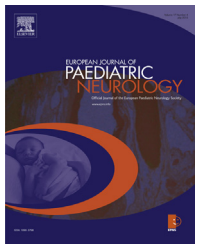
EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2014) 1–4

ELSEVIER

Official Journal of the European Paediatric Neurology Society



Case study

Viral triggering of anti-NMDA receptor encephalitis in a child – An important cause for disease relapse

Ronny Wickström [a,*], *Åsa Fowler* [a], *Gerald Cooray* [b], *Alex Karlsson-Parra* [c], *Pernilla Grillner* [a]

[a] *Neuropediatric Unit, Department of Women's and Children's Health, Karolinska Institutet, Sweden*
[b] *Department of Clinical Neurophysiology, Karolinska University Hospital, Sweden*
[c] *Department of Immunology, Genetics and Pathology, Uppsala University, Sweden*

ARTICLE INFO

Article history:
Received 21 January 2014
Received in revised form
20 March 2014
Accepted 28 March 2014

Keywords:
Herpes simplex 1
Autoimmune
CNS
Pediatric
Infant
Extreme delta brush
EEG

ABSTRACT

Herpes simplex encephalitis (HSE) in children is a potentially devastating condition which is occasionally complicated by a clinical relapse. An autoimmune component has long been suspected in these relapses and recent findings suggest that antibodies against N-methyl-D-aspartate receptors (NMDARs) may be part of this mechanism.

We here report an 11 months old girl with acute HSE and with negative NMDAR antibody serology at presentation who after an initial response to antiviral treatment deteriorated with seizures, abnormal movements, focal neurologic deficits and psychiatric symptoms. We show that this relapse occurred as production of NMDAR antibodies developed and that clinical improvement followed immunotherapy with a concomitant decrease in NMDAR antibody titers in CSF. She also developed a characteristic 15–20 Hz activity over both hemispheres which has been previously described as an electroencephalographic presentation of anti-NMDAR encephalitis.

We conclude that relapse or persisting symptoms in HSE in children may represent an immune-mediated mechanism rather than a viral reactivation and that NMDAR antibodies should be analyzed as this may be of importance for the choice of therapy.

1. Introduction

Acute encephalitis due to herpes simplex virus infection remains one of the more severe forms of childhood encephalitis in western countries. The clinical course of herpes simplex encephalitis (HSE) is occasionally complicated by a clinical relapse which usually occurs a few weeks after the initial infection and often during antiviral therapy. It has long been suggested that such a relapse may be due to secondary immune mechanisms rather than a true viral relapse[1] and antibodies against N-methyl-D-aspartate receptors (NMDARs) in particular have been implicated.[2]

Abbreviations: HSE, herpes simplex encephalitis; NMDAR, N-methyl-D-aspartate receptor.

* *Corresponding author*. Neuropediatric Unit, Q2:02, Astrid Lindgren's Children's Hospital, Karolinska University Hospital, 171 76 Stockholm, Sweden. Tel.: +46 (0) 8 517 706 27.
E-mail address: ronny.wickstrom@ki.se (R. Wickström).

http://dx.doi.org/10.1016/j.ejpn.2014.03.011

In children, a link between HSE and anti-NMDAR encephalitis was observed with the finding of NMDAR antibodies 4 months after an initial HSE in a 2 year old girl.[3] Furthermore, in a study of 7 children with a clinical relapse following HSE NMDAR antibodies were found in two cases. In one of these, NMDAR antibodies were negative in serum on initial presentation but positive after clinical relapse.[4] Although retrospective in nature, these studies strongly suggest a causal relationship between HSE and anti-NMDAR encephalitis. Single case reports have also prospectively found synthesis of NMDAR antibodies following HSE in an adult[5] and a recent study of 4 infants corroborates the possibility of a viral triggering of anti-NMDAR encephalitis.[6]

We here report an 11 months old with acute HSE and negative NMDAR antibody serology at presentation, and demonstrate a clinical relapse that was due to production of NMDAR antibodies.

2. Case study

A previously healthy girl, with no family history of neurologic disorders, presented at the age of 11 months with status epilepticus preceded by one day of high fever, vomiting and diarrhea. Her seizures were generalized but with a possible right-sided predominance. CSF analysis showed a monocytic pleocytosis (24 monocytes/microL) but a normal albumin, lactate, and glucose. Whereas an initial CT scan was normal, the acute EEG showed a focal left sided abnormality with increased delta activity with spikes and sharp waves. Intravenous antiviral treatment with acyclovir was initiated on day 2. Results from PCR of the CSF were positive for Herpes simplex type 1 (HSV1) and it was noted that the mother had mouth blisters a few weeks earlier. Seizures were treated with midazolam boluses followed by a midazolam infusion and subsequent oral phenobarbital treatment. She was also included in a prospective study of childhood encephalitis and therefore sampled according to study protocol.

On day 4–5 the girl was noted to be irritable, with abnormal tongue movements, abnormal hand movements on right side, as well as truncal instability. Repeated EEG showed persisting delta activity over the left temporal lobe but no epileptiform activity. A repeat lumbar puncture was performed on day 12 and revealed a persisting monocytic pleocytosis (26 monocytes/microL) whereas PCR for HSV1 was negative. During weeks 2–3 there was a slight improvement in the EEG with a reduction in the high amplitude delta activity and absence of electrographic seizures, consistent with clinical improvement. Our standard protocol for antiviral treatment recommends iv acyclovir for 3 weeks, but this was slightly shortened to 19 days, followed by oral treatment for 2 days due to difficulties with iv access.

Between days 15–19 she again developed a fever and displayed a progressive change in behavior that was perceived as aggressive in combination with oral and truncal choreoathetosis or dystonia. A CT scan was repeated and demonstrated changes consistent with necrosis due to herpes encephalitis (Fig. 1). A third lumbar puncture on day 21 again showed elevated monocytes (30/microL) and now also elevated albumin levels (359 mg/L) but a normal opening pressure. PCR for HSV1 was still negative but IgG for HSV1 were detected in the CSF. At this time, a distinctly different EEG pattern with 15–20 Hz activity was seen over both hemispheres (Fig. 2).

The troublesome and deteriorating clinical picture during the third week after initial presentation with severe behavioral change, irritability, sleep disturbance and poor motor control with choreoathetotic movements of head and trunk as well as decreased motor control in right arm and hand, together with negative findings in the CSF of PCR for HSV 1 suggested a secondary inflammatory response to the HSV1 infection. Therefore anti-inflammatory treatment with intravenous immuno globulin-treatment (IVIG, 1 g/kg for 2 days) was initiated on day 25. Despite IVIG treatment no significant improvement was seen and she was started on prednisolone (2 mg/kg*day) on day 35 for 1 week and tapered over 2.5 weeks. Starting on day 40 she gradually improved with better motor control, started eating and

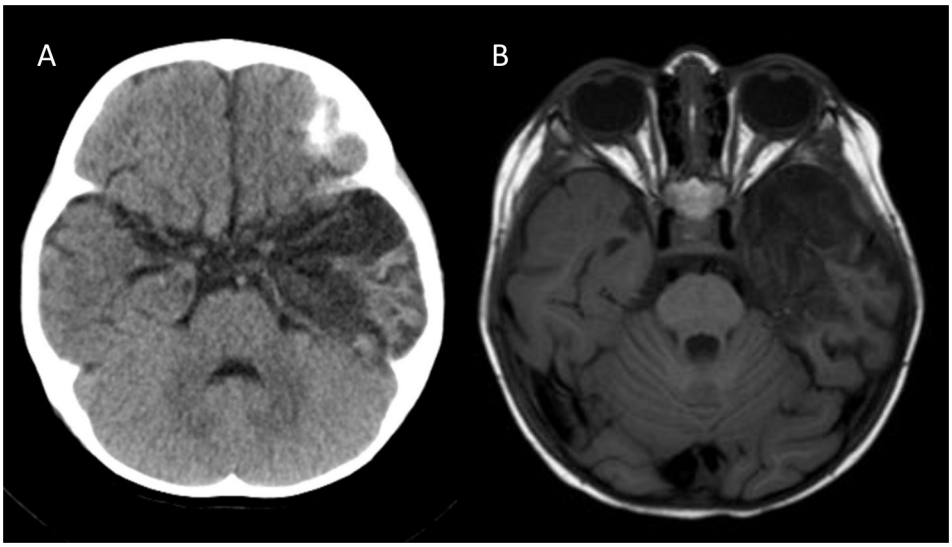


Fig. 1 – CT scan (day 20, A) and MRI (day 30, B) showing focal necrosis mainly affecting the left temporal lobe consistent with herpes simplex encephalitis.

Please cite this article in press as: Wickström R, et al., Viral triggering of anti-NMDA receptor encephalitis in a child – An important cause for disease relapse, European Journal of Paediatric Neurology (2014), http://dx.doi.org/10.1016/j.ejpn.2014.03.011

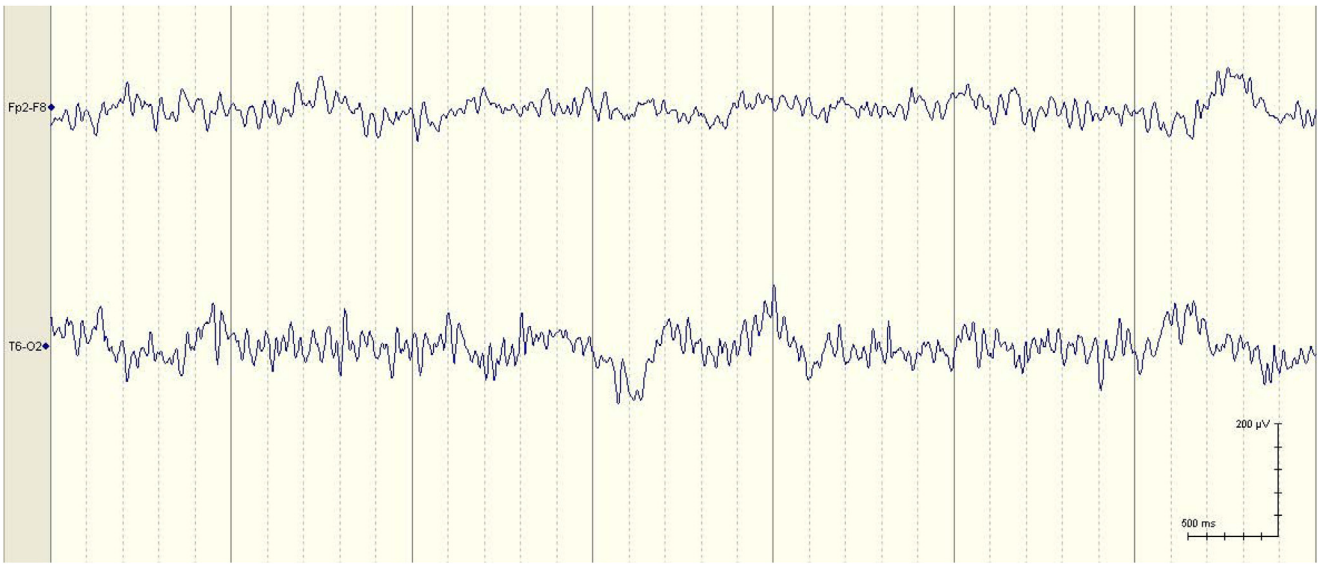


Fig. 2 – Bipolar EEG-registration from lateral sensors (Fp2-F8 and T6-O2) showing increased fast rhythmic activity with posterior dominance.

drinking and displayed a better emotional contact and general well-being. MRI performed after one month revealed changes typical for HSE with destruction of basal frontal lobe, insula, and anterior temporal lobe of the left side.

Subsequent analysis of the prospectively sampled serum and CSF confirmed that she did not have NMDAR antibodies in either serum or CSF at presentation or on day 12 but displayed such antibodies on day 21 in serum (IgG 1/64, IgM 1/64) and CSF (IgG 1/16, IgM 1/16). She was still positive in serum on day 36 but has since then been negative in serum for NMDAR antibodies at 9, 15 and 23 months. No CSF sampling was performed after day 30.

Currently, at the age of 3 years, she has no apparent motor deficits but is hyperactive, delayed in her cognitive and speech development and with intractable epilepsy. Treatment with ACTH analogs has shown positive effect on seizures and general behavior.

3. Discussion

This case demonstrates an NMDAR antibody-associated relapse post HSE in an 11 months old girl. When included in the prospective encephalitis study, she was negative for NMDAR antibodies in serum and CSF. The appearance of antibodies at the time of her relapse clearly suggests the viral infection as the trigger of her anti-NMDAR encephalitis. Although a coincidental development of both disorders is theoretically possible it is unlikely because of the low incidence of both HSVE and anti-NMDAR encephalitis. Also, the temporal association with the viral infection preceding the autoimmune response makes this further unlikely.

This case resembles previously described cases of HSE relapses where an autoimmune activation has been suggested as the mechanism for deterioration[4,6] with a clinical picture including seizures, abnormal movements, and focal neurologic deficits in addition to psychiatric symptoms. Clinical improvement followed immunotherapy with a concomitant decrease in NMDAR antibody titers in CSF which illustrates the importance of considering an autoimmune etiology in HSE relapses in the absence of viral reactivation.

Although previous studies of NMDAR encephalitis have shown a substantial improvement in 85% of cases with 60% making a full recovery, this girl developed sequela following her initial disease. It is, however, impossible in this case to ascertain to what extent these are due to the initial HSE and what role the autoimmune response has played. It is also possible that a persisting inflammatory state within the CNS is responsible for the remaining symptoms. This area should be addressed in future research and may be of uttermost clinical importance as this may direct therapy choices and duration. In considering immunosuppressing therapy, the risk of reactivation of latent viruses also needs to be considered. In immunocompromised children such reactivation is a well-known phenomenon for several viruses including HSV1.

The multiple EEGs performed show two different patterns with an initial picture compatible with HSE. Upon readmission to the hospital she had developed a characteristic 15–20 Hz activity over both hemispheres, which might be related to the development of anti-NMDAR encephalitis. Although she was not treated with benzodiazepines, the ongoing treatment with phenobarbital may induce beta activity. However, as EEGs prior to day 21 (and during phenobarbital treatment) showed markedly less beta activity, we speculate that the increase in beta activity was not pharmacologically induced.

Extreme delta brushes with a beta activity of 15–25 Hz superimposed on high amplitude delta activity have been described as a characteristic finding in anti-NMDAR encephalitis.[7] We suggest that the findings described above could be a slightly atypical electroencephalographic presentation of anti-NMDAR encephalitis.

The mechanism by which herpes simplex virus acts to trigger the production of NMDAR antibodies remains to be elucidated. It may represent a primary autoimmune response

Please cite this article in press as: Wickström R, et al., Viral triggering of anti-NMDA receptor encephalitis in a child – An important cause for disease relapse, European Journal of Paediatric Neurology (2014), http://dx.doi.org/10.1016/j.ejpn.2014.03.011

following the viral destruction of neurons exposing tissue normally shielded from systemic immunity, but may also be carried out by a B-cell activation as seen in other types of CNS inflammation such as multiple sclerosis.

It is becoming increasingly clear that relapse or persisting symptoms in HSE may rather represent an immune-mediated mechanism and that NMDAR antibodies should be promptly analyzed as this may affect treatment. If future studies demonstrate that NMDAR antibody production is indeed frequent in HSE, anti-inflammatory treatment should be considered as routine treatment of this severe CNS condition.

REFERENCES

1. De Tiege X, Rozenberg F, Des Portes V, et al. Herpes simplex encephalitis relapses in children: differentiation of two neurologic entities. *Neurology* 2003;**61**(2):241–3.
2. Pruss H, Finke C, Holtje M, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann Neurol* 2012;**72**(6):902–11.
3. Armangue T, Titulaer MJ, Malaga I, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr* 2013;**162**(4):850–6.
4. Hacohen Y, Deiva K, Pettingill P, et al. N-methyl-D-aspartate receptor antibodies in post-herpes simplex virus encephalitis neurological relapse. *Mov Disord* 2014 Jan;**29**(1):90–6.
5. Leypoldt F, Titulaer MJ, Aguilar E, et al. Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. *Neurology* 2013;**81**(18):1637–9.
6. Armangue T, Leypoldt F, Malaga I, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. *Ann Neurol* 2014;**75**(2):317–23.
7. Schmitt SE, Pargeon K, Frechette ES, et al. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012;**79**(11):1094–100.

Please cite this article in press as: Wickström R, et al., Viral triggering of anti-NMDA receptor encephalitis in a child – An important cause for disease relapse, European Journal of Paediatric Neurology (2014), http://dx.doi.org/10.1016/j.ejpn.2014.03.011