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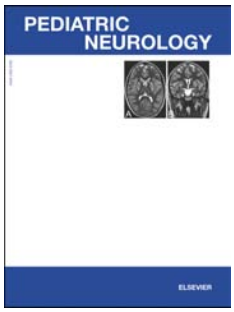

"Light switch" mental status changes and irritable insomnia are two particularly salient features of NMDA receptor antibody encephalitis

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Title: “Light switch” mental status changes and irritable insomnia are two particularly salient features of NMDA receptor antibody encephalitis

Short title: Distinct features of NMDA encephalitis

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ABSTRACT

BACKGROUND: N-methyl-D-aspartate (NMDA) antibody encephalitis is becoming increasingly recognized as a cause of acute and subacute encephalopathy in both adults and children. The typical features of this disorder include some degree of encephalopathy, seizures, and often a movement disorder component. However, there is wide variability in its presentation, and diagnosis based on clinical features alone is often delayed.

PATIENTS: We report a case series of 4 out of a total of 12 patients observed at our children's hospital from 2011 through 2013 that we chose as particularly representative examples of two distinct clinical features.

RESULTS: In this case series of NMDA receptor antibody encephalitis, we note a very rapid on-off state between responsiveness and nonresponsiveness and/or insomnia accompanied by extreme irritability. We describe the abrupt mental status shift as "light switch," as the patients can awake in seconds from a complete nonresponsive state. The insomnia noted in our patients was also impressive and often present early in the patients' courses.

CONCLUSIONS: "Light switch" mental status changes and irritable insomnia are important early features of NMDA receptor antibody encephalitis that can signal the presence of this disorder. The exact pathophysiology of these two symptoms has not been fully elucidated, and we feel that presence of one or both of these symptoms early in the disease course should prompt immediate concern for this disorder.

INTRODUCTION

Since its description in 2007, there have been several articles detailing the heterogeneity of presentations of N-methyl-D-aspartate (NMDA) receptor antibody encephalitis. The "classic" presentation consists of a subacutely progressive disturbance in behavior and/or mental status, seizures, and a movement disorder component. In addition, various psychiatric manifestations have been reported: hallucinations, delusions, socially inappropriate behaviors, agitation, depression and other mood shifts/changes, and amnesia.[1-5] Both progressive mental status changes and insomnia have been described, but we have noted distinct presentations of these two symptoms in children with this autoimmune disorder that we have followed. The first, we describe as "light switch"

mental status changes, are consistently described by parents and observed by our group clinically. The second feature, what we describe as irritable insomnia, is another generally early feature of the disease. We describe several cases below of confirmed NMDA receptor antibody encephalitis that illustrate our observations.

Case 1: The patient was a 4 year-old female who was previously healthy and neurodevelopmentally normal who was admitted following several seizures approximately 10 days following an upper respiratory infection. Following her admission, she was noted to have extreme agitation with crying and screaming but then she would "abruptly shift" to a calm demeanor with normal mental status. It was noted at times that she was completely unresponsive, although appearing awake, when consultants would enter the room, and, minutes later, another physician would find she was able to follow commands well. About 10 days after admission, she started to have persistent insomnia for several nights at a time, sleeping as little as 1-2 hours per 24 hour periods. While appearing awake, the patient was extremely agitated, often screaming and crying, and sometimes complaining of muscle pain or discomfort. The patient's initial laboratory investigations revealed 12 white blood cells/mm3 with a normal glucose and protein and negative CSF cultures, negative herpes simplex virus (HSV) DNA by polymerase chain reaction (PCR), negative enterovirus DNA by PCR, and a negative arbovirus serology panel. In addition, her MRI of her brain, a computed tomography (CT) scan of her chest, abdomen and pelvis, and a positron emission tomography (PET) scan of her body were normal. An initial routine one-hour electroencephalogram (EEG) had rare interictal spikes without evidence of status epilepticus and no electrographic seizures, although two

follow-up prolonged video EEGs had polymorphic delta slowing only without any epileptiform abnormalities. Her more prolonged EEGs were obtained later in her course when her rapid mental status changes were not prominent. Because there was a concern about an autoimmune encephalitis from her initial presentation, an NMDA receptor antibody test was sent from her serum, which came back positive. Initial treatments with intravenous immunoglobulin and steroids had no appreciable effect. She then underwent plasma exchange for a total of 5 exchanges and was given a dose of cyclophosphamide. Following this combination, she started to gradually recover and had made significant progress at an outpatient follow-up visit 4 months following the onset, although she still had difficulty following commands consistently, she was awake and alert. At her follow-up visit 7 months after her initial presentation, she was almost completely normal with only some mild intermittent behavior problems.

Case 2: The patient was a 4 year-old neurodevelopmentally normal male who had persistent intermittent fevers for a month followed by several seizure-like episodes and progressive mental status decline. His parents felt he was initially declining following the seizures, although he started to have clear speech regression, and he started to exhibit aggressive behavior – such as kicking and biting when corrected. His cerebrospinal fluid examination showed 16 white blood cells/mm3 and a protein of 632 mg/dL. Testing in either the CSF or serum for Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus-6 (HHV-6), varicella-zoster virus (VZV), HSV, Mycoplasma pneumoniae, and Lyme disease was negative. An MRI of his brain showed subtle increased T2 signal in his left hippocampus. A CT scan of the chest, abdomen, and pelvis and an ultrasound

of the testes were normal. Because of concern about an autoimmune encephalitis, he was started empirically on high-dose steroids, to which he had no response. Following the steroids, testing in his serum came back with an elevated titer to NMDA receptor antibodies – 1:160. He was started on plasma exchange and received a total of 7 exchanges. When we examined him prior to the onset of plasma exchange, he was noted to have abrupt changes in his mental status multiple times during even brief examinations. The patient would be staring, nonresponsive with diffuse choreiform movements and occasionally would be drooling for several minutes at a time, and, as if we "flipped a light switch" he would be completely communicative, answering simple questions with ease and would follow simple commands only to be followed again by a sudden lapse into an unresponsive state. This was noted to occur several times throughout the early course of his treatment and these findings were found to have no clear EEG correlate consistent with seizures, although his staring spells had started to wane when a video EEG was obtained, which showed only a mixture of polymorphic delta and theta slowing without epileptiform abnormalities and findings on video capturing examples mostly of his movement disorder. He started to improve markedly following his 5^{th} and 6^{th} exchanges, and by a 5 month follow-up assessment, he had returned to his normal state, recovered all of his speech, and was continuing to develop normally.

Case 3: The patient was a 17 year-old previously healthy male who presented with a subacutely progressive disorder comprised predominantly of disturbances in his behavior. Following a gastrointestinal illness with vomiting and diarrhea, he began to drag his leg over a week and then had two generalized tonic-clonic seizures that brought him to the

emergency department. He was started empirically on valproic acid, but he started to develop marked behavior disturbances such as excessive cursing, socially inappropriate behaviors such as urinating or masturbation in public, and he was progressively irritable. At about this time, his mother noted that he had very little sleep for several weeks, despite seeming fatigued and agitated. She told us he would be "fine one minute and then not answer questions the next." Prior to his admission to our service, he had 4 lumbar punctures, none of which showed an elevation in the cerebrospinal fluid white blood counts or protein. Laboratory testing in the CSF and serum for EBV, HHV-6, and HSV was negative. His MRI of his brain was normal. The patient had multiple EEGs during his early course, the first was a video EEG that was normal, although had no captured events. A follow-up routine EEG had bifrontal infrequent spike and slow wave discharges and one episode of sharply contoured alpha activity associated with an arousal, although no video correlate was present. Two other routine one-hour EEGs obtained later in his course after treatment was initiated were normal and the captured behaviors were nonepileptic. Serum testing, performed twice, for NMDA receptor antibodies was negative, but CSF testing for NDMA receptor antibodies was positive at a titer of 1:1 – this was repeated and again noted to be positive at 1:1. The patient had no response to intravenous high-dose steroids, but he was started on plasma exchange, and he had an excellent clinical response while still in the hospital. After he received a total of 5 exchanges, he was discharged home. By his follow-up assessment in 3 months, he had returned to school, resumed all his classes, and his family felt he was back to his baseline.

Case 4; The patient was a 2 year-old neurodevelopmentally normal female who presented after a precipitous behavioral decline over two weeks. Her mother first noted she was sitting up in bed at night talking to herself and not going to sleep. She would do this more and more at night, while getting progressively more agitated. She started to pace around the room during the day and night, muttering to herself. In addition, she would have episodes of becoming extremely violent, and she would bite her mother and other people, throw things, or scream incessantly. We observed her transitioning from a state of playing with her mother to one of extreme agitation and lack of responsiveness with screaming and biting in a matter of seconds. She was started empirically on high-dose steroids because of the concern about an autoimmune encephalitis. She had no elevation in her CSF white blood cells and her CSF protein was normal. An MRI of her brain and a CT scan of the chest, abdomen, and pelvis were normal. Testing for HSV and EBV was negative. A routine EEG did not show any epileptiform abnormalities, although none of her abrupt behavioral transitions were captured. Her NMDA receptor antibody titer in her CSF was elevated to 1:40 and her serum titer was elevated to 1:1280. Because of a poor response to steroids, she was started on plasma exchange, and, after 7 exchanges, she had a marked improvement. We are currently still following her progress.

DISCUSSION

NMDA receptor antibody encephalitis has a variety of symptomatic presentations that have been noted by several authors.[1-5]However, the propensity for several of these patients to rapidly alternate between normal and altered mental status states has been a

particularly profound feature in our experience. Our retrospective review of EEG data has not clearly elucidated any specific EEG findings with these episodes, and we are planning to prospectively analyze this further. One paper notes that the particular altered mental state may be due to status dissociatus, which the authors postulate is a complete breakdown of brain electrical state variation with regards to wakefulness and sleep states.[6] We feel that more rigorous video EEG monitoring with particular focus on these episodes, accompanied with mental status clinical assessment with observed "light-switch" mental status changes should be a target for future studies. Furthermore, the insomnia in children often accompanies extreme irritability and agitation and can be refractory to several treatment modalities. Certainly, sleep disturbances are not specific only to this disorder, as they can be noted in other neuroimmunologic disorders, such as opsoclonus-myoclonus syndrome, but the early timing of the insomnia and irritability and their refractory nature to treatment are impressive in our experience.[7] Although seizures, movement disorders, and encephalopathy are the "classic" features of this disease, the cases presented here suggest a "light switch" mental status change not associated with seizure activity. Furthermore, this rapid change in mental status and the irritable insomnia as noted above should prompt immediate concern for NMDA receptor antibody encephalitis until proven otherwise.

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