concerning for CTE,[8] but details surrounding the pathology in this case are not yet published. These associations are further bolstered by reports of mild CTE pathologic changes in 2 young soccer players.[3,6] Therefore, this case report suggests that more studies are warranted to determine the connection among soccer, CTE, neurodegeneration, and dementia.

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1. Stern RA, Daneshvar DH, Baugh CM, et al. Clinical presentation of chronic traumatic encephalopathy. Neurology 2013;81:1122–1129.
2. Martland H. Punch drunk. JAMA 1928;91:1103–1107.
3. McKee AC, Daneshvar DH, Alvarez VE, Stein TD. The neuropathology of sport. Acta Neuropathol 2014;127:29–51.
4. McKee AC, Stein TD, Nowinski CJ, et al. The spectrum of disease in chronic traumatic encephalopathy. Brain 2013;136:43–64.
5. Omalu B, Bailes J, Hamilton RL, et al. Emerging histomorphologic phenotypes of chronic traumatic encephalopathy in American athletes. Neurosurgery 2011;69:173–183.
6. Geddes JF, Vowles GH, Nicoll JA, Revesz T. Neuronal cytoskeletal changes are an early consequence of repetitive head injury. Acta Neuropathol 1999;98:171–178.
7. Maher ME, Hutchison M, Cusimano M, Comper P, Schweizer TA. Concussions and heading in soccer: a review of the evidence of incidence, mechanisms, biomarkers and neurocognitive outcomes. Brain Inj 2014;28:271–285.
8. BBC News. Jeff Astle: West Brom Legend "killed by boxing brain condition." 2014. Available at: http://www.bbc.com/news/uk-england-birmingham-27654892. Accessed June 4, 2014.

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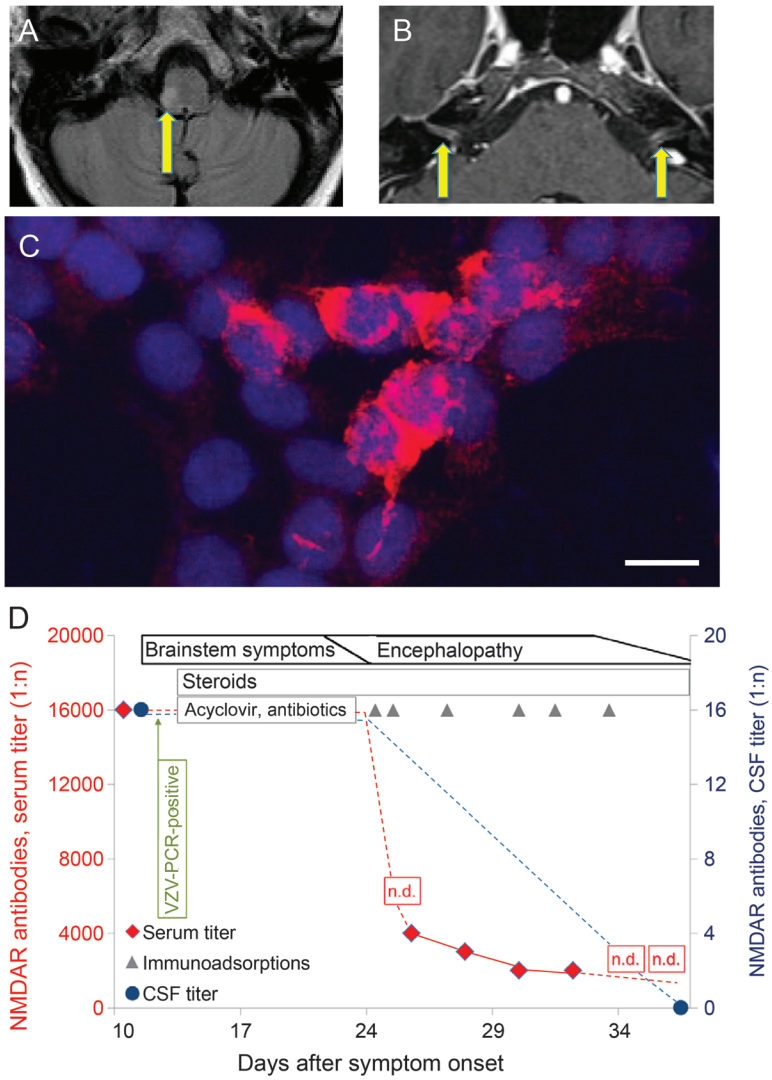
VZV BRAINSTEM ENCEPHALITIS TRIGGERS NMDA RECEPTOR IMMUNOREACTION

After its discovery, anti-NMDA receptor (NMDAR) encephalitis was quickly recognized as "sleeping" neurologic disease, presumably heavily underestimated. This autoimmune disease is defined by the presence of immunoglobulin G (IgG) antibodies against cell surface epitopes of the NR1 subunit of the NMDAR.[1] The disease phenotype is best characterized as encephalopathy and was initially described by Dalmau et al.[2] in young women presenting with a prominent change of behavior, psychosis, memory deficits, seizures, abnormal movements, coma, and autonomic dysfunction. Whereas in cases of an underlying tumor (usually teratoma in the ovary) the cause of the disease is viewed as paraneoplastic, in many cases without a tumor the trigger for the NMDAR antibody production is unknown. Recently it has been observed that herpes simplex virus 1 (HSV-1) may account for relapses of HSV encephalitis (HSVE) by inducing NMDAR immunoreactivity causing the full clinical picture of anti-NMDA-R encephalopathy[3] or a choreatic condition.[4–6]

Case report. A 76-year-old patient was transferred from an external ear, nose, and throat department, where she was treated for dysphagia and dysphonia. Upon admission to our department, there was left hypoglossus paresis, dysphonia due to hypophonic vocal cord paresis, left velum paresis, right oculomotor paresis, saccadic eye movements, horizontal nystagmus, and left hemihypesthesia.

Lumbar puncture 12 days after symptom onset revealed 138 cells/μL (lymphocytes and a few monocytes), elevated protein of 701 mg/dL, glucose-CSF/serum ratio of 0.45, lactate 3.62 mmol/L, positive oligoclonal bands in CSF/serum indicating intrathecal IgG production, and a positive PCR of varicella-zoster virus (VZV). All other tests for neurotropic viruses and other bacteria had negative results. Upon search for antineural antibodies (to GAD65, GAD67, $GABA_BR$, NMDAR, AMPAR1/2, AQP4, Glycin receptor, LGI1, CASPR2, amphiphysin, CV2, PNMA2 [Ma-2/Ta], Hu, Ri, and Yo), NMDAR antibodies were detected in serum and CSF. The specific antibody index for anti-NMDAR calculated as $(\text{anti-NMDAR titer}_{CSF}/\text{anti-NMDAR titer}_{serum})/(IgG_{CSF}/IgG_{serum})$ was <1, demonstrating absence of intrathecal NMDAR antibody production (figure, C). The MRI showed inflammatory lesions in the left brainstem (figure, A) and several enhancing cranial nerves (figure, B). The patient showed no signs of skin VZV disease or other sign of immunosuppression. The diagnosis of a classical VZV brainstem encephalitis combined with polyneuritis cranialis was made and the patient was initially treated with IV ceftriaxone, acyclovir, and ampicillin plus IV steroids over 5 days (500 mg methylprednisolone) following oral tapering.

Figure MRI, antibody presence, and time course under treatment



(A) High-field (3T) MRI of the brainstem. Note the enhancement in the lower pons in fluid-attenuated inversion recovery images (arrow in A); arrows in (B) show enhancement of caudal cranial nerves. (C) Patient serum and CSF were incubated with acetone-fixed HEK293 cells expressing NMDA receptors (NMDAR) composed only of NR1 subunits (Euroimmun, Lübeck, Germany). On visualization by a fluorescence-labeled antihuman immunoglobulin G antibody, a specific signal on serial dilutions down to 1:16,000 (serum) and 1:16 (CSF) was visible. Mild counterstaining of nuclei with Hoechst 33342, diluted 1:10,000. Bar: 10 μm. (D) Two-phasic clinical, serologic, and therapeutic course. The follow-up anti-NMDAR serum titers were determined in samples collected immediately after immunoadsorption sessions 2, 3, 4, 5, and a week after the final session. The dotted lines indicate "extrapolated" titer courses for the sake of easier readability of the figure. n.d. = not determined; VZV = varicella-zoster virus.

On this treatment, the patient recovered partially (hemihypesthesia and oculomotor symptoms improved), but she developed in the further course of the disease optical and scenic hallucinations, illusions, disturbance of orientation, and cognitive impairment. These later symptoms were attributed to NMDAR autoimmunity, and anti-NMDAR encephalitis was diagnosed; the patient was additionally treated with 6 immunoadsorption sessions. In brief, 2 plasma volumes passed through the immunoadsorption system containing the nonspecific IgG absorber Globaffin (Fresenius Medical Care, Bad Homburg, Germany). On this treatment (the patient was still on oral prednisolone), NMDAR antibody titers declined (figure, D), the psychic and cognitive symptoms slowly improved over the next 3 weeks, and the patient could be transferred to a rehabilitation unit.

Discussion. We report for the first time that VZV encephalitis may trigger the occurrence of NMDAR antibodies leading to an encephalopathy complicating the initial disease. This finding is novel and important because it extends the recently reported constellation with HSVE as a trigger of anti-NMDAR encephalitis. Currently unclear is the pathophysiologic cause of this condition. The neurotropic viruses from the herpes group induce an intense inflammation either in limbic structures (HSVE) or in the brainstem as in our case, thereby probably releasing and presenting abundantly expressed local NMDAR epitopes to the immune system, breaking tolerance and initiating an autoimmune response.[7] These findings shine a broader light on occurrence and relevance of anti-NMDAR encephalitis. It is likely that other neurotropic viruses can induce similar pathology.

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1. Gleichman AJ, Spruce LA, Dalmau J, Seeholzer SH, Lynch DR. Anti-NMDA receptor encephalitis antibody binding is dependent on amino acid identity of a small region within the GluN1 amino terminal domain. J Neurosci 2012;32:11082–11094.
2. 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.
3. Leypold 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.

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. 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.
6. Armangue T, Leypoldt F, Málaga I, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. Ann Neurol 2014;75:317–323.
7. 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;32:251–254.

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VZV brainstem encephalitis triggers NMDA receptor immunoreaction

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