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NEUROPSYCHIATRIC AND COGNITIVE SEQUELAE FOLLOWING HERPETIC ENCEPHALITIS

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ABSTRACT

Herpes Simplex Encephalitis (HSE) is one of the most severe sporadic viral infections of the central nervous system and remains associated with significant neurological and psychiatric morbidity despite early antiviral treatment. Long-term cognitive and neuropsychiatric sequelae remain insufficiently recognized and may lead to major impairment in patients' functional abilities and autonomy.

We report the case of a patient who developed progressive memory impairment, executive dysfunction, behavioral disturbances, and loss of autonomy consistent with an early major neurocognitive disorder following herpetic encephalitis.

This case highlights the potential severity of long-term neuropsychiatric sequelae after Herpes Simplex Encephalitis and emphasizes the importance of early recognition, multidisciplinary assessment, and long-term psychiatric follow-up. It also underlines the diagnostic challenges posed by post-infectious cognitive syndromes, which may mimic neurodegenerative or primary psychiatric disorders. Further studies are needed to better understand the underlying pathophysiological mechanisms and to optimize therapeutic and rehabilitative strategies.

KEYWORDS: Herpes Simplex Encephalitis; neuropsychiatric sequelae; cognitive impairment; early-onset dementia; major neurocognitive disorder.

INTRODUCTION

Herpes Simplex Encephalitis (HSE) is one of the most common sporadic viral encephalitides in developed countries, with an estimated annual incidence ranging from 2 to 4 cases per million inhabitants. It is predominantly caused by Herpes Simplex Virus type 1 (HSV-1), whereas HSV-2 is less frequently involved, particularly in neonates and immunocompromised patients.

Despite significant diagnostic and therapeutic advances, particularly the early administration of Acyclovir, HSE remains associated with substantial neurological and psychiatric morbidity. The predominant involvement of the medial temporal and limbic regions accounts for the high frequency of cognitive, memory, behavioral, and emotional disturbances observed during the course of the disease.

Post-encephalitic neuropsychiatric and cognitive sequelae represent a major healthcare challenge, as they may profoundly impair patients' autonomy and quality of life. Reported manifestations include memory deficits, executive dysfunction, personality changes, psychotic symptoms, anxiety and mood disorders, as well as early major neurocognitive disorders.

These clinical manifestations may mimic neurodegenerative diseases or primary psychiatric disorders, making diagnosis and management particularly challenging.

Understanding the long-term neuropsychiatric consequences of Herpes Simplex Encephalitis remains essential for improving early detection, multidisciplinary assessment, and cognitive and psychiatric rehabilitation strategies.

Through this work, we report a clinical case illustrating the importance of cognitive and behavioral sequelae following Herpes Simplex Encephalitis, while discussing the main findings from the literature regarding the underlying pathophysiological mechanisms, diagnostic aspects, and therapeutic implications.

Case Report

Mr. E.B., a 56-year-old man, had a medical history significant for smoking cessation, untreated Chronic Obstructive Pulmonary Disease (COPD), and a previous episode of status epilepticus occurring six years earlier in the context of Herpes Simplex Encephalitis (HSE), which had been treated with sodium valproate, currently discontinued.

One year prior to presentation, the patient reportedly developed recurrent focal epileptic seizures in a febrile context, involving the right hemibody and associated with deviation of the head and eyes, without recovery of consciousness between seizures.

This episode required admission to the intensive care unit for 40 days with mechanical ventilatory support, followed by transfer to the neurology department. Biological investigations revealed a white blood cell count of 9,900/mm³ with neutrophil predominance and a C-reactive protein level of 77 mg/L. Lumbar puncture demonstrated clear cerebrospinal fluid with pleocytosis of 76 cells/mm³ predominantly composed of lymphocytes. Polymerase chain reaction (PCR) testing revealed a positive multiplex panel, whereas electroencephalography (EEG) showed no significant abnormalities. A diagnosis of Herpes Simplex meningoencephalitis was retained, and the patient was treated with Levetiracetam with regular neurological follow-up.

Four months later, the patient progressively developed apraxic disturbances characterized by difficulty coordinating and executing previously learned voluntary movements, associated with both anterograde and retrograde amnesia. Behavioral disturbances subsequently emerged, including agitation, hetero-aggressive behavior, nocturnal shouting episodes, insomnia, and emotional lability.

Given this clinical presentation, the patient was referred by his neurologist for psychiatric evaluation.

Psychiatric assessment revealed a demential syndrome characterized by impairments in attention, concentration, and memory, associated with behavioral disturbances and depressive mood symptoms.

Brain magnetic resonance imaging (MRI) demonstrated bilateral temporolimbic sequelae with predominant hippocampal involvement, associated with cortico-subcortical atrophy consistent with chronic sequelae of Herpes Simplex Encephalitis.

Neuropsychological assessment was based on the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) for global cognitive evaluation.

The MMSE score was 21/30, revealing memory, attentional, and executive impairments consistent with a major neurocognitive disorder.

The MoCA score was 16/30, showing predominant impairment of executive functions, episodic memory, and attentional abilities.

The final diagnosis was major neurocognitive disorder secondary to herpetic encephalopathy.

The patient was treated with Risperidone 2 mg/day, Sertraline 50 mg/day, and Quetiapine 25 mg/day, resulting in progressive improvement in mood symptoms and behavioral disturbances.

DISCUSSION

Pathophysiology of Neuropsychiatric Sequelae

Herpes Simplex Viruses type 1 and 2 are neurotropic viruses capable of establishing latent and reactivable infections within the host organism [1]. Primary HSV infection generally occurs during childhood or adolescence, whereas in adults, Herpes Simplex Encephalitis (HSE) most commonly results from viral reactivation [2]. The latent virus constitutes a persistent reservoir that partially escapes both immune surveillance and currently available antiviral therapies [3].

HSE remains the leading cause of sporadic viral encephalitis in developed countries, with an estimated incidence ranging from 2 to 4 cases per million inhabitants annually [4]. Despite the early introduction of Acyclovir therapy, this condition continues to be associated with substantial neurological and psychiatric morbidity [5].

The pathophysiology of neuropsychiatric sequelae is mainly related to the neurotropism of HSV-1 for the medial temporal and limbic structures [6]. The virus preferentially involves the hippocampus, amygdala, insula, and orbitofrontal regions through olfactory and trigeminal pathways [7]. This anatomical distribution explains the high frequency of memory, emotional, and behavioral disturbances observed following the acute phase of the disease.

In our case, brain magnetic resonance imaging demonstrated bilateral temporolimbic sequelae with predominant hippocampal involvement, consistent with findings reported in the literature. Hippocampal lesions are strongly associated with severe impairment of episodic memory and the development of persistent amnestic syndromes [8].

Several pathophysiological mechanisms appear to contribute to the development of chronic neuropsychiatric manifestations, including direct neuronal injury secondary to viral replication, hemorrhagic necrosis, persistent neuroinflammation, dysfunction of frontolimbic neural networks, and post-infectious autoimmune mechanisms [9].

Recent studies have shown that HSE may trigger secondary autoimmune encephalitis with anti-NMDA receptor antibody production, potentially explaining delayed or persistent psychiatric manifestations observed in some patients [10].

Furthermore, the status epilepticus experienced by our patient may have aggravated preexisting cerebral lesions through glutamatergic excitotoxicity and hippocampal neuronal injury [11].

Clinical Manifestations and Neuropsychological Findings

The clinical presentation of HSE classically includes fever, confusion, impaired consciousness, focal seizures, and focal neurological deficits [12]. However, certain psychiatric-predominant presentations may delay diagnosis, particularly in elderly patients [13].

Post-herpetic cognitive sequelae predominantly affect memory, executive functions, attention, and behavior [14], with memory impairment remaining the most frequent manifestation due to bilateral hippocampal involvement.

In our observation, the patient presented with anterograde and retrograde amnesia, apraxic disturbances, executive dysfunction, agitation associated with hetero-aggressive behavior, emotional lability, and persistent insomnia.

These manifestations are consistent with the literature describing polymorphic neuropsychiatric syndromes that may persist for several years following the acute infectious episode [15].

Cognitive evaluation using the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) revealed global cognitive impairment predominantly involving memory and executive functions. The MoCA appears particularly sensitive for detecting early executive and frontal dysfunction [16].

Neuroradiological and Diagnostic Findings

Historically, the diagnosis of Herpes Simplex Encephalitis relied on the detection of anti-HSV IgG and IgM antibodies in the cerebrospinal fluid (CSF), as well as intrathecal antibody synthesis and suggestive CSF/serum antibody ratios. However, these methods demonstrated limited sensitivity during the early stages of the disease.

Currently, polymerase chain reaction (PCR) detection of HSV DNA in the CSF is considered the diagnostic gold standard because of its excellent sensitivity and specificity, exceeding 95% and 98%, respectively. PCR allows rapid and early diagnosis and has significantly reduced the need for invasive diagnostic procedures such as brain biopsy.

Nevertheless, HSV serology may still be useful in specific clinical situations, particularly in cases of negative PCR despite strong clinical suspicion or in the assessment of post-infectious autoimmune complications.

Neuroimaging also plays a major role in the diagnosis of HSE. Magnetic resonance imaging is currently considered the neuroradiological examination of choice because of its high sensitivity during the early stages of the disease [17].

Typical MRI findings include medial temporal T2/FLAIR hyperintensities, asymmetric limbic involvement, hippocampal abnormalities, and occasionally hemorrhagic changes [18]. In chronic forms, MRI may demonstrate medial temporal atrophy, temporolimbic gliosis, and cortico-subcortical necrotic sequelae [8].

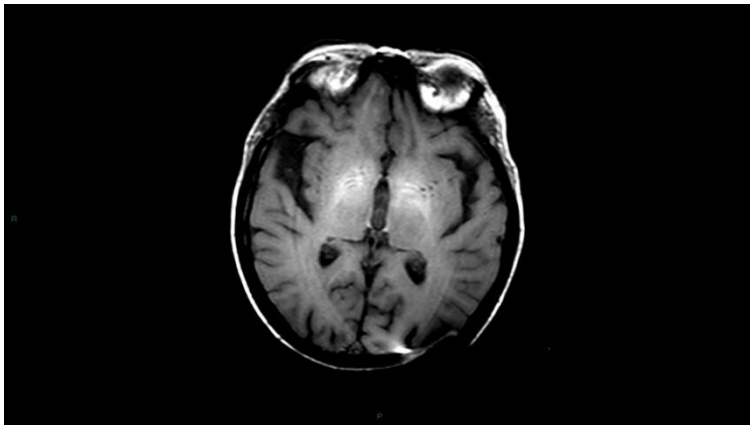

Image 1: MRI of a patient with Herpes Simplex Encephalitis.

Differential Diagnosis

Neurodegenerative or psychiatric disorders:

- **Alzheimer's disease**: characterized by severe memory impairment and hippocampal atrophy.
- **Frontotemporal dementias**: associated with behavioral disturbances and disinhibition [21].

Infectious, autoimmune, vascular, and toxic/metabolic conditions:

- Autoimmune encephalitis
- Cerebral abscesses
- Cerebral vasculitis
- Toxic or metabolic encephalopathies [22]

Finally, in cases of secondary clinical deterioration or atypical psychiatric presentations, post-herpetic autoimmune encephalitis should always be considered and actively investigated [10].

Therapeutic Management

Herpes Simplex Encephalitis is a medical and neurological emergency requiring the early initiation of intravenous Acyclovir as soon as the diagnosis is suspected, without waiting for virological confirmation [23].

The management of neuropsychiatric sequelae is based on a multidisciplinary approach involving neurologists, psychiatrists, and neuropsychologists [24].

1) Symptomatic treatment:

Behavioral disturbances may require cautious use of low-dose atypical antipsychotics.

In our case, Risperidone and Quetiapine led to a progressive improvement in agitation and hetero-aggressive behavior.

Associated mood symptoms may justify the introduction of an antidepressant such as Sertraline [25].

2) Cognitive rehabilitation:

Cognitive rehabilitation represents a key component of management. Several studies emphasize the benefit of early neuropsychological interventions in improving functional autonomy and patients' quality of life [14].

Prognosis and Outcome

Before the era of Acyclovir, mortality associated with Herpes Simplex Encephalitis (HSE) reached 70–80% [27]. Advances in diagnostic tools, intensive care management, and the early introduction of antiviral therapy have significantly improved the overall prognosis [28].

However, moderate to severe neuropsychiatric sequelae remain common among survivors, even after appropriate treatment [29]. The main unfavorable prognostic factors include delayed diagnosis, the extent of temporolimbic lesions, the occurrence of status epilepticus, and the persistence of cognitive impairment [30].

Despite partial clinical improvement under treatment, our patient continued to present persistent cognitive deficits consistent with a major neurocognitive disorder secondary to herpetic encephalopathy.

This case highlights the importance of long-term neuropsychiatric follow-up in patients with a history of Herpes Simplex Encephalitis, even several years after the acute episode.

CONCLUSION

Neuropsychiatric and cognitive sequelae of Herpes Simplex Encephalitis represent a severe and often underrecognized complication of this central nervous system infection. This case illustrates the potential progression toward a major neurocognitive disorder characterized by amnestic syndrome, executive dysfunction, and severe behavioral disturbances occurring months after the acute infectious episode.

These cognitive impairments are most commonly related to preferential involvement of the temporolimbic structures, particularly the hippocampus. Associated psychiatric

manifestations may complicate the diagnostic process by mimicking primary neurodegenerative or psychiatric disorders.

This observation underscores the importance of early detection of cognitive and behavioral disturbances in patients with a history of Herpes Simplex Encephalitis, as well as the need for a multidisciplinary management approach involving neurologists, psychiatrists, and neuropsychologists.

Long-term neuropsychiatric follow-up and tailored cognitive rehabilitation appear essential to optimize functional outcomes and patients' quality of life.

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