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Frequency, syndromes, risk factors, and outcome of autoimmune encephalitis following herpes simplex encephalitis: a prospective observational study and a retrospective analysis of cases

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Authors' contributions

TA, did the study design, literature search, data collection, data interpretation, radiological analysis, statistical analysis, development of figures, writing, critical approval of the final paper, and obtained funding. MS did the figures, data interpretation, and critical approval of the paper. SM, MCC, EIM-H, SL, JM, did the radiological analysis critical approval of the final manuscript. AV, MEE, LA, GM, LMG, ICC, CM, MT, LB, GS, HA, EuM-H, MJ, MAM, LA, AS, and MRR did the data collection and critical approval of the final paper. FG participated in the study design, data interpretation, critical approval of the final paper. JD participated in the study design, data interpretation, writing, critical approval of the final paper, and obtained funding.

Conflicts of interest:

Dr. Dalmau holds patents for the use of Ma2, NMDAR, GABAbR, GABAaR, DPPX and IgLON5 as autoantibody tests. Dr. Graus holds a patent for the use of IgLON5 as an autoantibody test. Dr. Rosenfeld holds patents for the use of Ma2 and NMDAR as autoantibody tests. Drs. Dalmau, Graus, and Rosenfeld receive royalties related to autoantibody tests from Athena Diagnostics and Euroimmun, Inc. The rest of the authors have no conflicts of interest.

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Abstract

Background: Herpes simplex encephalitis (HSE) can trigger autoimmune encephalitis (AE) that leads to neurological worsening. We aimed to assess the frequency, syndromes, risk factors, and outcome of this complication.

Methods: Prospective observational study of patients with HSE diagnosed between January 1st 2014 and October 31st 2017 by neurologists, pediatricians, and infectious disease specialists in 19 secondary/tertiary Spanish centers (Cohort-A). Outpatient follow-up was obtained at 2, 6 and 12 months; patients who died within the first 3 weeks or with delay in recruitment >10 days were excluded. Another group of patients was retrospectively studied after they developed AE post-HSE (Cohort-B). Multivariable binary logistic regression models were used to assess risk factors for AE.

Findings: Cohort-A included 51 patients (median age 50 years, IQR 6–68; 29 male); 14 (27%) developed AE and all (100%) had neuronal antibodies (9 NMDAR, 5 other); the other 37 did not present AE and 11 (30%) developed antibodies (3 NMDAR, 8 other) ($p<0.001$). Antibody-detection within 3 weeks post-HSE often heralded AE (OR 11.5; 95% CI 2.7–48.8, $p=0.001$). Within 2 months post-HSE, antibody sensitivity, specificity, positive and negative predictive values for AE were 100%, 76%, 61% and 100% (if only NMDAR considered: 64%, 95%, 82%, 88%; in youngest children: all 100%). Cohort-B included 48 patients (median age 8.8 years, IQR 1.1–44.2; 27 male), 44 with AE (34 NMDAR, 10 other). In both Cohorts ($n=58$ AE), patients ≥ 4 years old frequently presented with psychosis (18/31, 58%; younger children not assessable). Patients ≥ 4 years (27) were more likely to have shorter HSE-AE intervals (median 26 vs 43 days, $p=0.0073$), choreoathetosis (27, 100% vs 0, $p<0.001$), impaired consciousness (26, 96% vs 7, 23%, $p<0.001$), NMDAR antibodies (24, 89% vs 19, 61%, $p=0.033$), and worse outcome at 1 year (median modified Rankin Scale, 4 vs 2, $p<0.001$; seizures, 12/19 [63%] vs 3/23 [13%], $p=0.001$).

Interpretation: AE occurs in 27% of patients with HSE. It follows the development of neuronal antibodies and usually presents within 3 months post-HSE; the symptoms are age-dependent, and the outcome is worse in young children. Prompt diagnosis is important because patients, mainly those older than 4 years, respond to immunotherapy.

Introduction

Herpes simplex virus encephalitis (HSE) is the most frequent cause of sporadic infectious encephalitis in western countries, with a worldwide incidence of 2–4 cases per million population per year.¹ It affects patients of either sex, with a bimodal age distribution in which children and elderly persons are the most frequently and severely affected. The fatality rate among patients treated with acyclovir is 10–25%, and the proportion of cases that are able to resume activities of daily living is 40–55%.² A separate problem is the

development of neurological relapses or worsening of deficits, which have been reported in a proportion of cases ranging from 5–26%.^{3–6} These complications tend to occur within the first 2 months of completing treatment with acyclovir and can affect children and adults. In some patients the relapsing symptoms are caused by reactivation or persistence of the herpes simplex virus (HSV), as shown by detection of viral DNA in the cerebrospinal fluid (CSF),⁶ but in many cases viral testing is negative and treatment with acyclovir ineffective. The observation that symptoms may improve or stabilize with steroids suggested that inflammatory or immune mechanisms underlie some of these complications.^{5,6} This hypothesis has gained support from recent reports describing IgG antibodies against synaptic receptors and other neuronal surface proteins in patients' serum or CSF.^{7–14} In preliminary studies, children with this type of autoimmune encephalitis (AE) predominantly developed choreoathetosis –a previously known late complication of HSE,¹⁵ whereas adults developed psychiatric and cognitive deficits.^{8,16} It has been reported that immunotherapy is effective in these patients, but most of the findings are based on small, retrospective case series in which patients were selected for autoantibody testing.^{7–11} In the current study we used two cohorts comprising 99 patients with HSE to further investigate some of the outstanding questions related to relapsing syndromes post-HSE, including the frequency of these complications, main clinical syndromes in children and adults, risk factors, frequency of neuronal autoantibodies, response to immunotherapy, and long-term outcome.

Methods

Study design and participants

After the observation that some patients with HSE developed a delayed neurological deterioration associated with IgG antibodies against N-methyl-D-aspartate receptor (NMDAR),^{7,9} we designed a prospective multicenter observational study, defined as Cohort-A, with the aim to better characterize the syndrome and immunological associations. This cohort included patients with new onset HSE prospectively recruited between January 1, 2014 and October 31, 2017 in 19 participating centers in Spain (*Appendix*). All patients had HSE confirmed with cerebrospinal fluid (CSF) polymerase chain reaction (PCR) positive for HSV type 1 or 2. Patients who died within the first 3 weeks of recruitment, or with an interval between symptom onset and recruitment of more than 10 days were excluded. Clinical information was obtained with standardized questionnaires that were completed at different time points: at diagnosis of HSE, after discontinuing treatment with acyclovir (~21 days) and at 2, 6, and 12 month follow-up from HSE onset. Brain MRIs obtained at diagnosis were centrally reviewed at IDIBAPS-Hospital Clinic, University of Barcelona (*Appendix*). IgG antibodies against NMDAR and other neuronal surface proteins were determined in serum and CSF obtained at diagnosis and after completing acyclovir, and in serum obtained at 2, 6, and 12 months follow-up. Investigators performing the autoantibody testing were blinded to clinical data and the treating physicians were blinded to results unless patients developed new neurological symptoms or unexplained progression of previous deficits; if this occurred, new paired CSF/serum samples were examined and results along with those of previous samples were provided to the treating physician.

In parallel, we obtained clinical information using the indicated questionnaires on all patients whose serum and CSF were sent for neuronal autoantibody investigations to our center with the suspicion of AE post-HSE between October 7, 2011 and October 31, 2017 (Cohort-B). These patients were studied while they had symptoms of AE and therefore the only part of the information that was retrospective was that related to HSE; in these cases antibody testing results were provided to the physicians. Patients from Cohort-B who had an interval of more than 4 months between symptom onset and determination of serum and CSF antibodies were excluded from analysis.

Patients were considered to have probable AE post-HSE if within the first 12 months after completing treatment with acyclovir they developed new onset CNS symptoms or worsening of pre-existing deficits that lasted for more than 24 hours, associated with a negative CSF PCR for HSV, and the symptoms could not be explained by other complications (e.g., metabolic derangement, drug toxicity, stroke) or residual lesions caused by the viral encephalitis (e.g., isolated new onset epilepsy).

Procedures

Follow-up of neurologic function was assessed using the modified Rankin Scale (mRS).^{17,18} Studies related to neuronal autoantibody testing were performed at IDIBAPS-Hospital Clinic, University of Barcelona, using previously reported techniques (*Appendix*).^{19,20} As far as treatment is concerned, all patients were started on standard dose of intravenous acyclovir (1500mg/m² for younger children, 30 mg/kg/day for older children and adults, divided every 8 hours for 14–21 days) as soon as HSE was diagnosed. Concomitant use of steroids (and/or immunotherapy for patients who developed AE) was at the physician's discretion.

Standard protocol approvals, registrations, and patient consents

Written informed consent for participating in the study was obtained from all patients or their guardians. Studies were approved by the Internal Review Board of Hospital Clinic, University of Barcelona. The funders of the study had no role in the design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Statistical analyses

Analysis of demographics and clinical features of patients who developed AE compared with those who did not develop AE, or according to age group (children < 4 years compared with patients > 4 years), was performed using Fisher-Exact and Wilcoxon-rank sum test as appropriate for the data set. Patients were considered to have good outcome if the mRS score at the last follow-up was 0–2, and bad outcome if > 2. Multivariate binary logistic regression models were explored to identify predictor variables of developing AE post-HSE. All variables with a cut-off $p < 0.1$ (likelihood ratio test) in univariate binary logistic models and variables of high biological value (patients' age, % volume involvement on MRI, CSF pleocytosis and protein concentration at 21 days) were considered for the multivariable binary logistic regression models, and approached by forward stepwise procedure

(*Appendix*). When the variables were collinear, the predictive power with one or the other variables was compared. First order interactions between variables were explored. Odds ratio (OR) and 95% confidence interval (CI) were used to measure the effect of predictors and adjusted for relevant variables (if a clinical relevant change in the OR was noted).^{21,22} In all analyses, a bilateral type I error of 5 % was applied without a formal correction for multiplicity. STATA version 13.1 (StataCorp, Texas, USA) program package was used for statistical analyses.

Results

Cohort-A

Fifty-one patients with HSE (50 HSV1 and 1 HSV2) were included for analysis after excluding three patients who died during the first 3 weeks of the disease (Figure 1). Median time from neurological symptom onset to inclusion in the study was 4 days (range 0–10); 29 (57%) patients were male. Forty-eight (94%) patients were followed for a minimum of 6 months (2 who died at 9 and 10 weeks and 1 with < 6 month follow-up were excluded) and 40 (78%) were followed for 1 year (additional patients excluded: 1 who died at 9 months, 1 lost to follow-up, and 6 with less than 1 year follow-up).

Thirty-seven of the 51 (73%) patients included for analysis had progressive neurologic improvement or stable deficits; 3 of them died at 9, 10 and 36 weeks of aspiration pneumonia (11 year-old patient), malignant thymoma (30 year-old) and lung complications (84 year-old) respectively. Fourteen (27%) patients developed new onset CNS symptoms or worsening of previous deficits consistent with probable AE post-HSE (Table 1). Median time from HSE until probable AE was 32 days, IQR 22–43 days, range 7–61 days. Whereas all infants and toddlers (n=6, median age 9 months, IQR 3–12, range 2–15 months) developed a syndrome associated with choreoathetosis, all the teenagers and older patients (n=8, median age 66 years, IQR 40–78, range 13–81 years) developed a syndrome without choreoathetosis in which behavioural and psychiatric manifestations predominated (Table 2).

Brain MRI studies at onset of HSE demonstrated no significant FLAIR or DWI differences in volume lesion between patients who developed AE and those who did not (Table 1, *Appendix*). Among patients who developed AE, MRI studies at onset of AE showed that 9/11 (82%) had contrast enhancement comparable to that found during the viral encephalitis; similar findings were observed in patients who did not develop AE and had MRI at 1–3 months follow-up (6/10, 60%, p=0.269) (Figure 4). Patients who developed AE were more likely to have necrosis with cystic lesions in MRIs obtained at follow-ups later than 4 months post-HSE (9/9 [100%] vs 7/14 [50%], p=0.019) (Figure 4). No differences were noted regarding progression of local white or grey matter abnormalities, or local atrophy, between patients who developed AE and those who did not (*Appendix*).

CSF studies at onset of HSE and at 3 weeks post-HSE demonstrated no significant differences between patients who subsequently developed AE and those who did not (Table 1 and *Appendix* Table S1). At onset of AE the CSF HSV1–2 PCR was negative in all patients, and all showed mild pleocytosis (median 17 WBC, IQR 7–54) and elevated protein concentration (median 61 mg/dL, IQR 39–88).

At onset of HSE, none of the 51 patients had antibodies against neuronal surface antigens. During the follow-up, all 14 (100%) patients who developed symptoms consistent with AE tested IgG antibody-positive at the time of symptom onset, including 9 patients with NMDAR antibodies (64%, 1 with co-existing gamma-aminobutyric acid A receptor [GABA_AR] antibodies), and 5 with antibodies against unknown antigens (36%) (Figure 2A and Figure 3). Nine of these 14 (64%) patients were already antibody positive at the 3 week follow-up (in 6 preceding symptoms of AE); an example of progressive NMDAR antibody development is shown in *Appendix*, Figure S1. In contrast, among the 37 patients who did not develop AE, only 11 (30%) tested IgG antibody positive during the follow-up ($p<0.001$), including 3 (27%) against NMDAR and 8 (73%) against unknown antigens (Figure 2B). Compared with patients with AE, only 5 of these 37 (14%) patients tested antibody positive at the 3 week follow-up ($p=0.001$). At 1 year follow-up, 7/14 (50%) patients with AE post-HSE and 1/26 (4%) without AE had antibodies detectable in serum ($p=0.001$) (Figure 2A and B). The outcome of AE patients who had persistent antibodies at 1 year follow-up was worse than that of patients who became antibody negative (at 1 year, median mRS 4 (3–5) vs mRS 3 (IQR 3–3), $p=0.030$).

Considering that the longest interval between HSE and AE was 61 days, the detection of neuronal surface antibodies within 2 months post-HSE had a sensitivity, specificity, positive predictive value, and negative predictive value for AE of 100%, 76%, 61% and 100%. If only NMDAR antibodies were considered: 64%, 95%, 82%, and 88%, and for children 4 year-old: all 100% (*Appendix*, Table S2).

In paired serum/CSF testing the antibodies were always present in CSF (19/19) and less frequently in serum (11/19) (Figure 2A and B). In 6 patients who did not develop AE, the antibodies were detected during the clinical follow-up when only serum was tested according to the study design.

In the exploratory multivariate logistic regression analysis, the presence of autoantibodies at the 3 week follow-up (OR 11.5; 95% CI 2.7–48.8, $p<0.001$) was identified as risk factor for AE (*Appendix* Table S1). Adjustment by patient's age and other possible effect modifiers did not associate with a clinically relevant change of OR.

At 1 year follow-up, patients who developed AE had more neurological deficits (median mRS 3 (IQR 3–4) vs 2 (IQR 1–2), $p<0.001$) (Table 1) and were more frequently treated with antiepileptics (10/14, 71% vs 9/26, 35%, $p=0.046$) than those who did not develop AE.

Cohort-B

This retrospective cohort included 48 patients (median age 8.8 years, IQR 1.1–44.2; 27 male) who after completing treatment with acyclovir developed new onset or worsening neurological symptoms not caused by HSV reactivation (Figure 1). Of these 48 patients, 44 (92%) had neuronal surface antibodies, 34 (77%) against NMDAR and the other 10 (23%) against uncharacterized antigens (*Appendix*, Table S3). Antibodies were more frequently detected in CSF (44/44, 100%, median titers 1/40, IQR: 1/10–1/160) than in serum (25/33, 76%, median titers 1/800, IQR: 1/400–1/3200) (Supplementary Table 3).

The median time from HSE until symptoms of probable AE was 31 days (IQR 25–49 days, range: 11–306 days). Similar to the patients from Cohort-A, patients who were ≤ 4 years old ($n=21$, median age 10.6 months, IQR 7–20, range 4.5–48 months) developed a syndrome associated with choreoathetosis, whereas those who were >4 years old ($n=23$, median age 34 years, IQR 16–56, range 6–69 years) developed a syndrome in which behavioural and psychiatric manifestations predominated (*Appendix*, Table S3). The remaining 4 (8%) patients did not have neuronal surface antibodies and their main clinical features were epileptic seizures in 3 and behavioural change in 1 (*Appendix*, Table S4).

Syndromes associated with AE pos-HSE

Considering all 58 patients from cohorts A and B who developed antibody associated AE post-HSE, two age-related syndromes were identified (Table 3): patients ≤ 4 years ($n=27$) developed prominent choreoathetosis, behavioural change, decreased level of consciousness, truncal hypotonia, dysphagia, and frequent refractory seizures. Six (22%) of these patients developed infantile spasms during the acute phase of AE, and another two at later stages (12 months follow-up). In contrast, patients >4 years ($n=31$) developed prominent change of behaviour and psychiatric symptoms, less frequent seizures or decreased level of consciousness, and absent choreoathetosis. Eighteen of these patients (58%) presented with psychosis (in younger children, psychosis was not assessable). Compared with the older group, patients ≤ 4 years old (all with choreoathetosis, $p<0.001$) were more likely to have a shorter interval between HSE and AE (median 26 vs 43 days, $p=0.0073$), seizures (15/27, 56% vs 7/31, 23%, $p=0.015$), impairment of the level of consciousness (26/27, 96% vs 7/31, 23%, $p<0.001$), NMDAR antibodies (24/27, 89% vs 19/31, 61%, $p=0.033$), and worse outcome at 1 year including a higher mRS score (median 4 vs 2, $p<0.001$) and more frequent seizures (12/19 [63%] vs 3/23 [13%], $p=0.001$).

Compared with patients with antibodies other than NMDAR ($n=15$), those with NMDAR antibodies ($n=43$) were more likely to be younger (median age 2.2 years, IQR 0.9–25 vs 56 years, IQR 25–75, $p=0.005$) and develop psychosis (15/19 vs 3/12, $p=0.008$), choreoathetosis (24, 56% vs 3, 20%, $p=0.033$), decreased level of consciousness (28, 65% vs 5, 33%, $p=0.04$), and dysautonomia (15, 35% vs 0, 0%, $p=0.006$). No differences in outcome were noted between AE patients with NMDAR antibodies and those with other neuronal surface antibodies (*Appendix* Table S5).

Discussion

We found that 27% of patients with HSE developed symptoms of AE within 3 months of completing treatment with acyclovir, and that the neurological syndrome, response to immunotherapy, and long-term outcome varied according to the patients' age. Patients that were 4 years old or younger developed a syndrome punctuated by choreoathetosis, decreased level of consciousness and frequent seizures or infantile spasms, whereas older children and adults developed predominant change of behaviour and psychiatric symptoms sometimes accompanied by seizures. In addition, older children and adults were more likely to respond to immunotherapy. Similar findings regarding age-related syndromes and different outcomes

were demonstrated in a retrospective cohort where patients who developed unexplained neurological symptoms were investigated for antibodies against neuronal surface proteins.

When the prospective cohort was interrogated for risk factors of AE the main feature identified was the detection of neuronal antibodies at the 3 week follow-up. Considering that none of the patients harbored these antibodies at onset of HSE, the finding suggests the viral infection triggered the immune response. We do not know whether any of these immune responses occurred as a result of viral-induced release of NMDAR and other proteins, or by mechanisms of molecular mimicry, such as similarity between NMDAR and HSV proteins. The high frequency of antibodies against several different neuronal antigens supports the first possibility but does not rule out that molecular mimicry may also be involved. A recent study showed that patients with classic anti-NMDAR encephalitis (not HSE-related) were more likely to have HSV antibodies than a control age-matched population suggesting the possibility of molecular mimicry between HSV and NMDAR.²³ Although an HLA predisposition to develop anti-NMDAR encephalitis is still unclear,^{24,25} future studies should determine whether there is a predisposition to develop AE among patients with HSE.

In cohort-A, the prospective clinical and immunological follow-up showed that the development of autoantibodies preceded the onset of AE, and that not all antibody positive patients developed neurological worsening. Moreover, at 1 year follow-up, 50% of patients who developed AE remained IgG antibody positive despite the use of intensive immunotherapy, whereas only 4% of those who did not develop AE, and therefore did not receive immunotherapy, remained antibody positive. These findings indicate that HSE can initiate, in some patients, a transient and subclinical synthesis of neuronal antibodies that becomes undetectable several months after the infection. Only a longer follow-up of these patients will clarify if they have a propensity to develop AE; in fact, 4 adult patients from cohort B (in whom antibodies were not prospectively followed) developed late symptoms of AE (306 days) or relapses at 60, 699, and 723 days post-HSE.

The syndrome associated with AE post-HSE varied according to the patient's age, and partially resembled the symptom onset of classical anti-NMDAR encephalitis.¹⁹ Children with this disorder usually present with seizures, behavioural change, choreoathetosis, or decreased level of consciousness^{9,26–28} whereas teenagers and adults are more prone to present with behavioural, psychiatric, cognitive changes, and less frequently seizures.^{29–31} These age-related symptoms may explain why the relapsing neurological symptoms post-HSE have been more frequently described among pediatric than adult patients. Indeed, new onset choreoathetosis and other movement disorders are readily identified on clinical grounds, but changes of behaviour, cognition, and memory can be attributed to residual deficits of HSE.⁸ The susceptibility of young children to develop post-infectious movement disorders or seizures has been noted in other disorders such as post-streptococcal (Sydenham) chorea and fever-induced seizures, suggesting an enhanced vulnerability of specific synaptic networks to inflammatory or autoimmune mechanisms.^{32,33} A similar type of vulnerability may explain why 22% of younger but not older children with NMDAR antibodies post-HSE developed early infantile spasms as part of the AE.³⁴ The time frame of this complication is different from that of classical infantile spasms that typically develop several months after a precipitating event, such as a brain infection or another type of brain

injury.³⁵ Indeed, two other patients with AE post-HSE and two without AE or antibodies developed classical infantile spasms 6–12 months after HSE (data not shown).

In the current cohort, the prognosis of young children with AE post-HSE was substantially worse than that reported in patients with classical anti-NMDAR encephalitis,^{27–29} and also than that reported in smaller case series of AE post-HSE.^{7–11} Although older children and adults with AE post-HSE had better outcomes than the younger children, their outcomes were notably worse than those described in patients of the same age with classical anti-NMDAR encephalitis.^{29,36} A reason for this worse outcome may be related to the presence of clinical or subclinical deficits caused by the viral encephalitis.² Additional mechanisms, such as complement or T-cell mediated cytotoxicity, which do not seem to play major pathogenic roles in classical AE,^{37,38} may be more relevant in cases of AE post-HSE, and deserve future study. For example, in a previous study we found that only 33% of patients with classic anti-NMDAR encephalitis had brain MRI abnormalities, and these rarely enhanced with contrast.²⁹ In comparison, 82% of patients with AE post-HSE in the current study had areas of contrast enhancement (similar to those found during the viral encephalitis), suggesting blood-brain-barrier disruption with the potential for entry of complement and other pro-inflammatory molecules.³⁹ Whether a systematic use of anti-inflammatories or immunotherapy during the viral phase of the disease could prevent the development of AE is a task for the future. We did not find a significant difference in the use of steroids among patients who developed AE and those who did not, but the number of cases is small and not all patients were treated similarly.

This study has several limitations, 1) the number of cases in the prospective cohort is relatively small (14 of 51 with AE post-HSE), 2) although all patients of this cohort had paired serum/CSF antibody testing at two different time points (diagnosis of HSE, and three weeks later), and additionally if they developed AE, only serum testing was performed in later follow-ups. Because of this, it is possible that we underestimated the number of patients who without neurological worsening may have developed CSF antibodies at a later time, 3) the identity of some of the cell-surface antigens is unknown. These cases were extensively studied for reactivity with known neuronal cell-surface antigens using cell-based assays, rat brain immunostaining, and cultured live neurons, with positive results only seen with brain tissue and live neuronal staining. Although dopamine 2 receptor antibodies were previously reported in some patients with AE post-HSE,¹¹ we did not identify these antibodies in these cohorts. Further work is needed to identify these unknown targets, and 4) in Cohort B, the retrospective collection of information through a questionnaire sent to clinicians can be perceived as a limitation, but only the information related to HSE was obtained retrospectively.

The current study raises awareness for AE triggered by HSE, and reveals a predictable time frame of approximately 3 months in which 27% of patients with HSE develop AE associated with immune responses against NMDAR and other neuronal surface proteins. AE should be strongly considered in patients who within this time frame develop new neurologic or psychiatric symptoms, punctuated in children by choreoathetosis, and in older children and adults by cognitive and behavioral impairment or psychosis. In this context, detection of NMDAR or other neuronal surface antibodies is confirmatory of AE. Recognition of this

complication is important because a substantial number of patients, mainly older children and adults, respond to immunotherapy. The challenges are now to determine the mechanisms involved, whether anti-inflammatory/immunotherapy prophylaxis during HSE prevent AE, if there are predisposing genetic factors, and whether earlier diagnosis and treatment may improve outcome.

Research in context

Evidence before this study:

It has been known for long time that some patients with HSE develop neurological relapses a few weeks after successful treatment of the viral infection. Autoimmune mechanisms were considered but the evidence was circumstantial and the target antigens unknown. These targets were recently identified as the NMDAR and other neurotransmitter receptors, but the frequency of this complication, spectrum of symptoms, risk factors, and prognosis are largely unknown.

We searched in Medline and Embase databases up until April 01, 2018 for articles published in English with the search terms “herpes simplex encephalitis”, “relapsing encephalitis”, “post-herpes simplex encephalitis”, “choreoathetosis”, “NMDA receptor antibodies” and/or “N-methyl-d-aspartate receptor antibodies” [MeSH Terms]. We restricted searches to human studies. We also reviewed the reference lists of the papers identified by this search.

Added value of this study:

This study describes the frequency, clinical features, risk factors, and prognosis of autoimmune encephalitis post-herpes simplex encephalitis (HSE) in two cohorts of patients. Cohort-A, is a prospective multicenter study of patients diagnosed with HSE (January 2014 - October 2017). Cohort-B is a retrospective study of patients who developed neurological worsening after HSE. The clinical features of AE post-HSE and outcome were derived from both cohorts, and the frequency, risk factors, and outcome (compared with patients without AE) after 1 year follow-up were derived from Cohort-A. The findings show that AE post-HSE is frequent (27% of HSE patients) and the associated syndrome varies with patients' age. Compared with patients >4 years old, those <4 years were more likely to develop choreoathetosis, impaired level of consciousness, and refractory seizures (often with infantile spasms). In contrast, older children and adults were more likely to present with cognitive changes and psychiatric symptoms. The syndrome in younger children corresponds to that previously known as “choreoathetosis post-HSE”, but the frequent presence of infantile spasms had not been previously reported. The clinical features in older children and adults were less known, and we show that psychosis is a frequent symptom presentation in this group (mainly if NMDAR antibodies are present). Importantly, the main risk factor for AE post-HSE was the detection of autoantibodies (NMDAR or against unknown cell-surface antigens) at the 3 week follow-up, and the outcome was worse in young children.

Implications of all available evidence:

Findings from this study should raise awareness for AE post-HSE. Detection of antibodies to NMDA and other neurotransmitter receptors 3 weeks after the diagnosis of HSE significantly associates with development of AE. Prompt recognition of this complication is important because patients, mainly older children and adults, respond to immunotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AE	autoimmune encephalitis
CI	confidence interval
CSF	cerebrospinal fluid
GABA_AR	gamma-aminobutyric acid A receptor
HSE	herpes simplex encephalitis
HSV	herpes simplex virus
IQR	interquartile range
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NMDAR	N-methyl-D-aspartate receptor encephalitis
OR	Odds ratio
PCR	polymerase chain reaction

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Figure 1: Patients included in Cohorts A and B Algorithm demonstrating the total number of patients studied (107) and those who fulfilled the inclusion criteria (99). Overall, 58 patients had antibody confirmed AE post-HSE.

A

Case	Sex	Age, years	Sample	HSE	d21	d60	d180	d365	Antigen	Serum titers (higher*→d365)
1	M	0,2	CSF Serum	-	d7 +	+	+	+	NMDAR	1/3200 → 1/800
2	M	0,3	CSF Serum	-	d24 +	+	+	+	NMDAR	1/1600 → 1/400
3	F	0,6	CSF Serum	-	d25 +	+	+	+	NMDAR	1/12800 → 1/800
4	M	0,9	CSF Serum	-	d19 +	+	+	+	NMDAR	1/3200 → 1/1200
5	M	1,0	CSF Serum	-	d39 +	+	+	-	NMDAR	1/3200 → -
6	M	1,2	CSF Serum	-	d27 +	+	+	+	NMDAR**	1/3200 → 1/200
7	M	13	CSF Serum	-	d43 +	+	+	+	NMDAR	1/3200 → 1/400
8	F	34	CSF Serum	-	d45 +	-	-	-	NMDAR	1/200 → -
9	M	45	CSF Serum	-	d44 +	-	-	-	NMDAR	(only positive CSF)
10	F	56	CSF Serum	-	d39 +	-	-	-	Unknown	(only positive CSF)
11	F	75	CSF Serum	-	d37 +	-	-	-	Unknown	(only positive CSF)
12	M	77	CSF Serum	-	d22 +	+	+	+	Unknown	1/1600 → 1/800
13	F	78	CSF Serum	-	d17 +	-	-	-	Unknown	(only positive CSF)
14	F	80	CSF Serum	-	-	d63 +	-	-	Unknown	(only positive CSF)

B

Case	Sex	Age, years	Sample	HSE	d21	d60	d180	d365	Antigen	Serum titers (higher*→d365)
15	F	1,1	CSF Serum	-	+	+	+	n.a.	Unknown	1/12800 → n.a.
16	M	2,2	CSF Serum	-	+	-	-	-	Unknown	(only positive CSF)
17	F	22	CSF Serum	-	+	-	-	-	Unknown	(only positive CSF)
18	F	49	CSF Serum	-	-	+	+	+	Unknown	1/1600 → 1/1200
19	M	51	CSF Serum	-	+	-	-	-	Unknown	1/400 → -
20	F	55	CSF Serum	-	-	+	+	-	Unknown	1/400 → -
21	M	59	CSF Serum	-	-	+	-	-	Unknown	1/200 → -
22	M	61	CSF Serum	-	-	+	+	-	NMDAR	1/800 → -
23	F	63	CSF Serum	-	+	-	-	-	NMDAR	(only positive CSF)
24	F	66	CSF Serum	-	-	-	+	-	NMDAR***	1/200 → -
25	M	71	CSF Serum	-	-	-	+	-	Unknown	1/400 → -

Figure 2: Timing of antibody detection, development of AE, and follow-up of serum testing and neurologic status.

(A) Patients from Cohort-A, who developed neuronal surface antibodies in association with AE. None of the patients had neuronal surface antibodies at the time of HSE onset, but all were antibody positive at onset of symptoms of AE. In all patients the presence (+) or absence (–) of neuronal cell-surface antibodies in serum was followed for 1 year. The neurological status was measured with the modified Rankin Scale (mRS) and is color coded. (B) Patients from Cohort-A, who developed neuronal surface antibodies without AE. These patients became antibody negative sooner than those of patients with AE. *In all patients, the highest serum titers were identified within the first 2 months of follow-up; ** NMDAR

antibodies with co-existing GABA_AR antibodies; ***NMDAR antibodies with co-existing GAD65 antibodies; at 1 year follow-up only GAD antibodies remained detectable (not shown). AE, autoimmune encephalitis; CSF, cerebrospinal fluid; d, day; F, female; HSE, herpes simplex encephalitis; M, male; mRS, modified Rankin score; na, not available.

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Figure 3: Antibodies against neuronal surface antigens.

Sagittal sections of rat hippocampus immunostained with CSF from a patient with NMDAR antibodies (**A**), CSF from a patient with antibodies against unknown neuronal antigens (**C**), or CSF from a patient without neuronal antibodies (**E**). The same patients' samples were used to immunolabel primary cultures of live rat hippocampal neurons (**B**, **D**, **F**) respectively. In **B**, **D** and **F**, the nuclei of the neurons are shown with DAPI. Scale bars in **A**, **C**, **E** = 500 μ m; Scale bars in **B**, **D** and **F** = 10 μ m.

Figure 4: MRI follow-up in patients who developed AE compared with those who did not develop AE.

Each row corresponds to a different patient and includes MRIs obtained at diagnosis of HSE, at 1–3 month follow, and at 6–9 month follow-up. The first three columns of images correspond to FLAIR sequences, and the last 3 columns to T1 sequences, all with contrast (except case 1 last follow-up). Patient 1 (first row): 10 month-old boy (case #4) who developed AE post-HSE with NMDAR antibodies. Patient 2 (second row): 56 year-old woman (case #10) who developed AE post-HSE with antibodies against unknown neuronal surface antigens. Patient 3 (third row): 49 year-old woman who developed HSE without AE or neuronal antibodies (she had history of lung adenocarcinoma, brain metastasis, and cranial radiotherapy). Patient 4 (fourth row): 66 year-old woman (case #24) who developed NMDAR and GAD65 antibodies but without symptoms of AE. In all patients the MRIs obtained at the 1–3 month follow-up show areas of FLAIR hyperintensity (larger or similar to those obtained at diagnosis of HSE); however, the MRIs of patients who developed AE (1st and 2nd patients) show more extensive areas of post-necrotic cystic abnormalities than

those who did not develop AE (3rd and 4th). Note that all patients, except patient 4th, have areas of contrast enhancement at 1–3 month follow-up.

Table 1:

General clinical features of patients in Cohort-A

	All	AE Post-HSE		
	N =51	Yes (14)	No (37)	<i>p</i> value *
Age, in years, median (IQR)	50 (5–68)	24 (0.9–75)	51 (13–68)	0.290
Infants (< 4 years)	13 (25%)	6 (43%)	7 (19%)	0.089
Children (5–17 years)	5 (10%)	1 (7%)	4 (11%)	0.182
Male sex	29 (57%)	8 (57%)	21 (57%)	0.980
Symptoms at diagnosis of HSE				
Fever	49 (96%)	13 (93%)	36 (97%)	0.490
Altered consciousness	35 (69%)	11 (79%)	24 (65%)	0.335
Abnormal behaviour	21 (41%)	5 (36%)	16 (43%)	0.624
Memory deficits, n=36 **	26/36 (72%)	6/8 (75%)	20/28 (71%)	0.841
Aphasia, n=36 **	28/36 (78%)	7/8 (88%)	21/28 (75%)	0.431
Seizures	32 (63%)	11 (79%)	21 (57%)	0.139
Motor deficit	21 (41%)	8 (57%)	13 (35%)	0.156
CSF at HSE onset				
WBC (median, IQR, cells/mm ³)	77 (22–170)	77 (22–122)	77 (22–190)	0.545
Protein (median, IQR, mg/dL)	60 (38–78)	62 (37–74)	57 (38–82)	0.872
Brain MRI changes at HSE onset ***				
FLAIR, mean % volume (SD)	3.9% (3.3)	4.5% (3.9)	3.4% (2.9)	0.344
DWI, mean % volume (SD)	3.7% (3.3)	3.6% (2.9)	3.8% (3.6)	0.904
Contrast enhancement, n=34	21/34 (62%)	6/8 (75%)	15/26 (58%)	0.368
Treatment of HSE				
Start acyclovir **** (median days, IQR)	1 (0–2)	2 (1–2)	1 (0–3)	0.193
Acyclovir duration (median days, IQR)	21 (16–21)	21 (18–23)	21 (15–21)	0.548
Steroids ****	20 (39%)	5 (36%)	15 (41%)	0.752
ICU admission	27 (53%)	9 (64%)	18 (49%)	0.315
Antiepileptic drugs	40 (78%)	12 (86%)	28 (76%)	0.422
Modified Rankin Scale (median, IQR)				
At 6 months, n=48	2 (1–3)	3 (3–4)	2 (1–3)	<0.001
At 12 months, n=40	2 (1–3)	3 (3–4)	2 (1–2)	<0.001

* likelihood ratio test;

** Not assessable in 15 patients (<3 years old, or severe decrease of the level of consciousness);

*** For lesion volume calculation, axial FLAIR sequences were available in 33 patients (19 without AE and 14 with AE), and axial DWI sequences in 46 patients (32 without AE and 14 with AE).

**** The number of days from HSE symptom onset to initiation of acyclovir.

Seventeen patients were treated with intravenous dexamethasone and 3 with intravenous methylprednisolone (2 of them along with intravenous immunoglobulins). AE, autoimmune encephalitis; DWI, diffusion weighted imaging; FLAIR, fluid-attenuated imaging recovery; HSE, herpes simplex encephalitis; IQR, interquartile range; SD, standard deviation

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Table 2:

Clinical Features of patients with AE post-HSE in Cohort-A

# sex, age	mRS post- HSE *	Day of onset and main symptoms of AE post-HSE	Maximum mRS during AE post-HSE	Antibody findings at diagnosis of AE		Immunotherapy	mRS at 12 months	Outcome at 12 months follow up
				Serum (Titer)	CSF (Titer)			
#1 M, 2 months	2	D7: Choreoathetosis	3	NMDAR 1:200	NMDAR 1:40	None	4	Developmental delay, refractory epilepsy, infantile spasms, cortical blindness, microcephaly
#2 M, 3 months	2	D23: Choreoathetosis, refractory seizures, LCE, hypotonia, dysphagia	5	NMDAR 1:1600	NMDAR titer n.a.	Day 26: IV MP, PEX, RTX	3	Developmental delay, right hemiparesis, microcephaly
#3 F, 7 months	2	D25: Choreoathetosis, refractory seizures, status epilepticus, infantile spasms, LCE, decreased consciousness, hypotonia, dysphagia	5	NMDAR 1:800	NMDAR 1:20	Day 25: IV MP, IVIg, Day 60: RTX, CYC	4	Developmental delay, spastic tetraparesis, anarthria, and controlled epilepsy
#4 M, 11 months	1	D19: Refractory seizures, infantile spasms, LCE, hypotonia, dysphagia, choreoathetosis	5	NMDAR 1:200	NMDAR 1:160	Day 20: IV MP, IVIg, RTX, CYC, ketogenic diet Day 70: PEX	5	Developmental delay, spastic tetraparesis, refractory epilepsy
#5 M, 12 months	2	D31: Choreoathetosis, loss of language skills, LCE, hypotonia, dysphagia	5	NMDAR 1:800	NMDAR 1:160	Day 32: IV MP, IVIg, RTX	3	Delay in language skills
#6 M, 15 months	2	D28: Refractory status epilepticus, hypotonia, LCE, decreased consciousness, dysphagia, choreoathetosis	5	NMDAR ** 1:200	NMDAR ** 1:80	Day 28: IV MP, induced coma Day 44: PEX, RTX	4	Developmental delay, refractory epilepsy
#7 M, 13 years	4	D42: Aggressive behaviour, headache, high blood pressure	4	NMDAR 1:800	NMDAR 1:160	D190: IV MP	3	Residual motor and cognitive deficits
#8 F, 34 years	2	D38: Insomnia, anxiety, irritability, fear, sleep fragmentation and nightmares	3	NMDAR 1:200	NMDAR 1:80	D60: IV MP	0	Complete recovery
#9 M, 45 years	3	D44: headache, confusion, agitation, insomnia, delusional thoughts	4	Negative	NMDAR 1:20	D140: IV MP	3	Residual aphasia
#10 F, 56 years	4	D30: Emotional lability, suicidal ideation, confusion	4	Negative	Unknown Ag 1:40	D160: IV MP	3	Anterograde amnesia
#11 F, 75 years	4	D37: Confusion, aggressive behaviour, insomnia	4	Negative	Unknown Ag 1:20	D180: IV MP, IVIg, RTX, CYC	4	Anterograde amnesia
#12 M, 77 years	3	D24: Progressive irritability, paranoid thoughts	4	Unknown Ag 1:800	Unknown Ag 1:20	D159: IV MP	4	Anterograde amnesia and irritability

# sex, age	mRS post- HSE*	Day of onset and main symptoms of AE post-HSE	Maximum mRS during AE post-HSE	Antibody findings at diagnosis of AE		Immunotherapy	mRS at 12 months	Outcome at 12 months follow up
				Serum (Titer)	CSF (Titer)			
#13 F, 78 years	3	D18: Fever, seizures, irritability, abnormal behaviour, confusion, apathy	5	Negative	Unknown Ag 1:10	D21: steroids, IVIg, RTX, CYC	3	Anterograde amnesia
#14 F, 80 years	4	D61: Progressive depression, apathy	4	Negative	Unknown Ag 1:160	D90: IV steroids, IVIg	3	Anterograde amnesia

* For all patients the mRS corresponds to 3 weeks post-HSE, except for patients 1, 4 and 13 who developed AE before the 3 week follow-up (additional information in Figure 2A).

** Coexisting GABA_AR antibodies, AE, autoimmune encephalitis; Ag, antigen; CSF, cerebrospinal fluid; CYC, cyclophosphamide; D, day; F, female; GABA_AR, gamma-aminobutyric acid A receptor; HSE, herpes simplex encephalitis; M, male; IV, intravenous; IVIg, intravenous immunoglobulins; LCE, loss of contact with environment; MP, methylprednisolone; mRS: modified Rankin Scale; n.a., not available; NMDAR, N-methyl-D-aspartate receptor; PEX, plasma exchange; RTX, rituximab.

Table 3:

Age-related syndromes of AE post-HSE in 58 patients (Cohorts A and B)

	Patients ≤ 4 years 27 (47%)	Patients > 4 years 31 (53%)	p
Median age (IQR, range)	11 months (IQR 7–17, range 2–48 months)	42 years (IQR 18–60, range 6–80 years)	
Interval HSE to AE, median (IQR, range)	26 days (IQR 24–32, range 7–61)	43 days (IQR 25–54, range 11–306)	0.007
Main symptoms of AE	Change of behaviour, * 26 (96%) Seizures, 15 (56%) ^a Choreoathetosis, 27 (100%) Decreased consciousness, 26 (96%) Dysautonomia, 9 (33%)	Change of behaviour, * 28 (90%) Seizures, 7 (23%) ^b Choreoathetosis, 0 (0%) Decreased consciousness, 7 (23%) Dysautonomia, 6 (19%)	0.615 0.015 <0.001 0.247
Antibodies	NMDAR, 24 (89%) ^c Unknown antigens, 3 (11%)	NMDAR, 19 (61%) Unknown antigens, 12 (39%)	0.03 0.03
Immunotherapy	No immunotherapy, 2 (7%) 1st line, 25 (93%) ^d 2nd line, 15 (56%) ^f	No immunotherapy, 4 (13%) 1st line, 27 (87%) ^e 2nd line, 8 (26%) ^g	0.675 0.675 0.03
Seizures at 1 year follow-up	12/19 (63%)	3/23 (13%)	0.001
Antiepileptics at 1 year follow-up	19/19 (100%)	13/23 (57%)	0.001
mRS median (IQR) at follow-up	6 months: mRS 4 (4–5) 12 months: mRS 4 (4–4)	6 months: mRS 3 (2–3) 12 months: mRS 2 (2–3)	<0.001 <0.001

* In very young children manifested as irritability and poor response to stimuli and environment. In adults, 18 patients developed full-blown psychosis.

^aTen with status epilepticus (6 with infantile spasms).

^bFour with status epilepticus;

^cOne with co-existing GABA_AR antibodies;

^dCombined IV MP and IVIg (n=13), combined IV MP, IVIg, and plasma exchange (7), IV MP alone (3), IVIg alone (1), plasma exchange alone (1).

^eCombined IV MP and IVIg (11), combined IV MP, IVIg, and plasma exchange (3), IV MP alone (12), IVIg and oral corticosteroids (1).

^fAll 15 patients were treated with rituximab and 6 also received cyclophosphamide.

^gAll 8 patients were treated with rituximab and 4 also received cyclophosphamide. Abbreviations: AE, autoimmune encephalitis; GABA_AR, gamma-aminobutyric acid A receptor; HSE, herpes simplex encephalitis; IQR, interquartile range; IV, intravenous; IVIg, intravenous immunoglobulins; MP, methylprednisolone; mRS: modified Rankin Scale; NMDAR, N-methyl-D-aspartate receptor