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Case Reports

Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis Presenting With Features of Kleine-Levin Syndrome and Demyelination

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Introduction

Anti–*N*-methyl-D-aspartate (NMDA) receptor (NMDAR) encephalitis is an autoimmune disorder leading to severe neurologic and psychiatric symptoms. NMDARs are ligand-gated channels with the NR1 subunit binding to glycine and NR2 binding to glutamate.[1] In anti-NMDAR encephalitis the patient forms antibodies to the GluN1 subunit of the receptor[2] in either an autoimmune or paraneoplastic disease state. A current review indicates that more than one-third of NMDAR encephalitis cases are attributable to a paraneoplastic process with an identifiable tumor.[3] The antibodies cause a decrement and eventually a depletion of these receptors, which is thought to be the reason for the multistage symptomology of this disease.[4] Immune-modulating treatment has been shown to be successful in cases without tumor, with only 12–20% relapse following first-line therapy and further reductions in relapse with second-line therapies.[3]

The most prominent features of the disease include acute psychiatric illness, autonomic instability, memory deficit, dyskinesias, and speech problems.[3] The psychiatric presentation classically includes psychosis, anxiety, agitation, mania, sexual disinhibition, or catatonia.[2] The presenting neurologic symptoms are usually limited to dyskinesias and speech difficulties, with rare cases involving focal neurologic deficits.[3] Only 35% of anti-NMDAR cases reveal magnetic resonance imaging (MRI) findings at initial presentation and approximately 50% over the entire course of disease.[3] When present, the typical patterns for NMDAR encephalitis demonstrate transient T2, FLAIR, or contrast-enhancing abnormalities.[4] These abnormalities are most commonly located in the hippocampi, cortices, and basal ganglia, and, infrequently in the brainstem and spinal cord.[5] Most imaging findings have been reported as mild or transient and follow-up MRIs either remain normal or show minimal change despite the severity and duration of symptoms.[4]

Case Presentation

Ms. A, a 23-year-old woman with borderline intellectual function (reported IQ in high school of 70), childhood sexual trauma, and borderline personality disorder, bulimia nervosa in remission, extensive substance use (cocaine, ecstasy, methamphetamine, marijuana, and remote intravenous heroin), and a family history of bipolar disorder type 1, presented to the emergency department for evaluation of behavior changes, falls, and episodes of unresponsiveness.

The timing of symptom onset was unclear. Although her family reported severe impulse control problems for the preceding 3 months, she always had

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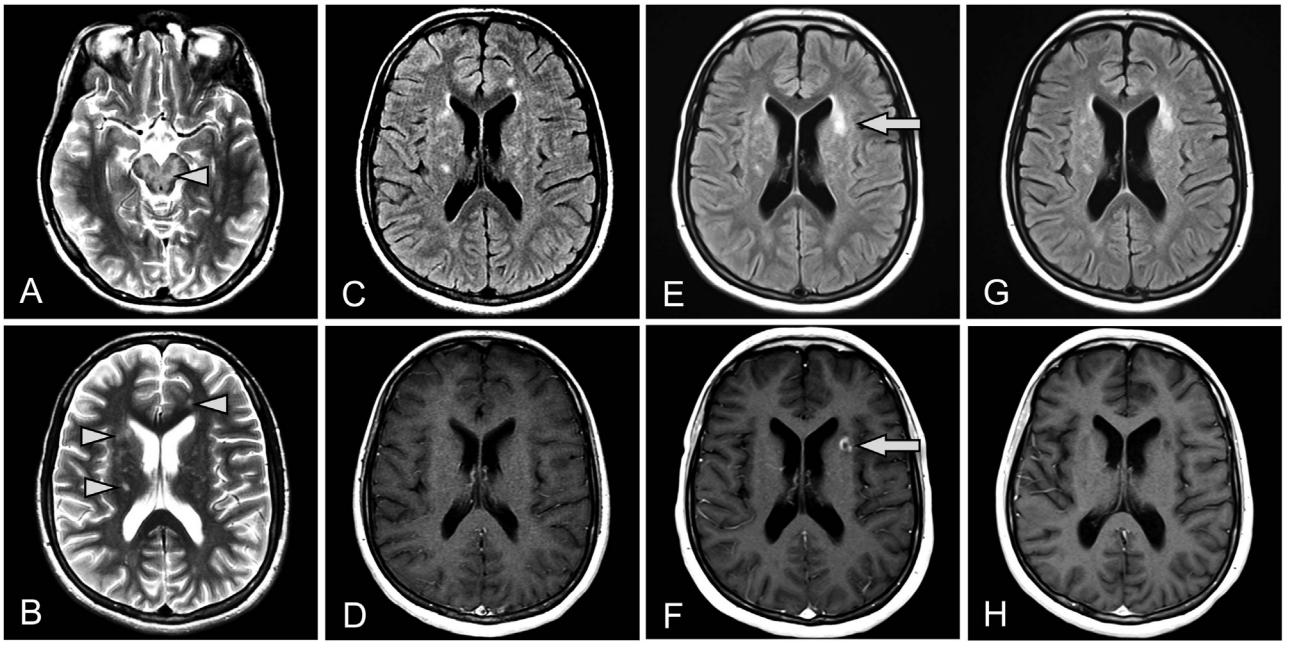
behavioral difficulty in school and had started using substances years before. She had experienced worsened enuresis in the last 3 months, yet her mother reported a history of the same dating to age 17 years.

Further confounding the identification of symptom onset, a diagnosis of narcolepsy had been considered before hospitalization. She had complained to her primary provider of worsening abrupt somnolence following the birth of her child 16 months earlier. A sleep study revealed minimal obstructive sleep apnea and short rapid eye movement onset latency. Owing to abnormal and impulsive behavior during the study, she did not complete the multiple sleep latency test; thus a diagnosis of narcolepsy could not be determined. Her sleep symptoms had worsened since that time to the point of loss of consciousness from a standing position, resulting in injury.

In the 3 months before presentation she was psychiatrically hospitalized 3 times for abnormal behavior and impulsive acts, such as running into the highway. Her symptoms prompted 2 MRI studies of the brain that showed midbrain T2 hyperintensity (Figure) but this finding was felt to be nonspecific. On each occasion her neurologic examination had only minor findings, such as a left positive Babinski.

Owing to impulsivity Ms. A was admitted to our combined internal medicine and psychiatry service to simultaneously address behavioral control and workup, for which neurologic consultation was requested. On examination she was unarousable from sleep despite sternal rub and intermittent apnea. When awake, her neurologic findings included left exotropia, partial intranuclear ophthalmoplegia bilaterally, limited eye abduction bilaterally, and poor ocular smooth pursuits. Psychiatrically, the primary presenting symptoms were periods of alternating somnolence and impulsivity, accompanied by hyperphagia. Initial laboratory study results were unremarkable, including a negative serum NMDAR antibody (Athena Diagnostics). A lumbar puncture was performed with an

FIGURE. Imaging Findings on Initial Presentation (A and B) and Evolution. (A) Axial T2-Weighted MRI Shows Diffuse Abnormal Signal Involving the Midbrain (Arrowhead), a Finding That Persisted on All Follow-Up Studies. (B) Axial T2-Weighted Image Through the Level of the Ventricles Shows Multiple Foci of Hyperintensity in the Deep and Periventricular White Matter (Arrowheads). (C and D) Axial FLAIR and T1 Postcontrast Images Obtained 3 Months After Initial Presentation Show Multifocal White Matter Lesions That Have Persisted From the Initial Scan. (E and F) Axial FLAIR and T1 Postcontrast Images Obtained 12 Months After Initial Presentation Show the Development of a New Ring-Enhancing Lesion in the Left Corona Radiata (Arrows). (G and H) Axial FLAIR and T1 Postcontrast Images, Obtained 6 Days After the Scan Shown in (E and F), show Resolution of the Enhancement, But Persistence of Abnormal T2 Hyperintensity at the Site of the Prior Lesion. The Patient Underwent Plasmapheresis During the Interval Between the 2 Scans.



opening pressure of 16-cm H_2O, and normal cell counts and glucose and protein levels. Oligoclonal bands were present in the cerebrospinal fluid, and a Mayo paraneoplastic panel result was negative, which at that time did not include testing for an NMDA antibody.

Many differential diagnoses were considered in this case. Based on the history alone the diagnosis of Kleine-Levin Syndrome (KLS) was considered given the reports of hyperphagia, hypersomnolence, and impulsivity. The details of KLS and the parallels to this case are discussed later. Additionally, we considered drug-induced behavioral change, drug-induced vasculitis, nutritional deficiency, metabolic encephalopathy, and demyelinating diseases, such as multiple sclerosis or neuromyelitis optica. Despite this broad differential, the MRI and examination findings prompted the multidisciplinary team to proceed with empiric treatment of autoimmune encephalitis using intravenous steroids followed by 5 sessions of plasmapharesis. This resulted in significant improvement in her cranial nerve deficits, ataxia, hypersomnia, and hyperphagia. Prominent impulsivity was observed during treatment, requiring pharmacologic intervention including trials of valproic acid, benzodiazepines, low potency neuroleptics, and alpha$_{2A}$ agonists (e.g., guanfacine). She was discharged and then readmitted twice in the next year for recurrence of hypersomnolence, dysmetria, and dysphagia.

The patient's third admission was complicated by apneic episodes that became progressively more severe, resulting in a period of endotracheal intubation. Given this severity, repeat testing was undertaken and NMDAR autoantibodies were positive in the cerebrospinal fluid (Mayo laboratories). A battery of imaging studies showed no evidence of ovarian teratoma or other malignancy. Another 5 rounds of plasmapheresis were administered, followed by a course of Rituximab, resulting in decreased somnolence, resolution of apnea, and improved speech and movements. However, she continued to exhibit significant impulsivity that was unresponsive to multiple medication trials. Owing to concerns about her ability to be safe in the community, guardianship proceedings were initiated and she was transferred to an inpatient psychiatric hospital with a medical-psychiatric ward to facilitate monitoring for recurrence of encephalitis symptoms.

MR images from the outside hospital early in her course showed midbrain T2 hyperintensity (Figure). The initial MRI brain scan 3 months later revealed punctate and confluent areas of abnormal T2 signal centered primarily in the posterior limbs of the internal capsules, midbrain, and around the cerebral aqueduct, but also involving the basal ganglia and subcortical and periventricular white matter. There was no diffusion restriction or enhancement. At 3 and 5 months, follow-up MRIs showed stable T2 lesions. On her third admission, about 1 year after getting the initial images, her MRI showed interval decrease in the described T2 abnormalities but 2 new areas of enhancement. The first was in the left corona radiata, with an incomplete ring of enhancement, and the second was in the left parietal deep white matter. After 5 days, and after initiation of plasmapheresis, an MRI showed resolution of the areas of abnormal enhancement.

Discussion

Our patient had markedly atypical symptoms, examination results, and imaging findings for anti-NMDAR encephalitis, on the background of a complex history.

As mentioned earlier, the treating psychiatric team identified parallels between the patient's behaviors and those described in KLS, a distinct neuropsychiatric illness. KLS is a rare disease usually affecting teenagers and young adults, characterized by hypersomnia, confusion, derealization, apathy, altered mood, hallucinations, and disinhibited behavior, usually in the form of hypersexuality and hyperphagia. Authors posit an autoimmune etiology for KLS given the recurrent nature of episodes and histopathologic evidence of focal inflammation,[6] and roughly 10% of cases are secondary to various genetic, inflammatory, vascular, or paraneoplasic conditions.[7] Meanwhile, hyperphagia[8] and sleep disorders[9] have been described in anti-NMDAR encephalitis. The apnea exhibited by our patient is reflective of central hypoventilation, which is a well-known feature of anti-NMDAR encephalitis.[3] However, our search reveals that this is the first patient with anti-NMDAR encephalitis described with both hyperphagia and hypersomnia. Although parallels exist between the sequelae of anti-NMDAR encephalitis and KLS, as well Kluver-Bucy Syndrome,[4] in this case

the hypersomnia and hyperphagia were clearly part of the active phase of disease and responded to treatment.

In addition to the overlap with KLS, there are other neuropsychiatric conditions that anti-NMDAR encephalitis can mimic, including mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome,[10] HaNDL syndrome,[11] Rasumussen syndrome,[12] and psychogenic nonepileptiform spells.[13] These similarities indicate that NMDA antibody testing may be prudent even when the presentation appears consistent with another known neurologic or neuropsychiatric entity.

The lack of psychosis or catatonia is atypical in adults with anti-NMDAR encephalitis, but not children, who may present with more subtle behavioral changes.[14] Symptom categories described in a large review fit this case, including speech disorder, movement disorder, loss of consciousness, and central hypoventilation.[3] However these authors identified behavioral symptoms in more than 95% of patients, defined as delusions, psychosis, and catatonia.[3] None of these features were observed in this case despite close monitoring by experienced clinicians. Noting the correlation that this intellectually disabled patient presented with symptoms more typical of pediatric cases of anti-NMDAR encephalitis,[14] we hypothesize that this may represent a pattern. We encourage the consideration of autoimmune encephalitis early when patients with cognitive impairment present with behavior change.

The focal neurologic deficits and neuroimaging findings were present for this patient for months, and may have led to an earlier diagnosis if suspicion had been higher for an autoimmune disorder. At the time of her presentation in 2013, the overlap between anti-NMDAR encephalitis and demyelinating syndromes had not been widely described. Though her initial MRI images did include T2 signal abnormality, the distribution was not typical for demyelinating disorders. She then developed abnormal contrast enhancement a year after symptom onset despite similar symptoms months earlier, which may have indicated demyelination. The images also did not fit well with prior descriptions of anti-NMDAR disease, as the lesions were neither mild nor transient. In hindsight, this patient may fit the newly described overlap category between anti-NMDAR encephalitis and a demyelinating syndrome,[15] given that she presented with focal cranial nerve deficits and MRI findings concerning for demyelination. Test result for aquaporin-4 antibodies was negative, but anti-myelin oligodendrocyte glycoprotein antibodies were not tested. In future cases, subtle examination and imaging findings may prompt earlier testing and diagnosis of antibody mediated conditions.

The decision to treat was ultimately not controversial among the providers in this case by the time her symptoms included focal neurologic deficits and dramatic MRI findings. However, a strong multidisciplinary team was required for recognition of the behavioral and neurologic syndrome to pursue the proper workup, to monitor for treatment response, and then to monitor for recurrence and treat relapse early. The involvement of psychiatric expertise was critical to differentiate new symptoms from her baseline, to identify and describe her symptoms, to monitor for improvement, and to manage impulsivity to facilitate care. Given the uncertainty of her examination result and imaging findings, and the overlap of her presentation with other known neurologic diseases, neurologic expertise was essential for diagnosis and treatment as well.

Conclusions

We hypothesize that Ms. A's cognitive impairment and complex psychological history contributed to an atypical presentation of anti-NMDAR encephalitis, and delayed the recognition of her symptoms, diagnosis, and treatment. Patients with cognitive deficits may present with atypical symptoms of autoimmune encephalitis for adults, and providers should be aware that more subtle behavioral changes could represent a new disease process. We highlight hypersomnia and hyperphagia as behavioral symptoms that should trigger consideration of this diagnosis, and additionally emphasize the consideration of autoimmunity when encountering other neuropsychiatric syndromes previously thought to be idiopathic, such as KLS. This case also contributes to the growing evidence for an overlap between anti-NMDAR encephalitis and demyelinating disorders, and so close monitoring for focal neurologic findings could contribute to earlier diagnosis in similar cases. As prompt treatment may lead to improved cognitive outcomes,[16] early diagnosis and treatment should be our goal. Finally, diagnosis and management of the complex

constellation of symptoms and findings in this case would not be possible without superb collaboration across medical specialties.

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