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Herpes Simplex Virus 2 Encephalitis Followed by Anti NMDAR Encephalitis in an Immunocompetent Adult: Five Year Follow Up Case Report

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Abstract: ***Background: Autoimmune encephalitis following HSV2 encephalitis is exceptionally rare in immunocompetent adults. Purpose: To describe a longitudinal clinical course of Herpes Simplex Virus 2 (HSV2) encephalitis followed by anti NMDAR encephalitis. Methods: Detailed clinical, neuroimaging, electrophysiological, and cerebrospinal fluid analyses with five years follow up were conducted. Results: The patient developed post infectious autoimmune encephalitis characterized by focal seizures, cognitive behavioral changes, and positive NMDAR antibodies, responding to corticosteroid and antiepileptic therapy. Conclusion: This case highlights the need for long term autoimmune surveillance after HSV2 encephalitis and suggests favorable prognosis with early immunotherapy.***

Keywords: HSV2 encephalitis, autoimmune encephalitis, anti NMDAR antibodies, immunocompetent adult

1. Introduction

Herpes Simplex Virus 2 (HSV2) is a sexually transmitted infection. About 15% of global population is infected (Dass, 2025). In most of the cases HSV2 is at latent state and the most frequent presentation, if activated, is relapsing genital herpes. HSV2 encephalitis (HSV2E) represents 10% of all Herpes Simplex encephalitis, but it is more typical for infants and immunocompromised individuals (Dass, 2025). HSV2E is extremely rare in immunocompetent adults (<2% of all cases of herpes simplex virus (HSV) encephalitis) (Li, 2024). Unlike HSV1, HSV2 might damage not only orbitofrontal cortex and temporal regions, but also brainstem and typically produces pronounced inflammation and necrosis (Dass, 2025). The development of autoimmune encephalitis after HSV encephalitis is rare, the most frequent type is anti-N-methyl-D-aspartate receptor encephalitis (NMDARE) (Brás, 2019; Kreye, 2025). NMDARE develops 28 to 90 days after the onset of the viral encephalitis (Bras, 2019) and is strongly more frequent in cases with HSV1 (Kreye, 2025). NMDARE after HSV2 is extremely rare with several isolated cases worldwide (Brás, 2019, Li, 2024).

We present a case of 45 years old white man with HSV2E followed by NMDARE.

Initial infection: May 2020 (at 40 years of age), after 2 week complaints of headache, fatigue and low grade fever, without rash, the patient developed severe continuous convulsive epileptic status and high grade fever and was admitted to another hospital at comma state. The previous medical history was unremarkable, except for pituitary gland (PG) apoplexy (2020). He had no history of alcohol or drug abuse. The blood examinations at that time showed mild leukocytosis (see table1). Head, thoracic and abdominal computed tomography (CT) were unremarkable. The lumbar puncture of the patient revealed mild pleocytosis and elevated cerebrospinal fluid (CSF) protein. The polymerase chain reaction (PCR) examination of CSF was positive for HSV2, but negative for other viruses and Mycoplasma. Human immunodeficiency virus (HIV), syphilis, tuberculosis and Viral Hepatitis were excluded. Intravenous Acyclovir and antiepileptic (AEM) treatment (Valproic acid (VAL), followed by Thiopental) was started. The patient was discharged at the second month, fully conscious, without fever, with normal neurological examination except right positive Babinski sign. He was left on continuous VAL (1000mg/d) treatment. Possible onset of autoimmune encephalitis (not proven): One week after the discharge he developed bilateral tonic-clonic seizures (BTCS) and VAL was increased to 2000mg/d. Soon after, he complained of worsened psychological and cognitive changes, alopecia, multiple episodes of derealization and short term BTCS, which became more frequent over the time of 2 months. Carbamazepine was added, but the patient complained of rush and symmetric tremor so it was replaced by Levetiracetam (LEV; 2000mg/d). On September 2020 he was hospitalized in our clinic at relatively good state, with normal somatic examination (except bilateral omarthrosis) and normal vital signs. The neurological status revealed right pyramidal sign and mild left peroneal nerve palsy. The patient was fully conscious, but showed some cognitive and psychological changes (magical ideation and cognitive rigidity, emotional lability, episodes of anxiety). The blood count and serum biochemistry were normal, electromyography revealed mild peroneal palsy, due to compression and low amplitude high frequent synchronous hand tremor. Electroencephalography (EEG) was abnormal (table1). Head Magnetic Resonance Imaging (MRI, fig.1) showed PG apoplexy. Although the suspicion of autoimmune encephalitis, at that time, the patient and his relatives refused other examinations and he was discharged on VAL (2000mg/d) and LEV (3000mg/d).

Proven diagnosis of NMDARE and possible relapse: The patient was hospitalized in our clinic again in May 2022, because of worsening of epileptic seizures of focal origin, increasing in frequency and duration, headache, dizziness, fatigue, sleepiness and personal and cognitive changes, despite taking his AEM (see fig. 2). He had also several episodes of short-time BTCS (approximately once per month). His relatives noticed additional personal changes – emotional instability, temper irritability, episodes of aggressive behavior (mostly verbal) and intolerance to noise, work and long conversations. The patient also changed his

daily routine. His glucose, thyroid stimulating hormone, thyroid hormones, cortisol and testosterone levels and urine analysis were normal. Head MRI and EEG showed no dynamic. The LP revealed mild pleocytosis. CSF electrophoresis showed polyclonal intrathecal gamma globulin elevation. The patient was negative for Lime disease and HIV. CSF and serum examination showed slightly increased titer of antibodies against NMDAR (indirect immunofluorescence (IIF) for anti NMDAR IgG in CSF was 1:25 (<1:10) and in serum 1:52 (N <1:20)). Our patient met the criteria for NMDARE: he had subacute development of abnormal psychiatric, behavior or cognitive dysfunction, seizures and tremor, abnormal EEG, CSF with pleocytosis and oligoclonal bands and positive NMDAR IgG IIG in CSF and serum (Nguyen, 2023). He was treated with intravenous corticosteroids (CS) and discharged on VAL (2000mg/d), LEV (3000mg/d), Lamotrigine (LTG in slowly increasing dosages to 100mg/d) and oral low-dosage CS. During the follow-up, systemic diseases and vasculitis were also excluded. The patient improved with regard to the frequency and duration of his seizures and the severity of headache and stopped his oral CS on January 2023, although continued taking his AEM.

Follow up and possible relapses: During the winter-spring 2023 he noticed weight loss (about 12kg for 2 months) and since the beginning of June 2023 he complained of worsening of dizziness and sleepiness as well as frequent episodes of subjective aura like episodes, despite taking AEM. He independently started to take oral dexamethasone, with "some but not enough improvement" and was again hospitalized. The gastroenterological examination with echography and contrast fluoroscopy were unremarkable. On October 2023, he suffered a traffic accident with head trauma without loss of consciousness. Since then, he again started to have dizziness and "seizure feeling" and was hospitalized on November 2023 because of disorientation and full loss of memory for more than 3 hours. During the hospitalization, several focal clonic seizures at right facial zone were seen. The patient was discharged on VAL (2000mg/d), LEV (3000mg/d) and increased dosages of LTG (gradually to 200mg/d) and dexamethasone (4mg/d) for 1 week. He had no additional complains and no generalized seizures on this therapy until July 2025, when he realized several BCTS, followed by headache, severe dizziness and sleepiness and the dosages of LTG were increased to 300mg/d. On December 2025, because of complaints of cognitive changes and several seizures with focal origin, Brivaracetam (100mg/d) and Donepezile (5mg/d) were added. On this therapy, the patient improved with regard to cognitive functioning and seizure frequency (see table1).

2. Discussion

We presented an extremely rare case of HSV2 encephalitis in immunocompetent adult male, soon followed by NMDARE. The possible mechanism of NMDARE development after HSV2 is immune cross reactivity, induced by HSV2 (Bras, 2020). Unlike the other presented cases (Bras, 2020; Li, 2024), our patient had PG apoplexy 10 years before the presentation of the encephalitis with possible disruption of blood-brain barrier at this region. However, his other previous medical history was unremarkable. The first symptoms of NMDARE occurred within the previously reported interval (Bras, 2019), although the existence of NMDAR antibodies was proved 2 years after the onset. NMDARE is associated with systemic diseases and some tumors (Bras, 2019), which were excluded in our case. Unlike the severe clinical picture of NMDARE after HSV2 encephalitis reported before (Bras, 2019; Li, 2024), our patient had relatively benign course with good response to CS therapy and AEM treatment only.

3. Conclusions

This report documents a rare progression from HSV2 encephalitis to anti NMDAR encephalitis in an immunocompetent adult, demonstrating that delayed autoimmune complications may occur despite initial recovery. Early recognition and immunotherapy were associated with favorable long term neurological and cognitive outcomes, underscoring the importance of sustained clinical surveillance after viral encephalitis."

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Table 1: The blood, cerebrospinal examinations, EEG, Magnetic-Resonance Imaging and Neuropsychological Examination of our patient.

	MAY 2020	SEP 2020	MAY) 2022	JUN 2023	NOVr 2023	JUL 2025	MAR 2023
Blood leuco x109/l	14	4.48	2.99 6.5	6.5	11.28	6.73	NA
CRP (mg/L)	10	NA	1.4 1.5	1.6	0.2	1.3	NA
CSF Leuco $x10^6$/l	134	Refuse LP	14	Refuse LP	Refuse LP	Refuse LP	NA
CSF Protein (g/L)	0.81		0.29				
EEG	NA	Desorganized, SSW, predominantly at left T	Disorganizedlow amplitude SSW at left T	SW at left T	grouped SW at left T	diffuse SW and single sharp waves at both T	Single SW waves at both T
Head MRI	NA	PG apoplexy	PG apoplexy	NA	NA	PG apoplexy	NA
MMSE (p.)	NA	25	25	27	27	24	29
IST (p.)	NA	23	20	25	29	32	34
10WT (average of 5 trials)	NA	3	2.7	3.5	3.7	3.7	5
DR (w.)	NA	0	0	1	0	0	1
Recognition	NA	12/20	13/20	14/20	13/20	15/20	16/20
DST F (p.)	NA	5	4	5	4	5	5
DST R (p.)	NA	0	0	0	2	2	3

Legend CRP – Creactive protein, CSF – cerebrospinal Fluid; EEG – electroencephalography; MRI – magnetic resonance imaging; T – temporal region; MMSE – Mini Mental State Examination; 10WT – 10 words test; DR – delayed recall; DST – Digit Span Test F – forward B – backward; LP lumbar puncture; Leuco – leucocyte count; SSW – sharp-and slow waves; SW – slow waves; PG – pituitary gland

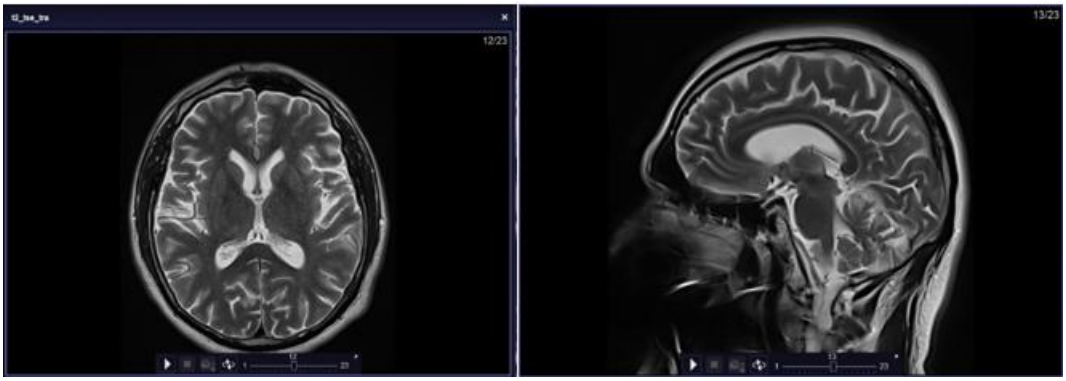

Figure A: Magnetic Resonance Imaging (MRI) of our patient

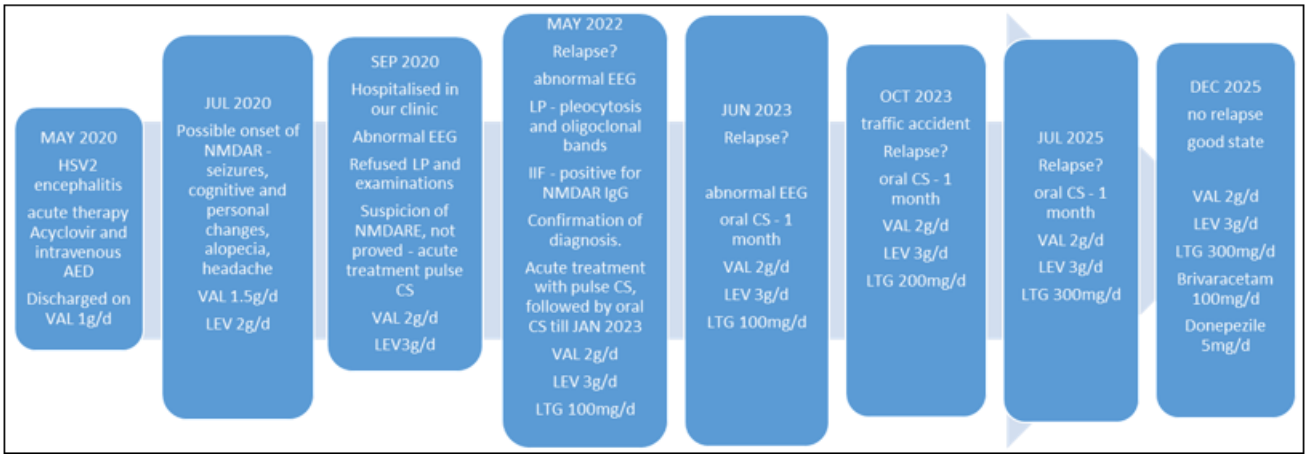

Figure 2: Course of the disease – timeline.

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