N-methyl-D-aspartate (NMDA) receptor antibodies encephalitis mimicking an autistic regression

YAEL HACOHEN[1,2]* | SUKHVIR WRIGHT[1,3]* | JONATHAN GADIAN[2] | ANGELA VINCENT[1] | MING LIM[2]* | EVANGELINE WASSMER[3] | JEAN-PIERRE LIN[2]

1 Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford; **2** Paediatric Neuroscience, Evelina Children's Hospital @ Guys and St Thomas' NHS Foundation Trust, Kings Health Partners Academic Health Science Centre, London; **3** Department of Paediatric Neurology, Birmingham Children's Hospital, Birmingham, UK.

Correspondence to Ming Lim at Children's Neurosciences, Evelina Children's Hospital @ Guys and St Thomas' NHS Foundation Trust, Kings Health Partners Academic Health Science Centre, Lambeth Palace Road, London SE1 7EH, UK. E-mail: ming.lim@gstt.nhs.uk

***These authors contributed equally to this work.**

This article is commented on by Dale on pages 1002–1003 of this issue.

PUBLICATION DATA
Accepted for publication 11th April 2016.
Published online 3rd June 2016.

ABBREVIATIONS

NMDAR-Ab	*N*-methyl-D-aspartate receptor antibodies

Expressive dysphasia and mutism are common clinical features in children and adults with *N*-methyl-D-aspartate receptor antibodies (NMDAR-Ab) encephalitis, and are likely to result from NMDAR hypofunction. A prodromal loss of social and communication skills can typify that of an autistic regression, particularly when presenting under the age of 3 years. Here we describe two toddlers who presented with developmental regression, particularly of their social communication skills, mimicking an autistic regression, who were found to have NMDAR-Ab in the serum and cerebrospinal fluid. Although both patients had some other neurological features, they were subtle, which resulted in delayed diagnosis of NMDAR-Ab encephalitis. Importantly, immunotherapy was beneficial in both patients, with significant improvement of their language skills and behaviour.

N-methyl-D-aspartate receptor antibodies (NMDAR-Ab) encephalitis is a well-recognized, clinical-immunological syndrome. Milder phenotypes have been described predominantly in polysymptomatic patients without an encephalopathy.[1] Expressive dysphasia and mutism are typically seen in patients with encephalitis and in patients with partial phenotypes, and word-finding difficulties can be a useful clue for the diagnosis.[2] A prodrome of loss of social and communication skills, however, can also lead to a diagnosis of autistic regression. Here we report two females, both aged 2 years, who presented with acute onset regression of social and communication skills who were found to have NMDAR-Ab in serum and cerebrospinal fluid (CSF).

CASE 1

A previously well 2-year-old female, with a normal antenatal and developmental profile, presented with an acute onset of behavioural change, disrupted sleep, and loss of motor, language, and social communication skills. She was initially treated for encephalitis, and investigated for an organic brain syndrome with brain magnetic resonance imaging (MRI), electroencephalogram (EEG), and CSF studies, which were all normal; she was discharged home 1 week later. However, she continued to regress over the next 4 weeks and was readmitted with drowsiness and significant speech and motor impairment with irritability. On admission she was mute and had orofacial and right hand stereotypies (Video S1, online supporting information). She did not understand or initiate any verbal or non-verbal interaction, but had some situational understanding.

The EEG was in keeping with encephalopathy, with diffuse background slowing and disorganization without epileptiform discharges, and abnormal sleep architecture with spikes in the right frontal region. Neurometabolic, genetic, and inflammatory screening revealed positive NMDAR-Ab in the serum and CSF, with normal CSF cell count and protein, but positive oligoclonal bands. On day 3 of admission she was commenced on 15μg clonidine three times a day. with rapid improvement in return of oral feeding but no change in social inattention or mutism. Further treatment on day 5 with 30mg/kg intravenous methylprednisolone (for 3d) and then a total intravenous dose of 2g/kg immunoglobulin administered as five daily doses, was complicated by borderline hypertension that did not require pharmacological management. She had an improvement in confusion, sleep, and a resolution of dyskinesias at day 21, but remained aphasic. A repeat EEG 2 weeks later showed minimal background improvement with more apparent frontal discharges, and therefore plasma exchange was initiated but discontinued after only 1.5 cycles because of a line infection and catheter-related thrombosis necessitating line removal. She was discharged home on high-dose 25mg (i.e. 2mg/kg/d) steroids for a week, then three daily consecutive doses of 340mg

 DOI: 10.1111/dmcn.13169

(600mg/m^2) intravenous methylprednisolone. Over the course of the next month, and 4 months from symptom onset, she had a significant improvement in speech and social communication skills, with normalization of sleep, gross motor function, and EEG. At follow-up, aged 4 years, 2 years from symptom onset, she is well, has age-appropriate language acquisition, no behaviour and psychiatric concerns, and remains relapse-free.

CASE 2

A previously well 2-year-old female, with a normal antenatal and developmental profile, presented with an episode of unresponsiveness lasting 40 minutes. She was thought to be postictal, was diagnosed with a first afebrile seizure, and was discharged home the following day. Three days later she re-presented with abnormal behaviour with biting, pinching, and banging her head, and irritable insomnia, which gradually got worse. Over the next 3 weeks she deteriorated with fluctuating unsteadiness, poor comprehension, aggressiveness, and loss of speech. Neurometabolic screening included normal brain MRI, white cell enzymes, and ophthalmology review, which were normal. Sleep EEG revealed occasional focal and generalized epileptiform discharges. To help her behaviour and sleep, she was commenced on clobazam and melatonin. She had a further regression with loss of speech and interaction, increasing ataxia, and food refusal (choking on solid food). Repeat EEG showed general slowing. The CSF was acellular with normal glucose and protein but positive oligoclonal bands. An autoinflammatory screen identified NMDAR-Ab in the serum and CSF.

Treatment with 30mg/kg once daily for 5 days intravenous methyl-prednisolone (2mo after onset of symptoms) brought short-lasting improvement. Ten days later she went on to have five cycles of plasma exchange followed by four doses of 375mg of rituximab once a week (commenced 3mo after onset of symptoms); at 5 months from symptom onset she was commenced on mycophenolate mofetil. Full-body MRI and paraneoplastic antibodies showed no evidence of malignancy. At 12 months from onset, on maintenance mycophenolate mofetil, there have been significant improvements in her speech, gait, and swallowing, but she continues to suffer from ongoing behavioural concerns and sleep disruption.

DISCUSSION

Autistic spectrum disorders form a group of conditions classified as neurodevelopmental disorders, which present with impairment in social communication and repetitive or stereotypical behaviour, with onset before 3 years of age. Atypical features – which may suggest an alternative diagnosis, and warrant further investigations to exclude both congenital and acquired causes – include severe learning difficulties, the presence of an early onset epileptic syndrome, or an associated movement disorder. The onset of symptoms outside the usual age, or a sudden acute onset of autism with or without fluctuation of symptoms, would also point to an alternative diagnosis. Although the two cases presented here had the typical age of onset, the sudden acute onset together with the lack of developmental arrest before the regression were all suggestive of an alternative aetiology. Moreover, other atypical features were seen in both cases. Case 1 had orofacial dyskinesia in addition to the right arm motor stereotypies of repetitive rubbing of the right side of the head, a movement disorder not typically seen in children with autistic spectrum disorders. Case 2 presented with a possible seizure, had an abnormal EEG, and later developed swallowing and gait difficulties.

What this paper adds

- *N*-methyl-D-aspartate receptor antibodies should be tested in infants with regression of social and communication skills, particularly in the presence of additional neurological symptoms.
- Early diagnosis and treatment of these patients is associated with a much-improved outcome.

There was considerable overlap in features between these two children and patients with NMDAR-Ab encephalitis. The motor stereotypies seen in Case 1 can be seen in children with autistic spectrum disorders. However, although there are some stereotypical features, the movements are more complexed with some repetitive elements, motor restlessness, and some writhing elements; features previously reported in patients with anti-NMDAR encephalitis.[3] The involuntary movements seen in patients with NMDAR-Ab encephalitis are hypothesized to arise secondary to loss of cortical and brainstem inhibition (because of the loss of surface NMDARs by antibody-induced internalization), resulting in release of primitive patterns of bulbar and limb movement.[4] Case 1 received beneficial symptomatic treatment with clonidine. A recent retrospective study of 27 children with anti-NMDAR encephalitis[5] has indeed shown that symptomatic treatment with long-acting benzodiazepines, anticonvulsants, and clonidine can be beneficial, but patients appear vulnerable to antipsychotic-related adverse effects.

Expressive dysphasia and mutism are typically seen in patients with full-blown anti-NMDAR encephalitis and can mimic an autistic regression, particularly if present under the age of 3 years. The exact mechanism is unknown but as a reduction in verbal fluency is often seen with NMDAR antagonists, this phenomenon is also likely to be secondary to NMDAR loss of function.

Perturbation of function of the NMDAR may also result from mutation in the NMDAR subunit *GluN2A*, equivalent to NMDAR *NR2A*. Mutations in this gene have been reported in children with epilepsy–aphasia spectrum disorders ranging from benign epilepsy with centrotemporal spikes through acquired epileptic aphasia (Landau–Kleffner syndrome), to continuous spike and wave during slow-wave sleep syndrome;[6–8] disorders with behavioural manifestations that overlap with autistic spectrum disorders. Although genetically predetermined, these conditions do not manifest at birth but present later, possibly related to the age-dependent physiological switch from *GluN2B* to

GluN2A.[9] Interestingly, hypofunction of NMDAR was also found to be the underlying molecular cause of impaired social interaction in *Shank2*-mutant mice, which recapitulate many of the behavioural phenotypes that are characteristic of autistic spectrum disorders.[10]

Acquired reversible autistic syndrome with an acute encephalopathic illness has previously been reported in three children.[10] Although phenotypically similar to patients with NMDAR-Ab encephalitis, the patients described[10] were not tested for the antibodies. In other reports, a 3-year-old male[11] and a 9-year-old[12] male presenting with acute autistic regression were found to have NMDAR-Ab, and their symptoms responded to immunotherapy resulting in re-acquisition of language and social skills as seen in our cases. In a recent UK surveillance study of children with NMDAR-Ab, 29% of paediatric presentations were under the age of 3 years, highlighting the importance of testing for NMDAR-Ab even in very young children.[13]

In conclusion, NMDAR-Ab should be tested in cases of regression of social and communication skills with additional neurological symptoms such as a movement disorder or seizures. Unlike autism, early diagnosis and treatment of NMDAR-Ab encephalitis is associated with a much improved outcome.[14]

ACKNOWLEDGEMENT

The authors have stated that they had no interests which might be perceived as posing a conflict or bias.

SUPPORTING INFORMATION

The following additional material may be found online:

Video S1: A video clip of Case 1 taken during her acute admission demonstrates orofacial dyskinesia in addition to the right arm motor stereotypies of repetitive rubbing of the right side of the head. The movements are coarse with motor restlessness and writhing elements. Of note, the child looks disengaged and does not understand or initiate any verbal or non-verbal interaction, in keeping with other reports of patients with anti-NMDAR encephalitis, with patients rarely being 'unconscious or drowsy'; instead, the eyes are open but they are unresponsive to their environment.

REFERENCES

1. 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.
2. Hacohen Y, Dlamini N, Hedderly T, et al. *N*-methyl-D-aspartate receptor antibody-associated movement disorder without encephalopathy. *Dev Med Child Neurol* 2014; **56**: 190–93.
3. Mohammad SS, Fung VS, Grattan-Smith P, et al. Movement disorders in children with anti-NMDAR encephalitis and other autoimmune encephalopathies. *Mov Disord* 2014; **29**: 1539–42.
4. Kleinig TJ, Thompson PD, Matar W, et al. The distinctive movement disorder of ovarian teratoma-associated encephalitis. *Mov Disord* 2008; **23**: 1256–61.
5. Mohammad SS, Jones H, Hong M, et al. Symptomatic treatment of children with anti-NMDAR encephalitis. *Dev Med Child Neurol* 2016; **58**: 376–84.
6. Lemke JR, Lal D, Reinthaler EM, et al. Mutations in *GRIN2A* cause idiopathic focal epilepsy with rolandic spikes. *Nat Genet* 2013; **45**: 1067–72.
7. Carvill GL, Regan BM, Yendle SC, et al. *GRIN2A* mutations cause epilepsy-aphasia spectrum disorders. *Nat Genet* 2013; **45**: 1073–76.
8. Lesca G, Rudolf G, Bruneau N, et al. *GRIN2A* mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction. *Nat Genet* 2013; **45**: 1061–66.
9. Paoletti P, Bellone C, Zhou Q. NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat Rev Neurosci* 2013; **14**: 383–400.
10. Won H, Lee HR, Gee HY, et al. Autistic-like social behaviour in *Shank2*-mutant mice improved by restoring NMDA receptor function. *Nature* 2012; **486**: 261–65.
11. Scott O, Richer L, Forbes K, et al. Anti-*N*-Methyl-D-Aspartate (NMDA) receptor encephalitis: an unusual cause of autistic regression in a toddler. *J Child Neurol* 2014; **29**: 691–94.
12. Creten C, van der Zwaan S, Blankespoor RJ, et al. Late onset autism and anti-NMDA-receptor encephalitis. *Lancet* 2011; **378**: 98.
13. Wright S, Hacohen Y, Jacobson L, et al. *N*-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. *Arch Dis Child* 2015; **100**: 521–26.
14. Byrne S, Walsh C, Hacohen Y, et al. Earlier treatment of NMDAR antibody encephalitis in children results in a better outcome. *Neurol Neuroimmunol Neuroinflamm* 2015; **2**: e130.