

## A Case Report of HIV-Related Encephalitis with Psychiatric Presentation: Behavioral Anomalies, Differential Diagnosis and Therapeutic Strategies

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## 1. Abstract

The difference between a primary psychiatric disorder and the psychiatric manifestation of a defined medical condition is often blurred and represents an utmost clinical challenge, especially in the context of an emergency service in which it is essential to achieve a correct and timely differential diagnosis.

We thought interesting to share our experience at the Psychiatry Operative Unit - Lomellina, Vigevano (Pavia, Italy), in collaboration with the Infectious Diseases Operative Unit of the "Policlinico San Matteo" - Pavia, about a case of behavioral disorder and psychomotor agitation secondary to a Reversible Posterior Encephalopathy Syndrome: this case allows to describe the clinical process from the Emergency Department to the Psychiatric and Infective Unit with in-depth discussion of therapeutic options.

## 2. Introduction

The differential diagnosis between a primary psychiatric disorder and the psychiatric manifestation of a defined medical condition, represent an utmost clinical challenge, especially in the context of an emergency service [1]. This challenge becomes even more complex when the patient manifests a series of symptoms that, according to the current DSM-5 criteria (Diagnostic and Statistical Manual of Mental Disorders), do not lead to an easy diagnosis [2]. The clinician's approach should be guided, first of all, on a careful anamnestic collection and on the performance of a complete psychic examination taking also into account what might emerge from

a possible instrumental investigation. Unfortunately, only few laboratory and imaging tests are available in A&E, even in western countries, and the sensitivity of these tests appear generally quite poor for the differential diagnosis of many psychiatric conditions [3-4].

With reference to the above, there are cases where the boundary between psychiatry, neurology and infectious diseases is blurred. Advanced imaging appeared to be an effective first tool in guiding towards an initial differential diagnosis, allowing the best clinical approach to be outlined [3-5]. In the optimal scenario, when light has been shed on the diagnostic hypothesis, the approach to be followed is undoubtedly multidisciplinary, bringing into play several services and several professional figures, creating a network of professionals who make possible to delineate the course to be followed and the best therapy to be set up [6-7-8].

With reference to the above, in literature, only few studies show clinical cases in which the patient is taken care of by several specialists working together to formulate a complex diagnosis. We believe that this would make it possible to outline an appropriate therapy to ensure, if possible, a more rapid recovery.

For this reason, we thought interesting to share our experience at the Psychiatry Operative Unit (UOP) - Lomellina, Vigevano (Pavia, Italy), in collaboration with the Infectious Diseases Operative Unit of the Policlinico IRCCS San Matteo - Pavia, of a case of behavioral disorder and psychomotor agitation, secondary to a Reversible Posterior Encephalopathy Syndrome (PRES), which

led to the differential diagnosis of AIDS-related Progressive Multifocal Leukoencephalopathy (PML) versus AIDS-related dementia.

### 3. Clinical Case

A 48-year-old man with no history of psychiatric illness came to our attention manifesting a dissociative state. No substance abuse disorder, episodic alcohol abuse. No psychiatric familiarity. Only bronchial asthma in medical history.

The patient was taken by the Police, alerted by family members, for episodes of psychomotor agitation with fits of rage and heteroaggressiveness towards objects (not people), which increased in the last few months until reaching a peak in the last few days.

The patient was admitted under compulsory in-patient care for a clinical picture characterized by altered state of consciousness with fluctuations of consciousness, episodes of confabulation, disorientation and confusion. The patient presented altered consciousness of ego with absence of criticism of the illness, thought disorder with grandeur and querulous delusions and persecutory behavior that affect therapy and food intake; furthermore, it was also observed an alteration of sense of perception with microzootic visual dispersions.

This clinical picture, in particular the presence of disorders of consciousness, confusion in addition to psychotic symptoms, in absence of history of psychiatric illness, substance abuse disorder and psychiatric familiarity, was suspicious for an organic etiology.

Therapy was started with aripiprazole up to 30 mg per day intramuscularly and delorazepam 6 mg per day with progressive improvement of the psychopathological picture and reduction of behavioral alterations. We chose this drug because of its efficacy in the management of agitation, safe and well tolerated by patients [9]. Moreover, aripiprazole is indicated in the CANMAT guidelines for the management of manic agitation and mixed mood disorders [10]. However, this topic will be explored further in the conclusions.

In addition, as shown in Table 1, we report the laboratory examinations that we considered necessary to conduct in order to make a correct diagnostic assessment.

To complete the diagnosis, instrumental examinations (some of which had already been carried out in the emergency room) were also performed. We must also specify that the MRI was conducted following the abnormalities shown on the CT scan, in order to better frame the neurological picture.

- Chest X-ray: slight hypodiaphany in the left area, with modest reinforcement of the peribronchovascular interstitium in the absence of coarse layers of pleural effusion.

- ECG: on admission SR, 100 bpm, QTc 491ms; at discharge SR, QTc 465ms.

- Encephalus CT scan without contrast medium: showed a blurred densitometric change with difficult differentiation between poste-

rior occipital white and gray substance bilaterally, suspected for posterior reversible encephalopathy (PRES).

- MRI of the brain without and with contrast medium: in the bilateral occipital subcortical supratentorial site, predominantly on the right and, to a lesser extent, in the bilateral frontal and parietal subcortical site, shaded hyperintense signal alterations are observed in the long TR sequences that correspond in the DWI sequences to areas of slight reduction of the diffusivity of water molecules, hyperintense in the b1000-weighted sequences and hyperintense in the ADC map, with substantial isointensity in the T1-weighted sequences; after intravenous administration of contrast medium, there is no clear intraparenchymal contrastographic impregnation but only a slight diffuse leptomeningeal contrastographic impregnation is observed. The findings described are not of unambiguous interpretation but appear compatible with a PML meningo-encephalitis picture although PRES cannot be excluded. Punctiform signal alterations are found at the level of the bridge, although non-specific. There is a slight diffuse enlargement of the supratentorial ventricular system and cortical convexity furrows in relation to age.

Following the findings of laboratory and instrumental examinations, we deemed it necessary to carry out an investigation test for HIV. The diagnostic suspicion arose due to a clear and continuous reduction in the lymphocyte population, to the evidences of CT and MRI images and to the period of sexual promiscuity witnessed by the patient's ex partner, after the interruption of their relationship.

Table 2 and 3 show the results of the tests that confirmed HIV positivity. In addition, the lymphocyte subpopulations have been investigated in order to gain a more detailed view of the overall clinical picture.

Based on HIV positivity and suspected encephalitis, it was decided to transfer the patient to the Infectivology Department of the San Matteo Hospital in Pavia, in order to study the case more thoroughly.

Haematochemical tests, HIV-RNA and HIV resistance on blood, lymphocyte profile, serology for Treponema Pallidum, Cryptococcus Neoformans, Toxoplasmosis on serum and Quantiferon test were scheduled.

The spinal tap was positive for HIV-RNA and Epstein Barr Virus and negative for cytomegalovirus, Herpes Virus 6, Herpes Simplex, Enterovirus and Varicella Zoster Virus, and also for JC virus. Due to HIV infection, antiretroviral therapy, antifungal therapy for oral candidiasis and antibiotic therapy for syphilis were started.

Due to the subsequent clinical/neurological worsening, which resulted in a picture of drowsiness, a new spinal tap was performed, which confirmed HIV-RNA positivity and a picture of AIDS-related dementia.

Once the patient reached a better clinical state, based on the marked improvement of both the organic picture and the psychic sphere, in which a good insight was shown, in the absence of psychotic symptoms, discharge was ordered.

**Table 1:** Blood chemistry tests

|  | Admission | Intermediate | Discharge |
|--|-----------|--------------|-----------|
| HB   | 13,7 g/dL | 11,7 g/dL    | 12,6 g/dL |
| WBC  | 2900/uL   | 2280/uL      | 2000/uL   |
| NEU  | 2000/uL   | 1300/u/L     | 1200/uL   |
| LIN  | 600/ul    | 600/uL       | 500/uL    |
| Na   | 133 mEq/L | 138 mEq/L    | 144 mEq/L |
| PCR  | <1 mg/L   | 2,50 mg/L    | 2,69 mg/L |
| Molecular Nasopharyngeal Swab for Sars-CoV2: Neg |           |              |           |
| TPHA: 1:1280                                     |           |              |           |
| HBsAg: Neg                                       |           |              |           |
| HCV: Neg   |           |              |           |
| Urinoculture/Emoculture: Neg                     |           |              |           |
| Pharyngeal swab positive for: Candida Albicans   |           |              |           |
| HZV-2 e toxoplasmosis IgM: Neg                   |           |              |           |
| ANA, Anti-dsDNA: Neg                             |           |              |           |

**Table 2:** Analysis of lymphocyte subpopulations

|  |                |
|--|----------------|
| Lymphs TOT                                       | 500 cells/ul * |
| Lymphs CD3+ (T Lymphs tot)                       | 85%            |
| Lymphs CD3+ (T Lymphs tot)                       | 425 cells/ul * |
| Lymphs CD4+ (CD4+/CD3+) (T helper inducer)       | 3% *           |
| Lymphs CD4+ (CD4+/CD3+) (T helper inducer)       | 15 cells/ul *  |
| Lymphs CD8 (CD8+/CD3+) (T suppressor cytotoxic)  | 81% *          |
| Lymphs CD8+ (CD8+/CD3+) (T suppressor cytotoxic) | 405 cells/ul   |
| Ratio Helper/Suppressor                          | 0,03           |
| Lymphs NK (CD16+ 56+/CD3-)                       | 14%            |
| Lymphs NK (CD16+ 56+/CD3-)                       | 70 cells/ul *  |
| Lymphs B (CD19+/CD3-) (B Lymphs tot)             | 1% *           |
| Lymphs B (CD19+/CD3-) (B Lymphs tot)             | 5 cells/ul *   |

**Table 3:** Western-Blot-analysis

|                      |                    |
|----------------------|--------------------|
| S- HIV 1 / 2 Ab-Ag   | Positive           |
| S-INNO-LIA HIV 1 / 2 | Positive for HIV 1 |
| sgP 120              | Positive           |
| gP 41                | Positive           |
| p 31                 | Positive           |
| p 24                 | Positive           |
| p 17                 | Negative           |
| sgP 105              | Negative           |
| gP 36                | Negative           |

## 4. Discussion

### 4.1. Focus on Posterior Reversible Encephalopathy Syndrome and Progressive Multifocal Leukoencephalopathy

The posterior reversible encephalopathy syndrome (PRES) is a neurological disorder of subacute/acute onset. The main signs are neurological symptoms, including headache, mental changes, disorders of consciousness, confusion, seizures and focal neurological deficits [11,12].

Computed tomography (TC) and magnetic resonance images (MRI) in PRES can help in the early diagnosis and treatment [13]. Neuroimaging frequently shows a distinctive parieto-occipital pattern with a symmetric distribution reflecting vasogenic edema [11]. PRES develops in clinical conditions as hypertensive encephalopathy, preeclampsia/eclampsia, autoimmune diseases, after transplantation, infections and as an adverse effect of immunosuppressive drugs or chemotherapy [12].

The overall prognosis is favorable, since clinical symptoms as well as imaging lesions are reversible in most patients[11].

Progressive multifocal leukoencephalopathy (PML) is a CNS infection caused by JC Virus (JCV), a polyomavirus that commonly establishes a persistent and asymptomatic infection in the general population. However, the disease results when JC virus reactivation occurs in a subject with impaired cellular immunity [14]. Usually affects the white substance of the brain, caused by the infection that targets cells that make myelin [15]. Clinical suspicion of the disease is typically when MRI shows focal neurological deficits and associated demyelinating lesions; in any case, the diagnosis of certainty is made by identification of JCV in cerebrospinal fluid or brain tissue [16].

The most typical symptoms are clumsiness, physical weakness, visual language and, often, personality disorders [15].

However, current anti-HIV therapy with antiretroviral drugs (ART), which effectively restores the function of the immune system, enables the survival of as many as half of HIV-PML patients, also witnessing the elimination of JCV from the cerebrospinal fluid. [15,16,17].

The reasons for variability in the natural history of progressive multifocal leukoencephalopathy and treatment responses are largely undefined, and more specific and rational approaches to management are needed [16].

### 4.2. Aripiprazole and its uses

**4.2.1. Relation between JC virus, PML and antipsychotics:** It was recently discovered that the cellular receptor for the JC virus is the serotonin 5HT2A receptor, involved in the initial attachment of virus to cells with a mechanism not totally discovered [18].

Only 5-HT2 receptors were found to support infection by JCV. None of the other 11 isoforms of serotonin receptors supported JCV infection [18].

In a fundamental study, the researchers used the older antipsychotic medications chlorpromazine and clozapine to block the serotonin 5HT2A receptor and block JC virus cell entry. Unfortunately, despite the excellent receptor blockade, chlorpromazine and clozapine have such significant side effects and toxicities, e.g., extrapyramidal symptoms and the possibility of bone marrow dyscrasias - that they may be problematic to use clinically [18,19].

These results, however, gave other studies the opportunity to focus on blocking the serotonin receptor, trying to avoid possible side effects in clinical practice.

Although data in the literature are still limited, aripiprazole also showed a good efficacy profile in blocking the serotonin 5-HT2A receptor, as well as an excellent safety profile, in the absence of significant side effects [20].

This makes it possible, on the one hand, to highlight the important role that antipsychotics, in particular atypicals, could play in the prophylaxis of PML, as well as the management of behavioral abnormalities in acute cases; on the other hand, they represent a remarkable opportunity for further study, providing new guidelines in the management of this syndrome.

**4.2.2. Aripiprazole and AIDS:** In November 2007 the Food and Drug Administration (FDA) approved the use of aripiprazole as an adjunctive, or add-on, treatment to antidepressant therapy in adults with major depressive disorder (MDD). Aripiprazole is the first medication approved by the FDA as an add-on treatment for MDD, modulating the dopaminergic system [21].

Lento-viral replication seems to be enhanced in peripheral blood mononuclear cells partially through dopaminergic activity. Dopamine acts through dopamine receptors (DRs), and classically DRs have been studied on neurons. In addition, DR expression has been reported in several types of peripheral blood leukocytes, including T lymphocytes and monocytes. Dopamine receptors have been shown to modulate the immune function of T lymphocytes [22,23].

Although the effect of aripiprazole in these situations is still unknown, clinical cases are presented in the literature in which the drug has been used on forms of resistant depression, somatoform disorder and panic disorder in an HIV-infected subject treated with aripiprazole as augmentation therapy. In this case, aripiprazole led not only to a significant improvement in depressive symptoms, but also to an improvement in CD4 cell count and viral load [24].

Furthermore, other studies in literature have shown that aripiprazole (in combination with a benzodiazepine) is the treatment favored in cases of psychomotor agitation, psychosis and even catatonia in HIV patients [25].

**4.2.3. Aripiprazole and Neurosyphilis:** There is no consensus on treatment regimens for patients with neurosyphilis and psychotic features in terms of which neurotrophic agents to use and at what dose. Hung et al. found that treatment with penicillin alone resolved their neurosyphilis (NS) patient's auditory hallucina-

tions and religious delusions [26]. In a case report documenting a 40-year-old male positive for neurosyphilis, antipsychotic treatment was attempted but was not found to be a beneficial measure [27], in another case report 400 mg of valproate twice a day was used to reduce agitation symptoms effectively [28]. There have also been many cases described of using both antipsychotic medications in combination with antibiotics. Sanchez and Zisselman described a series of five case reports of neurosyphilis patients treated effectively with antipsychotics in combination with antibiotics [29].

## 5. Conclusions

The case observed offers numerous points for reflection, both of clinical and pharmacological utility.

Our case report, in fact, underlines how, in the approach to a complex patient, it is important to have a multidisciplinary management as much as possible, involving different teams in a fruitful collaboration, in order to take charge of all aspects of the pathology, also from a diagnostic point of view. Moreover, remaining in the clinical sphere, the importance of instrumental examinations (CT and MRI) emerges, which are often still little used in psychiatry departments, allowing doubts to be resolved and a correct differential diagnosis to be made.

The second domain, pharmacology, was one of our main objectives. The HIV+ patient is, in itself, a complex patient. The range of symptoms is broad, multiform and leads to the intervention of many different specialists.

In our study it emerged how aripiprazole is a drug to be favored in many situations. Potentially, it was shown to have an excellent action profile in patients with Progressive Multifocal Leukoencephalopathy as, by blocking the serotonin 5-HT2A receptor, it prevents the virus from entering the receptor. The competition between the drug and the virus causes an arrest of virus damage, a reduction in symptoms (especially behavioral) and plays, among other things, a prophylactic role in JCV infection.

A further aspect that emerged from our study is that aripiprazole is not only to be favored in states of psychomotor agitation (as it is already known) but specifically to be used in agitations occurring in HIV+ patients. Dopamine regulation, in fact, on the one hand reduces tension, anger, hetero- and self-aggression; on the other hand it has a modulatory action on the immune function of T lymphocytes, leading to an overall increase in CD4 count and a reduction in viral load.

With regard to neurosyphilis, however, there are few studies in the literature. The first intervention to be favored is certainly antibiotics. However, even in this case, antipsychotics may play an important role in the management of psychiatric symptoms resulting from the damage caused by the infection in progress.

Lastly, it should be emphasized that aripiprazole is also to be preferred because it has demonstrated a high safety profile as well as

efficacy. It is very well tolerated by patients, thus allowing greater adherence to treatment, even when this is prolonged over time.

With the limitations of a single clinical case, we think that these areas are undoubtedly worthy of further and more structured clinical studies, capable of providing both diagnostic and therapeutic tools, in the context of contemporary psychiatry.

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