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CASE REPORT

Anti-*N*-methyl-D-aspartate receptor encephalitis after Herpes simplex virus-associated encephalitis: an emerging disease with diagnosis and therapeutic challenges

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Abstract
Introduction Morbidity and mortality of Herpes simplex virus encephalitis (HSE) remain high.Relapses of neurological signs may occur after initial clinical improvement under acyclovir treatment.
Methods We report here a case of post-HSE anti-N-methyl-d-aspartate receptor-mediated encephalitis in an adult and perform a systematic search on PubMed to identify other cases in adults.
Results We identified 11 previously published cases, to discuss diagnostic and therapeutic management.Symptoms in adults are often inappropriate behaviors, confusion and agitation. Diagnosis of anti-NMDA-Rencephalitis after HSE is often delayed. Treatment consists in steroids, plasma exchange, and rituximab.Prognosis is often favorable.
Conclusion Anti-NMDA-R antibodies should be searched in cerebrospinal fluid of patients with unexpected evolution of HSE. This emerging entity reopens the hot debate about steroids in HSE.

Keywords Herpes simplex virus · Encephalitis · Anti-NMDA-receptor antibodies · Neurological relapses · Autoimmune encephalitis

Introduction

Herpes simplex virus (HSV) is the leading cause of infective encephalitis [1], HSV encephalitis (HSE) resulting in great morbidity and mortality [1]. In spite of successful antiviral treatment, patients with a history of HSE are frequently readmitted to hospital for neurological or neuropsychiatric disorders [2]. Recently, increasing reports of autoimmune encephalitis associated with anti-*N*-methyl-D-aspartate receptor (NMDA-R) antibodies have been published. This post-HSE autoimmune encephalitis may in part explain the still great morbidity of HSE at the era of acyclovir. We report here a rare case of post-HSE anti-NMDA-R antibody-mediated autoimmune encephalitis in an adult, and reviewed the published cases in adults to discuss diagnosis approach and therapeutic management of this emerging entity.

Case report

A previously healthy 52-year-old woman was admitted to emergency department with non-fluent aphasia for 48 h. She had no fever. Brain magnetic resonance imagery (MRI) demonstrated hyperintensity lesions on temporal areas predominating in left side (Fig. 1a). She received intravenous (IV) aspirin (250 mg) and enoxaparin 40 mg a day, as the diagnosis of an ischemic stroke was retained. Two days later, body temperature increased to 38.5 °C associated with confusion and impaired consciousness. A brain CT confirmed extensive necrotical lesions in left temporal lobes with edema. She was transferred to intensive care unit. A first cerebrospinal fluid (CSF) analysis performed on day two post-admission showed 50 leukocytes/mL with 95% of lymphocytes, 220/mL red blood cells (RBC) and hyperproteinorachia (3 g/L). Cefotaxime (300 mg/kg/day), amoxicillin (200 mg/kg/day), gentamicin (3 mg/kg/day) and acyclovir (10 mg/kg/8 h) and dexamethasone (10 mg/6 h during 4 days) were started. As the detection

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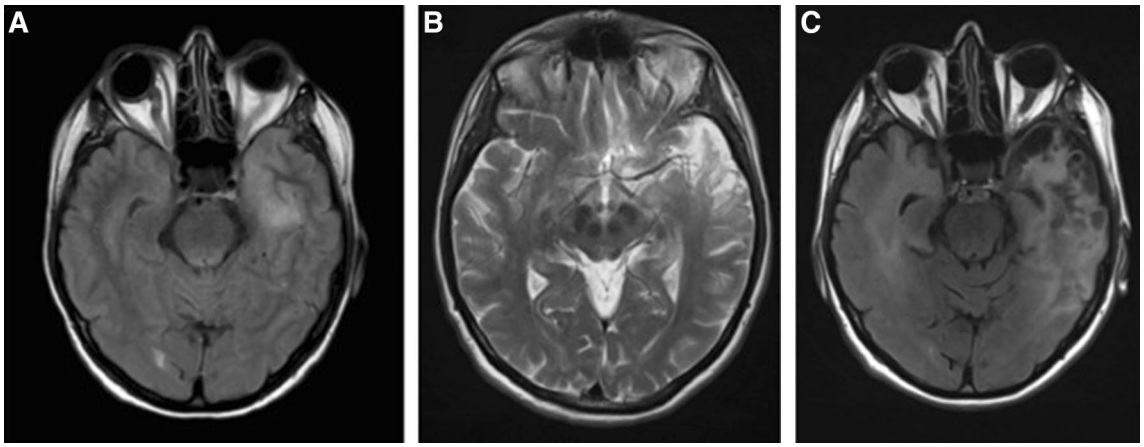

Fig. 1 Successive brain MRI in a patient experiencing post-HSE autoimmune encephalitis. **a** December 2014, FLAIR sequence, showing hyperintensity in bilateral limbic and temporal areas in axial view, with predominance in the *left* temporal lobe. **b** T2 sequence (performed in January 2015), showing extensive oedema in both temporal lobes. Hypersignal in *left* temporal lobe shows early necrosis lesions. **c** FLAIR sequence, performed for neurological relapse after HSE outcome, and showing extensive oedema in *right* temporal lobe, and hyposignal of *left* temporal lobe showing extensive necrotic lesions compared with precedent brain imagery

of HSV by polymerase chain reaction (PCR) in CSF was strongly positive (extraction and amplification BDMAX® [3]), antimicrobials except acyclovir were stopped. She recovered slowly with residual aphasia, anterograde amnesia and both spatial and temporal disorientation. She was discharged for rehabilitation twenty days later.

One week later, she was readmitted for catatonia, mutism, anorexia, aphasia, and urinary retention. A CSF analysis showed 12 lymphocytes/mL, 2 RBC/mL, proteinorachia at 0.79 g/L, glycorachia 3.50 mmol/L (glycemia at 6 mmol/L), with PCR negative for HSV. Anti-NMDA-R IgG were highly positive in CSF. Retrospectively, Anti-NMDA-R IgG were also found in the first CSF specimen. MRI showed no new necrotical lesions but extensive bilateral white matter hyperintensities predominating in fronto-temporal areas (Fig. 1b, c). Intravenous immunoglobulins (IgIV) (0.4 g/kg/day) and methylprednisolone (1 g/day) for 5 days were started. Despite three cures of IgIV, there was no clinical improvement, and cyclophosphamide (0.6 g/m^2 twice a month the first month, then 1 per month during six months) was started in addition to IgIV. After one year of follow-up, speech, memory, and autonomy in daily activities improved despite conserved severe neuro-psychological sequelae (Rankin score 4).

Discussion

Anti-NMDA receptor encephalitis was first described in women with teratoma and is known as being the first non-infectious cause of encephalitis in young people, tumor being very inconstant. In 2000s, relapses after HSV encephalitis were reported. Negative HSV PCR in CSF and inefficacy of antivirals during relapses suggested that other mechanisms than HSV neuropathogenicity were involved such as immune-mediated encephalitis or secondary infections by another viral agents [4, 5]. The first cases suggesting the role of anti-NMDAR antibodies in relapses after HSE were described in 2013 in a child and an adult [6]. To better assess the importance of anti-NMDAR encephalitis in the prognosis of HSE in adults, we performed a systematic review of the literature on Pubmed between 1990 and 2016 including as key words: "HSE and neurological relapses", "NMDA-R encephalitis and HSE", or "autoimmune encephalitis and HSE".

Our search permits to identify eleven supplementary cases of post-HSE anti-NMDAR encephalitis in adults or teenagers (Table 1). Clinical signs are similar between teenagers and adults but different from children. Age ranged from 13 to 67 years, sex ratio (M/F) was 1.4. Mean delay between HSE and neurological relapses due to anti-NMDAR antibodies was 48 days (±18); it was of 50 days in our case. Modification in behavior, psychiatric disorders, abnormal movements and headache were at the forefront of clinical manifestations in adults and teenagers [6–11], in contrast with children who often developed choreoathetosis. Most of the patients had rapid onset of clinical signs of anti-NMDAR encephalitis. The delay between HSE and the diagnosis of anti-NMDAR encephalitis ranged from 28 to 90 days. A prompt CSF analysis with screening anti-NMDAR antibodies should be recommended in patients experiencing incomplete recovery or neurological relapses of HSE. In our patient, anti-NMDA-R antibodies were retrospectively tested and found positive in the first CSF, questioning about different pattern of evolution between patients who rapidly develop auto-antibodies and

Table 1 Characteristics of the published adult and teenage cases of anti-NMDA receptor encephalitis secondary to HSE

References	Age (years)	Gender	HSE treatment	Delay between HSE and relapse (days)	Clinical manifestations of relapses	Treatment	Outcome
[6]	24	M	21-d IV acyclovir	41	Loss of memory, aggressive behavior	IV MP 1000 mg/a day for 5 days	Full recovery
[7]	20	M	21-d IV acyclovir	28	Inappropriate behavior	Plasma exchange, IV polyvalent Ig, cyclophosphamide	Partial recovery
[8]	41	M	14-d IV acyclovir	49	Confusion, headache, weakness, inappropriate behavior, weakness	Immunotherapy	Full recovery after 1 year
[8]	45	F	14-d IV acyclovir	74	Headache, seizures, weakness	NR	NR
[9]	30	F	21-d IV acyclovir	30	Aggressive behavior	IV polyvalent Ig, plasma exchange	Full recovery
[10]	13	M	21-d IV acyclovir	42	Aggressive behavior, headache	IV methylprednisolone	Partial recovery
[10]	15	M	21-d IV acyclovir	51	Aggressive behavior, cognitive impairment	IV and oral methylprednisolone, IV polyvalent Ig	Full recovery
[10]	45	M	21-d IV acyclovir	44	Headache, confusion, agitation	No specific treatment	Spontaneous resolution, mild persisting aphasia
[10]	50	M	14-d IV acyclovir	40	Headache, psychiatric disorders, suicidal ideation, termor, aggressive behavior	IV methylprednisolone, IV polyvalent Ig, rituximab, cyclophosphamide, plasma exchange	Partial recovery with moderate behavioral deficits
[10]	34	F	14-d IV acyclovir	38	Insomnia, delusions, restlessness	IV methylprednisolone	Improvement of behavior, mild aphasia (2-month follow-up)
[11]	67	F	21-d IV acyclovir	90	Confusion, headache, seizures	IV polyvalent Ig, rituximab 1000 mg, Cyclophosphamide	Full recovery
Our case	52	F	21-d IV acyclovir	50	Confusion, urinary retention, catatonia, mutism, abasia	IV methylprednisolone, IV polyvalent Ig, cyclophosphamide	Partial recovery

M male, *F* female, *D* days, *IV* intravenous, *Ig* immunoglobulins, *NR* not reported

Table 2 Diagnostic criteria for probable anti-NMDA receptor encephalitis (Grauss et al. [15])

Diagnostic criteria for probable anti-NMDA receptor encephalitis (diagnosis can be made when all three of the following criteria have been met)
Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms
Abnormal (psychiatric) behavior or cognitive dysfunction
Speech dysfunction (pressured speech, verbal reduction, mutism)
Seizures
Movement disorder, dyskinesias, or rigidity/abnormal postures
Decreased level of consciousness
Autonomic dysfunction or central hypoventilation
At least one of the following laboratory study results:
Abnormal EEG (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush)
CSF with pleocytosis or oligoclonal bands
Reasonable exclusion of other disorders

the others. In 2012, Prüss et al. identified anti-NMDA-R antibodies in blood and CSF of 13/44 patients treated for HSE [12]. They did not identify any difference in clinical course of patients with or without NMDA receptor antibodies during HSE; however, the follow-up was short [12]. Interestingly, the delay between onset of the symptoms and hospital admission was longer in patients with auto-antibodies probably because of difference in clinical signs such as high frequency of psychiatric disorders. This brain auto-immunity may contribute to neurological relapses several weeks after the completion of antiviral regimen in HSE, with no detection of HSV DNA by PCR in CSF at the time of relapse as observed in our case. In contrast with this report, in a retrospective study where only one patient experienced relapse, no anti-NMDAR antibodies were detected in 61 cases of HSE [13]. Considering the possible great proportion of the patients with HSE who had auto-antibodies in CSF [12], the hot debate of steroids in the treatment of HSE is re-opened. Although our patient had received steroids, she developed autoimmune encephalitis. In our case, steroids were administered early after the diagnosis of HSE.

Most of the patients received immunotherapies (steroids, intravenous immunoglobulins, cyclophosphamide, and/or plasma exchange) and experienced full or partial recovery as in the present report (Table 1). These treatments were in accordance with practice for other anti-NMDA-R encephalitis [14].

To reduce the delay in diagnosis and treatment of anti-NMDA-R encephalitis, guidelines were recently published (Table 2). Even if these guidelines do not specifically deal with HSE, at readmission our patient and most of the others patients fulfilled the criteria for a probable anti-NMDA-R encephalitis [15]. An evaluation of these criteria in post-HSE autoimmune encephalitis might be interesting to measure sensitivity and specificity. Physicians taking care of patients with HSE need to be aware of this emerging entity, post-HSE anti-NMDA-R encephalitis that probably contributes to the great morbidity of HSE.

We suggest to promptly assess the presence of these auto-antibodies in CSF of the patients who developed relapses in the 3 months following HSE or with unfavorable outcomes of HSE, and to early start immunotherapy after having ruled out a new central nervous system infection or reactivation of HSV by PCR. However, due to the high frequency of anti-NMDA-R antibodies in CSF of patients with HSE without clinical signs for autoimmune encephalitis, the specificity of these antibodies remained uncertain but seems to play an important role in pejorative prognostic of HSE when they are present.

Compliance with ethical standards

Conflict of interest We do not have any conflict of interest. We did not receive any financial support for this work.

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