Anti-*N*-Methyl-D-Aspartate Receptor Antibody Mediated Neurologic Relapse Post Herpes Simplex Encephalitis

A Case Series

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Abstract: Despite the advent of antiviral therapy, herpes simplex encephalitis (HSE) remains a devastating condition with significant morbidity and mortality. Neurologic relapse after initial improvement is generally attributed to herpes simplex virus reactivation. In 2013, inflammation caused by anti-*N*-methyl-D-aspartate receptor antibodies was reported in association with cases of neurologic relapse after herpes simplex encephalitis. We present 3 such cases and discuss diagnostic and management dilemmas.

Key Words: herpes simplex encephalitis, *N*-methyl-D-aspartate receptor, relapse of herpes simplex encephalitis, movement disorder post herpes simplex encephalitis

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Relapse of herpes simplex encephalitis (HSE) presents as 1 of 2 distinct neurologic patterns.[1–3] The first, caused by new viral replication, presents with fever, seizures, focal neurologic signs and new areas of necrosis on neuroimaging. It responds to treatment with acyclovir. The second is characterized by choreoathetoid movements, absence of new areas of necrosis on neuroimaging, and poor response to acyclovir treatment. Recently, cerebrospinal fluid (CSF) anti-*N*-methyl-D-aspartate receptor (NMDAR) antibodies have been detected in cases of HSE relapse with choreoathetosis in children and adults.[4–11] We present 3 recent pediatric cases of anti-NMDAR antibody positive neurologic relapse with choreoathetosis complicating HSE that illustrate the variable clinical presentation and the management dilemmas that arise.

CASE REPORTS

Initial Presentation

Between 2014 and 2015, 3 previously healthy infants presented with herpes simplex virus-1 (HSV-1) encephalitis. All presented with a short preceding history (less than 48 hours) of fever, lethargy and poor feeding or new onset focal seizures. All received empiric intravenous (IV) acyclovir [20 mg/kg three times daily (TDS)] promptly on admission and showed significant early clinical improvement. Neuroimaging was characteristic of HSE (Fig. C, D, F and G, Supplemental Digital Content 1, http://links.lww.com/INF/C481). Diagnosis was confirmed by polymerase chain reaction (PCR) detection of HSV-1 DNA in CSF (Table1).

Relapse With Choreoathetosis

Case 1

On day 13 of IV acyclovir (20 mg/kg 8 hrly) for HSE, a 15-month-old female infant had a prolonged focal seizure requiring transfer to pediatric intensive care unit. Magnetic resonance imaging (MRI) brain showed bilateral temporoparietal and minor right thalamic hemorrhages with edema (Fig. A, Supplemental Digital Content 1, http://links.lww.com/INF/C481). By day 28, further deterioration was evident with behavioral change, irritability and dramatic hemiballismic and choreiform movements. Repeat MRI showed no acute changes. CSF showed 25 white blood cells (WBC)/cmm (80% lymphocytes). HSV-1 PCR was negative. IV acyclovir (20 mg/kg 8 TDS) was continued. Management of ballismic movements was challenging and required combinations of benzodiazepines, chloral hydrate, dexamedetomidine, haloperidol, gabapentin and tetrabenazine. Empiric immunomodulation with IV methylprednisolone (30 mg/kg), plasma exchange (PLEX) and IV immunoglobulin (IVIG; 400 mg/kg/d for 5 days) was started without significant improvement. Anti-NMDAR antibodies were detected in CSF from day 30. In all 3 cases, neat CSF was tested for anti-NMDAR-antibodies using a cell-based (HECK243) assay at the Clinical Neuroimmunology Service at Oxford Radcliffe Hospital Trust. Two doses of IV rituximab (375 mg/m^2) were administered over 2 weeks. Over the following 2 months, movement disorder and encephalopathy gradually improved. Antiviral treatment was changed to valacyclovir (30 mg/kg TDS) for a further 5 weeks. Five months after admission, she developed fever, lethargy, new right-sided seizures and exacerbation of her movement disorder. Lumbar puncture was deferred due to a mild coagulopathy. IV acyclovir (20 mg/kg) and methylprednisolone (30 mg/kg) were recommenced, and IVIG replacement (400 mg/kg/d ×5) was started. Repeat MRI 9 days later showed new and extensive T2 hyperintensity of left temporal, occipital and parietal lobes and left thalamus, suggestive of active inflammation (Fig. B, Supplemental Digital Content 1, http://links.lww.com/INF/C481). Repeat CSF showed 19 WBC/cmm (95% lymphocytes); enterovirus and HSV-1 PCR, and anti-NMDAR antibodies were negative. Enterovirus RNA was detected in stool. She was discharged home 1 month later with dense right and mild left hemiplegia, language delay and bulbar difficulties requiring gastrostomy feeding. She remains hypogammaglobulinemic and continues to receive IVIG replacement and valacyclovir (30 mg/kg/twice daily).

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TABLE 1. Clinical Features, Laboratory Findings and Imaging at Initial Presentation

Case	1	2	3
Presenting symptoms	Fever, focal seizure	Poor feeding, fever, vomiting	Lethargy, fever, focal seizure
Duration of symptoms	12 h. Seizure on arrival	24 h	<24 h
CSF			
WCC (% DIF)/cmm	6	373 (67% polymorph)	51 (100% monocytes)
RCC/cmm	0	15	0
Protein mg/L	190	444	317
Glucose/serum mmol/L	3.2/5	3.3/4.8	3.3/NA
HSV 1 PCR	Positive	Positive	Positive
Neuroimaging	Normal CT brain	Normal CT brain MRI brain D2: consistent with encephalitis (Fig. C, Supplemental Digital Content 1, http://links.lww.com/INF/C481)	CT brain: multiple areas of cortical hyperdensity MRI brain D2: consistent with extensive encephalitis (Fig. F and G, Supplemental Digital Content 1, http://links.lww.com/INF/C481)
Treatment commenced on presentation	Immediate IV acyclovir 20 mg/kg and cefotaxime 50 mg/kg	Immediate IV acyclovir 20 mg/kg and ceftriaxone 80 mg/kg	Immediate IV acyclovir 20 mg/kg and cefotaxime 50 mg/kg

Case 2

On day 10 of IV acyclovir (20 mg/kg 8 hrly) for HSE, a 5-month-old male infant developed orofacial dyskinesia. Repeat CSF showed 51 WBC/cmm (100% lymphocytes); HSV-1 PCR remained positive. Oral prednisolone (2 mg/kg) was added for suspected autoimmune encephalitis. CSF anti-NMDAR antibodies were negative. After 21 days, IV acyclovir, oral valacyclovir (30 mg/kg TDS) was commenced. Prednisolone was weaned to 0.5 mg/kg/d on day 26. On day 27 of illness, he had a further focal seizure, and by day 31, worsening orofacial dyskinesia, chorea and ballismic limb movements were noted. Neuroimaging demonstrated no acute changes (Fig. E, Supplemental Digital Content 1, http://links.lww.com/INF/C481). CSF showed 28 WBC/cmm (100% lymphocytes); HSV-1 PCR was negative. Prednisolone was increased to 2 mg/kg/d and IVIG (400 mg/kg/d ×5) started. Chorea resolved and orofacial dyskinesia improved within 5 days. Anti-NMDAR antibodies were detected subsequently in CSF from day 28. Six weeks later, he was discharged on valacyclovir (30 mg/kg TDS for 6 months). At 12 months of age, he had made good developmental progress without further seizures or abnormal movements. Repeat CSF anti-NMDAR antibodies were negative.

Case 3

A 16-month-old female infant made a good neurologic recovery from HSE after completing 21 days IV acyclovir (20 mg/kg TDS). CSF HSV-1 PCR was negative before discharge. She was readmitted 3 days later, with altered consciousness, orofacial dyskinesia and chorea. Repeat MRI showed persistent bilateral frontal lobe and left perisylvian restricted diffusion (Fig. H and I, Supplemental Digital Content 1, http://links.lww.com/INF/C481). CSF showed 47 WBC/cmm (80% mononuclear); HSV-1 PCR remained negative. IV acyclovir (20 mg/kg TDS), methylprednisolone (30 mg/kg) and IVIG (400 mg/kg/d) were started. Further deterioration required transfer to pediatric intensive care unit. Trial of PLEX was discontinued because of hemodynamic and autonomic instability. Ballismic movements persisted despite midazolam and clonidine infusions, choral hydrate and tetrabenazine. On day 25, CSF was anti-NMDAR antibody positive. IV rituximab (375 mg/m^2 2 weeks apart) was started. Over the following weeks, she improved slowly. MRI at 13 weeks showed no acute changes and CSF HSV PCR and anti-NMDAR antibodies were negative. She was discharged home 3 months later. At 6-month follow-up, she is ambulatory and the movement disorder has resolved. She continues on valacyclovir (30 mg/kg twice daily).

DISCUSSION

Anti-NMDAR encephalitis was first described in women with ovarian teratomas presenting with memory deficits, psychiatric symptoms, decreased consciousness and hypoventilation.[12] Primary anti-NMDAR encephalitis in children presents predominantly with abnormal movements, seizures and focal neurological deficits, in association with intrathecal production of antibodies against the NR1 subunit of the NMDAR.[5,13] Recently, evidence is emerging of the association of neurologic relapse after HSE and production of anti-NMDAR antibodies (Table 2).

Clinical features and timing of presentation of our cases (day 25–31 of illness) are similar to documented cases of anti-NMDAR encephalitis and previous descriptions of presumed autoimmune relapse with choreoathetosis and movement disorder post HSE (Table 2).[1,2] However, differentiating between relapse caused by new viral replication and that caused by autoimmune processes can be difficult. In case 2, initial orofacial dyskinesia occurred earlier (day 10 of HSE); CSF anti-NMDAR antibodies were negative and HSV PCR remained positive, suggesting ongoing viral replication. CSF anti-NMDAR antibodies were detected later on day 28 of illness in the setting of more florid dyskinesia. Desena et al[10] reports a similar infant with features of both HSV infection and autoimmunity 6 months after successful treatment of perinatal HSV-2 eye infection, presenting with orofacial dyskinesia, abnormal movements and positive CSF HSV-2 PCR and delayed positive CSF anti-NMDAR antibody. As in our case, clinical improvement ultimately required additional immunomodulation.

No consensus exists regarding initial choice or timing of immunomodulation in anti-NMDAR encephalitis post HSE (Table 1). First-line therapy typically involves empiric steroids, IVIG and PLEX. Dose and duration of medications vary between centers. However, PLEX in young infants is not without risk, and in our experience, it was made more complex by violent ballismic movements and hemodynamic instability. More recently, cyclophosphamide and rituximab are used as second-line agents. It is suggested that the earlier use of rituximab could improve outcome in NMDAR encephalitis as proposed in ospoclonos myoclonus ataxia syndrome.[14,15] Two of our cases ultimately required rituximab to control the encephalitis and movement disorders. However, treatment was delayed until the presence of CSF anti-NMDAR antibodies was confirmed. Resolution of symptoms was associated with disappearance of CSF NMDAR antibody, as has been reported previously in the literature.[6,11,13] Treatment of cases where residual herpes infection and evolving autoimmunity overlap may

TABLE 2. Clinical, Laboratory and Radiological Features of Reported Cases of Anti-NMDAR Encephalitis Post HSE

	Age	Days to Relapse	Neurological Presentation at Relapse	Anti-NMDAR abs	MRI Findings at Relapse	Treatment	Outcome
Case 1	15 mo	28	Seizures Oral dyskinesia Chorea	Serum CSF	No acute change	Methlyprednisolone IVIG PLEX Rituximab, IV Acyclovir	Movement disorder resolved Residual hemiplegia and language delay
Case 2	5.5 mo	31	Seizures Oral dyskinesia Chorea	Serum CSF	No acute change	Prednisolone Valacyclovir IVIG	Movement disorder resolved Ongoing developmental progress
Case 3	16 mo	25	Oral dyskinesia Chorea	Serum CSF	Persistent restricted diffusion	Methlyprednisolone IVIG Rituximab Acyclovir PLEX IV	Movement disorder resolved Ongoing developmental improvement
Mohammad et al[4]	7 yr	15	Chorea Dysautonomia Dystonia	CSF and serum	Persisting right temporal lobe changes	Methlyprednisolone IVIG 2 g/kg Cyclophosphamide Valacyclovir	Improvement Chorea when agitated
	8 mo	16	Chorea	Serum*	Evolution of previous changes	Methlyprednisolone 2g/kg of IVIG Acyclovir	Movement disorder resolved dystonic CP
Armangue et al[5]	2 yr	28	Extreme agitation Chorea orofacial dyskinesia Autonomic dysfunction	CSF and serum	Unchanged	Methlprednisiolone IVIG 0.4 g/kg for 5 d Rituximab Cyclophosphamide acyclovir	Improvement at 5 wks post rituximab
Hacohen et al[6]	3 yr	31	Encephalopathy Behavioral change Chorea Facial dyskinesia	Serum	Evolution of frontotemporal lesions	Steroids MMF Rituximab IV Acyclovir PLEX	Movement disorder improved Ongoing hyperactivity
	10 mo	40	Florid dyskinetic moment disorder Orofacial dyskinesia	Serum*		IVIG given at 10 yr IV Acyclovir at 40 d	Improved cognition and seizure control
	15 yr	60	Headache Concentration difficulties Sleepiness Disinhibition	Serum*	Extensive white matter lesions frontal, temporal and parietal lobes	Methylprednisilone Cyclosporine	Improvement Residual behavioral problems
Bamford et al[7]	16 mo	21	Evolving right sided movement disorder	CSF and serum	MRI; extensive right sided encephalomalacia	PLEX Acyclovir Oral	5-mo follow-up: movement disorder improved Severe global dev delay Gastrostomy feeding
Wickström et al[8]	11 mo	15	Behavioral change Irritability Sleep disturbance Poor motor control Chorea	Negative serum and CSF D12* Positive CSF and serum D 21	Necrosis on CT	Prednisolone IVIG 1 g/kg × 2/7	Gradual improvement Hyperactive, cognitive delay Intractable epilepsy
Yushvayev-Cavalier et al[9]	6 mo	16	Irritability Sleep disturbance Choreoathetoid movements Dysautonomia	CSF	No change	IV Corticosteroids IVIG Rituximab Cyclophosphamide	3-mo follow-up: movement disorder resolved
Desena et al[10]	<1 yr		Severe encephalopathy Almost continuous choreathetosis	CSF		IVIG 0.4 g/kg for 5 d PLEX	2 mo follow-up: improved neurological status. Regaining motor milestones

*Tested retrospectively.

be particularly difficult. Nevertheless, in our experience, immunomodulation did not worsen or reactivate HSV disease or further compromise undiagnosed immunodeficiency.[7] Indeed, case 2, where high dose prednisolone was added to IV acyclovir on day 10 of illness (with persistent positive CSF HSV-1 PCR), had a more benign course and resolved without rituximab.

The precise mechanism by which HSV induces anti-NMDAR antibody production remains unknown. It is suggested that CNS necrosis caused by HSV exposes and leads to release and presentation of local NMDAR epitopes, breaking tolerance and initiating an autoimmune response.[16–18] Demonstration of anti-NMDAR antibodies in 13/44 (30%) adult patients with HSE but in none of 20 control patients with less destructive Varicella Zoster Virus and enterovirus encephalitides supports this hypothesis.[18] A similar break in immune tolerance is proposed in children with anti-dopamine-2 receptor antibody encephalitis and chorea post HSE.[4]

While the outcome of primary anti-NMDAR encephalitis is generally good, prognosis in anti-NMDAR encephalitis post HSE is heavily influenced by the severity of the initial HSV infection.[4–10] Nevertheless, the role of continuing antiviral treatment in anti-NMDAR encephalitis post HSE is unclear. Although CSF HSV PCR remained undetectable in all our cases at relapse, we continued IV acyclovir during immunomodulation treatment. In case 1, where antivirals were discontinued at 16 weeks, subsequent neurologic deterioration and extensive T2 hyperintensity of left cerebral hepisphere on MRI at 5 months was concerning for reactivation of HSV but could not be proven due to a delay in CSF sampling. Detection of enterovirus in stool in this case raises the possibility of enterovirus encephalitis, in the setting of hypogammalobunemia post rituximab, or enterovirus-triggered reactivation of NMDAR encephalitis. Autoimmune encephalitis has been reported after a number of infectious agents (eg, mycoplasma and influenza A)[5,19,20]

Little is known regarding the need for continued antiviral prophylaxis in the setting of hypogammaglobulinemia post rituximab. While cell-mediated immunity is more important in the initial clearance of viremia, complement dependent and independent antibody neutralization of HSV has been demonstrated in small animals and appears to reduce HSV spread into the nervous system.[21] In addition, clinical and experimental evidence suggests that primary or secondary hypogammaglobulinemia is associated with increased risk of viral reactivation and severe and recurrent herpes simplex infection.[21–23] We elected to continue oral valacyclovir prophylaxis in our cases post rituximab.

Anti-NMDAR encephalitis is a newly recognized complication of HSE that undoubtedly remains underdiagnosed. Anti-NMDAR antibodies should be checked in cases of apparent relapse post HSE, particularly when associated with movement disorder. While recognition of anti-NMDAR encephalitis post HSE is likely to increase, the timing, choice, dose and duration of immunomodulation and role of suppressive antiviral treatment remain to be determined. Nevertheless, our experience suggests that the benefit of early immunomodulation in suspected autoimmune encepahalitis triggered by HSE may outweigh the putative risk of viral reactivation.

REFERENCES

1. De Tiège X, Rozenberg F, Des Portes V, et al. Herpes simplex encephalitis relapses in children: differentiation of two neurologic entities. *Neurology*. 2003;61:241–243.
2. Hargrave DR, Webb DW. Movement disorders in association with herpes simplex virus encephalitis in children: a review. *Dev Med Child Neurol*. 1998;40:640–642.
3. Sköldenberg B, Aurelius E, Hjalmarsson A, et al. Incidence and pathogenesis of clinical relapse after herpes simplex encephalitis in adults. *J Neurol*. 2006;253:163–170.
4. Mohammad SS, Sinclair K, Pillai S, et al. Herpes simplex encephalitis relapse with chorea is associated with autoantibodies to N-Methyl-D-aspartate receptor or dopamine-2 receptor. *Mov Disord*. 2014;29:117–122.
5. Armangue T, Titulaer MJ, Málaga I, et al.; Spanish Anti-N-methyl-D-Aspartate Receptor (NMDAR) Encephalitis Work Group. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr*. 2013;162:850–856.e2.
6. 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;29:90–96.
7. Bamford A, Crowe BH, Hacohen Y, et al. Pediatric herpes simplex virus encephalitis complicated by N-Methyl-D-aspartate receptor antibody encephalitis. *J Pediatric Infect Dis Soc*. 2015;4:e17–e21.
8. Wickström R, Fowler A, Cooray G, et al. Viral triggering of anti-NMDA receptor encephalitis in a child—an important cause for disease relapse. *Eur J Paediatr Neurol*. 2014;18:543–546.
9. Yushvayev-Cavalier Y, Nichter C, Ramirez-Zamora A. Possible autoimmune association between herpes simplex virus infection and subsequent anti-N-methyl-d-aspartate receptor encephalitis: a pediatric patient with abnormal movements. *Pediatr Neurol*. 2015;52:454–456.
10. Desena A, Graves D, Warnack W, et al. Herpes simplex encephalitis as a potential cause of anti-N-methyl-D-aspartate receptor antibody encephalitis: report of 2 cases. *JAMA Neurol*. 2014;71:344–346.
11. Leypoldt F, Titulaer MJ, Aguilar E, et al. Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. *Neurology*. 2013;81:1637–1639.
12. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol*. 2007;61:25–36.
13. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10:63–74.
14. Pranzatelli MR, Tate ED, Travelstead AL, et al. Rituximab (anti-CD20) adjunctive therapy for opsoclonus-myoclonus syndrome. *J Pediatr Hematol Oncol*. 2006;28:585–593.
15. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. *Neurology*. 2014;83:142–150.
16. Titulaer MJ, Leypoldt F, Dalmau J. Antibodies to N-methyl-D-aspartate and other synaptic receptors in choreoathetosis and relapsing symptoms post-herpes virus encephalitis. *Mov Disord*. 2014;29:3–6.
17. Höftberger R, Armangue T, Leypoldt F, et al. Clinical Neuropathology practice guide 4-2013: post-herpes simplex encephalitis: N-methyl-Daspartate receptor antibodies are part of the problem. *Clin Neuropathol*. 2013;32:251–254.
18. Prüss H, Finke C, Höltje M, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann Neurol*. 2012;72:902–911.
19. Gable MS, Gavali S, Radner A, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. *Eur J Clin Microbiol Infect Dis*. 2009;28:1421–1429.
20. Baltagi SA, Shoykhet M, Felmet K, et al. Neurological sequelae of 2009 influenza A (H1N1) in children: a case series observed during a pandemic. *Pediatr Crit Care Med*. 2010;11:179–184.
21. Brockman MA, Knipe DM. Herpes simplex virus as a tool to define the role of complement in the immune response to peripheral infection. *Vaccine*. 2008;26(suppl 8):194–9.
22. Olson NY, Hall JC. Chronic cutaneous herpes simplex and X-linked hypogammaglobulinemia. *Pediatr Dermatol*. 1987;4:225–228.
23. Rice CM, Johnston SL, Unsworth DJ, et al. Recurrent herpes simplex virus encephalitis secondary to carbamazepine induced hypogammaglobulinaemia. *J Neurol Neurosurg Psychiatry*. 2007;78:1011–1012.