N-methyl-D-aspartate receptor antibody-associated movement disorder without encephalopathy

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PUBLICATION DATA
Accepted for publication 31st August 2013.
Published online 16th October 2013

ABBREVIATIONS

ASOT	Anti-streptomycin O titres
NMDAR	N-methyl-D-aspartate receptor

N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis is a well-recognized clinico-immunological syndrome that presents with a movement disorder, cognitive decline, psychiatric symptoms, and epileptic seizures. A pure monosymptomatic presentation is rare; however, some patients present predominantly with a movement disorder in the absence of encephalopathy. Here, we describe three paediatric patients with an NMDAR antibody-mediated movement disorder: a 5-year-old female with acute onset hemichorea, a 10-year-old female with generalized chorea, and a 12-year-old male with abdominal myoclonus. These patients did not develop the characteristic encephalopathy syndrome seen in NMDAR encephalitis, but all three had other associated subtle cognitive deficits. The patients demonstrated good responses to immunotherapy.

Immune-mediated disorders are a common cause of acute movement disorder in children, occurring as an isolated central nervous system (CNS) syndrome with encephalopathy, or in conjunction with systemic features of autoimmunity.[1] Some of these conditions present as a post-infectious phenomenon and have been linked previously to a number of infective organisms, particularly streptococcal infections.[1] These groups of post-infectious conditions that target the basal ganglia range from Sydenham chorea, where evidence of autoimmunity is derived from clinical studies and identification of specific autoantibodies,[2,3] to diseases where the autoimmune link is less clear, such as paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection and Tourette syndrome.[1]

Antibodies to neuronal surface antigens have been shown to be pathogenic in a number of immune-mediated conditions,[4] with antibodies against the N-methyl-D-aspartate receptor (NMDAR) most commonly reported in children.[5] Patients typically present with a well-characterized encephalopathy syndrome with prominent psychiatric symptoms, movement disorder, and seizures.[6] The cell-surface target antigen is disrupted by the antibodies (resembling symptoms associated with NMDAR antagonists) and symptoms can be reversed with immunotherapy (frequently prolonged).[6] Although initially described as a paraneoplastic syndrome in young adult females with ovarian teratoma, it is now recognized that NMDAR encephalitis in children is more typically post-infectious.[5] Milder or incomplete phenotypes of the disease are less commonly reported,[6] although this may either represent a referral bias or under-recognition of these milder presentations.

Here, we describe three paediatric patients who presented primarily with movement disorders. All three patients were positive for NMDAR antibodies and responded to immunotherapy. They did not have associated neoplasms.

Written informed consent for the publication of the case descriptions and videos was obtained for all three patients.

CASE 1

A 5-year-old female presented to her local hospital with acute onset intermittent right-sided choreiform movements (proximal and fine distal chorea with dystonia; Video S1, online supporting information) and one brief episode of generalized seizure. One year previously, she had been given a diagnosis of discoid lupus after a biopsy of a hyperpigmented upper truncal lesion. She had no other medical problems and was performing well at school. She had three further seizures and developed a more florid unilateral movement disorder. She was noted to have an expressive dysphasia with word finding difficulties, which on retrospective questioning were likely to have started 3 weeks before onset of the movement disorder. Brain magnetic resonance imaging (MRI) was normal. Cerebral spinal fluid (CSF) analysis was acellular with normal glucose, lactate, and proteins. Investigations revealed strongly positive NMDAR antibodies in the serum (CSF was not tested), after which she was treated acutely with intravenous immunoglobulins followed by a

 DOI: 10.1111/dmcn.12321

prolonged course of oral prednisolone (3-mo course of 2mg/kg and slow weaning over a further 3mo). She was positive for anti-neutrophil antibodies and granulocyte-specific IgM antibodies (with prolonged but asymptomatic neutropenia), rheumatoid factor, anti-streptomycin O titres (ASOT), and anti-double stranded DNA (transiently positive and normalized within the acute admission). An extended autoantibody screen (anti-nuclear, smooth muscle, mitochondrial, gastric parietal, and anti-basal ganglia) was negative. Her movement disorder improved dramatically with treatment and she was asymptomatic at 3-months' follow-up (Video S2, online supporting information). Her expressive language skills continue to improve, and at 6-months' follow up had returned to normal, with reduction of her antibody titres at 3 months and normalization at 1 year.

CASE 2

A 10-year-old female presented with an acute onset movement disorder, reduced fine motor coordination and deterioration of speech (with reported occasions of slurring). Examination revealed bilateral fine distal choreiform movements, alongside a postural and intension tremor. She was also noted to have spasmodic abnormal neck postures with dystonic spasms of her larynx affecting her speech and more generalized dystonic posturing of both upper limbs. Brain MRI was normal and CSF analysis was acellular with normal glucose, lactate, and proteins. Her ASOT and anti-DNAseB were raised, both measuring 400IU/mL, and she was found to have a positive IgG anti-cardiolipin antibody with subtle functional abnormality identified on the dilute Russell's viper venom test (DRVVT) and taipan snake venom time (TSVT), which normalized within 3 months. Extended autoantibody screen (anti-neutrophil, anti-nuclear, anti-dsDNA, smooth muscle, mitochondrial, gastric parietal, and anti-basal ganglia) was negative. She was diagnosed with a post-infectious acute onset movement disorder and had a good response to sodium valproate. She had a symptomatic relapse 3 months later, which was felt to be secondary to intercurrent illness. Six months later, she had a second relapse of her movement disorder, while not taking sodium valproate, with word finding difficulties detected on specific testing. Treatment was restarted, but with less dramatic improvement. She had a repeat MRI, an electroencephalogram (EEG), and an infective screen, which were all normal. At that time she was found to be positive for NMDAR antibodies in serum and CSF. She was commenced on oral prednisolone (60mg/day for 1mo, reduced to 30mg/day for a further month and slow weaning over 3mo), made a complete recovery, and remains relapse-free a year after stopping treatment, with normalization of serum antibody levels 2 months after initiation of treatment.

CASE 3

A previously well 12-year-old male developed generalized muscle ache (more severe in the legs) after an infectious illness with a sore throat. His neurological examination

What this paper adds

- NMDAR-Ab should be tested in patients with a movement disorder even without an encephalopathy.
- In patients presenting predominantly with a movement disorder, the other associated features should be checked.

was normal. He had a normal creatine kinase, raised inflammatory markers (erythrocyte sedimentation rate 99 and C-reactive protein 210) and ASOT (800IU/mL). Despite an initial improvement, the muscle aching remained problematic. Muscle MRI and electromyography were both normal. A few months later he developed frequent abdominal myoclonus, which happened every few minutes, more frequently when lying down. The movement disappeared with sleep, but worsened with excitement (Video S3, online supporting information). The distractibility as the patient began to speak, as seen in the video, prompted a psychological evaluation. Brain MRI, EEG, and CSF studies including neurotransmitters were all within the normal range. Antibodies to NMDAR were identified in the serum (CSF was not tested). The abdominal myoclonus resolved after a short course of oral prednisolone (6-wks course of 2mg/kg and slow weaning over a further 6wks), with normalization of antibody levels at 3 months. His general pain and fatigue persisted, but were managed successfully with intensive psychotherapy.

All three patients were empirically investigated by their physicians to exclude a range of infective, alternative inflammatory, and neurometabolic aetiologies, of which none were identified. Testing of all three patients' sera did not reveal the presence of antibodies to the voltage-gated potassium channel complex and the associated proteins (leucine-rich glioma-inactivated 1, contactin-associated protein-like 2, and contactin 2), glycine receptor, glutamic acid decarboxylase, and the dopamine receptors. All three patients were screened for occult malignancy (ultrasound scan of abdomen with/without ovaries and paraneoplastic antibodies), which were negative.

DISCUSSION

Autoimmune and inflammatory disorders are the most common causes of acute movement disorders in children. In a prospective study of acute movement disorders in children, 22 of the 52 patients (42%) were found to have an inflammatory or autoimmune aetiology.[7] In a paediatric cohort of autoimmune encephalitis, 18 out of 48 patients had a movement disorder, of which seven were positive for NMDAR antibodies and in 11 no antibody was identified, suggesting that a yet unidentified autoantibody might mediate this clinical entity.[8]

Autoimmune encephalitis secondary to NMDAR antibodies is now well recognized and increasingly diagnosed in children, presenting with similar clinical features to those described in adults; however, the presentation is typically more neurological than psychiatric and malignancy is less frequent.[9] In a large paediatric cohort, 84% of patients developed a movement disorder (frequently in the second

stage of the illness),[10] and in a smaller Spanish cohort all children had a movement disorder, with 30% having a movement disorder at the time of presentation.[9] The NMDAR is a member of the superfamily of receptors for glutamate, the major excitatory neurotransmitter in the CNS. The relatively high expression of NR1/NR2B receptors in basal ganglia makes them targets for the patients antibodies and could explain the movement disorders seen with NMDAR antibody-associated CNS diseases.[11] However, it is possible that the involuntary movement seen in NMDAR encephalitis is not generated in the basal ganglia, but, in fact, by the loss of cortical and brainstem inhibition (caused by NMDAR internalization) resulting in a release of primitive patterns of bulbar and limb movement as previously suggested.[12]

The most common movement disorders associated with this condition are orofacial dyskinesis, choreoathetoid, dystonic posturing, and stereotyped movements.[10,13] In a cohort of 20 paediatric patients with encephalitis lethargica, 10 were positive for NMDAR antibodies presenting with dsykinetic movement disorder with seizures, whereas the negative group had parkinsonism.[14] In a large observational cohort of 577 patients with anti-NMDAR encephalitis, only 1% of patients remained monosymptomatic at 4 weeks from symptom onset, suggesting that NMDAR antibodies causing a CNS disease without encephalopathy is uncommon.[15] Previously, a case of isolated hemidystonia was reported in a 19-year-old female who, similar to our cases, made a good response to immunotherapy.[16] Interestingly, she also had raised ASOT (as did all our cases), which supports the post-infectious trigger in some of the patients with NMDAR autoimmunity.[6] NMDAR antibodies were found in five out of 52 paediatric patients with new onset movement disorder,[7] but it is not clear if these patients went on to develop encephalopathy. As the majority of the reported literature comprises studies into NMDAR antibody-mediated encephalitis, the true incidence of presentation without encephalopathy may be under-recognized. However, in prospective studies looking into NMDAR antibodies in patients with new onset psychosis[17] and new onset epilepsy[18] the incidence was indeed low.

It remains unclear if patients presenting with the partial phenotype would proceed to full-blown encephalopathy as seen in other forms of autoimmune encephalopathies such as the leucine-rich glioma inactivated 1 antibodies, which were detected in two adults with subacute chorea, as the initial presentation before the development of the encephalopathy.[19] Both patients showed a good response to immunotherapy. Similarly, the faciobrachial dystonic seizures frequently seen in this condition, appear not to progress to limbic encephalitis when treated early and thus suggest a therapeutic window.[20]

Word finding difficulties, as seen in Cases 1 and 2, can be a useful clue to the diagnosis. Expressive dysphasia and mutism are typically seen in patients with full-blown encephalopathy. The exact mechanism is still unknown, but as reduction in verbal fluency is frequently seen with NMDAR antagonists, this phenomenon is likely to be secondary to NMDAR loss of function.

Interestingly, two of our patients (Cases 1 and 2) had a few features suggestive of lupus/anti-phospholipid syndrome-associated movement disorders; patients with these conditions previously have been shown to have neuronal surface antibodies.[21] Antibodies to the NR2 subunit of the NMDAR were found in some patients with systemic lupus erythematosus,[22] although their exact pathogenic role remains unclear, the possibility of cross-reactivity of the NR2 and anti-DNA antibodies has been suggested.[22] Our patients were reviewed by a paediatric rheumatologist, and were deemed not to fulfil the American College of Rheumatology Criteria diagnostic criteria of systemic lupus erythematosus.

Propriospinal myoclonus, as seen in Case 3, is frequently thought to be psychogenic,[23] which prompted the referral to a psychologist. In addition, the distractibility (as seen in Video S3) and the clinical improvement with a brief course of steroids (in contrast to what is usually seen in typical anti-NMDAR patients) would support a psychogenic movement disorder, and thus the antibody positivity would be an incidental finding and not clinically relevant. Nevertheless, the response to immunotherapy, albeit atypical, and the temporal relationship between the antibody and the clinical symptoms raises the question as to whether this could be mediated by NMDAR antibodies. Acute generalized and segmental myoclonus with raised ASOT was previously reported in three children and was thought to be an atypical variant of paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection;[24] however, testing for NMDAR antibodies was not available at the time of this report.

All three patients made a good response to immunotherapy with symptom control and antibody reduction, which resolved sooner than previously reported in children with NMDAR-Ab encephalitis.[8] The small numbers prevent us from making a direct comparison. Symptomatic treatment of movement disorders can be effective (as previously reported[13] and seen in Case 2), nevertheless it is likely that immunotherapy will be more effective in the NMDAR-positive group and be likely to reduce the risk of further relapse.

CONCLUSIONS

These cases illustrate the expanding spectrum of NMDAR antibody-associated CNS disorders to encompass a phenotype presenting predominantly with a movement disorder. Children with a new onset movement disorder (even unilateral) should be investigated for this treatable immune-mediated disorder.

ACKNOWLEDGEMENTS

This work was supported by the NIHR Oxford Biomedical Research Centre (YH, AV). We thank Dr Saif Huda for help with reviewing the video clips and preparation of video captions.

SUPPORTING INFORMATION

The following additional material may be found online:

Video S1: A video clip of the patient in Case 1 taken during her acute admission shows a unilateral right-sided hyperkinetic movement disorder, characterized by distal choreoathetoid right arm movements. In addition, there is dystonic dorsiflexion of the right foot and dystonic posturing of the right arm. No abnormality was seen on the left side. Of note, the patient is interacting normally and functioning well despite her movement disorder.

Video S2: A video clip of the patient in Case 1 at 3 months after immunotherapy, during an outpatient clinic appointment, demonstrating resolution of the movement disorder.

Video S3: A video of the patient in Case 3 demonstrates stereotyped repetitive abdominal myoclonus during a normal EEG recording. The movement disorder was not associated with an overwhelming urge or suppressibility. There is, however, suggestion of distractibility as the patient begins to speak. Overall, the clinical picture was felt to be consistent with an abdominal myoclonus of propriospinal origin.

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