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Anti-*N*-Methyl-D-Aspartate (NMDA) Receptor Encephalitis Mimicking a Primary Psychiatric Disorder in an Adolescent

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Abstract

Anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis likely has a wider clinical spectrum than previously recognized. This article reports a previously healthy 16-year-old girl who was diagnosed with anti-NMDA receptor encephalitis 3 months after onset of severe depression with psychotic features. She had no neurological manifestations, and cerebral magnetic resonance imaging (MRI) was normal. Slow background on electroencephalogram and an oligoclonal band in the cerebrospinal fluid prompted the search for anti-NMDA receptor antibodies. She markedly improved over time but remained with mild neuropsychological sequelae after a trial of late immunotherapy. Only a high index of suspicion enables recognition of the milder forms of the disease masquerading as primary psychiatric disorders.

Keywords

N-methyl-D-aspartate receptor encephalitis, depression, psychosis

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Anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis is a neuropsychiatric disorder that was originally associated with ovarian teratomas.[1] Cases occurring in men and children without any tumors have been recently identified.[2] Following nonspecific prodromes, sudden cognitive and behavioral changes appear coupled with anxiety, confusion, and hallucinations sharing common features with acute primary psychosis-like schizophrenia.[3] The condition rapidly worsens, with the onset of epileptic seizures, speech and movement disorders, impairment of consciousness, and occasional disturbances of autonomic functions leading to neurological investigations and search for NMDA receptor antibodies in serum and cerebrospinal fluid. Patients benefit from combined immunotherapy and early tumor resection in paraneoplastic form.[4] The outcome is usually favorable, but neuropsychological sequelae and relapses have been reported.[2] The clinical course is quite similar in adolescents, whereas psychiatric symptoms are more difficult to recognize in younger children, who can present with sudden behavioral changes or neurological manifestations only.[5] We report a case of a 16-year-old girl with anti-NMDA receptor encephalitis who presented with severe and prolonged behavioral changes but without other neurological manifestations and signs, mimicking a primary psychiatric disorder.

Case Report

In December 2009, a previously healthy 16-year-old girl of Vietnamese background, born in Switzerland, presented with sudden onset of extreme fatigue, behavior changes with excessive sadness, and hypersomnia of more than 24 hours per day after a birthday party. Sleep was restless, with shouting, crying, cursing, and incoherent speech. During wakefulness the young girl was most often prostrated, mute, and anorexic with periods of infantile or inappropriate behavior (running all over the place with her 5-year-old cousins). The girl was admitted to a pediatric emergency room 9 days after symptom onset. No toxic ingestion or traumatic events were reported. She had no personal medical history and functioned well socially despite

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some shyness. An uncle had a nonspecified psychiatric disorder. She was conscious and oriented. Neurological examination was normal, so she was sent home with a psychiatric appointment.

The consultant psychiatrist described a sad adolescent with a low voice and an inexpressive face. She was slow in her movements and ideation but able to answer questions in short coherent sentences and to express her anxieties about school. She had no suicidal thoughts. Neurological examination was again normal. The subsequent evolution was fluctuating, with periods when the girl could express her sadness and think rationally and periods of mutism and lack of initiative during a same day. During one psychiatric appointment, she suddenly became very angry and frustrated and adopted a catatonic fetal position for 2 hours, which resolved spontaneously. One month after disease onset, a return to school failed because of memory impairment and attention deficit. Thought disorders and auditory hallucinations (hearing a crowd or a dialogue) appeared 2 months after disease onset. Risperidone (0.75 mg/d) was administered without any improvement. At this time, the differential diagnoses included a psychotic disorder or a major depressive disorder with psychotic features, and a neuropediatric assessment was requested because of the sudden onset and fluctuating course. Two months after disease onset, the girl was still bradypsychic and sad with reduced speech and complete lack of initiative. Abnormal movements or other paroxystic events were never reported. Her neurological examination remained normal. A screening for neurological diseases with psychiatric features showed the following results: antinuclear antibodies slightly positive 1/80 but negative anti–extractable nuclear antigen antibodies (enzyme-linked immunosorbent assay), anti-DNA native, and anti-neutrophil cytoplasmic antibodies negative: C4 normal. Copper (blood and urine) and ceruloplasmin were normal; antithyroperoxidase and antithyroglobulin antibodies were negative; triiodothyronine, thyroxin and thyrotropin were normal. Serological tests for *Borrelia burgdorferi* and *Treponema pallidum* were negative. Brain magnetic resonance imaging (MRI) was normal, and cerebrospinal fluid analysis revealed 1 oligoclonal band but a normal cell count and normal glucose and protein levels. An electroencephalogram (EEG) performed 3 weeks after risperidone withdrawal showed a diffuse slow background rhythm and the absence of a physiological sleep pattern. NMDA receptor antibodies titers were strongly positive in serum (score 4, range 0-4, normal 0-0.5; semiquantitative assay, antibodies anti-NR1/NR2b performed by Professor A. Vincent, University of Oxford) but were not performed in cerebrospinal fluid (assay not routinely available at this time). An ovarian teratoma was ruled out.

A marked spontaneous improvement in mood and behavior was observed 4 months after neuropediatric assessment, so no treatment was initiated. However, a first neuropsychological evaluation 9 months after disease onset showed persistent memory and executive disorders. The EEG remained slow and a second brain MRI was normal. Combined immunotherapy (methylprednisolone and intravenous immunoglobulins) was administered. One month later, serum NMDA receptor antibodies titers decreased (score 2). An EEG, 2 months after treatment, showed reappearance of an alpha background rhythm. A repeat neuropsychological assessment 18 months after disease onset showed significant improvement (Figure 1). Twenty-two months after disease onset, the patient has returned to high school, is socially well integrated, and is considered healthy by her family.

Discussion

This case study is the first to document that proven anti-NMDA receptor encephalitis can present and evolve with psychiatric manifestations alone and can, therefore, be mistaken for a primary psychiatric disorder not only initially but during a prolonged time course.

It is well recognized that anti-NMDA receptor encephalitis can start with acute and severe psychiatric disturbances in adults and adolescents,[6] including anxiety and psychotic features like agitation, paranoia, and auditory and visual hallucinations that often require admission to psychiatric wards. However, clinical evolution with onset of abnormal movements, seizures, impairment of consciousness, or all of these together, soon suggests an underlying neurological disease that prompts further investigation.[6–8] Mild or incomplete forms with apparently isolated psychiatric symptoms were mentioned in a recent review by Dalmau et al.[9] The authors also underlined that subtle neurological manifestations, like facial dyskinesias, may be missed.[9] This could have been the case in our patient, even if the video review was not suggestive.

Our patient's initial symptoms met all the diagnostic criteria for severe depression following the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).[10] Psychotic manifestations started later, but no other neurological symptoms usually reported in anti-NMDA receptor encephalitis were observed. However, although initially diagnosed as a primary psychiatric disorder, the abrupt and severe onset as well as the sharp fluctuations of mood were considered unusual and led to a neurological consultation after 2 months of evolution.

It is also worth noting that the patient had sleep disturbances and an episode of catatonia, which is consistent with severe depression but has also been reported in anti-NMDA receptor encephalitis.[2,11,12]

Other than the EEG with background slowing and the finding of an oligoclonal band in the cerebrospinal fluid, the screening for a neurological disorder presenting with psychiatric features was negative. Both brain MRIs performed at 6-month intervals were completely normal, which is frequently the case in anti-NMDA receptor encephalitis, even if an involvement of the medial temporal lobe or white matter is known to occur.[2,4]

Our patient had strongly positive serum levels of NMDA receptor antibodies at diagnosis (score 4, normal 0-0.5), which were similar to those found in more severe cases with neurological manifestations. These levels decreased in correlation with clinical improvement, as has been reported in other cases.[4] Of high interest is the recent finding of mildly elevated NMDA receptor antibodies (scores 1-2) in 3 young adults of a cohort of 46 patients who presented with a first episode of psychosis

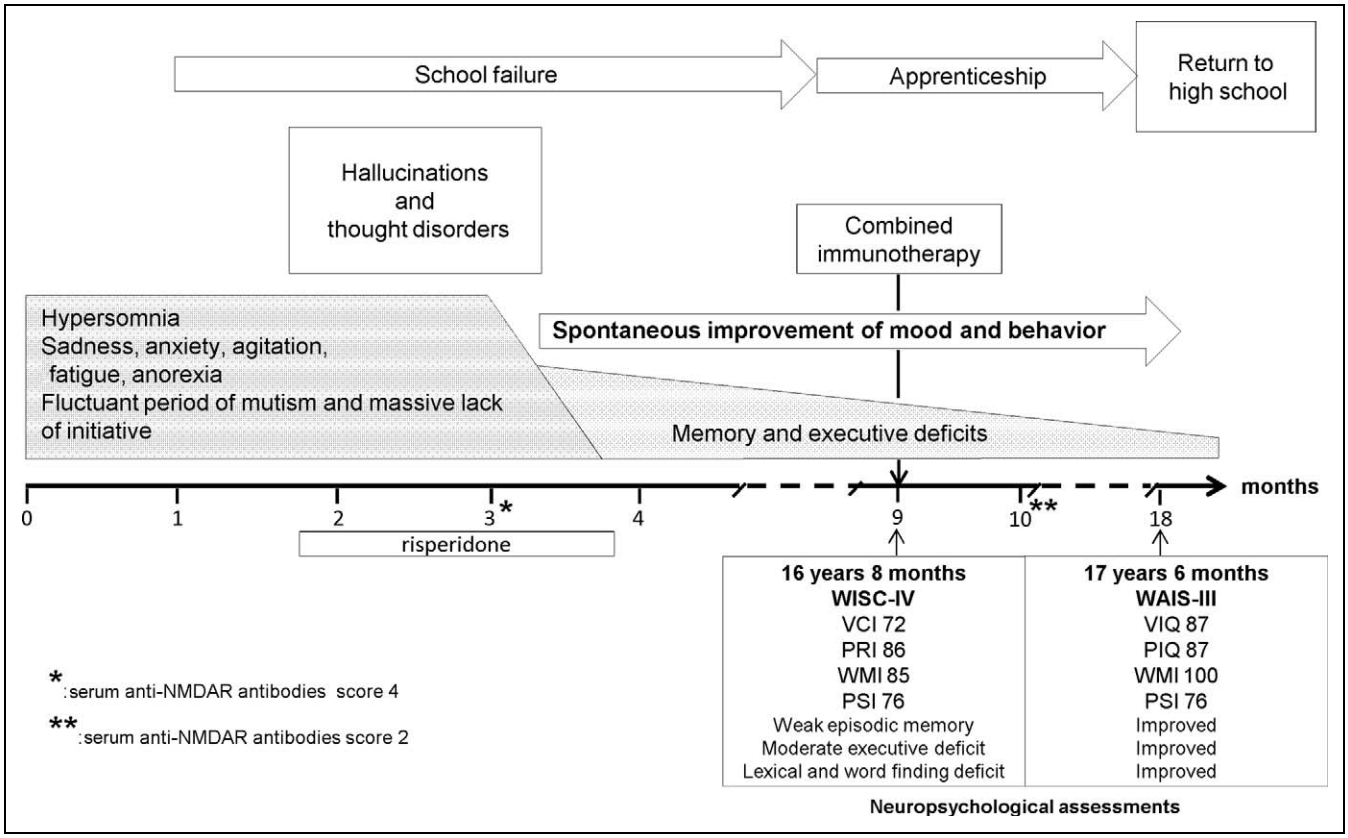

Figure 1. Time course of the disease and main neuropsychological results. PIQ, Performance Intelligence Quotient; PRI, Perceptual Reasoning Index; PSI, Processus Speed Index; VCI, Verbal Comprehension Index; VIQ, Verbal Intelligence Quotient; WAIS, Weschler Adult Intelligence Scale; WISC, Weschler Intelligence Scale for Children; WMI, Working Memory Index.

and were later diagnosed with typical schizophrenia. These findings were preliminary but suggest that NMDA receptor antibodies may have a pathogenic role in this disease that remains to be clarified.[13] NMDA antagonistic drugs can induce psychotic symptoms in humans, even though they usually act as powerful antidepressors.[14] Anti-NR2 antibodies have, however, been found in depressed patients with systemic lupus, suggesting a correlation between NMDA-mediated glutamatergic neurotransmission and mood regulation.[15] In this case, the evolution from depression to psychotic symptoms, as well as their remarkably strong fluctuations, was very remarkable and is difficult to explain.

Despite the initial marked spontaneous improvement in behavior and mood 4 months after disease onset, the patient still had significant executive and memory deficits 5 months later that justified an attempt of immunotherapy with the hope to hasten cognitive recovery. Seric antibody titers rapidly decreased, but neuropsychological functions improved so slowly (Figure 1) that a positive role of treatment is difficult to ascertain. Long-term neuropsychological sequelae in the executive and memory domains were recently documented in 9 adults who recovered from their severe psychiatric and neurological deficits, indicating that higher cognitive functions were the most vulnerable to NMDA receptor dysfunction. It is worth noting that all except one patient in this cohort had received immunotherapy and that those who were treated the latest had the worst outcome.[16] In our patient, improvement followed a similar, albeit faster, pattern of recovery, possibly explained by less severe initial involvement and younger age.[2]

Pediatric neurologists are now aware of anti-NMDA receptor encephalitis, and recommendations have been issued.[2] However, in our case the delay in diagnosis was mainly due to the absence of other psychiatric manifestations and physical neurological signs.[17]

Conclusion

Anti-NMDA receptor encephalitis should be considered in the differential diagnosis of unexplained severe and persistent psychiatric symptoms (depressive or psychotic), especially if onset is abrupt, in children and adolescents, even in the absence of further neurological manifestations.

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Author Contributions

SL, CMD, IP, CP, NS, and AG contributed to acquisition and interpretation of data. SL wrote the manuscript with the contribution and revision of ERP.

Declaration of Conflicting Interests

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Ethical Approval

As a case report, this project was not submitted for ethics committee approval. The authors obtained a consent form from the patient and her parents to publish clinical data, although care was taken to exclude any identifying details or images.

References

1. Dalmau J, Tuzun E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol*. 2007;61:25-36.
2. Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol*. 2009;66:11-18.
3. Kayser MS, Kohler CG, Dalmau J. Psychiatric manifestations of paraneoplastic disorders. *Am J Psychiatry*. 2010;167:1039-1050.
4. Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain*. 2010;133:1655-1667.
5. Lebas A, Husson B, Didelot A, et al. Expanding spectrum of encephalitis with NMDA receptor antibodies in young children. *J Child Neurol*. 2010;25:742-745.
6. Wandinger KP, Saschenbrecker S, Stoecker W, Dalmau J. Anti-NMDA-receptor encephalitis: a severe, multistage, treatable disorder presenting with psychosis. *J Neuroimmunol*. 2011;231:86-91.
7. Braakman HM, Moers-Hornikx VM, Arts BM, et al. Pearls & Oy-sters: electroconvulsive therapy in anti-NMDA receptor encephalitis. *Neurology*. 2010;75: e44-e46.
8. Le Foll J, Pelletier A. Psychiatric symptoms of a paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis: a case report. *Encephale*. 2010;36:166-171.
9. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10:63-74.
10. First MB, Frances A, Pincus HA. *DSM-IV-TR Guidebook*. Washington, DC: American Psychiatric Association; 2004.
11. Parratt KL, Allan M, Lewis SJ, et al. Acute psychiatric illness in a young woman: an unusual form of encephalitis. *Med J Aust*. 2009; 191:284-286.
12. Schimmel M, Bien CG, Vincent A, et al. Successful treatment of anti-N-methyl-D-aspartate receptor encephalitis presenting with catatonia. *Arch Dis Child*. 2009;94:314-316.
13. Zandi MS, Irani SR, Lang B, et al. Disease-relevant autoantibodies in first episode schizophrenia. *J Neurol*. 2011;258: 686-688.
14. Mitchell ND, Baker GB. An update on the role of glutamate in the pathophysiology of depression. *Acta Psychiatr Scand*. 2010;122: 192-210.
15. Lapteva L, Nowak M, Yarboro CH, et al. Anti-N-methyl-D-aspartate receptor antibodies, cognitive dysfunction, and depression in systemic lupus erythematosus. *Arthritis Rheum*. 2006; 54:2505-2514.
16. Finke C, Kopp UA, Pruss H, et al. Cognitive deficits following anti-NMDA receptor encephalitis. *J Neurol Neurosurg Psychiatry*. 2012;83:195-198.
17. Creten C, van der Zwaan S, Blankespoor RJ, et al. Late onset autism and anti-NMDA-receptor encephalitis. *Lancet*. 2011;378: 98.