SUBACUTE HIV ENCEPHALITIS IN AN ADOLESCENT WITH A CHRONIC HIV INFECTION

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ABSTRACT

We report the case of a 19 year old young man, with chronic HIV infection, diagnosed with HIV subacute encephalitis. The patient's therapy was changed 2 and ½ months before, because of immunological and virological failure to a HAART regimen with lower CNS penetration. Neurocognitive evaluation revealed the presence of cerebellar syndrome and moderate neurocognitive impairment. The patient had higher CSF HIV RNA levels compared to plasma and the MRI scan revealed minor periventicular demyelination. After switching to a regimen with better CNS penetration the neurocognitve performances and functionality improved, along with CD4 count restoration and virological suppression in both plasma and CSF compartments.

Key words: subacute HIV encephalitis, neurocognitive impairment, CNS penetration scores

We are presenting the case of a 19 years old patient (DPI), who was admitted to „Dr. Victor Babes" Hospital for Infectious and Tropical Diseases, Bucharest (VBH) on the 1st of October 2007, for vertigo, tremor of the upper limbs, unsteady gait and difficulty swallowing especially for liquids. The symptoms had appeared at home, a week before, in the absence of fever and they have been gradually worsening.

The patient was diagnosed with HIV infection in 1997, probably transmitted by horizontally route during the first years of his childhood when he was repeatedly hospitalized and received parenteral treatments. Other significant medical events were: pulmonary tuberculosis in 1997, thrombocytopenia secondary to the HIV infection and recurrent respiratory tract infections. Both hepatitis B and hepatitis C blood serologies were negative.

The patient has been monitored for CD4 levels in our clinic starting February 1999 when his CD4 count was 375 lf/mmc (10.9%). He has received highly active antiretroviral treatment (HAART) since July 5th, 1999 with CBV and NVP which was switched on July 23rd, 2007 because of immunological and virological failure (CD4=123 lf/mm^3, 8%, HIV VL 53000 copies/mm^3) with ABC+ddI+SQV/r. The new regimen was well tolerated. Both the patient and his caregivers declared a good adherence to the antiretroviral treatment.

Clinical examination at admittance: the patient had an altered general state, a temperature of 36,8°C, he was underweight and hypotrophic (G=39 kg, T=151, <p3), had facial desquamation– tinea-like appearance, bilateral cheilitis, generalized lymphadenopathy, the chest and heart examination was within normal limits, HR=92/min, BP=110/50 mmHg, the abdomen presented no guarding, rigidity or tenderness, the liver span was 11 cm, with an inferior hepatic edge at +2 cm under the rib cage, of normal consistency, the spleen could be palpated during profound inspiration, Tanner score was 4. The patient was conscious, oriented (person, place, time and situation), had bradilalia, severe anxiety, diminished ideation and motor performances, bilateral cerebellar syndrome, brisk peripheral reflexes, the cranial nerves, sensory and motor strength were grossly intact and the Babinski sign was absent bilaterally.

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Based upon the case history (relatively sudden onset with neurocognitive impairment) and the physical examination (which confirmed the cognitive deficit and the cerebellar syndrome) we suspected subacute encephalitis.

The laboratory examination found a moderate thrombocytopenia (34000/mmc) and no other relevant hematological or biochemical abnormality.

Specific laboratory tests for the HIV infection indicated the persistence of the severe immune suppression with a CD4 count of 150 lf/mm^3 (5%), and CD8 count of 1620 lf/mm^3, CD4/CD8=0.02. HIV plasma viral load was 2780 copies/ml (3.44 log10). The chest X-ray showed some per bronchial infiltration in the lower lobe of the right lung and no evidence of lymphadenopathy in the pulmonary hilum or the mediastinum. The ophthalmoscope examination was normal.

A lumbar puncture was performed and it showed a clear aspect of the CSF, with a normal evacuation pressure, 31 nucleate cells/ml, protein reaction +++, no germs on the Gram stain, and moderately frequent lympho-monocytes, very rare neutrophiles on the Giemsa stain, CSF albumin of 0,2 g/dl., CSF glucose of 0,58 g/dl, CSF chloride of 7,4 g/dl, negative China ink test and sterile bacterial cultures after 5 days. The CSF HIV RNA was 18700 copies/ml (4.27 log10).

We have further excluded CMV disease, measles and mumps viruses, toxoplasmosis, herpes simplex viruses 1 and 2, varicella virus, EBV and borreliosis as causes of these symptoms by means of blood and CSF serologies performed at admittance and by the absence of any other associated clinical signs. Molecular biology performed in the CSF excluded cerebral CMV disease and progressive multifocal leucoencephalopaty (negative JC virus DNA).

The cerebral MRI (fig. 1) showed leucoencephalitical demyelinising periventricular lesions and cortical atrophy.

Based on the clinical, laboratory and imaging findings, we have strongly suspected the diagnostic of subacute HIV encephalitis. This diagnosis was based on the subacute onset in the absence of fever, with neurocognitive impairment in a patient with a chronic HIV infection and severe immune supression. The higher CSF HIV RNA value than the corresponding plasma level in the absence of an altered blood-brain barrier (albumin index of 4.2), suggested the compartmentalization of the HIV infection in the central nervous system (CNS) and represented another positive argument for HIV encephalitis. The clinical presentation and the

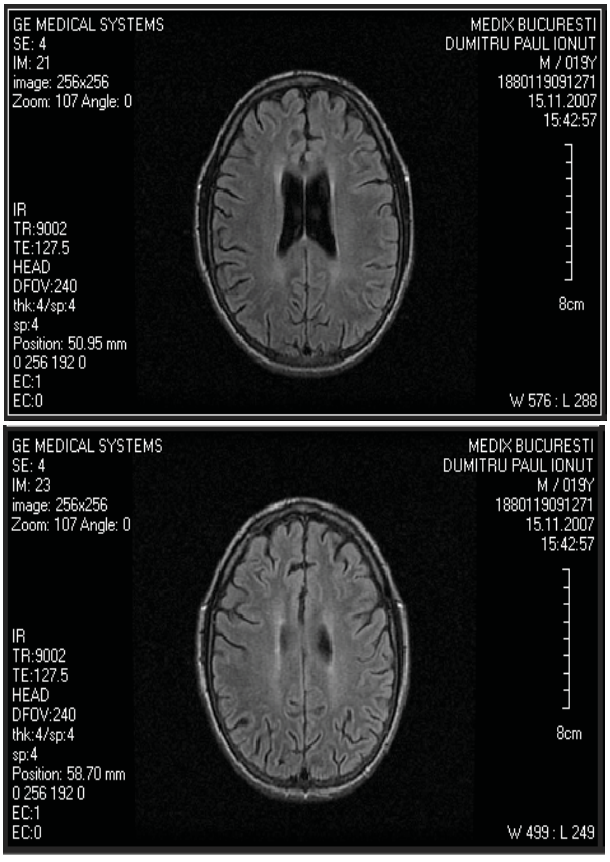

FIGURE 1. *Cerebral MRI (FLAIR) at the diagnosis of the subacute encephalitis showing periventricular lesions with increased signal, suggesting demyelinization.*

subacute onset could have suggested other viral aetiology or a cerebral opportunistic infection. The patient didn't describe any passed acute event that might have indicated the occurrence of a recent infectious disease and he has also denied contact with possibly contagious persons. Although he lived in a rural area, he had no interaction with animals. At the moment of the diagnosis he was a young adult with only 4 years of education because his mother decided to have him drop out of school after learning his HIV status. The patient lived with his family who insured a hyper protective environment and limited social contacts in order not to submit him to the risk of contracting any disease.

The neurological signs and symptoms aggravated progressively from admittance with an increase of the tremor especially during voluntary movements. A neurological evaluation was performed and it showed that the involuntary movements were non epileptic. It was also in favour at that point, of the extrapiramidal aetiology of the movement rather than the cerebellar one. The neurologist prescribed Rivotril in progressively augmenting doses (up to 2 mg/day) in the attempt to control the extrapiramidal

tremor to which we initially associated Sodium Valproate (Depakine). The clinical evolution was slowly favourable under this unspecific treatment and eventually the full control of the involuntary movements was obtained.

The thrombocytopenia, considered a manifestation of the HIV infection as it had previously been reported in the patient's history, initially started improving, reaching a value of 62300 trombocytes/mm^3, in the eighth day from admittance. At 14 days of hospitalisation, though, it dropped at 10.600/mmc, situation in which a substituve treatment was implemented associated with a short term systemic steroid therapy of 5 days. We have considered this aggravation as a side effect of the valproate and as such suspended this therapy. The patient responded with a normalisation of the thrombocytes value.

Given the HIV aetiology of this encephalitis as well as the impossibility to determine the HIV resistance genotype (neither at the last therapy switch nor at the moment of the neurological event) we have reconsidered the antiretroviral treatment according to other available data. The patient has had a therapy consisting of AZT, 3TC and NVP for 7 years to which we strongly believed he had acquired resistance. In the absence of the possibility to introduce Tenofovir (unavailable in Romania at that time), we considered ABC and ddI as the only options from the NRTI class. Resistance cross mutations selected by NVP had probably rendered the virus resistant to Efavirenz, too. Since three months prior to the neurological event, the plasma HIV VL had decreased from 53000 c/ml to 2780 c/ml, with a good declared adherence to treatment, we have considered that the virological response was an adequate one. Considering the low concentration and efficacy of SQV/r in the CSF (1) and the neurological impairment due to the absence of a good control of the viral replication at this site, we decided to switch SQV/r with a different protease inhibitor which has better effectiveness score in the CNS. As such, we have kept ABC and ddI – which were considered as potentially active, we intensified the treatment by adding T20 and we replaced SQV/r with LPV/r, in order to support the action of the two NRTIs by a third molecule which is active in the CNS. The new HAART has been well tolerated both clinically and biologically.

A neurocognitive evaluation has been conducted after improvement of involuntary extrapiramidal movements. At the screening with the international HIV dementia scale (2), the patient obtained 11 out of a maximum of 12 points. The neurocognitive evaluation was performed by means of the test battery provided by the HIV Neurobehavioral Research Centre in San Diego (HNRC) for the NIMH R21 MH0077487-01 trial (3). The results of this evaluation are shown in Table 1. The patient's global deficit score was 1, which is above the cut off value for the Romanian cohort. Two cognitive domains were found to be impaired: speed of information processing (moderate deficit) and

TABEL 1. *The neurocognitive evaluation using the HNRC test battery (7). We have evaluated 7 neurocognitive areas by means of a combination of tests. In order to interpret each test, we have used median T scores with a normal level of above 40. Lower values of the T score reflect the degree of the deficit in a particular area, as follows: 35-39 – mild deficit, 30-34 – mild-moderate deficit, 25-29- moderate deficit, 20-24- moderate-severe deficit, <20 severe deficit*

Cognitive area	**Tests**	**Median T score at baseline (12.11.2007)**	**Median T score at follow up (15.07.2008)**
Motor	Grooved peg-board	41,5	53,5
Speed of information processing	Digit symbol, Symbol search, Trails A, Color trails, Stroop word, color	29,4	38,8
Working memory	PASAT, spatial span	34,97	40,63
Verbal fluency	Animals, letters, actions	47,33	54,67
Recall	BVMT-R Delay, HVLT-R Delay	40,5	50,5
Learning	BVMT-R Total Learning, HVLT-R Total Learning	40,5	56
Executive functions	Category Test, WCST-64 Color Trails 2	41,5	57,75
Global deficit score *		1,00	0,35

*The cutt-off of the global deficit score for the Romanian cohort is 0,63.

working memory (mild-moderate deficit). In the self administered PAOFI (*Patient`s Assessment of Own Functioning Inventory*) test (4), the patient described having difficulties in the cognitive and motor and memory domains. In the self evaluation of his effectiveness during daily activities, he admitted to having difficulties in managing finance, providing supplies for himself and house activities but not in the self care and administering medication domains. Based on this evaluation which showed impairment in two cognitive areas and on the data regarding the patient's daily functioning level and according to the HIV associated neurocognitive impairment scale (5), we have diagnosted an HIV associated moderate nerocognitive deficit.

Interestingly, during the evaluation of the patient's level of functioning, the Beck II depression inventory (6) with a score of 10 points showed the presence of moderate state of depression.

After HAART switch, the follow up lumbar puncture (13/11/2007) showed normal levels of cells and biochemical markers (10 nucleate cells/mm^3, negative protein reaction, CSF albumin of 0.1g/l, CSF glucose of 0.61g/l and CSF chloride of 7.2 g/dl). As shown in Table 2, the HIV RNA level was still detectable in the CSF one month after HAART change and it became undetectable in the CSF as well as in the plasma after 3 months. We have also observed an increase in the cellular immunity (Table 2). Given the good clinical outcome as well as the immune restoration we have stopped the T20 treatment the 27th of January 2009.

At the neurocognitive evaluation 8 months after the acute episode, we observed an improvement of the patient's performance in all tested areas (Table 1) as well as in his daily functioning. The patient also scored 2 points on Beck II depression inventory which is consistent with the absence of depression.

DISCUSSION

The patient presented with subacute HIV encephalitis after 10 years of chronic evolution of the infection in a context of severe immune depression and of a low CNS penetration treatment. He received a HAART regimen consisting of CBV and NVP with a good CSF passage sustained by a penetration score of 10 according to the most recent classification (1). Thereafter, the HAART regimen was switched to ABC+ddI+SQV/r with a penetrability score of 6, given the immunological and virological failure. The HIV plasma VL diminished after 2.5 months of treatment suggesting a favourable evolution, but the neuro-cognitive symptoms appeared. Although we were unable to determine the plasma and CSF resistance profile of HIV, both the higher HIV RNA VL in CSF compared to plasma and the occurrence of the moderate neurocognitive impairment are favourable arguments for the compartmentalization of the HIV infection in the CNS.

There have been reports of HIV neurocognitive deficit which progresses under effective plasma antiretroviral treatment (8). The compartmentalization of the HIV infection with the emergence of different resistance profiles has been associated with neurocognitive clinical deficits (9-11). A possible explanation of this phenomenon is the week CNS penetrability of certain antiretroviral molecules which consecutively leads to suboptimal drug concentrations at this site and to the emergence of resistance mutations especially in certain cortical areas. (12,13). The patient's initial HAART regimen had a good CNS penetrability and a neuroprotector effect. Virological failure under the first regimen and the switch to a low penetrability one might have contributed to the autonomous viral replication in the CNS associating inflammatory immune activation mechanisms that led to the subacute clinical symptoms. Increased CSF HIV RNA levels with higher CNS values than corresponding plasma ones are associated with neurocognitive deficit (14-16). This has also been observed in our paediatric population at VBH (3). Furthermore, low or undetectable CSF HIV RNA levels determined by ultrasensitive methods can falsely indicate the lack of CNS alterations. In this context, as well as in the case in which the patient receives HAART and has

TABLE 2. *Evolution of the HIV infection markers after the subacute HIV encephalitis episode (Oct 2007) and after the HAART switch with ABC+3TC+ddI+LPV/r+T20*

	2/10/2007	13/11/2007	26/02/2008	15/07/2008	28/10/2008	27/01/2009	15/04/2010
CD4 (lf/mmc)	150	160	244	358	337	401	417
CD4%	5	7	7	12	11	12	15
CD8 (lf/mmc)	1620	1369	1907	1280	1750	1565	1669
CD4/CD8	0,09	0,12	0,13	0,28	0,19	0,26	0,25
HIV RNA(c/ml)	2780	168	<50	<50	<50	<50	N/A
CSF HIV RNA (c/ml)	18700	349	<50	<50	–	–	–

neurocognitive impairement, changing the ARV regimen may seem of minimal benefit (17). Letendre et al. has recently described the presence of more significant neurocognitive deficit in patients with HIV RNA levels <50 c/ml, who had detectable VL when using ultrasensitive tests as compared to those with strictly undetectable HIV RNA (<2 copies/ml) (18).

In the case of patients with discordant CSF and plasma HIV resistance profiles and neurocognitive impairment it is necessary to adapt the ARV therapy to the viral resistance profile found in the CSF (19). In the case presented here, we were unable to determine the HIV genotype and as such we have chosen a HAART regimen that reaches effective concentrations in the CSF. Given the limited choice in the NRTIs class, the good penetrability score of ABC (20) with a good control over the viral replication at this site (21) and the adequate score of ddI (2), as well as the fact that these two drugs along with SQV/r had decreased the plasma HIV VL, we have both these molecules in the new regimen. T20 has been added for intensification of the regimen. The penetrability of Enfuvirtide (T20) in the CSF is practically negligible, and thus it is not recommended for its onsite CNS effect (22). However, T20 has a benefice in the rapid increase of CD4 count and in reducing the plasmatic viral pool and as such it is also recommended for patients with HIV related neurocognitive impairment in association with three other antiretroviral agents with a good CSF penetrability (22,23). The reason for this approach is that controlling plasmatic viral replication leads to a positive modulation of the immune activation and thus has an indirect effect on the CNS (24).

Switching SQV/r with LPV/r has been justified by the fact that LPV/r reaches CSF levels that manage to control viral replication although these levels are much lower than plasma ones. LPV/r reaches CSF concentration above IC50, although it penetrates in a reduced fraction at this site due to plasma protein binding and efflux mechanisms (CSF and plasma concentration ratio of 0.22%) (25,26). Furthermore, it has been shown that both in patients with LPV/r monotherapy as well as in patients with HAART regimens containing LPV/r (27), LPV/r leads to a decrease in the CSF and plasma HIV RNA levels, reduces the onsite immune activation (27, 28) and improves the neurocognitive performances of the patients.(28).

The introduction of drugs with a good CNS penetrability in the HAART regimen led to the rapid improvement of neurocognitive performances. Eight months after the therapy switch we observed clear improvement in all seven tested cognitive areas, with the persistence of a minor deficit only in the speed of information processing domain. The lack of neurocognitive deficit has been maintained by means of a good adherence to treatment and of the same HAART regimen.

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