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Case report

Anti-NMDA Receptor antibody encephalitis with concomitant detection of *Varicella zoster virus*

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ABSTRACT

The typical presentation of anti-NMDA (N-Methyl-D-Aspartate) receptor encephalitis involves young women with psychiatric, neurologic and autonomic symptoms; it is often associated with mature ovarian teratomas. NMDA receptor encephalitis has been described following *Herpes simplex virus* (HSV) encephalitis. This case describes a classic presentation of anti-NMDA receptor encephalitis with the concomitant presence of *Varicella zoster virus* in the cerebrospinal fluid.

Autoimmune etiologies should be considered in the differential diagnosis of encephalitis syndromes. Recent clinical observations have postulated that *Herpes simplex virus* could potentially trigger anti-N-methyl-D-aspartate (NMDA) receptor encephalitis. There has only been one case that has linked a varicella zoster virus infection with anti NMDA receptor encephalitis. We present a second case with a classical presentation for anti-NMDA receptor encephalitis that had varicella zoster virus identified by polymerase chain reaction (PCR).

1. Case report

A 29 year-old woman, with no significant past medical history, complained of a 5 day history fever, runny nose, myalgia followed by severe headaches and mild changes in mood and behavior. She was brought to the emergency room and underwent a computerized tomography (CT) scan of the head that was normal and was discharged with a diagnosis of "bronchitis". Three days later she was found confused, with memory impairment and combative. She was brought back to the hospital and a lumbar puncture was performed which revealed a cerebrospinal fluid (CSF) white blood count (WBC) of 310 cells/mL (94% lymphocytes), glucose 60 mg/dL, and protein 0.55 g/L. Acyclovir 10 mg/kg of body weight was started every 8 h for possible herpes simplex virus (HSV) encephalitis. A magnetic resonance imaging (MRI) of the brain showed cortical thickening with increased signal intensity in the mesial temporal lobes bilaterally, suggestive of herpes limbic encephalitis. Another lumbar puncture was done 48 h later and it showed an improvement in the CSF pleocytosis (64 cells/mL). The patient was placed on intravenous vancomycin and piperacillin/tazobactam due to a new right lower lobe consolidation requiring mechanical ventilation. While attempting to win her off sedation and intubation, she was noted to have generalized convulsions that were treated with intravenous lorazepam and phenytoin.

The patient was transferred to our hospital 13 days later for higher level of care. Upon arrival her temperature was 37.2 °C, other vital signs were normal, during examination she was found not to be following commands, was unresponsive to painful stimulus, and had myoclonic jerks and muscle rigidity. Routine blood analyses were normal. Intravenous acyclovir was continued and on day 3 of hospitalization intravenous steroids were started for suspected autoimmune encephalitis (see Fig. 1). She was started on intravenous immunoglobulin 0.4 g/kg body weight/day for 5 days when the diagnosis of autoimmune encephalitis was confirmed, (see Fig. 1) and she continued on antiepileptic treatment, with levetiracetam 1500 mg two time's daily, lacosamide 50 mg twice daily and phenytoin 100 mg three times daily, due to seizure activity. She continued on acyclovir for 7 days in our hospital. She was on acyclovir for 20 days total. The Herpes simplex virus 1 & 2, Enterovirus, and the Varicella zoster virus (VZV) PCR (done at ViroMed laboratories) in the CSF that were sent prior to admission to our hospital were negative. An extensive infectious diseases work up was initiated with a third CSF that was done 10 days after her initial lumbar puncture at the outside hospital. The CSF showed a WBC of 68

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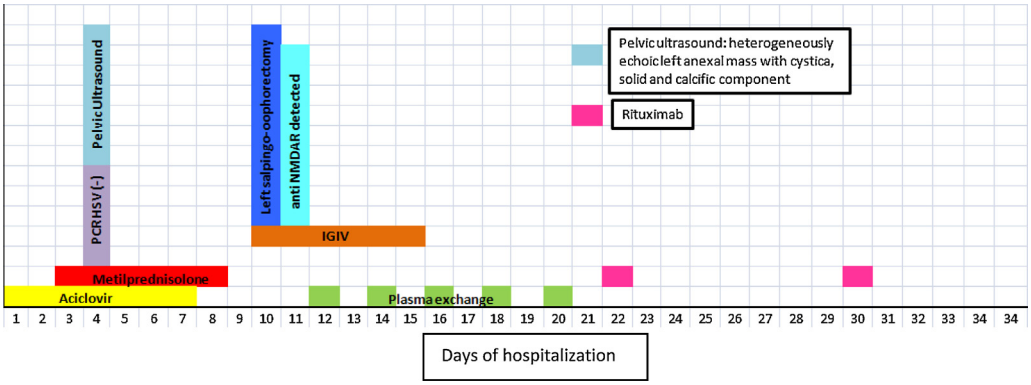

Fig. 1. Treatments and studies sent during hospitalization (antiviral and immunotherapy treatment).

with 95% lymphocytes, red blood cell (RBC) count of 22, protein 40 mg/dl, glucose of 51 mg/dl. This CSF also had the following negative tests: bacterial culture, *Herpes simplex virus* PCR, Epstein-Barr virus (EBV) PCR, VDRL, Enterovirus PCR, West Nile IgM, cryptococcal antigen, Arboviral panel, VZV PCR done at Focus diagnostics, and voltage-gated potassium channel antibodies. The CSF was positive for N-methyl-D-aspartate receptors antibodies. Besides the CSF studies mentioned above, an RPR, blood cultures, HIV (Human immunodeficiency virus) antibodies, HIV RNA PCR, arboviral panel (Western Equine Encephalitis, Eastern Equine Encephalitis, St Louis Encephalitis, California Encephalitis), a serum cryptococcal antigen test, *Histoplasma sp*. urine antigen, Influenza A y B nasal antigen, Lyme Western Blot, *Coccidioides sp* antibodies, and West Nile IgM were all negative.

Multiplanar multisequence magnetic resonance imaging (MRI) of the brain were obtained before and after the administration of 15 cc of Multihance. MRI showed no restricted diffusion, with a suggestion of a subtle increased T2 signal in the hippocampi, that was most prominently observed in the hippocampal tails. There was no abnormal parenchymnal of meningeal enhancement. Over the next days she started with dysautonomias and sympathetic storms, orofacial dyskinesia and hyperkinetic movements. She was placed on bromocriptine, lorazepam, clonidine and propanolol. The patient underwent tracheostomy and gastrostomy tube placement. An electroencephalogram showed poor reactivity to stimuli, lack of an anterior to posterior gradient, lack of a posterior dominant rhythm and excessive beta activity compatible with severe diffuse encephalopathy, without epileptiform activity. As she was clinically worsening and all her infectious diseases work up was negative, noninfectious etiologies were investigated. A pelvic ultrasound was done and was noted a 5 cm dermoid cyst on the left ovary that was confirmed with computerized tomography (CT) abdomen/pelvis. With these findings, N-methyl-D-aspartate receptors encephalitis was suspected. An order was placed to detect N-methyl-D-aspartate receptors antibodies, paraneoplastic and voltage-gated potassium channel antibodies in the left over CSF; in addition to that, a gynecologist evaluation was requested. The antibodies titers to N-methyl-D-aspartate receptors were identified as 1:1280 in the cerebrospinal fluid one week later. A diagnostic laparoscopy with left salpingoopherectomy was performed revealing a mature teratoma. Therapeutic plasma exchange was initiated (5 exchanges in 10 days). Rituximab was initiated, as there was no improvement noted and resulted in mild improvement on facial dyskinesia and hyperkinetic movements, two doses were given. Given the mild decrease in abnormal movements the patient was placed again on high doses of steroids for two weeks, then she was discharged and sent to neurology for follow up. The day of discharge, the patient didn't follow commands, had orodyskinesia and myoclonic jerks, and was not responding to painful stimuli. After discharge and as part of a clinical study, the third CSF saved during her hospitalization was sent to undergo testing with the Biofire® Film Array Meningitis Encephalitis panel that was positive for VZV in the CSF. The Biofire VZV PCR was confirmed with the quantitative PCR assay purchased from Genesig (Primerdesign, UK). Based on the qPCR results, 3.7×10^3 genome equivalents/uL of VZV were detected the sample. MRI and EEG two months after the first seizure were reported as normal.

2. Discussion

The patient had a classic presentation for anti-NMDA receptor encephalitis with headaches, changes in mood and behavior and seizures in a young female with an ovarian teratoma. Her MRI showed temporal lobe involvement prompting empirical therapy for *Herpes simplex virus* (HSV); however, bilateral temporal involvement is seen more frequently in autoimmune and other etiologies more than in HSV encephalitis [1]. Some etiologies that have been described to have a propensity for temporal lobes include paraneoplastic disorders, gliomatis cerebri, and infectious causes like tuberculosis, *Varicella zoster virus*, *Mycoplasma pneumoniae*, enterovirus and *Balamuthia mandrillaris* [1]. The most common inflammatory disease affecting the hippocampus is limbic encephalitis which occurs in three major forms: a paraneoplastic subtype which is related to onconeural antibodies in patients with malignant tumors, a non paraneoplastic subtype that is mainly caused by voltage gated potassium channel antibodies and an infectious subtype cause by herpes viruses [2].

Anti-NMDAR encephalitis was initially described as a paraneoplastic syndrome affecting young women with ovarian teratoma, but can also be associated with sex cord stromal tumors, small cell lung carcinoma and testicular teratomas [3]. NMDA receptors are found throughout the central nervous system, mediating synaptic transmission and plasticity. The main target epitopes are in the NR1/NR2 heteromers of the NMDAR [4]. The major antigen is NR1/NR2B, which is predominantly expressed in the hippocampus and forebrain. The NMDAR antibodies reacted with nervous tissue contained in the tumor [5]. In our case the patient had the NMDAR antibodies detected in the cerebrospinal fluid, but it can be detected also in serum, or only in CSF.

This disorder was reported more frequently in young women, but it also includes men. They often develop sudden behavioral and personalities changes [5], after a prodromal syndrome of mild hyperthermia, headaches, or a viral like process. We observed this in our patient who complained of a flu-like illness and headaches at the beginning of her illness. The clinical course is then followed by seizures, decreased level of consciousness, abnormal movements (orofacial and limb dyskinesia, dystonia and choreoathetosis), autonomic instability and sometimes hypoventilation [3]. The presence

of a tumor that expresses the NMDA receptor contributes to breaking immune tolerance. Given that most patients presented with prodromal symptoms, it is likely that BBB is transiently disrupted [6].

In about 40% of the cases, the MRI of the brain shows transient inflammatory changes in cerebral or cerebellar cortex, subcortical regions or hippocampus [3] as seen in our patient. A MRI was done two months after the first seizure and it was reported without abnormal changes.

NMDAR antibodies can be detected in patients with herpes simplex encephalitis. In a study by *Prüss* et al., 30% of the patients with herpes simplex encephalitis had NMDAR IgM, IgA or IgG antibodies detected in serum or CSF [6]. In our case the patient had the VZV detected with the CSF that was stored at −70C as part of a clinical study that evaluated the performance of the Biofire® Film Array Meningitis Encephalitis panel [7]. During the course of the illness, VZV was not detected by two PCRs, one done at ViroMed laboratories and one performed by Focus Diagnostics. The cause for this discordance is unknown but could be secondary to the Biofire® Film Array PCR being more sensitive or that this was a false positive result. As the Biofire VZV PCR was confirmed with the quantitative PCR assay purchased from Genesig, the former possibility is favored. There are studies that document a low sensitivity of a CSF VZV PCR [8]. In this study only 30% of patients had a + VZV PCR while intrathecal VZV IgG antibody production was documented in 93% of patients with VZV vasculopathy. Furthermore, a recent study evaluating the Biofire® Film Array Meningitis Encephalitis PCR demonstrated that the majority of discordant results seen are Film Array positive suggesting a higher sensitivity that with current assays [9].

To our knowledge, there is only case report that has linked varicella zoster infection with anti-NMDA receptor encephalitis [10]. These two cases suggests that other neurotrophic viruses such as VZV can also serve as triggers for anti-NMDA receptor encephalitis, most likely by causing inflammation and possibly exposing NMDAR epitopes [10]. Cell mediated immunity controls VZV, and it is thought that the CD4 response is responsible for the prevention of VZV reactivation [11]. It is also plausible that VZV reactivated due the severity of illness or due to the immunosuppressive therapies she received as it has been also been seen with other herpes viruses such as *Epstein Barr virus* and cytomegalovirus [12,13]. Our patient received steroids that can also affect the proliferation and differentiation of T cells, and plasma exchange that can be associated with a decrease in the CD4/CD8 ratio. This would be a less likely explanation for her reactivation as her immunophenotyping of peripheral blood by flow cytometry showed absent B cells but a normal T cell population.

VZV remains a rare cause of CNS infections but this is most likely the result of under diagnosis [14,15] or due to a low sensitivity of the current available CSF VZV PCR assays [8]. The role of VZV in patients with anti-NMDA receptor antibody encephalitis needs to be further evaluated.

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Conflicts of interest

R H is a consultant to Biomeriaux.

Competing interests

Rodrigo Hasbun is a consultant for Biomeriaux®.

Ethical approval

University of Texas Health Science Center Instituional Review Board and the Research Review Committee of the Memorial Hermann Health System.

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References

[1] F.C. Chow, C.A. Glaser, H. Sheriff, D. Xia, S. Messenger, et al., Use of clinical and neuroimaging characteristics to distinguish temporal Lobe Herpes simplex encephalitis from its mimics, Clin. Infect. Dis. 60 (2015) 1377–1383.
[2] A. Förster, M. Griebe, A. Gass, R. Kern, M.G. Hennerici, K. Szabo, Diffusion-weighted imaging for the differential diagnosis of disorders affecting the hippocampus, Cerebrovasc. Dis. 33 (2) (2012) 104–115.
[3] J. Dalmau, A.J. Gleichman, E.G. Hughes, J.E. Rossi, X. Peng, M. Lai, S.K. Dessain, M.R. Rosenfeld, R. Balice-Gordon, D.R. Lynch, Anti-NMDA receptor encephalitis: case series and analysis of the effect of antibodies, Lancet Neurol. 7 (2008) 1091–1098.
[4] M.F. Folstein, S.E. Folstein, P.R. McHugh, Mini-mental-state: a practical method for grading the cognitive state of patient for the clinician, J. Psychiatr. Res. 12 (1975) 189–198.
[5] J. Dalmau, E. Tüzün, H.Y. Wu, J. Masjuan, J.E. Rossi, A. Voloschin, J.M. Baehring, H. Shimazaki, R. Koide, D. King, W. Mason, L.H. Sansing, M.A. Dichter, M.R. Rosenfeld, D.R. Lynch, Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma, Ann. Neurol. 61 (1) (2007) 25–36.
[6] H. Prüss, C. Finke, M. Holtje, J. Hofman, C. Klingbeil, C. Probst, K. Borowski, G. Ahnert-Hilger, L. Harms, J.M. Schwab, C.J. Ploner, L. Komorowski, W. Stoecker, J. Dalmau, K.P. Wandinger, N-Methyl-D-Aspartate receptor antibodies in herpes simplex encephalitis, Ann. Neurol 72 (6) (2012) 902–911.
[7] S.H. Wootton, E. Aguilera, L. Salazar, A. Hemmert, R. Hasbun, Enhancing pathogen identification in patients with meningitis and a negative Gram stain using the BioFire FilmArray® Meningitis/Encephalitis panel, Ann. Clin. Microbiol. Antimicrob. 15 (2016) 26.
[8] M.A. Nagel, R.J. Cohrs, R. Mahalingam, M.C. Wellish, B. Forghani, et al., The varicella zoster vasculopathies:clinical, CSF, imaging and neurological features, Neurology 70 (11) (2008) 853–860.
[9] A. Leber, K. Everhart, J.M. Balada-Llasat, J. Cullison, J. Daly, S. Holt, et al., Multicenter evaluation of the Biofire Film Array Meningitis Encephalitis Panel for the detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens, J. Clin. Microbiol. (2016) (Posted online 22 June).
[10] W.R. Schabitz, A. Rogalewski, C. Hagemisteir, C.G. Bien, VZV brainstem encephalitis triggers NMDA receptor immunoreaction, Neurology 83 (2014) 2309–2311.
[11] C. Duncan, S. Hambleton, Varicella zoster virus immunity: a primer, J. Infect. 71 (Suppl 1) (2015) S47–53.
[12] M.J. Kelly, L.A. Benjamin, K. Cartwright, K.M.B. Ajdukiewicz, D.B. Cohen, M. Menyere, et al., Epstein-Barr coinfection in cerebrospinal fluid is associated with increased mortality in malawian adults with bacterial meningitis, J. Infect. Dis. 205 (2012) 106–110.
[13] F.G. Frantzeskaki, E.S. Karampi, C. Lottaridi, M. Alepaki, C. Routsi, M. Tzanela, et al., Cytomegalovirus reactivation in a general, nonimmunosuppressed intensive care unit population: incidence, risk factors, associations with organ dysfunction, and inflammatory biomarkers, J. Crit. Care 30 (2) (2015) 276–281.
[14] L. Nesher, C.M. Hadi, L. Salazar, S.H. Wootton, K.W. Garey, T. Lasco, A.M. Luce, R. Hasbun, Epidemiology of Meningitis with a Negative CSF Gram stain: under-utilization of available diagnostic tests, Epidemiol. Infect. 144 (1) (2016) 189–197.
[15] Q. Kaewpoowat, L. Salazar, E. Aguilera, S.H. Wootton, R. Hasbun, Herpes simplex and varicella zoster CNS infections: clinical presentations, treatments and outcomes, J. Infect. 44 (3) (2016) 337–345.