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Herpes Simplex Virus Encephalitis is a Trigger of Brain Autoimmunity

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CG has contributed in study design, data acquisition, interpretation and writing of the manuscript.
FG has contributed in data interpretation and writing of the manuscript.
JD has contributed in study design, collecting and analyzing data, writing of the manuscript

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Abstract

In five prospectively diagnosed patients with relapsing post-herpes simplex encephalitis (HSE), NMDAR-antibodies were identified. Antibody synthesis started 1–4 weeks post-HSE, preceding the neurological relapse. Three of five patients improved post-immunotherapy, one spontaneously, and one has started to improve. Two additional patients with NMDAR-antibodies, 9 with unknown neuronal surface-antibodies, and one with NMDAR and unknown antibodies were identified during retrospective assessment of 34 HSE-patients; the frequency of autoantibodies increased over time (serum p=0.004, CSF p=0.04). The three retrospectively identified NMDAR-antibody positive patients also had evidence of relapsing post-HSE. Overall, these findings indicate that HSE triggers NMDAR-antibodies and potentially other brain autoimmunity.

Keywords

Herpes Simplex virus; encephalitis; relapse; anti-NMDA receptor encephalitis

Introduction

Relapsing post-herpes-simplex-virus encephalitis (post-HSE) is a potentially lethal complication that occurs in 13–24% of the patients as a result of viral reactivation or suspected immunological mechanisms.[1–3] In the latter, patients frequently develop choreoathetosis, symptoms do not respond to acyclovir, and the HSV polymerase chain reaction (HSV-PCR) in cerebrospinal fluid (CSF) is negative.[1–4] These findings and the observation that some patients (11%) with HSE develop N-methyl-D-aspartate receptor (NMDAR) IgG antibodies,[5] led us to postulate that these antibodies could be involved in neurological relapses,[4] a hypothesis supported by a few case reports.[4,6–8] In the current study we provide a robust link between NMDAR antibodies and relapsing post-HSE by demonstrating novel NMDAR-antibody synthesis during the weeks that lapse between HSE and the development of new symptoms. We also show that HSE is a robust trigger of cell-surface/synaptic autoimmunity not limited to NMDAR. These findings are important because they assist in establishing the correct diagnoses and direct appropriate treatment approaches.

Patients and Methods

From June 2012 until May 2013, serum and CSF of 5 patients seen by the authors with relapsing post-HSE were studied at Hospital Clinic and August Pi i Sunyer Biomedical Research Institute (IDIBAPS), University of Barcelona. In addition, 34 patients with definite or probable HSE were included to determine the frequency of neuronal antibodies after HSE (Supplementary Table 1). From these 34 patients, archived serum and/or CSF obtained 1–88 days after HSE were available for study. Information was retrospectively provided by investigators of the California Encephalitis Project (Supplementary methods “Identification of patients”). All patients were examined for antibodies to cell-surface/synaptic antigens (Supplementary methods “list of antibodies tested, and techniques”).[9–12] The appearance of antibodies over time was assessed using the Mann-Whitney U test (IBM SPSS Version 20). Studies were approved by the internal review board of Hospital Clinic-IDIBAPS. Partial data on two patients (Case #2 and #5) were previously reported;[4,6] in this report we demonstrate NMDAR-antibody seroconversion post-HSE of Case #2.

Results

Prospective cases

The five patients prospectively identified included 4 children (median age 7 months, range 2–28; two female) and a 24 year-old man (Table 1). Detailed information and videos are provided in Supplementary material; the timing of initial antibody synthesis and symptoms is outlined in Figure 1. Overall, relapsing or new neurological symptoms started 7–41 days (median 24) after onset of HSE. In four patients the symptoms occurred after having improved from HSE, and in one (case #1) the symptoms (choreic-like movements) developed in contiguity seven days after hospital admission for HSE. In the four children, choreoathetosis was the most prominent finding (Supplementary Video); other symptoms included irritability, sleep disorder, and unresponsiveness. The adult patient developed abnormal behavior and personality change. CSF showed pleocytosis in 4/5 patients, with a white blood cell count (WBC) similar to that of the viral phase (HSE: median 49 WBC/μl, range 6–120; relapse: median 69 WBC/μl, range 10–153). Brain MRI did not show new T2/FLAIR signal abnormalities in three patients; patient#5 had a mild interval increase of a fronto-temporal T2/FLAIR abnormality without new necrotic lesions, and one patient did not have follow-up MRI.

All patients were treated for relapsing symptoms with a second 15–21-day course of intravenous acyclovir and four received immunotherapy (Table 1). Immunotherapy was not used in patient #1 who improved spontaneously (Supplementary video). Within four weeks of relapsing symptoms, only patient #5 improved with steroids; the other three did not respond to steroids and IVIg and were subsequently treated with rituximab (375mg/kg, weekly, four weeks) and cyclophosphamide (monthly IV pulses, first dose: 500 mg/m^2, second and subsequent doses: 750 mg/m^2). At the last follow-up, two patients have returned to the pre-relapse level (case#2, 24-month follow-up, case#3, 7-month follow-up), and the patient with the shortest follow-up (case #4, 4-month follow-up) has started to improve.

Serum and CSF samples of all five patients were available from the time of symptom relapse and in four from the time of HSE. None of the patients had NMDAR antibodies during HSE but all had high antibody titers, both in CSF and serum, 3–5 weeks later by the time of relapsing symptoms (Figure 1). All five patients had IgG and IgM NMDAR antibodies, and two had mild IgA antibody reactivity (Supplementary Table 2). All patients' serum/CSF reacted with the GluN1 subunit of the NMDAR but not with the subunit mutated at amino acid 368, as reported in anti-NMDAR encephalitis (Supplementary material).[15] Antibodies to the other indicated antigens were not identified.

Retrospective cases

Among the 34 patients with HSE whose archived serum/CSF samples were retrospectively studied, 17 had the samples obtained during the first week of the infection, 10 afterwards, and 7 during the first week and afterwards (Supplementary Table 1). Twelve of 34 patients had antibodies against neuronal cell-surface antigens, two of them against NMDAR, 9 against unknown antigens, and one both. In those two patients with only NMDAR antibodies (cases #6 and 7 in Supplementary Table 3, and vignette, case #7), the serum/CSF samples had been obtained after the first week of HSE (74 and 61 days). In case #8, CSF from the first week of HSE was available and showed extensive neuropil/cells-surface staining without NMDAR antibodies, suggesting an early presence of antibodies to uncharacterized antigens (Figure 2); however, NMDAR antibodies were identified on day 42 indicating seroconversion after the first week. For all three patients the antibody isotype was IgG (two also had IgM) against the GluN1 subunit of the receptor (Figure 2, Supplementary Table 2). In the three patients the reason for serum/CSF analysis was "new

onset or worsening neurological symptoms". The antibodies of the other 9 patients (4 detected during the first week of HSE and 5 afterwards) were directed against cell-surface antigens of unknown identity (one representative case shown in Figure 2).

Cell surface autoantibodies were identified in 1/17 sera and 5/22 CSF during the first week of HSE and in 5/13 sera and 7/12 CSF afterwards (Figure 2D). The frequency of autoantibodies increased over time in both serum and CSF (serum p=0.004, CSF p=0.04, Supplementary figure 1) suggesting that HSE triggers brain autoimmunity.

Discussion

This study shows that "relapsing post-HSE" is often anti-NMDAR encephalitis, that this immune response underlies different complications (e.g., choreoathetosis in children, abnormal behavior in adults), which may occur in contiguity or a few weeks after HSE, and that HSE is a trigger of cell-surface/synaptic autoimmunity.

The involvement of immune mechanisms in HSE has been previously suggested by the observation that immunocompetent patients have a more severe disease course than immunocompromised patients,[16] the beneficial effect of combining steroids with acyclovir,[17,18] and the recent identification of NMDAR antibodies in some patients with HSE.[4–6,8] We report here eight patients with relapsing post-HSE related to NMDAR antibodies, five of them with serum/CSF samples available from both the episode of HSE and the episode of neurological relapse. In these five patients (4 prospectively studied) the synthesis of NMDAR antibodies started shortly after HSE preceding the neurological relapse, providing a robust link between these entities. Altogether, 4/8 patients were children and all developed "choreoathetosis". In contrast, behavior, personality and memory deficits were the main symptoms in adults with only one (case #7) presenting abnormal movements. These differences regarding symptom presentation according to age are in line with those reported in non HSE-related anti-NMDAR encephalitis.[4,19]

Patient #1 (two months old), the youngest patient we know with NMDAR antibodies, developed choreic-like movements seven days after diagnosis of HSE. The awareness of one of the authors of "choreoathetosis post-HSE" led to antibody testing on day one of admission (without detection of NMDAR antibodies), and on day 24, which demonstrated NMDAR antibodies in serum and CSF. Subsequently, the patient improved spontaneously with a decrease of antibodies in CSF. The seroconversion demonstrated in this patient and in the other four prospectively identified cases, together with the detection of antibodies to cell-surface antigens in more than half of the patients tested after one week of HSE suggest that this infection often triggers brain autoimmunity which may fade spontaneously (e.g., case #1) or lead to progressive neurological symptoms.

Whether a mechanism of molecular mimicry or the release of antigens by viral neuronal lysis and inflammation leads to synaptic autoimmunity is unknown. We favor the second mechanism for three reasons; First, the broad immune response of some patients, mostly against unknown autoantigens, suggests release of multiple potential autoantigens; Second, the description of similar neurological complications in other viral encephalitis, such as Japanese B encephalitis, which may associate with a bimodal clinical course, including choreoathetosis and behavioral changes (to our knowledge, cell-surface autoimmunity has not been examined in these cases),[20] and third, the identification of other viruses such as Epstein-Barr or cytomegalovirus in the CSF of some patients with anti-NMDAR encephalitis, further supporting a non-specific viral-induced immunological mechanism (unpublished observations).

Findings from this study have several practical implications: 1) patients with prolonged, worsening or relapsing symptoms post-HSE should be tested for NMDAR and other antibodies to cell-surface/synaptic antigens, 2) identification of these immune responses is important because NMDAR-related symptoms are potentially responsive to immunotherapy, and 3) immunotherapy appears to be safe in patients with relapsing post-HSE. Future studies should determine prospectively the frequency of brain autoimmunity in patients with HSE, identify those who progress to develop post-HSE symptoms, characterize the unknown antigens, and further assess the effects of immunotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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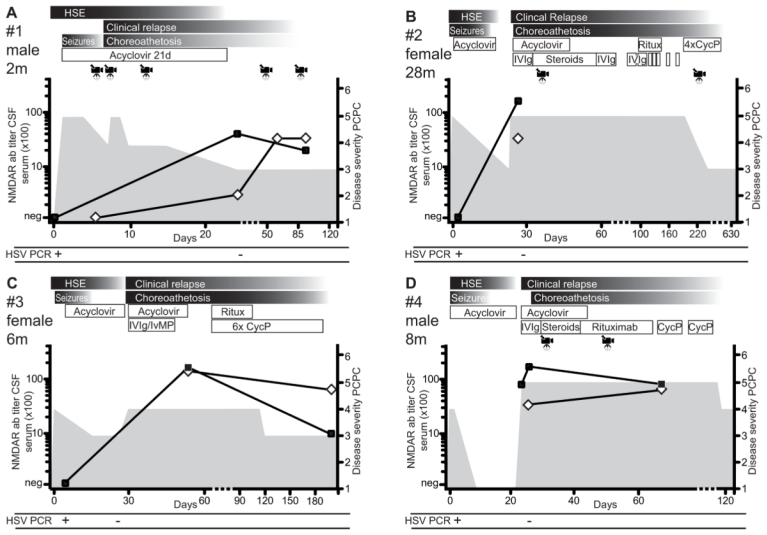

Figure 1. Clinical course, treatment, and CSF/serum NMDAR antibody titers in four patients with neurological relapses post-HSE

Scaling of X-axes is different in all patients reflecting length of follow-up. Broken x-axis represents discontinuous axis and change of tick interval. Right y-axis and grey curve: quantitative measure of disease severity Pediatric Cerebral Performance Category, PCPC[14](1=normal,2=mild disability, 3=moderate disability, 4=severe disability, 5= coma or vegetative state, 6=dead). Left y-axis: filled boxes NMDAR antibody titer in CSF, empty diamonds NMDAR antibody titer in serum (multiplied x100 to fit the same axis as CSF). Camera symbol represent available video segments in the supplementary video. IVIg: intravenous immunoglobulins, IvMP: intravenous methylprednisolone, or steroids: oral steroids, Ritux: rituximab, CycP: cyclophosphamide.

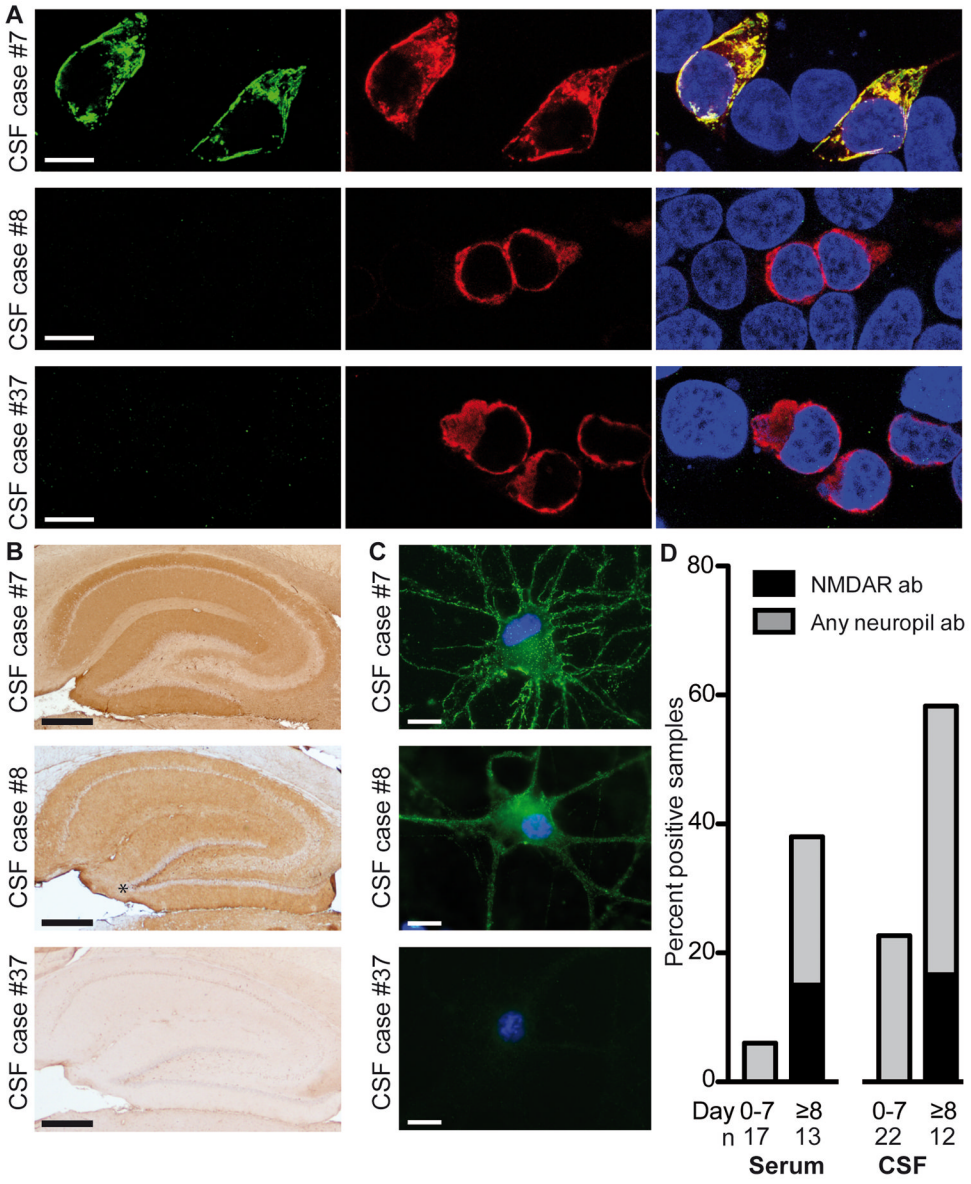

Figure 2. Determination and frequency of antibodies to NMDAR and uncharacterized cell-surface antigens in a retrospective cohort of patients with HSE

A: HEK cells expressing GluN1/GluN2 subunits of the NMDAR incubated with CSF of the indicated patients (left column, green fluorescence), and a monoclonal antibody to GluN1 (middle column, red); the merged immunostaining is shown in the right column. Nuclei of neurons demonstrated with DAPI. Scale bar 10μm. Note that only patient #7 had antibodies to NMDAR (a similar staining was obtained with cells transfected only with GluN1, not shown). B and C: Reactivity of the CSF of the same patients with sagittal sections of rat brain (B), and live rat hippocampal neurons (C). The CSF of patient #7 shows a typical pattern of NMDAR reactivity with the neuropil of hippocampus as well as with the cell-surface of neurons; the CSF of patient #8 shows reactivity with a neuropil antigen expressed on the cell-surface of neurons (the identity of the antigen is unknown), and the CSF of patient #37 was negative in both tests. Scale bar in B 500μm; Scale bar in C 10μm.

D: Percentage of patients' serum and CSF samples harboring IgG antibodies to NMDAR (black) or to other neuronal cell-surface antigens (grey) during and after the first week of

HSE; the identity of other neuronal antigens was unknown. Frequency increased over time (serum p=0.004, CSF p=0.04, Mann Whitney U test).

Table 1

Clinical features of patients prospectively identified with neurological relapse post-HSE

		HSV-1 ENCEPHALITIS						TIME TO RELAPSE (DAYS)	RELAPSE							OUTCOME (Follow-up after HSE onset)
#	AGE SEX	SYMPTOMS	CSF	MRI T2 LESIONS	HSV- PCR	TREATMENT	NMDAR ANTIBODIES		SYMPTOMS	CSF	MRI: NEW T2 LESIONS	HSV- PCR	NMDAR ANTIBODIES	INTRATHECAL SYNTHESIS NMDAR ANTIBODIES§	TREATMENT	
1	2 mo, m	Fever, focal seizures	WBC 77 prot. 78	Extensive bilateral occipital and right temporal	+	Acyc	−	7	Choreoathetosis, irritability, sleep disorder	WBC 120 prot. 249	n/a	−	+	75.41	Acyc	Day 130: Improved; deficits in visual tracking
2*	28 mo, f	Fever, irritability, focal seizures, dysphagia, dysarthria	WBC 18, prot. 25	Extensive bilateral temporal	+	Acyc	−	23	Fever, diarrhea, agitation, insomnia, choreoathetosis	WBC<5 prot.<45	−	−	+	18.85	Acyc, ivMP, IVIg, Ritux, CycP	Two years: Improved; normal exam, residual biopercular syndrome
3	6 mo, f	Fever, diarrhea, focal seizures. Residual right hemiparesis	WBC 10 prot. 38	Extensive bilateral temporal	+	Acyc	−	30	Fever, diarrhea, irritability, insomnia, choreoathetosis, unresponsiveness	WBC 6 prot. 45	−	−	+	4.71	Acyc, ivMP, IVIg, Ritux, CycP	Day 210:, Partial improvement: no chorea, residual dysphagia and hemiparesis
4	8 mo, m	Fever, irritability, focal seizures	WBC 85 prot. 36	Extensive bilateral frontotemporal	+	Acyc	n/a	24	Irritability, unresponsiveness, seizures, choreoathetosis	WBC 74 prot. 82 OCB	−	−	+	18.85	Acyc, ivMP, IVIg, Ritux, CycP	Day 120: slight improvement
5*	24 y, m	Confusion, delusions, coma. Residual memory impairment	WBC 153 prot.<45 OCB neg	Extensive bilateral temporal, insular	+	Acyc	−	41	Progressive mania, irritability, disorientation, memory dysfunction	WBC 24, prot. 86	+ (adjacent to prior lesions)	−	+	34.46	Acyc, IvMP	Day 119: Improved; residual memory impairment

*Partial data previously published[4,6].

§calculated according to [13] normal value ≤2.4;

Acyc: Acyclovir, CycP: monthly intravenous cyclophosphamide, f: female, IVIg: intravenous immunoglobulins, IvMP: intravenous methylprednisolone, m: male, mo: months, n/a: not available/not done, prot.: CSF total protein in mg/dL, Ritux: Rituximab, SIADH: syndrome of inappropriate anti-diuretic-hormone secretion, WBC: white blood cells/μl in CSF, y: years.