

## Short Report

# Catatonic features in children and adolescents with *N*-methyl-D-aspartate receptor antibody encephalitis

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Catatonia is a psychomotor dysregulation syndrome of diverse aetiology, increasingly recognised as a prominent feature of *N*-methyl-D-aspartate receptor antibody encephalitis (NMDARE) in adults. No study to date has systematically assessed the prevalence and symptomatology of catatonia in children with NMDARE. We analysed 57 paediatric patients with NMDARE from the literature using the Bush-Francis Catatonia Rating Scale. Catatonia was common (occurring in 86% of patients), manifesting as complex clusters of positive and negative features within individual patients. It was both underrecognised and undertreated. Immunotherapy was the only effective intervention, highlighting the importance of prompt recognition and treatment of the underlying cause of catatonia.

## Keywords

Clinical neurology; inpatient treatment; neuroimmunology; organic syndromes; drug interactions and side effects.

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Psychiatrists are increasingly involved in the diagnosis and management of patients with autoimmune encephalitis, and many patients present initially to psychiatrists. The commonest cause of autoimmune encephalitis in children and young people is *N*-methyl-D-aspartate receptor (NMDAR) antibody encephalitis (NMDARE), in which antibodies against the GluN1 subunit of NMDAR cause a severe and progressive neuropsychiatric syndrome characterised in the later stages by encephalopathy, seizures and movement disorder, but frequently presenting in the early stages with prominent psychiatric or behavioural symptoms that can be difficult to differentiate from primary psychiatric disease.<sup>1</sup>

The psychopathological features of NMDARE are well characterised in adults,<sup>2</sup> but less understood in children and adolescents, despite over a third of cases occurring in this group.<sup>3</sup> Diagnosis of autoimmune encephalitis in patients presenting with psychiatric symptoms is often delayed,<sup>4</sup> as earlier treatment is associated with a better outcome in both children and adults<sup>3,5</sup> recognition of psychiatric features in children is clearly important. Catatonia is frequently reported in adults with NMDARE but has never been systematically evaluated in children with the disease.<sup>4,6,7</sup> We therefore analysed individually reported paediatric patients with NMDARE to assess the prevalence and symptomatology of catatonia and the relationship to clinical characteristics and outcome.

## Method

We previously reported a MEDLINE literature search for first-episode cases of paediatric NMDARE, identifying individually reported data in 80 children ( $\leq 17$  years) across 34 publications (see Byrne et al Appendix e-1).<sup>5</sup> Only cases of patients with adequate detailed individualised information to reveal specific clinical characteristics and outcome were included. Outcome was dichotomised into either complete recovery (defined as modified Rankin Scale score of zero) or incomplete recovery at final follow-up, assessed

in each patient by three independent reviewers (S.B., M.L. and R.C.D.). In the present study we conducted a secondary analysis of this cohort to extract catatonic features using the validated screening instrument of the Bush-Francis Catatonia Rating Scale (BFCRS), comprising a checklist of 14 features in which the presence of  $\geq 2$  suggests a diagnosis of catatonia.<sup>8</sup> The BFCRS was applied to reports containing adequate detailed descriptions of movement and behaviour by two independent reviewers (S.B. and A.K.). The Mann-Whitney *U*-test was used to analyse group differences in BFCRS total score according to dichotomised clinical characteristics. Multivariate logistic regression was used to determine the independent association of BFCRS total score with complete recovery.

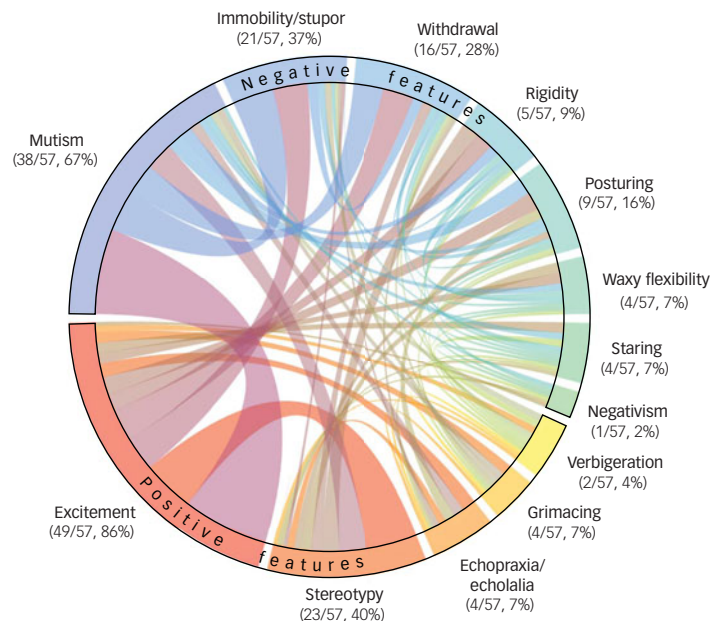
## Results

In total, the cases of 57 patients were analysed (median age 8 years, range 1.3–17; 40 females). A median of three catatonic features were identified per patient (range 0.5–10). Figure 1 details the frequency of each feature within the cohort, and co-occurrences of feature pairs within individual patients (shown as connections between features). Two or more catatonic features were present in 49/57 patients (86%), of whom 34 (69%) had both positive and negative features, 10 (20%) had positive features only, and 5 (10%) had negative features only.

Catatonia was recognised by the reporting physician in only 16/49 patients (33%). Patients with recognised catatonia were older (median 14.5 v. 7 years,  $P < 0.001$ ) and had a greater number of positive (median 2 v. 1,  $P = 0.034$ ) and negative (3 v. 1.5,  $P < 0.001$ ) catatonic features. Five (31%) were treated with lorazepam, without sustained response. Eleven (69%) were treated with antipsychotic medications, with adverse effects reported in five (45%): central nervous system depression and extrapyramidal signs with haloperidol ( $n = 3$ ), worsening dystonia with olanzapine ( $n = 1$ ), and orofacial dyskinesia with risperidone ( $n = 1$ ). In all patients, symptoms of catatonia improved only after initiation of immunotherapy.

Associations of clinical characteristics with catatonia score are detailed in Table 1. Higher catatonia score was associated with a

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**Fig. 1** Catatonic features and clinical characteristics in children and adolescents with *N*-methyl-D-aspartate receptor antibody encephalitis. Frequency of catatonic features and co-occurrence of features within individual patients.

Chord diagram: blue–green node segments represent negative features and red–yellow segments represent positive features of catatonia. *n/N* (%) indicates the frequency of feature occurrence within the whole cohort. Arc connections represent flow between features, such that arc thickness is proportional to the number of individual patients in which connected features co-occurred. Mannerisms were also reported in one patient, excluded from figure because of the absence of co-occurrence with any other features. Figure produced in Python 3.6 with code adapted from *Matplotlib-chord-diagram* (Feng Wang, MIT).

clinical history of prodromal infectious illness (median score 4 v. 3,  $P = 0.03$ ) and complete recovery from NMDARE (4 v. 3,  $P = 0.009$ ). Complete recovery occurred in 25/57 patients (44%). There was no significant difference in follow-up duration between those with complete recovery (median 7 months, interquartile range (IQR) = 4.5–17, range 2–54) and those without (median 9 months, IQR = 3–18.75, range 1.3–33) ( $P = 0.764$ ). To evaluate the independent association of catatonia score with complete recovery (controlling for differences in age and other clinical characteristics) we fitted a multivariate logistic regression model (Supplementary Table 1 available at <https://doi.org/10.1192/bjo.2020.55>). The presence of each additional catatonic feature (+1 BFCRS score) was associated with 2.08 (CI 1.20–3.60) times increased odds of complete recovery ( $P = 0.009$ ).

## Discussion

In total, 86% of children and adolescents with NMDARE had signs and symptoms consistent with catatonia, in keeping with previous reports of catatonia in 19–88% of NMDARE patients.<sup>4,6,7</sup> The symptomatology was complex, with 69% of affected patients manifesting both positive (hyperkinetic) and negative (hypokinetic) features. Only 33% were recognised as catatonic by the reporting physician. These were predominantly neurologists, who may tend to interpret movement disorders within a purely neurological paradigm, failing to recognise catatonia as a neuropsychiatric syndrome bridging across traditional symptom domains. Catatonia is not an aetiological diagnosis, but rather a psychomotor dysregulation syndrome with many causes; determination of the cause in the individual patient is of key clinical importance.

Symptomatic treatment with lorazepam was ineffective in this cohort, in keeping with previous reports in adult NMDARE,<sup>6</sup> and in contrast to the majority of patients presenting to general psychiatry with catatonia, 88% of whom improve with lorazepam.<sup>9</sup>

Lorazepam acts by potentiating the effect of the inhibitory neurotransmitter  $\gamma$ -amino-butyric acid (GABA) at the GABA-A receptor;<sup>10</sup> the hypothesised inactivation of GABAergic neurons in NMDARE<sup>11</sup> may explain the reduced efficacy of the drug in this disease. Failure to respond to lorazepam should therefore prompt careful evaluation for an underlying neurobiological disorder in patients who are catatonic. Adverse effects of antipsychotics occurred in 45% of those treated, in keeping with previous reports in paediatric NMDARE.<sup>12</sup> The reasons for this remain unclear, but likely result from complex interactions of cortical and subcortical NMDAR hypofunction with dopaminergic and other neurotransmitter pathways, confounded by a host of other factors experienced by the critically ill patient. The only effective intervention for catatonia in this cohort was early initiation of immunotherapy.

In our exploratory analysis of clinical characteristics associated with catatonia, contrary to previous reports of worse outcome with paediatric NMDARE with catatonia,<sup>13</sup> we surprisingly found complete recovery was associated with a greater number of catatonic features during the illness course. This is consistent with findings in adults with NMDARE, in which both status epilepticus and death occurred more often in patients without catatonia.<sup>6</sup> Recent research implicates dysregulation and hyperactivity of the cortical supplementary and presupplementary motor areas as a pathophysiological mechanism in catatonia;<sup>9</sup> it may be that patients who are more severely encephalopathic (who tend to have worse outcome) are unable to support any organised output of cortical motor circuits, and so are unable to manifest the behavioural signs of catatonia.

This retrospective study has a number of limitations, including scarcity of detailed information available in case reports for catatonia scoring, bias towards atypical cases in such reports, variable terminology used by authors (typically non-psychiatrists) to describe psychomotor signs and symptoms, and diagnosis that was not always confirmed with cerebrospinal fluid testing. In addition, our analysis of associations with clinical features was exploratory and uncontrolled for multiple comparisons. In summary, we found

**Table 1** Associations of clinical characteristics with catatonia score (Mann–Whitney *U*-test)<sup>a</sup>

	<i>n/N</i> (%)	Bush-Francis Catatonia Rating Scale total score, median (range)	<i>P</i>
Gender			
Female	38/57 (67)	3 (0.5–10)	0.515
Male	19/57 (33)	3 (1–9.5)	
Tumour			
Present	5/56 (8.9)	3 (2–10)	0.716
Absent	51/56 (91)	3 (0.5–9.5)	
Infectious prodrome			
Present	19/57 (33)	4 (1–10)	0.03
Absent	38/57 (67)	3 (0.5–9)	
Psychotic features <sup>b</sup>			
Present	17/57 (30)	4 (1–9)	0.077
Absent	40/57 (70)	3 (0.5–10)	
Movement disorder <sup>c</sup>			
Present	17/57 (30)	3 (2–10)	0.168
Absent	40/57 (70)	3 (0.5–9.5)	
Seizures <sup>c</sup>			
Present	18/57 (32)	3 (1–10)	0.728
Absent	39/57 (68)	3 (0.5–9)	
MRI brain			
Normal	18/33 (55)	4 (2–10)	0.301
Abnormal	15/33 (45)	3 (1–6.5)	
CSF pleocytosis <sup>d</sup>			
Present	22/34 (65)	3.25 (1–10)	0.659
Absent	12/34 (35)	3 (2–5.5)	
Recovery			
Complete	25/57 (44)	4 (1.5–10)	0.009
Incomplete	32/57 (56)	3 (0.5–6.5)	

MRI, magnetic resonance imaging.  
a. Electroencephalogram was abnormal in all 34 patients with data reported, and therefore not included in the analysis.  
b. Delusions, paranoia, hallucinations or thought disorder reported at any time.  
c. At presentation to hospital.  
d. >5 leucocytes/ $\mu$ L in cerebrospinal fluid (CSF).

features consistent with catatonia were highly prevalent in paediatric NMDARE. Catatonia was characterised by mixed or fluctuating symptomatology, resistance to lorazepam and antipsychotic intolerance. Symptoms resolved only with immunotherapy in all cases, highlighting the importance of prompt recognition and treatment of the underlying cause of catatonia.

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## Data availability

The search criteria and papers included in our previously reported systematic literature review are provided in Appendix e-1 of Byrne et al.<sup>5</sup>

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## Author contributions

M.E. contributed to data analysis and wrote the first draft of the manuscript. A.K. contributed to study formulation/design and data collection. E.B. and M.D.K. contributed to study formulation/design. T.P. contributed to data analysis. R.C.D. contributed to data collection and data analysis. S.B. and M.L. contributed to study formulation/design, data collection and data analysis. All authors contributed to data interpretation and drafting, revising and approving the final manuscript.

## Declaration of interest

M.E. reports a travel grant from Terumo BCT, outside the submitted work. R.C.D. reports honoraria from Biogen Idec and Merck Serono as invited speaker, outside the submitted work. M.L. reports personal fees from the Advisory Board Octopharma, and non-financial support from Advisory Board CSL Behring, outside the submitted work. A.K., E.B., M.D.K., T.P. and S.B. report no disclosures.

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## Supplementary material

Supplementary material is available online at <http://doi.org/10.1192/bjo.2020.55>

