Anti-N-methyl-D-aspartate receptor encephalitis during relapse of herpes simplex encephalitis in a young boy: A brief review of literature

Sir,

Herpes simplex virus (HSV) is an important cause of infectious encephalitis in young children and adults.[1] Approximately 14–26% of the patients with herpes simplex encephalitis (HSE) develop relapsing symptoms, usually in the form of choreoathetosis, a few weeks after viral therapy.[2,3] Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune-mediated disorder now being increasingly recognized as a cause of encephalitis in children, often in the absence of a tumor.[3] Recently, a strong association between these two discrete causes of encephalitis has been reported.[4,5] We report the case of a young boy with neurological relapse of HSE caused by antibodies to NMDAR. A brief review of similar cases in children is also presented.

A 9-month-old healthy boy, with normal birth and developmental history, presented to our institute with complaints of fever, partial seizures, and encephalopathy for 2 days. Initial investigations (including a hemogram, serum electrolytes, and transaminases) were normal. Cerebrospinal fluid (CSF) analysis showed 15 cells/μL (differential count: lymphocytes = 10, polymorphs = 5) and normal protein (38 mg/L) and glucose (52 gm/L). CSF viral study was positive for HSV using polymerase chain reaction (PCR).

Magnetic resonance imaging (MRI) of the brain showed asymmetrical abnormal signal intensity involving bilateral frontal, precentral and central subcortical white matter, deep gray and white matter, bilateral ventrolateral thalami, and left midbrain and pons along the corticospinal tracts [Figure 1a and b]. The electroencephalogram (EEG) revealed diffuse encephalopathy. He was started on intravenous acyclovir and antiepileptics (phenobarbitone, valproate, and levetiracetam). By day 5 of the illness, his sensorium worsened and he developed neurogenic stridor, required intensive care support, and invasive ventilation for two days.

He responded well to acyclovir therapy (given for a total of 21 days) and antiepileptics that improved his sensorium, with a good seizure control and hemodynamic stability. By the day 24 of the illness, he had deteriorated clinically with new-onset oromotor dyskinesias and choreoathetoid movements of limbs along with recurrence of fever and seizures. A repeat CSF study revealed increasing pleocytosis (cell count of 39/μL, all lymphocytes) and high protein (97 mg/L) and normal glucose (63 gm/L) levels. A relapse of HSE was considered; differentials being reactivation of HSV and autoimmune encephalitis triggered by HSV. At this time, CSF study for HSV PCR was negative. Meanwhile, serum and CSF anti-NMDAR antibody levels were found to be positive. Repeat MRI of the brain revealed scarred cortices with a large area of gliosis in bilateral frontoparietal perirolandic cortical and subcortical white matter as well as bilateral thalamocapsular region with subtle gyral enhancement and significant regression in the extent of restricted diffusion seen in the previous study [Figure 1c and d].

Then, he was given intravenous methylprednisolone therapy for 3 days followed by oral prednisolone (2 mg/kg/day), to which he showed gradual improvement. His abnormal movements and seizures stopped completely within the next 2 weeks, and he was discharged for domiciliary care on oral steroids. Three months after the discharge, he developed flexor spasms and partial seizures. EEG revealed hypsarrythmia pattern and oral vigabatrin was added to his medications. A repeat autoimmune panel was advised in view of ongoing encephalopathy. Serum anti-NMDAR antibodies were found to be negative; CSF study was refused by the parents. Further aggressive immunotherapy was not considered. With optimization of antiepileptic therapy, his spasms have stopped. He is now on oral steroids, valproate, and vigabatrin. He now attempts to roll over, recognizes parents and responds by nonverbal cues, and gets occasional partial seizures.

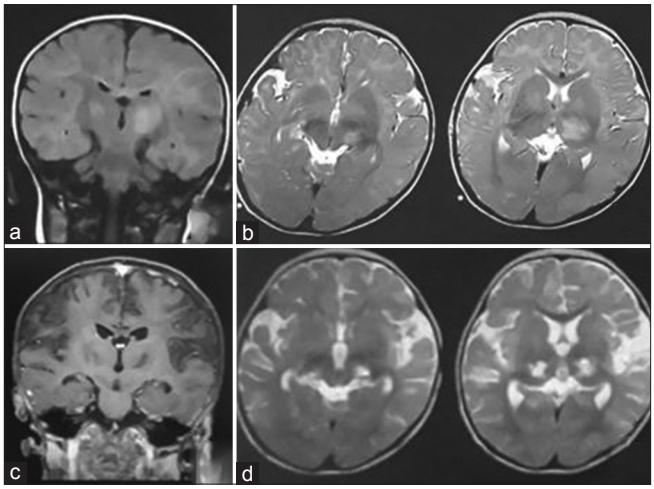

Figure 1: (a and b) Initial magnetic resonance imaging (MRI) of the brain; fluid-attenuated inversion recovery (FLAIR) and T2-weighted images (day 2 of illness) revealed asymmetrical abnormal signal intensity involving bilateral frontal, precentral, and central subcortical white matter, as well as deep gray and white matter, bilateral ventrolateral thalami, and in left midbrain. (c and d) MRI of the brain; FLAIR and T2 weighted images (day 28 of illness) revealing scarred cortices with large area of gliosis in bilateral frontoparietal perirolandic cortical and subcortical white matter as well as in bilateral thalamocapsular region

Anti-N-methyl-D-aspartate receptor encephalitis

Anti-NMDAR encephalitis is an immune-mediated disorder caused by IgG antibodies against the GluN1 subunit of the NMDAR.[3] It was first described by Dalmau *et al*., (2007) in young women with ovarian teratomas.[6] This disorder has now become a leading cause of encephalitis in children, often in the absence of a tumor.[3,7] The typical features observed are behavioral changes, hallucinations, seizures, amnesia, movement disorders, and/or dysautonomia. In young children, abnormal behavior, seizures, and movement disorders are frequent.[3] A tumor or prior infection may act as a trigger for autoimmune response via molecular mimicry.[7]

Postherpes simplex encephalitis neurological relapse

Neurologic relapses after HSE have been reported frequently in children more than in adults.[2,5,8-16] Two distinct clinical entities have been reported. A resumption of viral replication, a few days to years after the initial HSE, has been noted. It presents as fever along with several neurological symptoms without a prominent movement disorder. This is supported by evidence of increasing viral titres in CSF study and/or new necrotic hemorrhagic lesions exhibited on neuroimaging, improvement with acyclovir and presence of virus in brain biopsy.[2] A second entity typically characterized by new-onset cognitive regression, movement disorder or behavioral disturbance along with a negative HSV-PCR, absence of new necrotic MRI lesions, and no response to acyclovir is observed. It usually presents in a period of 4–6 weeks after acyclovir therapy.[2,5,8-16]

Association of autoantibodies in post-herpes simplex encephalitis neurological relapse

Pruss *et al*., in their study on acute serum samples of adult patients with HSE, found 30% of patients with serum positivity for NMDAR antibodies of IgA, IgG, and IgM subtypes.[4] Subsequently, researchers have demonstrated that 7% of the patients with HSE harbor anti-NMDAR IgG antibodies against the NR1 receptor.[5] These antibodies have been found in both adults and children with new-onset neurological relapses and movement disorders, especially post acyclovir therapy choreoathetosis.[5,8-16] Less frequently, antibodies against the dopamine-2 receptor and other brain proteins have been found.[12] A review of few similar studies and case reports has been presented in Table 1.[9-16]

Pathogenesis (possible hypotheses)

Molecular mimicry due to homology of synaptic receptors to the viral protein components has been strongly proposed. The

Table 1: Review of selected cases of post herpes simplex encephalitis with neurological relapse showing autoimmune reactivation

Study	Number of cases of HSE with NMDAR encephalitis, Median Age (Range)	Sex	Presenting symptoms at relapse	Abnormal MRI/EEG	Interval prior to onset of relapse	CSF HSV PCR		Treatment given	Anti-NMDAR antibodies		Follow-up	Outcome
						Initial (at diagnosis)	Follow-up (during relapse)		Initial (at time of relapse) Serum/ CSF	Follow-up Serum/CSF		
Yushvayev-Cavalier, *et al.* (2015)	1, 6 mo	F	Irritability, insomnia, dysautonomia, orolingual, facial, and limb choreodystonic movement	Yes/NA	4 wk	+	-	Rituximab Cyclophosphamide	+	Not done	3 mo	Normal
Wickström *et al.* (2014)	1, 11 mo	F	Seizures, abnormal movement, focal neurologic deficits, psychiatric symptoms	Yes/Yes	3 wk	+	-	IVIG, prednisolone	+	Decreased titres	2 yr	Cognitive and speech delay, intractable epilepsy
De Sena *et al* (2014)	2, 1 mo	M	Hyperkinetic movement, worsening sensorium	NA	6 mo	+	-	IVIG, plasma exchange, cyclophosphamide	+	NA	9 wk	Good
Mohamed *et al.* (2014)	3, 2.8 yr (8 mo-to 7 yr)	1-M, 2-F	Encephalopathy, Chorea +/- dystonia, dysautonomia	Yes/No	15d-6 wk	+	-	Steroids, IVIG, cyclophosphamide	+ **	-	9 mo, 13 yr, 14 yr respectively	Developmental delay, refractory epilepsy, intellectual disability, behavioural problems
Bamford A *et al.* (2014)	16 months	F	Encephalopathy, left hemiparesis, evolving right-sided movement disorder	Yes/No	21 d	+	-	Plasmapheresis	+	Decreasing titres	5 mo	Minimal movement disorder, improving cognition
Bektaş *et al.* (2014)	17 months	F	Orofacial dyskinesia, choreo-athetosis	Yes/No	28 d	+	-	MPS	+	NA	NA	Improvement
Armangue *et al.* (2014)	4, 1.04 yr (2 mo- 28 mo)	F-2, M-2	Fever, diarrhea, irritability, insomnia, choreo-athetosis, unresponsiveness	Yes/No	7-30 d	+	-	Acyclovir, MPS, IVIG, Rituximab, Cyclophosphamide	+	NA	9.7 mo (210 d, 2 yrs, 120 d, 130 d)	Minimal improvement, residual visual deficit
Hacohen *et al.* (2013)	3, 6.26 yr (10 mo, 15 yr, 3 yr)	F	Encephalopathy, choreoathetosis, orofacial dyskinesias, cognitive regression, seizures	NA/NA, Yes/Yes, Yes/NA	40 d, 16d 31 d	+ + +	- - -	IVIG, MPS, cyclosporine, MMF, rituximab	NA, +, +	+, NA, +	10 yr, 3 yr, 1 yr	Residual motor and cognitive decline

IVIG = Intravenous immunoglobulin; MPS = Methylprednisolone; MMF = Mycofenolate mofetil; NA = details not available; NMDAR = N-methyl-D-aspartate receptor; HSV = Herpes simplex virus; PCR = Polymerase chain reaction; +, Positive; -, Negative; **, (1- NMDAR positive, 1- dopamine receptor 2 Ab positive)

temporal relationship between infectious and autoimmune encephalitis in various cases reported in the literature suggests that autoantibodies may be a part of a secondary immune response to virus-induced neuronal damage. Viral destruction of the neurons and an inflammatory trigger to autoimmunity has been proposed as another mechanism.[2] An aberrant immune response triggered after neuronal cell surface antigen has been presented as being pathogenic to the circulating lymphocytes has been noted. This occurs especially after a loss of tolerance arising from HSV-mediated cellular damage.[5]

Role of immunotherapy and response to therapy

Prospective series show that immunotherapy has been beneficial in such patients.[3,12] The response to immunotherapy has been modest.[8-16] Titauler *et al*.,[2] and Bamford *et al*.,[13] have proposed diagnostic and treatment algorithms. A first-line therapy should be started immediately after evidence of anti-NMDA and/or anti-dopamine-2 receptor antibodies or other neuronal antibodies, with a negative study for HSV from the CSF (with/without serum) sample, is obtained. The studies differ in recommending the use of steroids as first-line therapy, with steroids being suggested to be avoided by the latter group. However, steroids alone or in combination with intravenous immunoglobulin or plasmapheresis have shown promising results.[10,12,14,16] Concurrent acyclovir therapy with immunotherapy has also been proposed in selected cases.[13] If first-line therapy fails, a second-line therapy has proven to be successful in these patients, including rituximab, cyclophosphamide, and mycophenolate mofetil.[3,9,12,13,15,16] Second-line therapy has shown to result in improvement in the patient's condition even after several years from the initial insult, although it has its own shortcomings such as the onset infections and immunological complications, especially secondary to rituximab.[12,13] Surveillance for HSV reactivation using blood/CSF PCR and titres of autoantibodies may be beneficial on follow-up visits and can be an adequate guide for treatment endpoint. The recommended interval between estimation of consecutive titres of autoantibodies has still not been defined. The neurological recovery of such patients depends on both the initial damage caused by HSV and additional autoimmune response triggered damage. The contribution of each to the resultant sequelae may be difficult to distinguish.[10,13]

Thus, autoimmune encephalitis triggered by HSV is being increasingly recognized in children. Prompt immunotherapy has been found to be associated with clinical improvement or substantial recovery. Neurological relapses of HSE should always be investigated for autoimmune antibodies from serum and CSF. Steroids may be routinely added to acyclovir in the context of HSE. Prospective studies will help to explore this causal association and provide newer insights into therapy.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Steiner I, Kennedy PG, Pachner AR. The neurotropic herpes viruses: Herpes simplex and varicella-zoster. Lancet Neurol 2007;6:1015-28.
2. 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.
3. Armangue T, Titulaer MJ, Málaga I, Bataller L, Gabilondo I, Graus F, *et al*. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr 2013;162:850-6.
4. Prüss H, Finke C, Höltje M, Hofmann J, Klingbeil C, Probst C, *et al*. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. Ann Neurol 2012;72:902-11.
5. Höftberger R, Armangue T, Leypoldt F, Graus F, Dalmau J. Clinical neuropathology practice guide 4-2013: Post-herpes simplex encephalitis: N-methyl-D-aspartate receptor antibodies are part of the problem. Clin Neuropathol 2013;32:251-4.
6. Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, *et al*. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25-36.
7. Peery HE, Day GS, Dunn S, Fritzler MJ, Prüss H, De Souza C, *et al*. Anti-NMDA receptor encephalitis. The disorder, the diagnosis and the immunobiology.Autoimmun Rev 2012;11:863-72.
8. Leypoldt F, Titulaer MJ, Aguilar E, Walther J, Bönstrup M, Havemeister S, *et al*. Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: Case report. Neurology 2013;81:1637-9.
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;52:454-6.
10. Wickström R, Fowler A, Cooray G, Karlsson-Parra A, Grillner P.

Viral triggering of anti-NMDA receptor encephalitis in a child-An important cause for disease relapse. Eur J Pediatr Neurol 2014;18:543-6.
11. Desena A, Graves D, Warnack W, Greenberg BM. Herpes simplex encephalitis as a potential cause of anti-N-methyl-D-aspartate receptor antibody encephalitis: Report of 2 cases. JAMA Neurol 2014;71:344-6.
12. Mohammad SS, Sinclair K, Pillai S, Merheb V, Aumann TD, Gill D, *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;29:117-2.
13. Bamford A, Crowe BH, Hacohen Y, Lin JP, Clarke A, Tudor-Williams G, *et al*. Pediatric Herpes simplex virus encephalitis complicated by n-methyl-d-aspartate receptor antibody encephalitis. J Pediatric Infect Dis Soc 2015;4:e17-21.
14. Bektaş Ö, Tanyel T, Kocabaş BA, Fitöz S, Ince E, Deda G. Anti-N-methyl-D-aspartate receptor encephalitis that developed after herpes encephalitis: A case report and literature review. Neuropediatrics 2014;45:396-401.
15. Hacohen Y, Deiva K, Pettingill P, Waters P, Siddiqui A, Chretien P, *et al*. N-methyl-D-aspartate receptor antibodies in post-herpes simplex virus encephalitis neurological relapse. Mov Disord 2014;29:90-6.
16. Armangue T, Leypoldt F, Málaga I, Raspall-Chaure M, Marti I, Nichter C, *et al*. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. Ann Neurol 2014;75:317-23.

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