



Catatonia in neurodevelopmental disorders: assessing catatonic deterioration from baseline

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Despite the inclusion of catatonia as a specifier of autism spectrum disorder in DSM-5, we—a team of child and adolescent neuropsychiatrists who specialise in paediatric catatonia and neurodevelopmental disorders—have identified a number of issues with the diagnosis and clinical management of catatonia in our patients. In this Personal View, we summarise the literature regarding catatonia in people with neurodevelopmental disorders, including autism spectrum disorder, describe our concerns, and offer a novel approach to addressing important issues with current diagnostic and treatment paradigms. We emphasise the need for a measure to diagnose and monitor people with catatonia and their history of neurodevelopmental disorders. This measure should consider previous complex and underlying motor, medical, functional, and neurobehavioural symptoms. We propose two concepts for understanding catatonia that relate to the baseline status of an individual: the personalised score at baseline, an estimate of premorbid neurobehavioral and motor symptoms, and the catatonic deterioration from baseline, an estimate of current features that are due to catatonia rather than an underlying neurodevelopmental disorder. We hope this measure will provide a practical tool for clinicians and researchers working with this underserved and high-risk population.

Introduction

Historically, catatonia has been most associated with adult psychiatric conditions, particularly schizophrenia and bipolar disorder.¹⁻³ However, in the past 10 years, paediatric catatonia has been increasingly recognised and underlying neurodevelopmental and genetic disorders have been shown to be substantial catatonia risk factors in both children and adults.⁴⁻⁷ In 2013, among other changes, catatonia was added as a specifier of autism spectrum disorder in DSM-5. However, we, a team of child and adolescent psychiatrists who specialise in paediatric catatonia and neurodevelopmental disorders, have identified several problems with the diagnosis and clinical management of catatonia in our patients.

Catatonia is under-recognised in some populations with neurodevelopmental disorders, including patients with profound symptoms of neurocognitive delay and intellectual disability, language impairment, and extensive care requirements. These populations include patients with intellectual disability associated with specific underlying causes, such as neurometabolic, genetic, and toxic causes, autoimmune conditions, and iatrogenesis. Many of these patients might meet the criteria for comorbid autism spectrum disorder. Our focus in this Personal View is on patients with a range of neurodevelopmental disorders that confer risk of catatonia; these patients often have intellectual disability or autism spectrum disorder, but not every individual with one of the neurogenetic, neurometabolic, or other syndromes discussed here has these comorbid diagnoses. Other forms of neurodevelopmental disorders, such as ADHD and Tourette syndrome, regardless of level of symptom severity, are not addressed in this Personal View. We are using the term profound in relation to neurodevelopmental disorders and autism as an extension of the concept described by Lord and

colleagues.⁸ Underlying repetitive behaviours, language disorders, motor stereotypies, and other common features seen in individuals with autism and neurodevelopmental disorders have been well documented to result in diagnostic confusion because of their overlap with core features of catatonia.^{6,9,10}

The presence of catatonia can worsen underlying symptoms, course, and outcomes for people with neurodevelopmental disorders,¹¹⁻¹³ resulting in a need to prioritise rapid diagnosis and treatment. No systemic studies have verified whether presentations of catatonia differ according to psychiatric versus neurodevelopmental causes, and further research is required to stratify these symptoms across underlying causes.

Prevalence estimates for children and young adults with catatonia vary from 0.6–17.0% in paediatric psychiatric inpatients.¹⁴⁻¹⁷ In adolescents and adults with autism, catatonia is estimated to occur in 4–17% of individuals.^{6,13,18,19} In some groups, rates can be considerably higher; for example, for people with Phelan-McDermid syndrome, in whom catatonia is estimated to occur in 53% of individuals.²⁰ People with Down syndrome appear to be at increased risk of development of catatonia because it can occur as a core feature of Down syndrome regression disorder.²¹ Catatonia has also been reported in individuals with 22q11 deletion syndrome, Prader-Willi syndrome, and many other genetic syndromes that we discuss in this Personal View.²²⁻²⁵ Catatonia has the highest mortality risk of any paediatric psychiatric diagnosis, with up to 20% mortality rate in untreated malignant catatonia.²⁶

Catatonia and regression

Catatonia and regression are sometimes confused in the literature, sometimes being used interchangeably and at other times referring to distinct phenomena. In our opinion, catatonia is a syndrome with severe, multimodal

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symptoms that can be triggered by psychiatric disorders, neurodevelopmental conditions, medical causes, therapeutic or recreational drugs, and trauma.^{5,16,27–29} Catatonia leads to behavioural and skill regression, but not all regressions are catatonia. Regression can be defined as pervasive functional decline, often characterised by loss of previously acquired skills, such as the management of daily activities. A retrospective study found that 3 of 20 of individuals with autism who that presented with regression during adolescence did not meet the criteria for catatonia,³⁰ supporting the idea that regression and catatonia are not always synonymous in autism. Nonetheless, catatonia can be associated with, or occur as an expression of, regression in various neurodevelopmental disorders, such as Down syndrome,^{21,31,32} *SHANK3*-related Phelan-McDermid syndrome,^{33–35} and epileptic encephalopathy.³⁶ As a result, catatonia should be considered and systematically assessed for in individuals with neurodevelopmental disorders presenting with new developmental regression. In these contexts, symptoms could improve with standard catatonia treatments and drugs to treat the underlying causes.¹⁶

Although some patients with regression show catatonic features, there are specific neurogenetic disorders in which regression is part of the natural history of the underlying disorder, is clearly not catatonia, and does not respond to catatonia treatments. This natural history of regression has been well described in individuals with neurodevelopmental disorders, such as Rett syndrome and Kleefstra syndrome,³⁷ and in paediatric neurodegenerative disorders, such as Batten disease or juvenile Huntington's disease.³⁸ Catatonia can occur alongside the progression of a disease or disorder in some of these individuals, further complicating classification (panel).

Diagnostic and treatment standards of care in paediatric catatonia

The Bush-Francis catatonia rating scale (BFCRS) is the gold standard for diagnosis and monitoring of catatonia.^{39,40} A version of the BFCRS, the paediatric catatonia rating scale (PCRS), has been validated in paediatric populations incorporating, for example, regression symptoms such as incontinence.⁴¹ Even with these validated approaches, challenges to the diagnosis and monitoring of catatonia in children with neurodevelopmental disorders remain—for example, when patient cooperation with a comprehensive catatonia examination is suboptimal.^{16,41}

Benzodiazepines, specifically lorazepam, are the first-line medication for paediatric and adult patients with catatonia.⁴² In a naturalistic study of 66 children and adolescents with catatonia, the response rate for benzodiazepines was approximately 65%.⁴³ Patients with catatonia and underlying autism spectrum disorder might require higher doses of benzodiazepines (eg, up to 30 mg per day) than those without autism spectrum

disorder.⁴⁴ Benzodiazepines are generally well tolerated in children and adolescents, and excessive sedation is the most frequently reported side-effect.⁴³ Successful use of diazepam and oxazepam were reported in adults^{45–48} but so far not in paediatric populations. No controlled studies support the preferential use of one specific benzodiazepine for paediatric catatonia. Electroconvulsive therapy can be considered in patients aged 13–21 years with catatonia that is resistant to benzodiazepines or, in severe cases, with life-threatening conditions, such as malignant catatonia.⁴⁹ Response rates of 76–92% were reported in patients aged 13–21 years with lorazepam-resistant catatonia,^{43,50–52} showing electroconvulsive therapy to be effective and safe in this population.

Catatonia in people with neurodevelopmental disorders

Catatonia and autism

Most data regarding catatonia in neurodevelopmental disorders focus on people with autism. Therefore, to provide a framework for the consideration of catatonia in other neurodevelopmental disorders, we will briefly review the conceptual history of the relationship between autism and catatonia. In 1979, Karl Leonhard⁵³ was the first to propose distinguishing catatonia from other mental conditions in youth (ie, preschool to teenage). He listed the differences between “infant catatonia”, autism, and the “state of feeble-mindedness”. In the late 1990s and early 2000s, various authors stressed the need to separate catatonia from motor dysfunctions associated with autism.^{6,13,51} In 2013, the American Psychiatric Association supported recognition of catatonia as a syndrome which can be associated with different medical and psychiatric diagnoses, including autism.^{14,28}

In 2000, Wing and Shah⁶ highlighted the substantial overlap of behavioural features shared by autism and catatonia. They proposed the idea that a diagnosis of catatonia should be made when the exacerbation of particular features of behaviour occurred to a notable degree, sufficient to interfere with movement and daily functions. The overlapping behaviours included echo phenomena, mannerisms, ritualised behaviours, and negativism. The authors emphasised the slowness, amotivation, and prompt dependence that often characterised catatonia in individuals with autism. They also questioned the nature of the relationship between the two disorders.⁶

Dhossche¹¹ then proposed a new hypothesis in 2004, suggesting that, in some cases, autism might be an early expression of catatonia. The relationship between autism and catatonia was elaborated by Dhossche and Rout⁵⁴ in 2006, and in the same year, Ohta and colleagues¹³ discussed the idea that catatonia in autism could be considered an epiphenomenon of autism or a manifestation of comorbidity in adolescence or early adulthood. Ohta and colleagues¹³ found that most of their

patients (eight [73%] of 11) had prodromal symptoms, typically a gradually emerging sluggishness with compulsive behaviours lasting for more than 1 year before the manifestation of typical catatonia.¹³

In 2019, Wachtel⁵⁵ published a retrospective cohort study of 22 patients with autism spectrum disorder and catatonia, highlighting the multiple aspects and facets of catatonia presentation in these patients. She proposed adding the symptoms of treatment-refractory and repetitive self-injurious behaviours devoid of environmental function as a recognised motor symptom of catatonia, reinforcing the overlapping connection between the two disorders.⁵⁵ According to this framework, stereotypies and related repetitive behaviours would be considered catatonic features if they exceeded baseline stereotypical behaviours as reported in the developmental history by parents or caregivers. Similarly, self-injurious behaviours, a form of stereotypy found in both catatonia and autism, would be considered a catatonia symptom if no specific social or operant function could be found during thorough behavioural evaluation.^{51,56}

Breen and Hare⁵⁷ proposed that catatonic features in autism might be attenuated behaviours, which can be assessed with a validated 34-item rating scale (ie, the Attenuated Behavior Questionnaire). This questionnaire has also been used in other genetic conditions, including Cornelia de Lange syndrome and fragile X syndrome.⁵⁸

The prevalence of psychiatric comorbidity among people with autism, including those with high cognitive functioning, is estimated to be around 70%.⁵⁹⁻⁶¹ Among the most frequent diagnoses are mood disorders, anxiety, and obsessive-compulsive disorder.⁵⁹⁻⁶¹ The high rate of comorbidities that have independent risks of catatonia, such as depression and schizophrenia, confounds establishing which cause is most responsible for the risk of catatonia, particularly in people with autism without intellectual disability. Psychomotor disturbances, social withdrawal, mutism, stereotypy, and echo phenomena are characteristics of both schizophrenia spectrum disorders and autism spectrum disorder. The presence of hallucinations in autism, although not common, has been reported, especially in high cognitive functioning individuals.^{62,63} Catatonia, psychosis, and autism, which have long been considered to be competing diagnoses, are now being evaluated as entities with at least some shared features, if not overlapping risk factors, genetic loci, and causes. Therefore, establishing catatonia in individuals with autism remains challenging for clinicians.

Catatonia in individuals with other neurodevelopmental disorders

A broad range of genetic conditions, with or without associated autism, have been described in association with paediatric catatonia.⁴ In a retrospective study of 89 patients with catatonia, these conditions included single-gene conditions (eg, Huntington's disease, fatal

Panel: Case vignettes

All families provided written informed consent for the anonymous use and publication of clinical data of their children for the purpose of this paper.

Case 1 involves an adolescent woman with stuporous catatonia in the setting of Down syndrome, consistent with Down syndrome regression disorder. The underlying cause was established to be neuroinflammatory due to high concentrations of cerebrospinal fluid inflammatory markers. Lorazepam and intravenous methylprednisolone were initiated, after multidisciplinary consultation, to treat catatonia with underlying autoimmune causes. Extensive tests for medical causes showed that antithyroid peroxidase antibody titres were substantially increased. The patient's catatonia was monitored with the Bush-Francis catatonia rating scale (BFCRS), which was 32 at the time of presentation before treatment. Catatonia symptoms included mutism, staring, posturing, grimacing, echolalia and echopraxia, stereotypy, mannerism, negativism, withdrawal, automatic obedience, passive obedience, so-called motor stuckness, and so-called anglepoise lamp arm (ie, *mitgehen*).

Case 2 involves a primary-school-aged girl with Rett syndrome presenting with mixed catatonia. Her catatonia was monitored with the paediatric catatonia rating scale (PCRS), which was 25 at the time of presentation. She was treated with 1 mg of lorazepam up to 8 times a day. Extensive tests were negative for known causes other than Rett syndrome. Catatonia symptoms included negativism, new-onset incontinence, echopraxia, posturing, waxy flexibility and rigidity, staring, and grimacing.

In both cases, in the setting of underlying neurodevelopmental disorders, catatonia rating scale scores remained high after extensive treatment (ie, BFCRS of 10 and PCRS of 13). There was substantial improvement compared with the time of presentation, but because of the the underlying motor and behavioural symptoms, whether treatment had been fully effective or whether further intervention might be required or lead to additional improvement was not clear based on rating scale scores alone.

For both patients, a personalised score at baseline was estimated on the basis of discussions with family members, reviewing old medical records, and watching home video footage provided by the families. The personalised baseline was scored at 9 for the patient in case 1 (with BFCRS) and 12 for the patient in case 2 (with PCRS). In the patient of case 1, symptoms that were present before the onset of catatonia included echo phenomena, stereotypies, manneristic behaviour, automatic obedience, passive obedience, and grasp reflex. In the patient of case 2, symptoms that were present before the onset of catatonia included axial stereotypies, psychomotor excitement, grimacing, fluctuating incontinence, staring, and persistent rigidity. Improvements in regression and other catatonia symptoms with lorazepam in the patient in case 2 suggest that this regression was consistent with catatonia rather than being caused by the natural course of Rett syndrome alone. Therefore, the catatonic deterioration from baseline for the patient in case 1 was 23 (with BFCRS) and 13 in the patient of case 2 (with PCRS).

Although their catatonia rating scale scores remained high after treatment, a final catatonic deterioration from baseline score of 1 was estimated for both patients on the basis of the catatonic deterioration from baseline scores. This score suggests that in the patients of both cases the personalised score at baseline had almost been reached after treatment, representing a near, but not entirely complete, resolution of catatonia symptoms. These cases suggest there might be additional, minor modifications that could be made to the regimen of each patient, and they show that a reduction of BFCRS or PCRS to 0 would not have been realistic for either patient because of their historical baseline.

familial insomnia, *PRODH* mutations, Kleefstra syndrome, and Sanfilippo syndrome), copy number variations (eg, 22q13.3 deletion including the *SHANK3* gene, 16p13 duplication, and 8p23.3 deletion), cytogenetic

atypicalities (eg, Down syndrome), and metabolic conditions.⁴

As with the challenges with co-occurring autism, atypicalities of movement in some of these disorders create additional confusion for clinicians. These atypicalities include bradykinesia and parkinsonism in juvenile Huntington's disease,⁶⁴ Rett syndrome,⁶⁵ and dopa-responsive dystonia;⁶⁶ motoric stereotypies in 22q11.2 mutation;²³ dystonia in cerebral palsy;⁶⁷ hypotonia in Prader-Willi syndrome;²⁵ and ataxia in Niemann-Pick type C.⁶⁸ The presence of catatonia in complex epilepsy syndromes, such as Lafora disease, has also been reported.⁶⁹

Neurobehavioral symptoms can create confusion for clinicians in the setting of catatonia. Examples of these symptoms include echo phenomena in fragile X syndrome,⁷⁰ changes in speech and swallowing in Wilson disease,⁷¹ and episodic regression and functional changes in Phelan-McDermid Syndrome.⁷² Automatic obedience can be confused with routine compliance, for example in an individual who is used to receiving considerable assistance with activities of daily living from adults or differential reinforcement and who thus might readily comply with requests. Onset of dysautonomia, which can be a sign of catatonia, might also create challenges for clinicians in properly diagnosing catatonia in specific populations. For example, this dysautonomia can occur in individuals with Rett syndrome who might already be prone to autonomic instability.⁷³ Some behavioural changes, such as food intake reduction, might be misattributed to underlying neurodevelopmental disorders and associated food selectivity even if they are a novel symptom for the individual that might be more consistent with catatonic negativism.

Confusion of clinicians as to whether these symptoms are part of an underlying neurodevelopmental disorder or whether they represent the onset of catatonia has considerable risk: for example, in the onset of malignant catatonia or the development of chronic catatonia, delayed onset of appropriate treatment unnecessarily extends the illness state.^{9,10,16,27} This risk highlights the need for measures that consider baseline neurological function in individuals with neurodevelopmental disorders in catatonia assessment and monitoring.

Because of the uncertainties in catatonia diagnosis and monitoring, we have tried to create an approach that uses existing, standardised catatonia rating scales while considering underlying baseline motor, behavioural, and functional status. The aim of this approach is to have a catatonia scale with a starting point that effectively equates to 0 for a patient with neurodevelopmental disorders, to be able to establish the extent of current catatonia and to know when treatment has been sufficient to return the patient to their baseline. The baseline catatonia score of an individual with neurodevelopmental disorders cannot be assumed to be 0, as might be expected in a typically developing

individual whose catatonia is judged to be due to underlying psychiatric conditions such as mood disorders or psychosis.

Assessment of personalised score at baseline and catatonic deterioration from baseline

To account for the uniqueness of each patient with neurodevelopmental disorders, we propose two concepts: personalised score at baseline and catatonic deterioration from baseline. The personalised score at baseline is an estimate that we define as the score an individual would have had on a standardised catatonia rating scale before the onset of catatonia. We then define catatonic deterioration from baseline, a concept drawn from the work of Wachtel,⁵⁵ as the difference between the patient's current score on a standardised catatonia assessment scale and their personalised score at baseline.

Because patients will not have had any reason for a scale, such as a BFCRS or PCRS, to have been completed before the onset of presenting symptoms, a clinician will not have a baseline for comparison at the time of their catatonia evaluation and testing. We recommend that when a patient presents for evaluation and catatonia is suspected, the clinician should first assess the patient's current catatonia status using a standardised assessment tool, such as the BFCRS or PCRS (figure). The personalised score at baseline can then be estimated on the basis of information provided by the family. We recommend the use of documented resources that are available, such as early-intervention reports, neuropsychological or psychoeducational testing, developmental paediatric notes, and individualised educational plans. Although evidence for recollection of past psychiatric history suggests variability in familial recall, we suggest that familial recollection of patient status before catatonia and other informal methods of data collection (figure) are included because families of individuals with neurodevelopmental disorders are often uniquely aware of their changes.⁷⁴ Furthermore, we ask specific questions of families to ascertain the patient's behavioural or mental health status before the onset of catatonia. Although a family might not be able to do a formal catatonia assessment, their recollection of these features could contribute to a clinician's estimation of baseline status that otherwise would not be available. The assessment of the baseline score might require an approximate estimation of when catatonia onset occurred, which might be difficult because of the often subacute or insidious onset in these populations.⁷⁵

As part of the evaluation to estimate the patient's score at baseline, we recommend that clinicians pay particular attention to six red-flag symptoms of catatonia that can easily be confounded or under-rated in individuals with neurodevelopmental disorders. These symptoms include the worsening of stereotypies, new-onset refusal to eat, new-onset or worsening incontinence (or urinary and faecal frequency without other cause), academic or

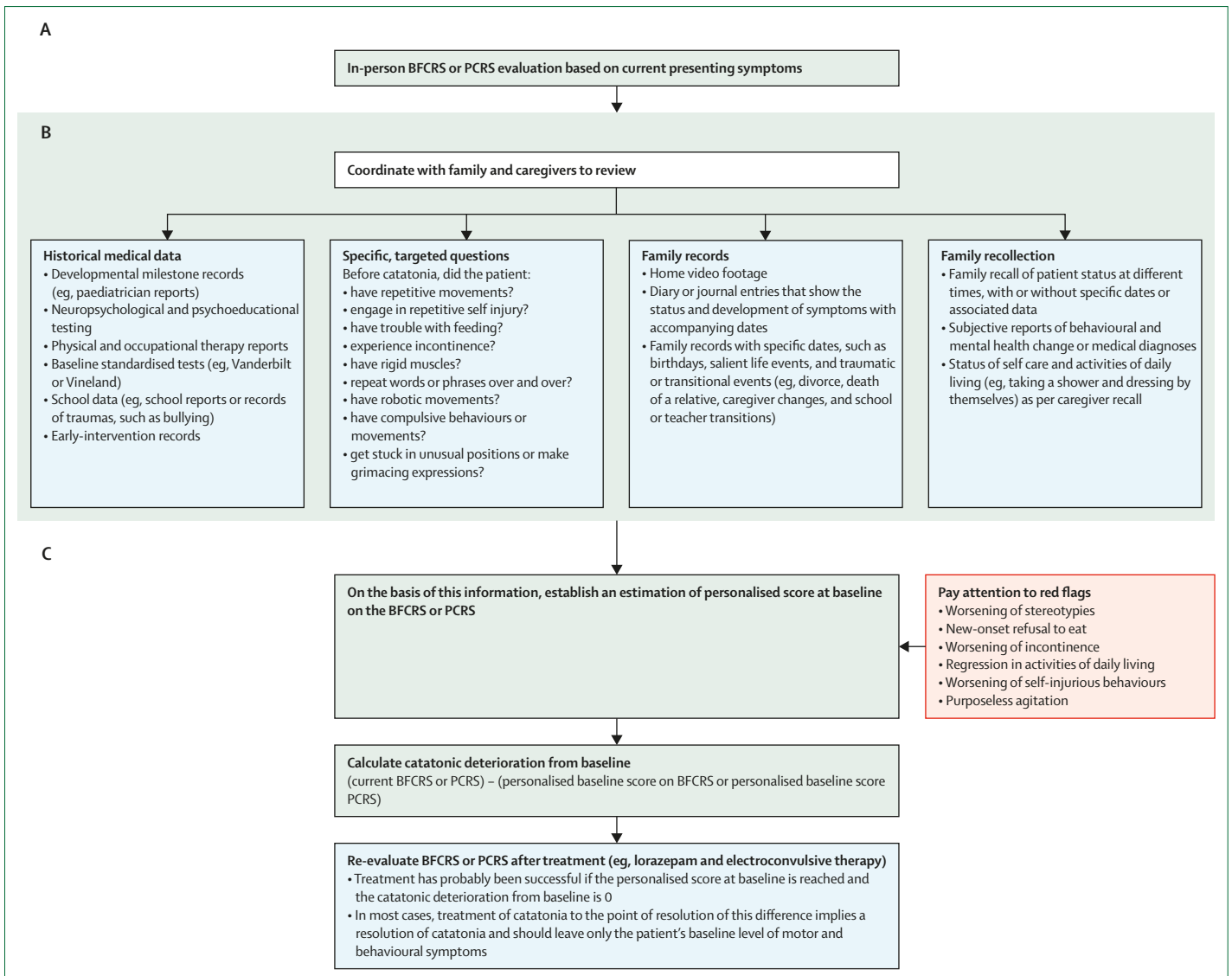


Figure: Assessment of personalised score at baseline and catatonic deterioration from baseline
 (A) Evaluation of catatonia signs and symptoms at the time of presentation. (B) Estimation of the personalised score at baseline for an individual patient with catatonia and underlying neurodevelopmental disability. (C) Assessment of catatonic deterioration from baseline score. BFCRS=Bush-Francis catatonia rating scale. PCRS=paediatric catatonia rating scale.

functional skill regression (or regression in activities of daily living without a known cause), onset or exacerbation of self-injurious behaviours, and purposeless agitation.^{7,16,51,55}

With the estimated personalised score at baseline and the BFCRS or PCRS at the time of clinical presentation, the catatonic deterioration from baseline can then be calculated as the difference between these values (figure). When treating catatonia to the point of resolution of this difference, the catatonic deterioration from baseline value can function as a marker of successful management. After treatment, the patient's baseline level of motor, vocal, and behavioural symptoms should remain. To show the practical challenges that this approach

addresses, we present two cases: one that used BFCRS for an adolescent young woman with Down syndrome and another that used PCRS for a primary-school-age girl with Rett syndrome (panel).

These cases show the extent to which the use of the catatonic deterioration from baseline score can help clarify when treatment has been adequate. Some patients with catatonia in the setting of neurodevelopmental disorders return to the baseline scores, whereas others continue to show features of regression.^{21,24,32} The use of the catatonic deterioration from the baseline score can still be helpful in evaluating adequate treatment and differentiating catatonic symptoms from other features of their presentation.

Conclusion

The use of the personalised score at baseline and catatonic deterioration from baseline might help diagnose catatonia in individuals with neurodevelopmental disorders and define treatment response. Because of the scarcity of existing protocols in this patient population, we feel these two scores potentially overcome a relevant issue in care, and we encourage further validation of this measure.

We also emphasise the need to consider other causes of catatonia in all patients with multiple disorders. Diagnoses, such as autoimmune encephalitis, can occur in individuals with underlying neurodevelopmental disorders, just as they might occur in developmentally typical paediatric patients, and commonly include components of catatonia.²⁴ Furthermore, regression or catatonia can be clinical features of neurodegenerative disorders of childhood. Therefore, the onset of these symptoms requires adequate medical evaluation and treatment of underlying illness. The treatment of catatonia should not occur at the expense of appropriate diagnostic testing and treatment of possible underlying conditions.^{4,5,16,29}

Some limitations of this measure should be considered and the use of the two scores will be appropriate for some but not all patients. For example, this approach assumes that there is a distinct period before catatonia that can be identified. For some individuals with neurodevelopmental disorders, this distinction might be difficult, such as for a non-verbal individual with severe motor stereotypies at baseline for whom catatonia onset was subacute or occurred in the remote past. Despite this limitation, we believe the personalised score at baseline and the catatonic deterioration from baseline will allow for minimisation of the risk of catatonia misdiagnosis in patients with neurodevelopmental disorders, and we hope that this tool will provide identifiable endpoints for symptomatic catatonia treatment.

Contributors

AJH and VF conceptualised the manuscript, searched the literature, and created the figure. AJH, VF, DC, and LW wrote the original draft. All authors reviewed and edited the manuscript, had full access to all the data in the study, and had responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

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