

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

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Abstract

Expressive dysphasia and mutism are common clinical features in both children and adult with N-methyl-D-aspartate receptor antibodies (NMDAR-Ab) encephalitis, and 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 CSF. 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 with significant improvement of their language skills and behaviour.

What this paper adds

1. NMDAR-Ab should be tested in infants with regression of social and communication skills particularly in the presence of additional neurological symptoms.
2. Early diagnosis and treatment of these patients is associated with a much-improved outcome.

Introduction

NMDAR-Ab encephalitis is a well-recognized clinical-immunological syndrome. Milder phenotypes have been described predominantly in polysymptomatic patients without an encephalopathy¹. Expressive dysphasia and mutism are typically seen in both patients with encephalitis and in patients with the partial phenotypes, and the word-finding difficulties can be a useful clue for the diagnosis². A prodrome of loss of social and communication skills, however, can also lead to a diagnosis of autistic regression. Here we report two girls, both age 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 girl 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; and was discharged home one week later. However, she continued to regress over the next 4 week and was readmitted with drowsiness and significant speech and motor impairment with irritability. On admission she was mute and had oro-facial and right hand stereotypies (Video 1). She did not understand or initiate any verbal or non-verbal interaction, but had some situational understanding.

EEG was in keeping with encephalopathy, with diffuse background slowing and disorganisation 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, protein but positive oligoclonal bands (OCB). On day 3 of admission she was commenced on clonidine 15 micrograms TDS with rapid improvement in return of oral feeding but no change in social inattention or mutism. Further treatment on day 5 with IV methylprednisolone (30mg/kg for 3 days) and then intravenous immunoglobulin (total of 2g/kg divided over 5 daily doses) were 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 two weeks subsequently showed minimal background improvement with more apparent frontal discharges, and therefore plasma exchange was initiated but discontinued after only 1.5 cycles due to a line infection and catheter related thrombosis necessitating line removal. She was discharged home on high dose steroids (25mg i.e. 2mg/kg/day) for a week then Methylprednisolone i.v three daily consecutive doses of 340mg (600mg/m²). Over the course of the next month, and four months from symptom onset, she had a significant improvement in speech and social communication skills, with normalisation of sleep, gross motor function and EEG. At follow-up, age 4 years, 2 year 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 girl with a normal antenatal and developmental profile presented with an episode of unresponsiveness lasting 40 minutes. She was thought to be postictal and 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 three weeks she deteriorated with fluctuating unsteadiness, poor comprehension, aggressiveness and loss of speech. Neurometabolic screen included normal MRI brain, white cell enzymes and ophthalmology review which were normal. Sleep EEG revealed occasional focal and generalised 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. CSF was acellular with normal glucose and protein but positive OCB. An autoinflammatory screen identified NMDAR-Ab in the serum and CSF.

Treatment with IV methyl-prednisolone course (30mg/kg once daily for 3 days, 2 months after onset of symptoms) brought short-lasting improvement. Ten days later she went on to have 5 cycles of plasma exchange followed by rituximab (4 doses of 375mg once a week commenced 3 months after onset of symptoms) and at 5month from symptoms onset she was commenced on Mycophenolate mofetil (MMF). Full body MRI and paraneoplastic antibodies showed no evidence of malignancy. At 12 month

from onset, on maintenance MMF, there has been a significant improvement of her speech, gait and swallowing but she continues to suffer from on-going behavioural and sleep disruption.

Discussion

Autistic spectrum disorders is 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 prior to the regression, were all-suggestive of an alternative aetiology. Moreover other atypical features were seen in both cases. Case one 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 ASD, and case 2 presented with a possible seizure, had an abnormal EEG and later developed swallowing and gait difficulties.

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 encephalitis³. The involuntary movements seen in patients with NMDAR-Ab encephalitis are hypothesised to arise secondary to loss of cortical and brainstem inhibition (due to the loss of surface NMDARs by antibody-induced internalisation) resulting in release of primitive patterns of bulbar and limb movement⁴. Patient 1 received beneficial symptomatic treatment with Clonidine. Recent retrospective study of 27 children with anti-NMDAR encephalitis⁵

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 the 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 frequently seen with NMDAR antagonists, this phenomenon is also likely to be secondary to NMDAR loss of function.

Perturbation of function of the NMDAR, which 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 [LKS]), to continuous spike and wave during slow-wave sleep syndrome (CSWSS)⁶⁻⁸; disorders with behavioural manifestations that overlap with ASD. Although genetically predetermined, these conditions do not manifest at birth and present later, possibly related to the age dependent physiological switch from GluN2B to GluN2A⁹. 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 ASD¹⁰

Acquired reversible autistic syndrome with an acute encephalopathic illness has previously been reported in three children¹⁰. Although phenotypically similar to patients with NMDAR-Ab encephalitis, the patients' described¹⁰ were not tested for the antibodies. In another report, a 3 year old¹¹ and a 9 year old¹² boys 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-Abs, 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 outcome¹⁴.

Video 1; A video clip of Case1 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' but instead their eyes are open but they are unresponsive with their environment.

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