Movement Disorders
CLINICAL PRACTICE
CASE SERIES

Partial Manifestation of Anti-NMDA-R Encephalitis with Predominant Movement Disorder

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Abstract: Childhood anti–*N*-methyl-D-aspartate receptor (NMDA-R) antibody encephalitis is a well-recognized autoimmune encephalitis presenting typically with a combination of varied movement disorders, seizures, mutism, behavioral and sleep disturbances, and autonomic changes. Monosymptomatic or incomplete forms of the disorder are rare, but have recently been reported. Here, we describe 2 children with nonparaneoplastic anti-NMDA-R encephalitis with partial presentation in the form of movement disorder and minor behavioral changes.

Since its seminal description in 2007, anti–*N*-methyl-D-aspartate receptor (NMDA-R) encephalitis is increasingly recognized worldwide as one of the most common forms of encephalitis surpassing any specific viral encephalitis.[1,2] The disorder still remains highly under-recognized in developing countries owing to a decreased awareness among the medical fraternity as well as a lack of easily available and reliable antibody testing.

The well-known clinical narrative in this encephalitis is that of a subacute onset multistage progressive encephalopathy with complex movement disorders, psychiatric manifestations, seizures, language disturbances, and autonomic dysfunctions.[1] Lesser known are the incomplete or forme frustes of the disorder, which have recently drawn interest.

Here, we describe 2 boys with anti-NMDA-R encephalitis presenting predominantly as a syndrome of ataxia and dyskinetic movement disorder without significant neuropsychiatric manifestations.

Case 1

The first patient was a 3.5-yr-old boy who had 3 episodes of afebrile, brief focal motor seizures over 2 days without intervening encephalopathy. Scalp EEG and cranial MRI were normal. Levitiracetam (LEV) was commenced, and 1 week later he developed gait difficulty. There were minor behavioral changes with irritability and sleep disturbances, though language and cognition remained normal. Neurological examination revealed normal mental status examination with ataxia, loss of postural reflexes, and significant chorea affecting primarily the lower limbs (see Video 1).

Considering these as drug adverse effects, LEV was discontinued, without benefit. Other normal investigations included a cerebrospinal fluid (CSF) routine examination, CSF lactate, and CSF total immunoglobulin (immunoglobulin G; IgG). Complete blood count and routine biochemistry were also normal.

Serum and CSF anti-NMDA-R antibody was then detected. Ultrasonography (USG) of the abdomen and scrotum were normal. The patient was initiated on intravenous immunoglobulin (IVIG) at a dose of 2 g/kg over 2 days, followed by a monthly single infusion of 400 mg/kg for 6 mo. Concomitant steroid therapy was offered, but refused by the parents. A gradual improvement in symptoms was noted with complete recovery by the fourth dose. Repeat serum NMDA-R antibody titer done 1 mo after completion of immune therapy was negative. The child remains asymptomatic at 1.5-yr follow-up.

Case 2

This 9-yr-old boy presented initially with a new-onset anxiety of heights. This was then followed by a gait disturbance with frequent falls and a change in voice in the form of slow scanning speech. He also had worsening of handwriting and continuous arrhythmic quasi-purposeful movements of both hands thought to be chorea by the treating physician at the time. Normal investigations at the time were routine blood counts, biochemistries, anti-streptolysin-O titers, serum ceruloplasmin,

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and anti-nuclear antibody. Cranial MRI and a two-dimensional echocardiogram were also normal. With a working diagnosis of Sydenham's chorea, sodium valproate and, subsequently, tetrabenazine were tried without clear benefit. Oral prednisolone (1.5 mg/kg/day) resulted in a prolonged remission lasting 3 mo. Steroid withdrawal led to a relapse of symptoms when he was referred to our institution. Cerebellar signs were prominent with gait ataxia, slow scanning speech, dysmetria, and dysdiadochokinesia. Though associated chorea was also observed, this was markedly reduced compared to the chorea recorded earlier on video (see Video 2). Language and cognitive skills were intact with normal behavior and no seizures.

An EEG was normal. CSF analysis revealed 22 cells (lymphocytes, 82%; neutrophils, 18%) with normal proteins, glucose, and lactate. Oligoclonal bands were present whereas CSF total IgG was normal.

Anti-GAD antibody was normal. However, anti-NMDA-R antibodies were detected in both serum and CSF. Screening for abdominal and scrotal neoplasms using ultrasound was negative.

Pulse methylprednisone followed by prolonged oral steroids tapered over 9 mo resulted in a complete remission of symptoms within 1 mo of starting treatment. His anti-NMDA-R antibody 1 mo after stopping steroids was negative. The child remains asymptomatic at 18-mo follow-up.

Discussion

Acute/subacute onset movement disorders in children are often related to autoimmune or inflammatory disorders of basal ganglia.[3] The prototype of these basal ganglia autoimmune disorders is Sydenham's chorea characterized primarily by chorea though hypotonia, speech difficulty, and emotional lability are common. Other less-defined disorders are pediatric acute-onset neuropsychiatric syndrome (PANS), which includes postinfectious disorders associated not only with streptoccocal infection, but also other microorganisms. This term is now preferred over the earlier term of PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections). Another recently described entity is basal ganglia encephalitis associated with dopamine 2 receptor antibodies.[4] Recently, autoantibodies have evoked a lot of interest in acute onset movement disorders with or without other neurological symptoms.[3–5]

NMDA-R encephalitis is a subacute onset progressive encephalopathy with a characteristic presentation first described in adolescent females with psychosis, dyskinetic movement disorder, seizures, and language and autonomic symptoms often associated with an ovarian teratoma.[1] Childhood series commonly report a movement disorder presentation, as opposed to the more common neuropsychiatric presentations in adolescents and young adults. Paraneoplastic etiology is less frequently observed in children, as compared to those above 12 yr.[6]

Oligosymptomatic illness without much progression in subsequent weeks is rarely described in NMDA-R encephalitis, and in a large observational cohort of 577 patients of NMDA-R encephalitis, only 1% were characterized as such at 1-mo follow-up.[7] Rare cases of oligosymptomatic presentations with NMDA-R autoimmunity have been reported recently; 3 children presenting with movement disorder, a 19-yr-old girl with hemidystonia, and 23 patients who developed isolated psychiatric symptoms either as the initial episode of the disease (5 patients) or as a later relapse (18 patients).[5, 8, 9] These reports highlight the incomplete presentations of the disorder.

Diverse bizarre movement disorders are well described in the NMDA-R syndrome, including orofacial dyskinesia, chorea, dystonia, catatonia, ataxia, and stereotypies often occurring in combination.[1,2,6] Movement disorder in children or psychosis in adults may be the sole symptom initially, and an encephalopathy may evolve subsequently as the disease progresses.

Both our cases evolved predominantly as a movement disorder. Case 1 had a predominant ataxia with some chorea distally. He also had infrequent easily controlled seizures, distal myoclonus, and mild irritability. Case 2 had initially a predominant chorea with mild anxiety and, in the relapse, had a prominent cerebellar syndrome. Psychosis, mutism, hypoventilation, depressed level of consciousness, and autonomic disturbances were notably absent in both during the entire course of the illness. This relatively confined phenotype could have been owing to early recognition of the disorder and appropriate treatment. Raised liver enzymes, as has been described in parainfectious cases, were absent in our patients.[5] Oligoclonal bands were observed in case 2, a finding well described in NMDA-R encephalitis. What was interesting was that both patients responded very well to single immunomodulating agents (IVIG in case 1 and steroids in case 2) with a persistent remission off medications at 18 mo. Repeat serum antibodies were negative in both in a relatively short time. However, they were not willing to have repeat CSF antibodies done when they were well.

Conclusions

Our cases highlight an oligosymptomatic presentation with predominant movement disorder in anti-NMDA-R encephalitis. This antibody should be tested in any new onset unexplained movement disorder with minor behavioral changes in an appropriate clinical setting. Early diagnosis hastens immune therapy and improves outcome.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

V.U.: 1C, 2C, 3B
N.D.: 1B, 3A, 3B
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Supporting Information

Videos accompanying this article are available in the supporting information here.

Video 1. Video of case 1 showing ataxia and dyskinesias of extremities at onset; latter part of video shows complete resolution of symptoms after immunotherapy.

Video 2. Video of case 2, who presented with generalized chorea, scanning speech, and ataxia; latter part of video shows marked resolution of symptoms after immunotherapy.

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