patients in chronic stages.

The symptomatology was various related both to the disease etiology as well as to neuroanatomical localization.

CMV is one of the most common causes of serious opportunistic viral infection in patients with HIV - infection. CMV infection caused an aseptic meningitis, at our patient, the clinical manifestations includes fever, stiff neck, lethargy; recovery was total because the CMV infection did not expand to become a meningoencephalitis.

We have a case, M.A. female, hospitalized with superficial coma, severe psychomotor agitation, stiff neck, vomiting, fever and rush. Rush can take multiple forms but it was generalized, truncal, urticarial exanthem
characterized by large raised, nonvesicular, erythematous plaques. We made biopsy of these lesions which reveals dilatation of the small blood vessels in the papillary dermis and infiltrates of lymphocytes and macrophages. Lumbar puncture evidences moderate increase in concentration of protein in the CSF and it was isolated Neisseria meningitidis. Clinical symptoms and evolution indicated Kawasaki disease and we considered the possibility that Kawasaki disease had been precipitated by a retrovirus.

Stroke is a common neurological complication of HIV infection.

We present the most special cases, having a various clinical symptomatology and different etiology:

- **First case**, MG, male, 37 – year old, hospitalized on March 2009 with left hemiparesis, VZV thoracic, hepatosplenomegaly. MRI Flair coronal image showing a 2 cm lesion in right frontal lobe (Fig. 1a) and 1,5 cm lesion in left temporal lobe (Fig. 1b) with aspect of ischemic stroke.

MRI abdominal shows hydatic hepatic and splenic cysts.

Laboratory:
- Western blot HIV-1 and HIV-2 positive (ELISA –MUREX, ELISA GEN SCREEN)
- CD4+ = 14 cell/ mmc (VN= 410- 1590 cell/ mmc).
- Viral load 121313 cps/ ml.
- CMV ( Ig G ) positive.
- Ebstein- Barr ( Ig M ) negative.
- Hepatic markers negative.
- Toxoplasma ( Ig G ) and Toxocara ( Ig G ) positive.
- Echinococcus ( Ig G ) negative.
- VDRL negative.

The patient had been under antiretroviral therapy for 18 month and he developed zidovudine myopathy. This is a toxic mitochondrial disorder that occurs with the insidious onset of proximal weakness and myalgia.

- **Second case**, DA, male, 19-year old, was hospitalized in June 2009 with left hemiparesis, seizures.

MRI T2 ( Fig. 2a, Fig 2b ) and Flair ( Fig 3b ) axial images shows wide areas with high signal into the white frontal matter bilaterally extended towards the right internal capsule and lentiform nucleus, which do not capture gadolinium and with aspect of leukoencephalopathy.

CSF albumine was 0, 817 g/ L.
ECHO cardiac: mitral valve prolapses, moderate aorta regurgitation, hyperechogenic pericardium.

Laboratory:
- Western blot HIV-1 and HIV-2 positive.
- CD4+ = 10 cell/mm cubic
- Viral load 112002 cps/ml.
- CMV (Ig G) POSITIVE.
- Ebstein-Barr (Ig M) negative.
- Hepatic markers negative.

The patient was under antiretroviral therapy for 12 months and we administrated him Levetiracetam + Carbamazepine for seizures.

- The third case, C.I., male, 28-year old, was hospitalized in September 2010 with right hemiparesis, motor aphasia, seizures, left lateral cervical ganglion diagnosed in May 2010 as chronic lymphadenitis TBC by biopsy, splenomegaly.

MRI T2 axial images shows five central necrosed lesions, between 1-3 cm with peripheral gadophilia and important edema (one in right temporal lobe- Fig. 3a; two in left frontal lobe- Fig. 3b and two in left parietal lobe- Fig. 3c), with aspect of cerebral tuberculomas.

Laboratory:
- Antibodies anti HIV-1 and HIV-2 positive, diagnosed at that moment.
- Hepatic markers negative.
- Tumoral markers (ACE and CA 19/9) negative.

The patient was under tuberculostatic treatment (Isoniazide, Rifampicine) for 4 months and we administrated him Levetiracetam + Carbamazepine for seizures.
EVOLUTION

Generally it was favorable. There was a case of death in one patient, female, 56 years with HIV infection, meningitis with Neisseria meningitidis, vasculitis (Kawasaki disease-like) and endocarditis. She died after 3 days of hospitalization.

TREATMENT

Etiological treatment—was made into large HIV clinics (Clinics “Matei Bals” – Bucharest and “Victor Babes” Timisoara).

Symptomatic treatment.

Therapy of depletion with Mannitol was performed for the patients with intracranial hypertension.

DISCUSSIONS

The neurologic complications of HIV-infection can be classified broadly as either primary or secondary (7).

Primary neurologic complications are those attributable directly to HIV—infections of the CNS. Secondary neurologic complications includes opportunistic infections and neoplasms facilitated by the HIV induced immunodeficiency states, cerebrovascular complication and toxic states. The risk of neurological complications increased with the progression of the HIV infection and decline of the CD4+ counts. These disorders affect every level of the neuraxis, and a certain patient may suffer more than one HIV-associated neurological disease (1).

Many patients develop neurologic manifestations caused by more than one etiology. Some patients develop parenchymal disease like: cerebral toxoplasmosis, primary CNS lymphoma, PML and stroke. Others develop meningeal disease.

PML is a demyelinating CNS disorder caused by reactivation of infection of oligodendrocytes and astrocytes with the JC virus (John Cunningham virus), a member of Papovavirus family (8). In HIV infected patients, PML usually occurs when the CD4+ cell count is less then 200 cells/mm3. The examined casuistry includes within the MRI and laboratory patterns from the field literature.

Stroke is a common neurologic complication of the HIV-infection. Mechanisms of stroke in HIV-infected patients vary with HIV vasculopathy reported in 20% of cases, followed by coagulopathies, hyperviscosity,
endocarditis and ruptured mycotic aneurysmus. Cerebral infarctions are more common than intraparenchymal hemorrhage (9). We have only ischemic stroke in our patients. In one of them, we describe that VZV thoracic can cause infectious vasculitis.

**CONCLUSIONS**

- Causes of ischemic stroke include coinfection with Toxoplasma, Toxocara and VZV which determines local vasculitis. Another cause of ischemic stroke at one patient with HIV- infection was non- bacterial thrombotic endocarditis and procoagulant states.
- In young patients with HIV – infection and symmetrical lesions predominantly located in the parieto – occipital white matter at the junction of gray and white matter, without mass effect, we should think at PML; this syndrome was caused by J.C virus and possible by metabolic disturbance. Our patient had spontaneous remission despite he presented CD4+ counts lower than 100/mm3 and HIV viral load higher than 500 copies/ml.
- Cerebral tuberculomas may develop in patients with HIV – infection and both their clinical and neuroimaging features are somewhat different from those of CNS tuberculomas that occur in HIV – seronegative patients. In our casuistry, the patient was diagnosed with left lateral cervical ganglion as chronic lymphadenitis TBC by biopsy four months ago and he was under tuberculostatic treatment. HIV – infection was diagnosed at that moment.
- We observed the development of different primary and secondary HIV – associated neurologic complications tends to parallel specific stage of HIV infection.
- Major HIV – associated neurological disorders may occur at any time from infancy to old age, but most reported cases have been in young patients.

**REFERENCES:**