Case Report

LATE-ONSET PSYCHIATRIC MANIFESTSTIONS REVEALING LIMBIC ENCEPHALITIS: A CASE REPOSRT OF 48 YEARS OLD MAN

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Abstract: Almost all psychiatric trouble usually happens in young adults, their late onset is often atypical, and an organic origin is frequently found. Many somatic etiologies like encephalitis remains poorly understood, and multidisciplinary management is necessary.

We present the case of a man hospitalized for the first time in the psychiatric ward of Monastir Tunisia at the age of 48 for behavioral disorders with atypical symptoms; Brain Magnetic resonance imaging showed bilateral signal abnormalities of the internal temporal region and hippocampal left lesions, suggestive of encephalitis. The autoimmune origin has been strongly suspected, and the determination of "onco-neuronal" antibodies and specifically the assay of anti Ma1 and anti Ma2 antibodies were positive. These elements lead us to evoke autoimmune encephalitis, and immunotherapy was initiated for the patient.

Keywords: Psychiatry; atypical symptoms; late-onset, limbic encephalitis; diagnosis.

INTRODUCTION Almost all psychiatric trouble usually happens in young adults, their late onset is often atypical, and an organic origin is frequently found. Psychiatric symptoms of late onset are often atypical, and organic origin remains to be eliminated at first. However, some of these somatic etiologies remain poorly understood, and multidisciplinary management is necessary. Among those diseases, autoimmune encephalitis tends to have a clinical presentation combining neuropsychiatric and somatic manifestations. In the early 2000s, it was described as a paraneoplastic manifestation, and then, with the discovery of disease-causing antibodies, it was shown to be nonparaneoplastic in many cases [1,2]. Clinically, the central nervous system's disorders are often represented by the limbic encephalitis that presents with rapidly progressive short-term memory deficits, psychiatric symptoms like depression or psychosis, and seizures [3].

The present study aimed to highlight the difficulties of diagnosis and treatment of behavioral disorders in limbic encephalitis.

CASE PRESENTATION Mr. WB 48 years old man, married, and father of four children, worked in a lead-smelting office for 19 years and having neither medical nor psychiatric history. He was taken to the psychiatric emergencies by his family for behavioral disorders: hetero aggressivity. There was an insidious onset of the symptoms, impassivity, and social withdrawal associated with an impaired concentration and judgment, and professional disinterest. His history revealed no fever, seizures, nor recent physical trauma. A few months later, persecution ideations and behavioral troubles appeared; he consulted a psychiatrist, who suspected a primary psychotic disorder. He was first treated with neuroleptic agents: amisulpride 400mg daily but showed no improvement after six weeks of medication. Then, he was hospitalized in the psychiatric ward for more investigations. A depressive syndrome was objectified

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associated with somatic manifestations: headache and asthenia. A selective serotonin reuptake inhibitor (Fluoxetine 20mg/day) was prescribed at the dose of 20mg daily for four weeks then 40mg daily for another four weeks, but the patient showed no improvement.

Neurocognitive tests found attention deficit, and the Raven's Standard Progressive Matrices (PM 38 test) was less than five percentiles.

The hypothesis of a somatic cause was strongly evoked: Given the late onset of the disease, the atypical clinical picture and non-response to treatment: thus, further workup ruled out the following etiologies:

- Thyroid dysfunction: but he had no other signs of thyroid disease such as tremor, tachycardia, intestinal transit disorder, and the thyroid function test was normal: (T4=10; TSH=2.5)
- Lead poisoning: was discussed in front of the work exposure, the difficulties with memory and concentration, the psychiatric disorder. But the level of lead in blood (LLB) was normal: (LLB=42.9 micrograms of lead per liter of blood (µg/L))
- Neurological diseases, such as:
- Wernicke Korsakoff syndrome: because of thiamine deficiency, common in chronic alcoholism, But Mr. WB was not used to consume alcohol.
- Dementia: In front of cognitive impairment Alzheimer's disease or Vitamin B12 deficiency can be suspected. But the dosage of Vitamin B12 and the Brain computerized tomography scan (CT scan) were normal, and the acute onset and course are against this diagnosis.
- Neoplasms: who have is a slight male predominance, but they appear more frequently in young adults, and there were no seizures in our case
- Infection of the central nervous system: especially herpes simplex virus (HSV) infection or neurosyphilis, but there was no history of unprotected sex with multiple partners. The serology was negative.
- The autoimmune origin has been strongly suspected.

INVESTIGATION

- The determination of onco-neuronal" antibodies and specifically the assay of anti-Ma 1 and anti-Ma 2 antibodies were positive.
- Brain Magnetic resonance imaging (MRI) showed bilateral signal abnormalities of the internal temporal region, and hippocampal left lesions suggest Limbic encephalitis (Fig. 1).
- Further workup to rule out paraneoplastic causes was ordered.
- Chest, abdomen, and pelvis computerized tomography scan and ultrasound of the pelvis did not find any tumors.

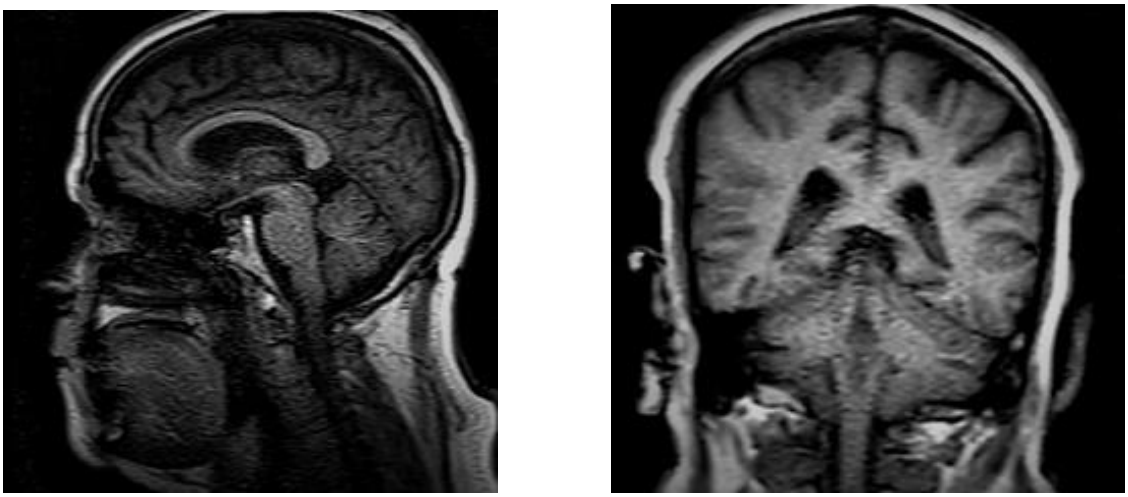

Figure 1: Brain Magnetic resonance imaging (MRI) showing bilateral signal anomalies of the internal temporal region and hippocampal left lesions.

OUTCOMES The patient was transferred to the neurology ward where treatment consisted of immunotherapy (IVIG, cyclophosphamide, and corticosteroid therapy). Unfortunately, Mr. WB kept severe cognitive troubles like delusional ideas of persecution, impaired concentration, judgment, and memory, and could not work anymore.

DISCUSION A few years ago, limbic encephalitis was thought primarily to be a paraneoplastic phenomenon, frequently encountered with cancer of the lungs or gonadal tumors, with associated antibodies to intracellular neuronal antigens [4]. Since then, this conceptualization has expanded to include conditions in which antibodies to cell membrane antigens in the neuropil of the hippocampus and cerebellum were present.

Patients with limbic encephalitis usually had some rapidly progressive neurological and psychiatric symptoms. Thus, they are often first hospitalized in psychiatric departments before being transferred to a neurology ward [5,6], making us wonder how many patients with primary psychiatric disease remained misdiagnosed [7,8].

Its prognosis largely depends on the rapid initiation of immunotherapy: any delay in diagnosis causes the worst morbidity like severe cognitive troubles and impaired functioning, while early treatment results in recovery in 70–80% of the patients [9–11].

It remains important for psychiatrists to be aware of clinical signs that should raise suspicion of autoimmune encephalitis. Several authors have proposed lists of clinical red flags (and some have proposed so-called yellow flags) that should raise suspicion of central nervous system autoimmunity in patients presenting with psychosis [12].

Clinical Yellow flag are [13]:

- Decreased levels of consciousness
- Abnormal postures or movements (orofacial, limb dyskinesia)
- Autonomic instability
- Focal neurological deficits
- Aphasia or dysarthria
- Rapid progression of psychosis (despite therapy)
- Hyponatremia
- Catatonia
- Headache
- Other autoimmune diseases (e.g., thyroiditis)

Clinical Red flags are [13]:

- Cerebrospinal fluid (CSF) lymphocytic pleocytosis or CSF-specific oligoclonal bands without evidence for infection
- Epileptic seizures
- Faciobrachial dystonic seizures
- Suspected malignant neuroleptic syndrome
- Brain Magnetic resonance imaging *(*MRI) abnormalities (mesiotemporal hyperintensities, atrophy pattern)
- EEG abnormalities (slowing, epileptic activity, or extreme delta brush)

The decreased level of consciousness, the presence of headache, and finally, the Brain Magnetic resonance imaging *(*MRI) abnormalities made us suspect the limbic encephalitis in the present case.
The diagnosis of limbic encephalitis is based on a clinical set of three associating [14]:

- Subacute onset of psychiatric symptoms, the deficit in working memory, or an alteration in mental status
- One or more of those manifestations: new focal neurological signs including seizures, pleocytosis in cerebrospinal fluid, Brain Magnetic resonance imaging *(*MRI) abnormalities
- Exclusion of potential other causes.

In our case, the late-onset symptoms in a man having no medical nor psychiatric history, the cognitive deficit with the abnormalities in the Brain Magnetic resonance imaging *(*MRI) were keys to limbic encephalitis diagnosis.

Many studies have led to the characterization of autoimmune encephalitis into two broad categories associated with antibodies to intracellular neuronal antigens and those associated with antibodies to cell membrane antigens in the neuropil of the hippocampus and cerebellum [15,16].

Diagnostic tests could be normal or show only nonspecific abnormal results. Both serum and cerebrospinal fluid testing for autoimmune antibody titers exist and should be performed as soon as possible. High rates of false positivity are found via serum testing. Thus, it's important to consider relevant a consistent clinical picture with a positive cerebrospinal fluid (CSF) result.

Clinicians should also be aware that not infrequently, autoimmune encephalitis can be seronegative, which

should highlight the importance of multidisciplinary collaboration (14). The latest European Federation of Neurological Societies guidelines (17) recommended total body fluorodeoxyglucose positron emission tomography (FDG-PET) if a patient is suspected of having a paraneoplastic syndrome and negative antibodies tests; sadly, not yet feasible in our context

Despite the limited data, the clinical experience suggests the following three general principles for treatment (18): First, if there is a presence of a tumor, we should remove and/or treat it, then we must consider immunotherapy, and finally, we have to start treatment as early as possible.

Psychiatric treatments described in the literature on autoimmune encephalitis focus primarily on the management of catatonia with electroconvulsive therapy (ECT). The use of multiple psychotropic medications, including conventional and atypical antipsychotics, mood stabilizers, and benzodiazepines, is detailed in several case reports. Still, concurrent use with other therapeutic modalities makes clinical outcomes difficult to assess.

As in this case, the most profound improvements in psychiatric and behavioral symptoms occur when the antibody response is suppressed or reversed. One particularly challenging aspect of this case involves the initial evaluation and subsequent surveillance.

CONCLUSION Once considered as a disorder related to cancer, and refractory to treatment, limbic encephalitis is now regarded as a disorder, often unrelated to cancer, and with some clinical immunologic variants that may respond to treatment.

Informed consent obtained for publication of this case report: Written informed consent was obtained from the patient's wife (since he was not able to give his consent) for the publication of this case report.

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