Herpes simplex encephalitis (HSE) is one of the most common causes of severe sporadic encephalitis. Herpes simplex virus (HSV) 1 is usually the responsible pathogen in adults and children, whereas HSV2 is mostly detected in neonates. Symptoms in the early stages in adults and children include fever, headache, fatigue, vomiting, seizures, confusion, somnolence, decreased consciousness, and focal neurological signs. HSE is characterized by unfavourable outcome with severe neurological sequelae or death in about 35% of patients. While HSE is usually a monophasic disease, relapses have been reported in 7.1% to 12.5% of adult patients, and in 14.3% to 26.7% of children. In some cases, the association of relapses with a low initial dose of aciclovir, the good response to a second course of aciclovir, or the detection of positive HSV-polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) have suggested incomplete viral inactivation or new viral replication. However, in other cases, the negativity of HSV PCR in CSF at relapse, the absence of new necrotic haemorrhagic lesions on brain magnetic resonance imaging, and the temporal separation of HSE and anti-NMDAR encephalitis suggest that these occurrences are different diseases. This paper aims to conduct a systematic literature review on patients with biphasic disease with herpes simplex virus (HSV) encephalitis followed by anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.
imaging (MRI), the poor response to aciclovir, and the efficacy of immune therapy have suggested that an immune-mediated mechanism may be responsible.8

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a condition characterized by multistage progression with psychiatric and behavioural symptoms, movement disorder, seizures, speech disturbances, decreased consciousness, and dysautonomias. After its description, it has been suggested that anti-NMDAR antibodies may be implicated in the immune-mediated relapses after HSE,9 and cases of anti-NMDAR encephalitis after HSE have been subsequently described both in adult and paediatric age.

We report the case of a 7-year-old female who recently presented to our hospital with anti-NMDAR encephalitis following an episode of HSE. As correct and early recognition of this condition is crucial for the commencement of appropriate therapy, this case prompted us to perform a systematic literature review of the literature on patients with biphasic disease with HSE followed by anti-NMDAR encephalitis (HSV-induced anti-NMDAR encephalitis) and on the relationship between central nervous system (CNS) HSV infection and anti-NMDAR antibodies.

METHOD

Case report and literature review

We illustrate a new case of biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis, and we present the results of a systematic literature review on the relationship between CNS HSV infection and the development of anti-NMDAR antibodies. A literature search was first done by one of the researchers (FC), and then carried out again by another researcher (MN), independently, in order to ensure inclusion of all relevant papers. The literature review was carried out in PubMed only (up to 10 December 2016), using the following search terms: ‘NMDAR’ OR ‘anti-NMDAR’ OR ‘anti-NMDAR encephalitis’ OR ‘NMDA receptor encephalitis’ OR ‘N-Methyl-D-Aspartate’ OR ‘Anti-N-Methyl-D-Aspartate Receptor’ OR ‘Anti-N-Methyl-D-Aspartate Receptor encephalitis’. The available results were searched manually for ‘herpes’, ‘HSV’, and ‘herpetic’.

Inclusion criteria

Patients with biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis were included in the literature review. We also included, separately, patients with HSE with detection of anti-NMDAR antibodies (in the absence of a clinical episode of anti-NMDAR encephalitis), and patients with anti-NMDAR encephalitis with concomitant positive HSV markers (in the absence of a preceding clinical or radiological episode of HSE). Both full-text and abstract-only articles were included.

Data extraction and collection

In the selected articles, a comprehensive data set was collected via a form designed for the present study. The form was created by one of the authors (MN) after reading the relevant literature, to capture core features and relevant data on published patients with biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis. The form consisted of an Excel spreadsheet (Microsoft, Redmond, WA, USA), where each column captured a different piece of information and data relative to each patient was recorded in a different line. When data were inadequate or insufficient for a definite piece of information, we recorded it as ‘not available’. Data of the individual patients were then pooled and analysed via the spreadsheet. A Microsoft Word document transposition of the form is provided as Appendix S1 (online supporting information).

Data extraction was first done by one of the researchers (FC), and then verified by another researcher (MN), who checked for accuracy and completeness of collected data. Other authors were involved in data analysis, interpretation, and supervision of the project. Data collection focused on symptoms during HSE and anti-NMDAR encephalitis, CSF data, evidence of CNS HSV infection, antibody status, antiviral and immune therapy, and outcome. Similar to other major published case series of anti-NMDAR encephalitis,10,11 we categorized the main symptoms of disease as encephalopathy (defined as altered level of consciousness persisting for >24h and including lethargy, irritability, or a change in personality and behaviour); psychiatric/behavioural changes or agitation; movement disorder; speech disturbances; cognitive deterioration; seizures; autonomic disturbances; and sleep–wake cycle disturbances.

We defined first-line immune therapy as corticosteroids, intravenous immunoglobulin and plasmapheresis, and second-line immune therapy as rituximab, cyclophosphamide, mycophenolate mofetil, azathioprine, and others. With regard to severity of disease and outcome, based on the clinical description available in the case reports, modified Rankin Scale (mRS) score was retrospectively assigned in different phases:13 at nadir of the episode of HSE; at recovery (before onset of anti-NMDAR encephalitis); at nadir of the episode of anti-NMDAR encephalitis; and at last available follow-up. mRS scores were assigned independently by two of the main investigators (MN and FC) and then compared. Discordant ratings were resolved by consensus. For paediatric patients, the Pediatric Cerebral Performance Category scale, as done by Armaungue et al.,14 was also applied (MN) in addition to the mRS scoring. Comparison of percentages and median values were used in most cases as main summary measures. The literature review was subject to publication bias and selective reporting within studies.

Statistical methods

Comparison of symptoms between the HSE and the anti-NMDAR encephalitis phases was done with McNemar’s
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RESULTS

Case report

A previously well 7-year-old female presented to the paediatric emergency department at the University Hospital of Padua (Italy) with a prolonged febrile generalized convulsive seizure followed by vomiting. The patient was lethargic, irritable, confused, and disoriented in space and time, and had a 3-day history of headache and fever. An electroencephalography showed significant bilateral slowing, more marked on the right side, with bilateral temporoooccipital epileptic discharges and subclinical focal temporal seizures (Fig. S1a, b; online supporting information). Brain MRI demonstrated diffusion restriction in temporal, mesial, and insular areas, prevalent on the right hemisphere (Fig. 1a–c), and a lumbar puncture showed 152/µL white blood cells (mostly mononuclear), no red cells, glucose 2.7 mmol/L, normal lactate and proteins, and negative anti-NMDAR antibodies. mRS score in the acute phase was 5. Antiepileptic drugs and empirical intravenous aciclovir (60 mg/kg/day) were started, and continued after confirmation of positive HSV PCR in CSF. At discharge after 21 days of antiviral treatment, the patient had regained normal consciousness and had no motor deficits, although she was not independent in activities of daily living and had residual cognitive deficits with slowed cognition, movements, and speech; inability to read; and prosopagnosia (mRS score 3).

Eight days after discharge (31d after onset of HSE), the patient returned to the emergency department with a 2-day history of lethargy, irritability, confusion, echolalia, nonsense talk, obsessions, sleep–wake cycle disturbances, drooling, dyskinesias, and stereotypes. Treatment with intravenous aciclovir was resumed. Electroencephalography showed poor organization of background activity, especially on the right hemisphere, bilateral frontotemporal slow waves, and epileptiform discharges (Fig. S1c). Brain MRI showed evolution of the previous lesions, in the absence of new areas of cytotoxic oedema (Fig. 1d, e), and the lumbar puncture disclosed negative HSV PCR and positive anti-NMDAR antibodies. mRS score in the acute phase of the relapse was 5. The patient received five plasma exchanges (started 9d after onset of anti-NMDAR encephalitis) and high-dose intravenous methylprednisolone (30 mg/kg/day for 5d, started 22d after onset of anti-NMDAR encephalitis) followed by oral prednisolone (1 mg/kg/day for 2mo, tapered in 1mo, total 3mo), with significant improvement. She was discharged on oral prednisone, carbamazepine, and olanzapine after 34 days of the relapse admission. At the 16-month follow-up from the onset of HSE, the patient had mild residual persistent prosopagnosia, mild mood disorder, and obsessive–compulsive behaviours (mRS score 2). She was back in mainstream school (with support), and she had normal sleep–wake cycle, no motor deficits, no seizures, and remained on carbamazepine.

Literature review

Biphasic illness: HSE followed by HSV-induced anti-NMDAR encephalitis

Our literature search led to the identification of 20 articles, published between 2013 and 2016, reporting a total of 42 patients who experienced biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis. The full text of all articles was available. With the addition of our case, a total of 43 patients with biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis were identified (31 children). Data on these patients are detailed in Table SI (online supporting information), and the main results are highlighted in the following sections.

Main clinical differences between the HSE and the anti-NMDAR encephalitis phases

Compared with the HSE phase, the anti-NMDAR encephalitis phase was characterized by a significantly lower rate of seizures (n=28/40 [70%] in HSE vs n=12/40 [30%] in anti-NMDAR encephalitis; p=0.001), and by a significantly higher frequency of movement disorder (n=1/40 [3%] in HSE vs n=30/40 [75%] in anti-NMDAR encephalitis; p<0.001). During anti-NMDAR encephalitis, the most frequent type of movement disorder (according to the terminology reported in the original papers) was choreoathetosis (n=22/30; 73%), followed by dyskinesias (n=16/30; 53%), ballismus or hemiballismus (n=7/30; 23%), dystonia (n=5/30; 17%), athetosis (n=3/30; 10%), and stereotypies, posturing, intentional tremor, and myoclonus (n=1/30; 3% each). Movement disorder was generalized in 48% (n=12/25), and the orofacial region was involved in 69% (18/26).

Main differences between children and adults during the anti-NMDAR encephalitis phase

The median time between onset of HSE and onset of anti-NMDAR encephalitis was significantly shorter in children (median 24d) than in adults (median 40.5d) (p=0.006). During anti-NMDAR encephalitis, movement disorder occurred significantly more often in children than in adults (n=26/30 [87%] in children vs n=4/10 [40%] in adults; p=0.006), whereas psychiatric symptoms were reported more frequently in adults than in children (n=9/10 [90%] in adults vs n=13/31 [42%] in children; p=0.025). No statistically significant differences between children and adults were detected in regards cognitive
deterioration, seizures, sleep–wake cycle disturbances, dysautonomias, and speech problems. The severity of disease measured with mRS score was slightly higher in children than in adults at nadir of anti-NMDAR encephalitis (median 5 vs 4; \( p=0.015 \)) (no statistically significant difference between children and adults was observed between median mRS at nadir of HSE, at recovery after HSE, or at last follow-up).

**Figure 1:** Brain magnetic resonance imaging (MRI) in our paediatric patient with biphasic disease with herpes simplex encephalitis (HSE) followed by herpes simplex virus (HSV)-induced anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. (a–c) Brain MRI 4 days after onset of HSE. (a) T2-weighted axial and coronal images; (b) diffusion-weighted images, axial; (c) apparent diffusion coefficient images, axial. The brain MRI at day 4 from onset of HSE demonstrated diffusion restriction in cortical–subcortical regions in the right temporal lobe, in the right insula, and the right parieto-occipital region. T2-weighted images also showed cortical thickening of the right temporomesial lobe with increased intensity of right parieto-occipital areas. A smaller area of increased intensity was shown in left temporoparietal cortex. (d, e) Brain MRI 4 days after onset of anti-NMDAR encephalitis (33 days from onset of HSE). (d) T2-weighted axial and coronal images; (e) diffusion-weighted images and apparent diffusion coefficient axial images. The brain MRI at day 4 from onset of anti-NMDAR encephalitis showed high signal in right temporal subcortical white matter, atrophic evolution of the known right parietal–insular–temporal lesion, ex vacuo dilatation of the temporal horn of the right ventricle, and small atrophic–degenerative cortical–subcortical areas in the left inferior and mesial temporal gyri. No cytotoxic oedema and no enhancement after gadolinium were observed.
Treatment during HSE and anti-NMDAR encephalitis phases, and disease recurrences

In total, 98% (n=40/41) of the patients with available information received aciclovir during the episode of HSE, and only 5% received additional intravenous immunoglobulin and/or corticosteroids (n=2/43).22,33

At the onset of anti-NMDAR encephalitis, 85% (33/39) of the patients were still on aciclovir from the previous episode of HSE or were started on a new empirical course. In these patients, duration of antiviral treatment from anti-NMDAR encephalitis was less than or equal to 7 days in 23% (n=5/22) and greater than or equal to 14 days in the remaining 77% (n=17/22) (data available for n=22/33); only four patients (n=4/22; 18%) received a prolonged course with oral valaciclovir/aciclovir (for 122d, 152d, 153d, and 243d respectively).20,24,31 During the episode of anti-NMDAR encephalitis, first- and second-line immune therapies were administered in 93% (n=38/41) and 53% (n=21/40) of patients respectively.

None of the patients who received immune therapy for HSV-induced anti-NMDAR encephalitis were reported to have new viral replication with recurrence of HSE at a median follow-up of 7 months (mean 15.9, range 1.2–160; data available for 39 patients).

Patients with HSE and detection of anti-NMDAR antibodies, and patients with anti-NMDAR encephalitis with concomitant positive HSV markers

HSE with detection of anti-NMDAR antibodies (in the absence of a clinical episode of anti-NMDAR encephalitis). The detection of anti-NMDAR antibodies during or after an episode of HSE, in the absence of a clinical episode of anti-NMDAR encephalitis, was reported in 25 adult patients described in one retrospective and one prospective series (both had available full text; top part of Table SII, online supporting information).9,34 All these patients had HSE confirmed by positive CSF HSV PCR, and positive anti-NMDAR antibodies in CSF and/or serum (n=25/25; 100%). In the prospective series by Westman et al.,34 antibodies were detectable only after 3 months in 10 of 12 positive cases. The rate of detection of anti-NMDAR antibodies (IgG type) in patients with HSE was 9% and 25% respectively, in the two studies.9,34 In the prospective series by Westman et al.,34 the development of anti-NMDAR autoantibodies was associated with significantly impaired recovery of neurocognitive performance. On the contrary, Prüss et al.9 were unable to detect significant clinical differences between the antibody-positive and antibody-negative patient groups.

Anti-NMDAR encephalitis with concomitant positive HSV markers (in the absence of clinical or radiological evidence of HSE). The detection of positive HSV PCR in CSF during an episode of anti-NMDAR encephalitis was reported in six patients, described in five articles (all had full text available).35–39 Data on these patients are limited (bottom part of Table SII). These patients had clinical anti-NMDAR encephalitis (confirmed by anti-NMDAR antibodies in serum and/or CSF in six of six patients [100%]), with detection of positive CSF HSV PCR (n=6/6; 100%) concomitantly or before detection of autoantibodies (in the absence of clinical or radiological evidence of HSE). In two of these patients the initial positive CSF HSV PCR was negative on subsequent testing, prompting the authors to consider it a spurious result.35,37 Interestingly, in one patient with anti-NMDAR encephalitis confirmed by positive anti-NMDAR antibodies in CSF, the detection of HSV in CSF by PCR discouraged the use of immune therapy, and the patient received only antiviral treatment with improvement in psychiatric symptoms but persistence of mild memory impairment.39

DISCUSSION

We present a comprehensive and up-to-date systematic literature review on the relationship between HSV and anti-NMDAR antibodies, and we describe a new illustrative paediatric case with HSE followed by HSV-induced anti-NMDAR encephalitis.

Clinical features of HSV-induced anti-NMDAR encephalitis

We were able to identify 43 patients with biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis. Our review confirms that the appearance of movement disorder is one of the main symptoms differentiating HSV-induced anti-NMDAR encephalitis from the preceding episode of HSE (Table S1).20 Choreoathetosis and dyskinesias were the most frequent types of movement disorder, and the orofacial region was often involved. In this respect, other case reports and series published before the description of anti-NMDAR encephalitis have pointed to movement disorder, especially choreoathetosis, as a key feature of relapses post-HSE, often reporting negativity of viral testing.4,40–44 With regard to the overall clinical manifestations during HSV-induced anti-NMDAR encephalitis, our literature review shows that the clinical picture is similar to that of anti-NMDAR encephalitis not preceded by HSE, including the known age-specific features of the disease. Indeed, psychiatric symptoms were more frequent in adults in our literature cohort, whereas neurological manifestations, such as movement disorder, were more represented in children (Table S1), similarly to what was previously reported in patients with anti-NMDAR encephalitis not preceded by HSE.11,45,46 Although it should be taken into account that under-reporting of psychiatry and cognitive features in young children is possible, we also observed a slightly more severe disease in children than in adults, and a shorter latency between HSE and autoimmune encephalitis in children.

Therapeutic decision-making in relapses after HSE

In case of recurrence of symptoms after HSE, high clinical suspicion should be maintained towards both the possibilities of a viral and an autoimmune relapse, and antiviral therapy should be started promptly. Subsequently, in the
absence of microbiological and neuroradiological findings consistent with a viral reactivation, early commencement of immune therapy should also be considered. Indeed, in view of the known pathogenicity of anti-NMDAR antibodies, immune therapy may be associated with a good response, especially if administered early. An algorithm for clinical and therapeutic approach in relapses after HSE is proposed in Figure 2.

**Pathogenic hypotheses**

The results of our literature review on patients with biphasic disease with HSE followed by HSV-induced anti-NMDAR encephalitis support the hypothesis that CNS HSV infection may trigger an autoimmune response in the CNS, resulting in the production of anti-NMDAR antibodies and in a fully-fledged autoimmune clinical syndrome. Indeed, an independent co-occurrence of viral and autoimmune encephalitis is unlikely given the relative rarity of both conditions. The mechanisms underlying the synthesis of anti-NMDAR antibodies following HSV infection remain unknown. As hypothesized by other authors, the virus-induced neuronal destruction may expose neuronal antigens to the systemic immunity, initiating a primary autoimmune response. Other possibilities may involve non-specific B-cell activation and/or molecular mimicry due to shared epitopes between HSV and NMDAR, as seen in other neurological diseases such as multiple sclerosis, acute disseminated encephalomyelitis, Guillain–Barré syndrome, and Sydenham chorea. The possibility of a common genetic predisposition between the two entities may also contribute. Different to the biphasic disease described above (HSE followed by HSV-induced anti-NMDAR encephalitis; Table SII, top part), in patients with HSE with concomitant detection of anti-NMDAR antibodies (in the absence of a clinical episode of anti-NMDAR encephalitis) the pathogenic role of antibodies remains unclear. In particular, whether some of the clinical manifestations observed in these cases during HSE may be due to an additional effect of anti-NMDAR antibodies is not
known. In this setting, the anti-NMDAR antibodies may be just a ‘silent marker’ of a postinfective autoimmune response without a specific contributory or causal role. Interestingly, no significant clinical differences were observed between the anti-NMDAR seropositive and seronegative subgroups of HSE patients reported by Prüss et al.,9 questioning whether the anti-NMDAR antibodies in these patients are therefore contributing to the disease.9 On the contrary, the development of anti-NMDAR autoantibodies was associated with significantly impaired recovery of neurocognitive performance in another prospective series.34

In the group of patients with clinical anti-NMDAR encephalitis and concomitant detection of HSV in the CSF by PCR (in the absence of a clinical or radiological episode of HSE),35–39 data are very limited (Table SII, bottom part). With regard to the (sometimes transient) detection of positive HSV PCR of CSF, a laboratory error was hypothesized by the authors in one-third of these patients (false positive);35,37 although definite conclusions cannot be drawn, it cannot be excluded that a previous subclinical CNS HSV infection may have triggered anti-NMDAR encephalitis.

Supporting these findings, an interesting recent work focused on the frequency of coexisting herpes viruses and autoantibodies in patients with encephalitis (herpes or autoimmune) in clinical laboratory service, disclosing that autoantibodies and herpes virus DNA frequently coexist in encephalitic CSF.56 In this study, as well as in other case reports, other types of herpes viruses beside HSV have been found in association with anti-NMDAR antibodies, including Epstein–Barr virus, human herpesvirus 6 and 7, and varicella zoster virus.56–60 However, other autoantibodies to neuronal surface antigens, in particular anti-dopamine-2 receptor,20 anti-γ-aminobutyric acid A receptor antibodies and antibodies against unknown neuronal cell surface proteins,27 have also been detected in patients with immune-mediated encephalitis (with negative CSF HSV PCR) occurring after HSE,16,27 suggesting that other antibodies may also be produced in this syndrome. In these cases, similarly to what is suggested for anti-NMDAR antibodies, it may be hypothesized more broadly that autoantibody production is triggered by herpes viruses infection, but further study for novel autoantibodies is required.

Insights into the use of immune therapy in HSE

The hypothesis that CNS HSV infection may trigger an autoimmune response sheds more light on the pathogenesis of HSE itself, supporting the observation that the cerebral insult in HSE results not only from neuronal cell death secondary to direct viral invasion, but also from secondary inflammatory changes and cerebral oedema due to the immune response to the virus. Therefore, in view of their anti-inflammatory action, corticosteroids could have an important role also in the management of the acute phase of HSE.61 So far, corticosteroid use has been limited by concerns that their immunosuppressive actions could increase viral replication and spread. However, experimental animal models of HSE have shown that the addition of corticosteroids to aciclovir treatment does not increase viral replication and dissemination.61,62 In this respect, it is noteworthy that in our literature cohort none of the patients treated with immune therapy for HSV-induced anti-NMDAR encephalitis (or for HSE) was reported to have recurrence of HSE, despite only very few receiving long-term antiviral therapy.20,24,31 Moreover, the beneficial effect of adjunctive steroids in HSE has been anecdotally described both in paediatric and adult age,63–66 and in an experimental study on a mouse model of HSE, the severity of long-term MRI anti-N-methyl-D-aspartate receptor (NMDAR) abnormalities was significantly reduced with add-on corticosteroids during acute HSE.62 The optimal timing for adjunctive steroid therapy has not yet been established,65 and while in some cases a beneficial effect has been reported after early simultaneous administration of aciclovir and steroids,64 in other cases steroid administration was delayed by a few days to weeks, with good results.65 Delayed but not early glucocorticoid treatment was associated with neuroprotection and survival in a study on experimental HSE in mice.67 Clinical trials in this field are under way.58

Limitations

The small number of patients and the retrospective nature represent the main limitations of our work. Moreover, disease severity scoring was likely subject to significant intrinsic biases, mostly relative to the availability and heterogeneity of information in the original papers, and the fact that the scoring was done retrospectively and by two researchers only. It is possible that the overall outcome may also be influenced by a reporting bias, due to unwillingness to report fatal outcomes. While the study of the outcome according to the administration of adjunctive immune therapy during HSE would be of great clinical interest, this could not be evaluated because only a few of the patients received immune therapy during HSE. Similarly, owing to the small numbers, a comparison between the outcome of patients with a clinical episode of anti-NMDAR encephalitis who did or did not receive immune therapy was not possible. Also, the study of the timing of appearance of anti-NMDAR antibodies after HSE could not be defined, in view of the different timing of antibody testing. The statistical analysis in our work was limited by the small number of patients and by the heterogeneity of data availability in the original papers; individual data for each patient were especially limited in case series compared with reports.19

CONCLUSION

The development of HSV-induced anti-NMDAR encephalitis, along with the detection of anti-NMDAR antibodies during HSE and of HSV in CSF with PCR...
during anti-NMDAR encephalitis, supports the likelihood that CNS HSV infection may trigger a secondary autoimmune response, resulting in the production of anti-NMDAR antibodies. Moreover, the hypothesis of an autoimmune response triggered by a CNS HSV infection supports the possibility that the pathogenesis and the neuronal damage of HSE involves not only a direct viral insult, but also a secondary autoimmune process, possibly providing arguments in favour of the rationale for the debated use of immune therapy in the acute phase of HSE. Interestingly, our review shows that despite the use of immune therapy for HSV-induced anti-NMDAR encephalitis, none of the patients experienced recurrence of HSE. Finally, while remaining vigilant for the possibility of new viral replication, high clinical suspicion toward an autoimmune aetiology should be maintained in case of relapses of HSE, in view of the different treatment and the good response to immune therapy. The identification of early predictors of autoimmune relapse post-HSE would allow early intervention and, possibly, prevention of secondary autoimmunity, and it remains among future challenges.

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REFERENCES


SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Form used for data collection for the literature review on patients with herpes simplex encephalitis followed by herpes simplex virus-induced anti-N-methyl-D-aspartate receptor encephalitis (Word document transposition of the Excel spreadsheet form).

Figure S1: Electroencephalography (EEG) tracings in a paediatric patient with biphasic disease with herpes simplex encephalitis (HSE) followed by herpes simplex virus (HSV)-induced anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. (a, b) EEG tracing 4 days from onset of HSE, showing significant bilateral slowing, more marked on the right side, with (a) bilateral temporo-occipital periodic epileptiform discharges and (b) subclinical focal temporal right seizures. (c) EEG tracing 4 days after onset of anti-NMDAR encephalitis (33 days from onset of HSE), showing slowed and poorly organized electrical activity, especially in the right hemisphere, with significant slow activity and epileptiform discharges in the frontotemporal areas bilaterally; no delta brush patterns nor seizures were recorded.

Table S1: Main results of our literature review: demographics, clinical data, laboratory investigations, treatment, and outcome of the paediatric and adult patients identified with biphasic disease with herpes simplex encephalitis (HSE) followed by herpes simplex virus (HSV)-induced anti-N-methyl-D-aspartate encephalitis, including our paediatric case (total 43 patients)

Table SII: Main results of our literature review on patients with herpes simplex encephalitis (HSE) with detection of anti-N-methyl-D-aspartate (anti-NMDAR) antibodies (in the absence of a clinical episode of anti-NMDAR encephalitis), and on patients with anti-NMDAR encephalitis and concomitant detection of positive polymerase chain reaction for herpes simplex virus in cerebrospinal fluid (in the absence of a preceding clinical or radiological episode of HSE)


