Clinical/Scientific Notes

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RESPONSE OF ANTI-NMDA RECEPTOR ENCEPHALITIS WITHOUT TUMOR TO IMMUNOTHERAPY INCLUDING RITUXIMAB

Paraneoplastic encephalitis with antibodies against NR1/NR2 heteromers of the NMDA receptor associates frequently with ovarian teratoma and has recently been established as a distinct clinical entity.[1] Most patients are young women who develop a syndrome with prodromal cold-like illness, intractable seizures, psychosis, dyskinesia, and hypoventilation.[1,2] However, about 40% of patients do not have a detectable tumor,[3] and the treatment of these patients remains unclear. We report a patient with anti-NR1/NR2 encephalitis without teratoma who showed a nearly complete recovery after intensive immunotherapy including rituximab.

Case report. A 42-year-old woman had cough and headache for 3 weeks. On the day before admission, she was found to be unresponsive for several minutes, and subsequently developed generalized seizures. On admission, her temperature was 38.2°C, and she had meningeal signs. CSF revealed mild pleocytosis (10/mm^3) and slightly elevated protein concentration (45 mg/dL) with normal glucose concentration and IgG index. MRI (figure, A) and EEG were unremarkable. After the seizures were controlled, minimal disorientation was observed. Acyclovir and ceftriaxone were started.

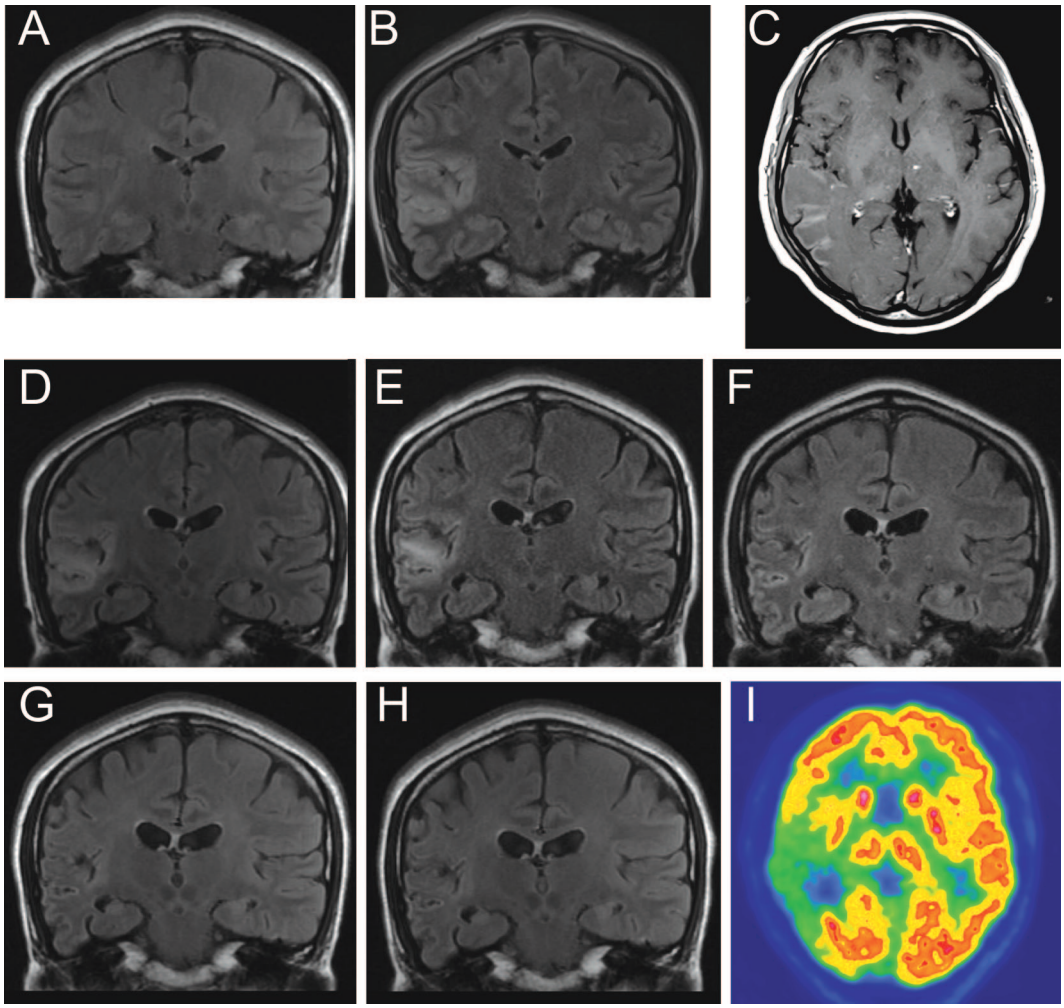
She developed pulmonary embolism on day 4. On day 9, partial motor seizures in the left side of the face and numbness in the left oral cavity were noted. On day 19, she developed personality changes with visual, auditory, and tactile hallucinations. MRI FLAIR revealed high-intensity areas (HIAs) mainly in the temporal cortex with meningeal enhancement (figure, B and C). EEG showed PLEDs-like waves with predominance in the right temporoparietal region. On day 21, the frequency of seizures increased; these included facial grimacing, spreading to changes in the respiratory pattern, resembling hiccup accompanied with apnea, followed by generalized tonic seizures. All these symptoms resolved after using midazolam. No mechanical ventilation was required, but the patient was almost unresponsive during this period.

CSF on day 24 revealed increased number of cells (30/mm^3), protein levels (78 mg/dL), and IgG index (1.0) (figure e-1 on the *Neurology*® Web site at www.neurology.org). After three courses of methylprednisolone (1 g/day, 3 days), she started to improve. The CSF findings became normal and HIAs on FLAIR were decreased (figure, D). Analyses for autoantibodies including Hu, amphiphysin, glutamate receptor (GluR)δ2,[4] and GluRε2 were all negative. Subsequently, antibodies to NR1/NR2 heteromers were identified in CSF (×320) and serum, using reported methods.[1] No teratoma was found despite comprehensive tumor screening. Given these results, we performed double-filtration plasmapheresis (DFPP). Seizures subsequently became controllable, allowing discontinuation of midazolam. Although the level of consciousness improved, she was found to have severe paranoia, and was extremely disoriented and uncommunicative. Because the CSF protein and IgG levels gradually increased again, with the CSF anti-NR1/NR2 antibodies remaining detectable (×10), and because her clinical and MRI improvement were limited (figure, E and F), we started treatment with weekly rituximab for six doses (375 mg/m^2 per week, following a protocol for malignant lymphoma) on day 93. After the first administration of rituximab, the proportion of CD20 positive B lymphocytes in the peripheral blood rapidly decreased from 8% to 0%. After the second administration, her psychiatric symptoms resolved and she became oriented and communicative. CSF findings improved and HIAs disappeared (figure, G and H), but FDG-PET revealed reduced metabolism in the right temporal region (figure, I). EEG showed symmetric alpha waves in the parieto-occipital regions with infrequent delta waves, and PLEDs-like waves were no longer observed. She recovered nearly fully and was discharged on day 160 (figure e-1).

Discussion. Although tumor removal has been shown to be effective for anti-NR1/NR2 encephalitis associated with teratomas,[1,5,6] the treatment strategy of patients without teratoma remains unclear. Our patient showed a dramatic clinical recovery as well as improvement of HIAs demonstrated by FLAIR MRI

Supplemental data at www.neurology.org

Figure MRI and FDG-PET studies of the brain



(A) On day 2, the FLAIR MRI was normal. (B) On day 18, the FLAIR image revealed new high-intensity areas in the right temporal cortex, insula, parts of the frontal, parietal, and occipital cortices, and hippocampus. These findings were accompanied by mild edema. High-intensity areas were also observed in the left inferior temporal cortex and hippocampus. (C) On day 18, the gadolinium-enhanced T1-weighted image showed meningeal enhancement. (D) On day 45, the FLAIR image obtained after methylprednisolone treatment showed partial improvement of the high-intensity areas. However, mild hippocampal atrophy was observed at the same time. (E) On day 61, the FLAIR image obtained after five treatments with DFPP was minimally changed compared with that of (D). (F) On day 86, the FLAIR image obtained before the beginning of rituximab therapy showed reduced high-intensity areas in the white matter; however, high-intensity areas in the cortex remained observed. (G) On day 123, the FLAIR image obtained after three times of rituximab administration revealed substantially diminishing high-intensity areas in the cortex. (H) On day 145, high-intensity areas in the FLAIR image as well as the cortical swelling had completely resolved after six treatment infusions of rituximab. The extent of hippocampal atrophy was almost the same as that of (D). (I) On day 145, a FDG-PET showed reduced glucose uptake in the right temporal cortex, as well as in the insula and frontoparietal cortices.

studies. These findings suggest that immunosuppressive therapy including IV corticosteroids, DFPP, and rituximab was effective. Given that multiple therapeutic treatments were given to the patient and that the symptoms had partially improved at the time of initiation of rituximab, it is difficult to evaluate the efficacy of rituximab. It should be noted, however, that after treatment with rituximab, the psychiatric symptoms showed a gradual but continuous improvement leading to virtually full recovery, and the CSF abnormalities also improved. These observations suggest that rituximab expedited recovery, although a spontaneous improvement cannot be completely ruled out. Analysis of anti-NR1/NR2 antibodies in patients with the indicated encephalitis (with or without teratoma) is important to demonstrate the autoimmune etiology and to promptly start immunotherapy to minimize the sequelae. Rituximab should be considered in patients without teratoma or those who do not improve with other immunosuppressive treatments.

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AUTISM SPECTRUM DISORDERS FOLLOWING IN UTERO EXPOSURE TO ANTIEPILEPTIC DRUGS

There is evidence that in utero exposure to teratogenic substances such as thalidomide and alcohol may increase the risk of developing autism spectrum disorder (ASD)[1] and that prenatal development may be a critical time. Animal model, case study, and retrospective reports have demonstrated that exposure to antiepileptic drugs (AEDs) in utero may also carry an increased risk for the development of ASD.[2-5]

Methods. The Liverpool and Manchester Neurodevelopment group is currently undertaking a prospective study to investigate the effects of exposure to AEDs in utero. Between 2000 and 2006, 620 women were recruited from antenatal clinics in both Liverpool and Manchester. Information has been collected on 632 live births; 296 births were to women with epilepsy (including 6 twin pairs), 249 of whom were exposed to AEDs at the beginning of gestation. Within the exposed group, 64 children were exposed to sodium valproate (VPA), 44 to lamotrigine (LTG), 76 to carbamazepine (CBZ), 14 to other monotherapy treatments, and 51 to polytherapy treatments. The remaining 47 births were to women with epilepsy who were not on medication. In addition, information has been collected on 336 live births (including two twin pairs) born to women without epilepsy who were not taking medication. Information was also collected during the pregnancy regarding the mother's epilepsy, medical history, lifestyle, education, and occupational details. Maternal epilepsy information and pregnancy and birth details were verified using medical case notes. Information was collected in respect to the father's age, medical history, education, and occupational details.

This prospective study is ongoing with the children undergoing assessment both medically and with a battery of neuropsychological tests at age 1, 3, and 6 years. Preliminary findings from this prospective cohort into the incidence of ASD following exposure to AEDs in utero are presented here.

Results. Out of the cohort of 632 children, 9 have been diagnosed with ASD. The diagnosis was made as part of a routine clinical referral independent of the study. All nine children were reported as meeting *DSM-IV* criteria for ASD. A further child has features of ASD including language impairment, a lack of attention, social difficulties, and restricted interests, and therefore is included in this article. The incidence of ASD is 1.6% of the total cohort.

Seven of the 10 children with ASD were exposed to AEDs in utero (2.8% of the exposed group). Of those seven children, four were exposed to VPA (4/64, 6.3%). Of the remaining three children, one child was exposed to VPA in combination with LTG (1/51; 2%), one child to phenytoin (PHT) (1/9:11%), and one child to LTG (1/44: 2%). Three control children (3/336: 0.9%) have also been diagnosed with ASD, one with autism and the other two with Asperger syndrome (table). According to interviews with parents, none of the children identified had a family history of autism or other pervasive developmental disorder.

Discussion. The finding that 6.3% of the children exposed to monotherapy VPA in utero have ASD or features of this disorder is seven times higher than the control group (0.9%) and higher than the reported incidence of 6 per 1,000 children in the general population.[6] Conclusions regarding the groups of children exposed to LTG or PHT cannot be made based upon a single case. No children exposed to CBZ, other monotherapy drugs, or children born to women with epilepsy who were not medicated during the time of the preg-