Autoimmune post–herpes simplex encephalitis of adults and teenagers

ABSTRACT
Objective: To report 14 patients with immune-mediated relapsing symptoms post–herpes simplex encephalitis (HSE) and to compare the clinical and immunologic features of the teenage and adult group with those of young children.

Methods: Prospective observational study of patients diagnosed between June 2013 and February 2015. Immunologic techniques have been reported previously.

Results: Among the teenage and adult group (8 patients, median age 40 years, range 13–69; 5 male), 3 had an acute symptom presentation suggesting a viral relapse, and 5 a presentation contiguous with HSE suggesting a recrudescence of previous deficits. Seven patients developed severe psychiatric/behavioral symptoms disrupting all social interactions, and one refractory status epilepticus. Blepharospasm occurred in one patient. Five patients had CSF antibodies against NMDA receptor (NMDAR) and 3 against unknown neuronal cell surface proteins. In 5/6 patients, the brain MRI showed new areas of contrast enhancement that decreased after immunotherapy and clinical improvement. Immunotherapy was useful in 7/7 patients, sometimes with impressive recoveries, returning to their baseline HSE residual deficits. Compared with the 6 younger children (median age 13 months, range 6–20, all with NMDAR antibodies), the teenagers and adults were less likely to develop choreoathetosis (0/8 vs 6/6, p < 0.01) and decreased level of consciousness (2/8 vs 6/6, p < 0.01) and had longer delays in diagnosis and treatment (interval relapse/antibody testing 85 days, range 17–296, vs 4 days, range 0–33, p = 0.037).

Conclusion: In teenagers and adults, the immune-mediated relapsing syndrome post-HSE is different from that known in young children as choreoathetosis post-HSE and is underrecognized. Prompt diagnosis is important because immunotherapy can be highly effective. Neurology® 2015;85:1736–1743

GLOSSARY
FLAIR = fluid-attenuated inversion recovery; HSE = herpes simplex virus encephalitis; HSV = herpes simplex virus; IDIBAPS = Institute of Biomedical Research August Pi i Sunyer; IgG = immunoglobulin G; IQR = interquartile range; IV Ig = IV immunoglobulin; NMDAR = NMDA receptor.

Herpes simplex virus (HSV) encephalitis (HSE) is a frequent cause of severe, potentially fatal encephalitis among children and adults worldwide. The disease usually follows a monophasic course but 12%–27% of the patients develop relapsing neurologic symptoms a few weeks after the CSF viral studies become negative and the treatment with acyclovir has been discontinued.1–3 Most of these patients are children who develop an encephalopathy with abnormal movements named choreoathetosis post-HSE or relapsing symptoms post-HSE.4 The hypothesis that the disorder is immune-mediated has received strong support by the recent discovery that many of these patients develop immunoglobulin G (IgG) antibodies against the GluN1 subunit of the NMDA receptor.5

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NMDA receptor (NMDAR)\textsuperscript{5–11} and sometimes to other known\textsuperscript{7} or unknown synaptic proteins.\textsuperscript{6} This clinical complication is less well-known in adults and teenagers, suggesting a lower frequency in these age groups or a different and less recognizable syndrome. Over the last 21 months, we have prospectively identified 14 new patients with relapsing symptoms post-HSE, 8 of them adults or teenagers. In the current study, we show that the clinical picture of these patients is indeed different from that of young children with choreoathetosis, leading to delays in diagnosis and treatment. Prompt recognition of this disorder is important because immunotherapy is effective in reducing the burden of the immune-mediated deficits and improving the quality of life of patients and families.

**METHODS** From June 2013 until February 2015, serum and CSF of 14 patients with nonviral relapsing symptoms post-HSE were prospectively studied at the Institute of Biomedical Research August Pi i Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona. Five of the patients (patients 3, 5, 8–10) were examined as part of a 2-year multicenter prospective Spanish study in which all patients with HSE are clinically and immunologically followed after being diagnosed with HSE. The other 9 patients were diagnosed either before this multicenter HSE study was initiated (January 1, 2014, patients 1, 4, 12) or at centers that do not participate in the study (2 from Spain, 4 from other countries). In the prospective multicenter study, physicians are blinded to the immunologic findings unless patients develop relapsing symptoms. Of 20 patients with HSE (6 children and 14 adults) enrolled to date, the indicated 5 cases (25%) have developed relapsing neurologic symptoms post-HSE.

CSF or serum of all patients were extensively examined for antibodies to cell surface/synaptic proteins, including NMDA, mGluR5, AMPA, GABA\textsubscript{A}, GABA\textsubscript{B} receptors, LGI1, Caspr2, and DPPX, using previously reported techniques that included tissue immunohistochemistry, live cultured neurons, and cell-based assays.\textsuperscript{12–14} All patients underwent repeat CSF PCR for HSV and MRI of the brain (9 with contrast and 5 without). Clinical information was obtained by the authors or from referring physicians. No data of any patient have been reported previously.

**Standard protocol approvals, registrations, and patient consents.** Written informed consent for participating in the study was obtained from all patients or guardians of patients. Studies were approved by the internal review board of Hospital Clinic-IDIBAPS and the ethical standards committee on human experimentation of IDIBAPS.

**Statistical analysis.** Comparative analyses between the group of teenagers and adults and the group of children were performed with STATA version 13.1 (StataCorp, College Station, TX), using Fisher exact test, Chi\textsuperscript{2} test, or Mann-Whitney U test when appropriate. The Wilcoxon rank-sum test was used for comparative studies between the CSF obtained during the stage of viral encephalitis and that obtained during the autoimmune relapse.

**RESULTS** Eight of the 14 patients with nonviral relapsing neurologic symptoms post-HSE were adults or teenagers (median age 40 years, range 13–69; 5 male) and the other 6 were young children (median age 13 months, range 6–20 months; 3 male). Repeat CSF PCR for HSV was negative in all patients. The 6 young children developed a classical syndrome of choreoathetosis post-HSE in association with IgG antibodies against the GluN1 subunit of the NMDAR and one of them also had antibodies against the GABA\textsubscript{B}R (figure e-1 on the Neurology\textsuperscript{®} Web site at Neurology.org). In many respects, these children were clinically similar to previously reported cases and are not the focus of this study (see information in table e-1, patients 9–14). In contrast, the 8 patients in the teenage and adult group did not develop choreoathetosis and are the main focus of this report (table 1, patients 1–8, and clinical vignettes in supplemental material).

In these 8 patients, the onset of relapsing symptoms started 12–51 days (median 39, interquartile range [IQR] 26–43 days) after onset of HSE. In 3 patients (2–4), symptoms presented acutely, mimicking a viral relapse (biphasic course), and all 3 patients were restarted on acyclovir along with antipsychotic drugs or benzodiazepines while waiting for the results of repeat CSF PCR studies. In the other 5 patients (1, 5–8), the symptoms developed while recovering in rehabilitation centers or at home, or in contiguity with those of HSE, without a clear biphasic stage, and none of the patients was initially considered to have relapsing symptoms. In these patients, the symptoms were initially attributed to a recrudescence of residual viral-related deficits and managed with antipsychotics and antidepressants. The severity and persistence of neuropsychiatric symptoms eventually led to reconsideration of the possibility of an independent complication. Three of these patients (3, 5, and 8) were diagnosed with immune-mediated symptoms when they returned for a routine outpatient visit as part of the prospective study.

Seven patients presented with acute or subacute change of behavior, agitation, aggression, suicidal ideation, confusion, or delusional thoughts, and one patient with refractory seizures and status epilepticus requiring mechanical ventilation and barbiturate coma (patient 6). An example of the severe alteration of mental functions and imaginary graphic representation is shown in the drawings of patient 8 (figure 1). In 3 patients (patients 1, 3, and 4), the neuropsychiatric manifestations were heralded by intense headache, accompanied in one case by drug-resistant high blood pressure (table 1, and case vignettes in supplemental data). In another patient (patient 7), the change of behavior was followed a few days later by fever, decreased level of consciousness, and severe blepharo-spasm. Except for this case, no abnormal movements were identified in the other patients.
Table 1  Clinical features of adults and teenagers with autoimmune relapsing symptoms post–herpes simplex encephalitis

<table>
<thead>
<tr>
<th>Patient/s</th>
<th>HSE</th>
<th>Symptoms</th>
<th>Brain MRI</th>
<th>CSF and immunologic studies</th>
<th>Treatment and response</th>
<th>Autoimmune relapse</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/13</td>
<td>HSE</td>
<td>Fever, seizures, aphasia, cardiorespiratory arrest</td>
<td>D2: left FT, right FB necrotic lesions with ADC restr</td>
<td>D5: HSV pos; D23: HSV neg, WBC 27, prot 51, neg NSAb</td>
<td>IV Acyc (21 d), motor and cognitive residual deficits</td>
<td>D42: aggressive behavior, headache, high blood pressure</td>
<td>D1186: no new necrosis</td>
<td>IV MP</td>
</tr>
<tr>
<td>2/M/15</td>
<td>HSE</td>
<td>Headache, focal seizures, encephalopathy</td>
<td>D3: bilateral FT necrosis + ADC restr, no enhanc</td>
<td>D2: HSV pos, WBC 2, prot 50</td>
<td>IV Acyc (23 d), complete recovery</td>
<td>D51: agitation, cognitive deficits, aggressive behavior</td>
<td>D186: no new necrosis</td>
<td>IV MP</td>
</tr>
<tr>
<td>3/M/45</td>
<td>HSE</td>
<td>Headache, fever, confusion, aphasia</td>
<td>D10: left T necrosis + ADC restr, mild enhanc; D23: no changes</td>
<td>D10: HSV pos, WBC 110, prot 74; D25: HSV neg, WBC 56, prot 78</td>
<td>IV Acyc (21 d), residual global aphasia</td>
<td>D44: headache, confusion, agitation, delusional thoughts, insomnia</td>
<td>D186: no new necrosis</td>
<td>IV MP</td>
</tr>
<tr>
<td>4/M/50</td>
<td>HSE</td>
<td>Fever, aphasia, memory deficits</td>
<td>D2: bilateral T necrosis + ADC restr, no enhanc</td>
<td>D2: HSV pos, WBC 239, prot 66</td>
<td>IV Acyc (14 d), good recovery</td>
<td>D40: headache, aggression, suicidal ideation, tremor, sleep disorder</td>
<td>D186: no new necrosis</td>
<td>IV MP</td>
</tr>
<tr>
<td>5/F/34</td>
<td>HSE</td>
<td>Fever, focal seizures, aphasia, memory deficits</td>
<td>D2: left T necrosis + ADC restr, enhanc NA</td>
<td>D2: HSV pos, WBC 460, prot 51, neg NSAb</td>
<td>IV Acyc (14 d), persistent aphasia and memory deficits</td>
<td>D38: insomnia, anxiety, restlessness, irritability, delusions</td>
<td>D186: no new necrosis</td>
<td>IV MP</td>
</tr>
<tr>
<td>6/F/69</td>
<td>HSE</td>
<td>Speech problems, confusion, fever, partial seizures</td>
<td>D2: normal brain CT</td>
<td>D2: HSV pos, WBC 52, prot ≤45</td>
<td>IV Acyc (21 d), improvement of seizures after 6 days of treatment</td>
<td>D12: confusion, new-onset nonconvulsive status epilepticus</td>
<td>D29: HSV neg, WBC 0, prot ≤45, pos NSAb also in serum</td>
<td>IV MP</td>
</tr>
<tr>
<td>7/M/29</td>
<td>HSE</td>
<td>Fever, respiratory failure, seizures, abnormal behavior</td>
<td>D3: right FT hypointensity in CT</td>
<td>D2: HSV pos, WBC 48, prot 60</td>
<td>IV Acyc (13 d), motor and cognitive residual deficits</td>
<td>D21: abnormal behavior, D60: fever, consciousness, blepharospasm</td>
<td>D58: HSV neg, WBC 2, prot 112; D90: HSV neg, WBC 12, prot 63, pos NSAb</td>
<td>IV MP</td>
</tr>
<tr>
<td>8/F/56</td>
<td>HSE</td>
<td>Fever, diarrhea, somnolence, catatonia</td>
<td>D7: bilateral T necrosis, no ADC restr, no enhanc</td>
<td>D7: HSV pos, WBC 250, prot 62; D23: HSV neg, WBC 90, prot 61</td>
<td>IV Acyc (15 d), residual anterograde amnesia</td>
<td>D30: emotional lability, suicidal ideation, confusion</td>
<td>D146: HSV neg, WBC 10, prot 45, pos OCB, pos NSAb (neg serum)</td>
<td>IV MP</td>
</tr>
</tbody>
</table>

Abbreviations: Ab = antibodies; Acyc = acyclovir; ADC restr = apparent diffusion coefficient restriction; CYC = cyclophosphamide; enhanc = contrast enhancement; FB = frontobasal; FT = frontotemporal; FU = follow-up; HSE = herpes simplex virus encephalitis; HSV = herpes simplex virus; IVlg = IV immunoglobulin; MP = methylprednisolone; NA = not available; neg = negative; NMDAR = NMDA receptor; NSAb = neuronal surface antibodies (unknown identity); OCB = oligoclonal bands; PEX = plasma exchange; pos = positive; prot = CSF total protein in mg/dL; RTX = rituximab; T = temporal; WBC = white blood cell count/μL in CSF; WM = white matter.
The median time between onset of relapsing symptoms and CSF routine and viral studies was 30 days (IQR 14–81, range 0–136), and for antibody testing 85 days (IQR 37–126, range 17–296). The PCR for HSV was negative in all 8 patients. Five patients had pleocytosis (median 10 leukocytes, IQR 7–10, range 5–27) and 4 had increased protein concentration (median 100 mg/dL, IQR 79–110). The level of pleocytosis was substantially lower than that previously found during the viral encephalitis (median 80 leukocytes, IQR 30–245, range 2–460, \( p < 0.01 \)). Patients 1–5 had IgG antibodies against the GluN1 subunit of the NMDAR (all 5 in CSF, 2 also in serum; figure 2 and figure e-2); patients 6–8 had antibodies against unknown neuronal antigens (all 3 in CSF, 1 also in serum). Archived CSF and serum obtained at the time of the HSE were available in 4 patients (patients 1, 3, 5, and 7) and all were negative for NMDAR or other autoantibodies (figure e-2).

All 8 patients underwent brain MRI; 6 had prior MRI studies obtained by the time of HSE, and the other 2 had CT scans (patients 6 and 7). In the 6 patients with repeat MRI, this showed mild to moderate interval progression of T2/fluid-attenuated inversion recovery (FLAIR) abnormalities compared with that obtained during HSE (figure 3, A–D). Gadolinium was used in 6 of the 8 patients at symptom relapse, showing in 5 contrast enhancement (4 intense, 1 mild) in the same areas with T2/FLAIR abnormalities (figure 3, F, G, and L). In 4 cases, the findings could be compared with those of the MRI obtained during HSE, which showed absence or mild enhancement. Several additional follow-up MRIs were obtained in 3 patients; 2 of them showed dramatic reduction or absence of contrast enhancement after clinical improvement (patients 3 and 8, figure 3H), and the third patient, who had not received immunotherapy and continued with severe deficits, showed persistent contrast enhancement 1 year after onset of relapsing symptoms (patient 4, figure 3L).

Before immunotherapy, 6 patients (patients 1, 2, 4, 6–8) received acyclovir, antipsychotics, or antidepressants, and all continued to deteriorate: 5 developed drug-resistant psychiatric symptoms (one of them, patient 7, progressing to coma), and 1 developed refractory status epilepticus needing barbiturate coma. Only one patient (patient 3) improved without immunotherapy (described below).
The median time between onset of relapsing symptoms and immunotherapy was 79 days (IQR 22–148, range 17–352 days). This included steroids in 4 patients, steroids and IV immunoglobulin (IVIg) in 1, and steroids, IVIg, and plasma exchange in the other 2 patients. In all 7 cases, a substantial improvement was noted after the immunotherapy was started. At last follow-up (median 12 months, IQR 4.5–15, range 2–20 months), 2 patients had full or near complete recovery (patients 2 and 6), and the other 5 had substantial improvement of the neuropsychiatric abnormalities or seizures, returning to their baseline residual deficits of HSE (table 1 and supplemental case vignettes). The patient with refractory status epilepticus improved transiently after the first plasma exchange but because of recurrent electrographic seizures he was started on IVIg and rituximab. This treatment resulted in complete seizure control and improved level of consciousness, but he was left with HSE-related residual aphasia and critical illness neuropathy.

The patient who was not treated with immunotherapy (patient 3, table 1 and case vignettes in supplemental data) was tested for antibodies 3 months after the neurologic relapse as part of the prospective multicenter study of patients with HSE. This patient on day 40 post-HSE developed agitation, delusional thoughts, and insomnia that improved with alprazolam. By the time he was found to have NMDAR antibodies in CSF (serum negative), his symptoms had substantially improved and the contrast enhancement in the MRI had decreased.

When the clinical features of these 8 teenagers and adults were compared with those of the 6 young children with autoimmune relapses (table e-2), the young children were more likely to have choreoathetosis (6/6 vs 0/8, \( p < 0.01 \)) and decreased level of consciousness (6/6 vs 2/8, \( p < 0.01 \)). In addition, 3/6 young children developed refractory seizures and status epilepticus (2 preceding choreoathetosis) while only 1/8 in the teenager and adult group had seizures. MRI with contrast was obtained in 3 young children; 1 showed contrast enhancement and the other 2, who had the study performed after immunotherapy, did not show enhancement.

The interval from onset of HSE to relapsing symptoms was similar in the teenager and adult group (median 39 days, range 12–51) and in the young children group (median 27 days, range 17–40, \( p = 0.25 \)), but the first group had a longer delay in the recognition of the relapsing symptoms than the young children.
group (interval onset of symptom relapse/antibody testing 85 days, range 17–296, vs 4 days, range 0–55 in children, \( p = 0.037 \)). Moreover, all young children were promptly treated with immunotherapy, while one of the adult patients did not receive immunotherapy and the other 7 were treated with substantial delay (interval from relapsing symptoms to immunotherapy in the teenager and adult group 79 days, range 17–352, vs 4 days, range 0–12, in the young children group, \( p = 0.043 \)).

**DISCUSSION** The recent identification of antibodies to NMDAR and other synaptic proteins has provided a proof of principle to the long-held theory that relapsing symptoms post-HSE (or choreoathetosis post-HSE) can be immune-mediated, and has increased awareness for this complication in children and adults.\(^{5,6,9}\) In the current study, we report several novel findings in the age group of adults and teenagers demonstrating that (1) the main clinical manifestations are different from those of young children; (2) the symptom presentation may occur as a relapse of encephalitis (biphasic course), or in contiguity with HSE, suggesting progression or recrudescence of residual deficits after the viral infection; (3) an immune-mediated pathogenesis is often not suspected, or is considered late in the course of the disease, likely explaining substantial delays in immunotherapy; (4) the brain MRI frequently shows contrast enhancement during the autoimmune relapse; (5) in addition to
NMDAR, patients may develop antibodies to GABA\textsubscript{A}R or other, unknown, neuronal cell-surface antigens; and (6) prompt diagnosis and immunotherapy improve symptoms and favorably affect the quality of life of patients and families despite persistence of HSE-related deficits.

The current data confirm that in young children the most characteristic manifestation of the disorder is choreoathetosis,\textsuperscript{4,6,17} which in some patients may be accompanied or preceded by refractory seizures or status epilepticus and the most common autoantibody is against NMDAR. In contrast, none of the teenagers or adults developed choreoathetosis; in these patients, the NMDAR antibodies also predominated in the antibody repertoire, but some patients had antibodies against unknown neuronal cell surface proteins. The novel finding of GABA\textsubscript{A}R antibodies in one of the young children with choreoathetosis and status epilepticus and a previous report demonstrating dopamine receptor antibodies\textsuperscript{4,6} support the concept that the viral encephalitis triggers an immune response against a wide number of antigens. Further support is provided by the reactivity of the CSF or serum of some patients with live neuronal cultures even when studies with cell-based assays expressing all known surface antigens are negative.\textsuperscript{6} Given that we have always found that CSF IgG antibodies to GluN1 associate with anti-NMDAR encephalitis\textsuperscript{8,19} and these antibodies are pathogenic in models of cultured neurons\textsuperscript{20} and mice,\textsuperscript{21} we postulate they contribute to patients’ symptoms. The pathogenic role of the other antibodies is unclear.

Preliminary data of our ongoing prospective study in which all patients with HSE are clinically and immunologically followed after the viral infection show that 5/20 patients (25%) developed immune-mediated neurologic symptoms, suggesting that this complication might be underrecognized. In teenagers and adults, the problem of syndrome underrecognition is worse than in younger children given that they had substantial longer delays in antibody testing (unless they were part of the prospective study) and initiation of immunotherapy. The 2 main reasons for these delays included the type of syndrome, which in teenagers and adults was less stereotyped (e.g., absence of choreoathetosis), and the initial symptom presentation, which in some patients was not suggestive of a clinical relapse. Indeed, the symptom presentation in most patients of the teenager and adult group was initially attributed to a progression or recrudescence of residual deficits and therefore not suspected to be autoimmune nor viral-induced; the clinical interval change noted in the scheduled visits suggested the autoimmune process. These findings have led to modification of the protocol to include early follow-up visits (e.g., 1 month after hospital discharge).

Compared with the brain MRIs obtained during HSE (which showed mild or absent contrast enhancement), the MRIs obtained during symptom relapse had intense contrast enhancement that decreased or disappeared after the use of immunotherapy and clinical improvement. This observation has not been previously reported and deserves further study with a larger number of patients in order to assess if contrast-enhancing MRI is a potential biomarker of the autoimmune response.

An important finding of this study is the symptom response to immunotherapy. In addition to the remarkable improvement of the patient shown in figure 1, the clinical response in other patients was similarly impressive despite their residual deficits caused by the viral encephalitis. Before the autoimmune relapse, all patients were collaborative or able to communicate and carry out some activities of daily living according to the expected limitations caused by the areas of viral-induced necrosis (usually affecting short-term memory and language). However, this clinical picture contrasted with that observed during the autoimmune relapse, when most of the patients were agitated, aggressive, not collaborative, some of them with suicidal thoughts, or with seizures or decreased level of consciousness progressing to coma. In all but one patient, who improved with symptomatic treatment, immunotherapy (usually first-line, such as steroids, IVIg, or plasma exchange) restored the clinical picture to the baseline deficits, allowing continuation of rehabilitation or discharge home.

The current findings suggest that patients with HSE should be carefully followed for any symptom relapse, worsening of deficits, or development of behavioral-psychiatric alterations with or without choreoathetosis or abnormal movements. Any of these symptoms should raise concern for a viral relapse or an immune-mediated complication. Determination of CSF and serum neuronal cell surface antibodies (mainly NMDAR) is a relatively new and important aid in the diagnosis of immune-mediated relapses post-HSE, and should be considered in all patients. If NMDAR antibodies are negative and testing for other antibodies is not available, a research laboratory should be contacted for further studies. Meanwhile, if the CSF PCR for HSV is negative, it seems reasonable to start these patients with empiric immunotherapy (e.g., first-line steroids, IVIg, or plasma exchange), and depending on the symptom response and antibody results, more intense therapies such as rituximab considered. The ongoing prospective multi-center study will clarify whether neuronal cell surface antibodies may occur without relapsing symptoms post-HSE, or if there is a titer threshold required for symptom development. The significance of MRI contrast enhancement in the areas previously affected by HSE, and the identity of additional target autoantigens, should be goals of future studies.
AUTHOR CONTRIBUTIONS

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DISCLOSURE
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