Catatonia: an under-recognised, acutely treatable condition in young people with intellectual disability/ASD.

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A case example

A 15-year-old girl with Down Syndrome was referred to neurology due to a neurocognitive decline over a two-month period. She had been socially active, happy, cheeky, talkative and an enthusiastic school attender. She had acquired basic self-care and hygiene skills, and achieved primary school educational skills. At a school swimming carnival, the girl was severely sunburnt. That night she became a little delirious and was uncharacteristically incontinent; this incontinence persisted. The next day she was found sitting in bed with arms out stiff and staring blankly. A GP review revealed nothing, with a normal urine screen. Over the next month she became progressively quieter until she became mute. She also became apathetic and lost interest in her craft activities and watching DVDs. This progressed on to the girl struggling to dress herself, and appearing confused.

Thorough neurological investigation for a progressive neurocognitive decline revealed nothing, including an EEG which was normal, and MRI which showed non-specific findings. Her course was somewhat fluctuating, recovering approximately 40% of her function before deteriorating again. She had also been eating less and lost some weight. At meals she would not hold her cutlery or would continue to spoon her food into her mouth when her bowl was empty. A differential diagnosis of post traumatic stress or catatonia was considered and she was referred to the Developmental Psychiatry Team approximately 6 months after the initial presentation. Presenting symptoms included anhedonia (see pg 10), decreased appetite, hypersomnia. She had mutism, withdrawal, immobility, bizarre posturing, muscle stiffness, waxy flexibility, extreme slowness, stereotypies, and was getting stuck in doorways. She was thought to have had seizure activity, for example, going stiff in her limbs following nocturnal enuresis (see pg 10). She was attentively cared for by her family. On examination, she had marked motor retardation and had a halted, slow, wide-based gait. She whispered inaudible words in the consultation and didn't respond to questions. She had waxy flexibility and mild increased muscle tone. She drew a few small indistinct pictures and was eventually able to write her name. She appeared to respond to unseen stimuli. There was no access to her internal mental state but she did laugh to herself regularly, out of context. It was not possible to assess her cognitive skills.

The girl was diagnosed with a psychotic disorder with catatonic features and started on olanzapine 2.5mg three times daily (tds), adding 0.5mg lorazepam tds a week later which was increased to 1mg tds two weeks later. There was clear improvement of about 35%, with the girl becoming more mobile, verbal and interactive but still extremely impaired. The olanzapine was changed, due to marked weight gain, to aripiprazole increasing from 5mg to 10mg and finally 15mg. She continued to slowly improve to 45% functional gain. On the assumption that lorazepam was a short term treatment, it was withdrawn after 6 weeks but there was an immediate deterioration back to a 20% gain and it was promptly restarted. However, her previous progress was not recaptured. Accordingly, 6 weeks later fluoxetine was added gradually, increasing from 5mg to 20mg.From this point, she made slow and steady improvement. The girl was able to restart school, began to slowly re-engage with peers and other family members, and she regained her pre-morbid personality with an increase in happiness and cheekiness. She became more relaxed and more able to contribute to the clinical interview. Her full recovery took 9 months from mental health presentation.

Description

Catatonia is a state of apparent unresponsiveness to external stimuli in a person who is apparently awake. It is a potentially life-threatening neuropsychiatric syndrome characterized by a variety of behavior and

movement traits. The individuals often can't provide a coherent history and family members describe the typical primary features including: immobility, stupor, posturing, rigidity, staring, grimacing, and withdrawal. The behavioural history includes mutism, negativism, echopraxia, echolalia (see pg 10), waxy flexibility and withdrawal. It also involves stereotypies, mannerism, verbigeration (stereotyped repetition of words or phrases) and rarely priapism. Patients are often immobile, mute, grimacing, posturing, rigid and refusing to eat or drink.

Alternatively, catatonia can present as an excited state possibly with impulsivity, combativeness and autonomic instability. This excited state is often short lived and not reported by family members. The excited state is often associated with bipolar disorder. Psychomotor manifestations of catatonia, when analysed by latent class statistics divided into four classes: withdrawal, automatic, repetitive and agitated/resistive.

Catatonia is difficult to differentiate from diffuse encephalopathy (see pg 10) and non-convulsive status epilepticus . Since I trained its status has changed from a dramatic presentation of 'non-verbal psychosis' to a broader neuropsychiatric disorder. Its presentation is observed in a wide variety of disorders with a considerable differential diagnosis and an urgency to identify treatable medical conditions.

Associated Medical Conditions

An initial interview with a patient must consider precipitating events including infection, trauma and exposure to toxins and other substances. In the emergency department treatable common causes need to be rapidly considered, including neuroleptic malignant syndrome, encephalitis, non-convulsive status epilepticus and acute psychosis. Comorbid disorders include affective disorders (46%), schizophrenia (20%), schizoaffective disorder (6%), psychological stressors, medical, neurological and obstetric conditions (16%), benzodiazepine withdrawal (4%) and other psychiatric disorders (8 %). It can be caused by various drugs such as levetiracetam, levofloxacin and rimonabant. Nine to fifteen percent of patients admitted to an acute care psychiatric service meet criteria for catatonia. The medical causes are varied, including neurological disorders (e.g., frontal tumour, petit mal epilepsy, metabolic disorders (including porphyria and ureamia), endocrine disorders (e.g., hyperparathyroidism), autoimmune disorders (e.g., systemic lupus erythematosus), intoxications (e.g., organic phosphates, carbon monoxide), and drug treatment (e.g., neuroleptics, disulfiram).

Treatment

One of the most dramatic clinical phenomena is the response of catatonia to treatment with benzodiazepines. In fact, catatonia has been conceptualized as a GABA (gama amino butyric acid) deficiency state. Within three hours of receiving lorazepam 1-3mg sublingually or intramuscularly, the majority of patients enjoy complete release from their frozen state (80% affective states, 70% schizoaffective, but less with schizophrenia). Some standardise the lorazepam test to last for 5 days. Electroconvulsive therapy (ECT) is the second line treatment. Case examples in the literature describe those that died, the life saving capacity of ECT in those that failed to respond to lorazepam and other psychotropics, but also how occasionally heroic doses of lorazepam and lorazepam for up to a year may be needed.

Literature review

Although Kahlbaum first described catatonia in 1874, his work was only translated into English in 1973. Kreplin included catatonia in his description of Schizophrenia or dementia praecox in 1896. Autism was first described in connection with schizophrenic negativism by Bleuler in 1910, although Kanner's description of autism was not published till 1944. The identification of catatonia as a distinct condition has

only occurred in the last 20 years, with factor analysis studies using reliable rating scales. Modifications of diagnostic categories in DSM-5 (APA, 2013) emphasises the importance of medical/neurological disorders.

Catatonia in ASD/ID

Catatonia is significantly associated with Autism Spectrum Disorder (ASD) and intellectual disability. The longitudinal study of ASD by Lockyer and Rutter (1970) found that 12% of the subjects showed neurologic regression marked by loss of language skills, inertia and intellectual decline accompanied in many cases with onset of seizures.

Wing and Shah (2000) did a diagnostic study of Catatonia in ASD, in which of 500 presentations to their ASD service, 17% (n=30) of those aged between 15-50 were diagnosed with catatonia which constituted 6% of all presentations. Their findings included:

- *Onset:* The age of onset for the vast majority (23) was between 10-19 years. A further eight had intermittent episodes, sometimes in only one setting such as school. In 15 individuals, the onset was immediately preceded by a period of very disturbed, often aggressive behaviour. Eight individuals developed obsessive-compulsive symptoms before they became catatonic. Six of these were among those who had shown disturbed, aggressive behaviour before the onset of catatonia.
- *Precipitating factors:* Possible precipitating factors were suggested for another 13 including bereavement, pressure at school, lack of structure after leaving school, and lack of occupation. These individuals did not communicate their feelings about these events and the connection with the onset of the catatonia was made by the parents or other caregivers.
- *Course:* Three individuals experienced a slow but steady deterioration in mobility and practical skills, 17 had a steady course once the catatonia was established, while four had shown minor and six had shown major fluctuations in severity.
- *Abnormalities of movement:* Most of the abnormalities of movement resulted in slowing or stopping activities, but episodes of excitement and sudden impulsive actions also occurred. Some could not stop actions once started. Incontinence resulted when the individual concerned did not initiate the movement needed to reach the toilet.
- *Other behaviours:* 12 individuals showed bizarre behaviour that could not be classified under other headings. For example, two individuals would never use one arm and hand (the left in one case and the right in the other), although no physical reason could be found. One man walked the same route to the same destination each day in order to stand motionless, staring for 2 hours at a spot where a building used to be before it was pulled down. Others had occasional visual hallucinations or paranoid ideas that did not fit any particular diagnosis. According to the accounts given by relatives or carers, none had ever had the first-rank symptoms of schizophrenia.
- *Communication skills:* All subjects showed abnormalities of speech, but these were indistinguishable from those found in autistic disorders. The quantity of speech was in all cases markedly reduced or absent when catatonia was present. Catatonia was seen more often in those who had impaired expressive language, and those who were passive in social interaction, before the onset of catatonia. Within the group of those who developed catatonia, however, the number of catatonic features and the degree to which the catatonia limited everyday activities had no significant relationship to expressive language ability or type of social interaction.
- *Level of intellectual disability:* Catatonia was found slightly more in those with profound or severe intellectual disability, although there was no significant association.

The main limitation of this fascinating clinical cohort is the lack of any account of treatment. Wing and Shah

(2000) considered these were manifestations of a motor/neurological disorder akin to an extrapyramidal disorder or parkinsonian syndrome or even comparing the features of encephalitic lythargica (caused by the influenza epidemic in the 1920s). Their findings emphasized the frequency in children and adolescents.

Catatonia in children and adolescents

Ghaziuddin and colleagues (2012) did a retrospective case review of 'high risk' child and adolescent psychiatric patients at a university hospital and found 17.8% met criteria for catatonia. Their selection of high risk cases included pervasive developmental disorder, psychosis not otherwise specified, intermittent explosive disorder, mental retardation, catatonia and neuroleptic malignant syndrome. The study's defined criteria were three or more of the following: unexplained agitation/excitement, disturbed or unusual movements, reduced movements, repetitive or stereotyped movements, or reduced or loss of speech. This was a strict criterion as DSM-IV (APA, 2000)only required two symptoms.

Analyses of the findings from the Ghaziuddin, Dhossche, & Marcotte (2012) case review revealed that only two out of their 18 cases were diagnosed by their treatment providers at the time, whereas others didn't receive the recognised treatment. Those identified in the study with catatonia who weren't diagnosed at the time included those presenting with pervasive developmental disorder, mental retardation, psychosis-NOS, intermittent explosive disorder, and neuroleptic malignant syndrome. Aggression was a common presentation in both those with catatonia and those without. Stereotyped or repetitive movements were poorly documented. Psychomotor retardation was less prominent than agitation/excitement, which should be considered a hallmark symptom. Males and previous use of antipsychotics were associated with catatonia, but there was only one case of schizophrenia in the series which was in the non-catatonic group.

The implications of the study are that catatonia is frequently missed, rarely treated with benzodiazepines, and CPK and EEGs are rarely performed. The agitated form of the catatonia is more frequent than the the classical motor retardation form. Although this study was limited by being a retrospective chart review, it does suggest that catatonia is not rare in child and adolescent psychiatry. In the 1980s catatonia was thought to be almost extinct , but recent adult prospective studies suggest that there is a prevalence between 7-17% in acute admission with affective or psychotic disorders. Identification can be increased with familiarisation with commonly used rating scales such as the Bush Francis Catatonia Rating Scale (Bush, et al., 1996), the Bräunig Catatonia Scale (Bräunig, et al., 2000) or the Northoff Catatonia Rating scale (Northoff, et al., 1999), that can measure change in symptoms. Catatonia needs to be separated diagnostically from psychosis and schizophrenia, as it is more associated with ASD and developmental disorders. It is also in the differential diagnosis of presentations of aggression or increasing obsessive/ repetitive behaviour.

DSM-5

DSM -5 (APA, 2013) diagnostic criteria requires three of the following the symptoms: Stupor, negativism, waxy flexibility, posturing, mimicking others' speech or movement, lack of response, agitation, grimacing, catalepsy, repetitive movements, echolalia, echopraxia. Although in DSM-5 (APA, 2013) catatonia remains a sub-specifier of psychosis and affective disorder, it has added a category of 'unspecified catatonia' which aims to increase the recognition in paediatric patients, on top of catatonia associated with another mental disorder, and catatonia associated with another medical condition (Dhossche, Goetz, Gazdag, & Sienaert, 2013).

"Catatonia is significantly associated with Autism Spectrum Disorder (ASD) and intellectual disability..."

Catatonia in paediatric patients

In paediatric patients catatonia can be associated with:

- *Developmental disorders:* ASD, childhood disintegrative disorders, intellectual disability of any cause, and Prader-Willi Syndrome.
- *Medical and neurological disorders:* A general medical condition (e.g., brain structural damage), seizures, metabolic, endocrine, and autoimmune disorders.
- *Psychiatric Disorders:* Psychotic disorders, mood disorders, substance-induced disorders, medication -induced movement disorders, tics and Tourette's Disorder.
- *Other disorders:* NMDAR encephalitis, paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), other aseptic encephalitides, Kleine-Levine syndrome, anaclitic depression and pervasive refusal disorder.

Catatonia may be more common in paediatric patients than realized. Prospective studies have found

catatonia in 12% of those with ASD, or 18% in psychiatric clinics, or in 33% in a retrospective study of first break adolescent psychosis. Benzodiazepines and ECT, including maintenance ECT are considered safe and effective in paediatric treatment. The range of aetiology indicates the extent of a medical work up that is required. Neuroleptics should be considered with caution because of the risk of Neuroleptic Malignant Syndrome. Although the lorazepam test is helpful, ECT may still be needed, even for a maintenance treatment. The concept of unspecified catatonia aims to draw attention to catatonia in milder mental disorders, and as a side effect of medications especially in the context of neuroleptic malignant syndrome, or where an associated condition is not identified and to support further research.

The diagnosis is under recognized because of unfamiliarity with the diagnosis, diagnostic overshadowing, where the symptoms are attributed to another condition such as ASD or neurodevelopmental disorders, segregation of mental health patients from mainstream medicine, perceived lack of effective treatment for catatonia, and the neglect of physical and neurological examination by child psychiatrists. Conversely the psychosocial contributors tend to be ignored such as deprivation, abuse or trauma, and labeled anaclitic depression or quasi-autism, reactive psychosis, dissociative disorders or pervasive refusal syndrome. This is then followed by the ambivalence to treatment with high-dose benzodiazepines or ECT. Under treatment or failure to treat, sometimes from legal barriers can have high costs for the patient.

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Investigation should include: 1 Full blood count, 2 Renal function tests 3 Liver function tests, 4. Thyroid function tests, 5 Blood glucose measurement, 6 Creatine phosphokinase measurement, 7 Drug screen of urine. Further investigations depending on findings on physical examination include: 8 Electrocardiography, 9 Computed tomography, 10 Magnetic resonance imaging, 11 Electroencephalography, 12 Urine culture, 13 Blood culture, 14 Test for syphilis, 15 Test for HIV, 16 Heavy-metal screen, 17 Auto-antibody screen, 18 Lumbar puncture (Rajagopal, 2006).

The mechanisms of catatonia

The exact cause of catatonia has not been elucidated, but a number of hypotheses have been offered (Rajagopal, 2006). These include a 'top-down modulation' of basal ganglia due to deficiency of cortical gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter of the brain. This explanation might account for the dramatic therapeutic effect of benzodiazepines, which cause an increase in GABA activity. Similarly, hyperactivity of glutamate, the primary excitatory neurotransmitter, has also been suggested as an underlying neurochemical dysfunction.

Alternatively, catatonia may be caused by a sudden and massive blockade of dopamine, explaining why dopamine-blocking antipsychotics are not generally beneficial in catatonia. Indeed, antipsychotics may actually precipitate a worsening of the condition by exacerbating dopamine deficiency. Clozapine-withdrawal catatonia is postulated to be due to cholinergic and serotonergic rebound hyperactivity.

In chronic catatonia with prominent speech abnormalities, positron emission tomography (PET) has identified abnormalities in metabolism bilaterally in the thalamus and frontal lobes. One interesting hypothesis suggests that catatonia may be understood as an evolutionary fear response, where catatonic stupor may represent a common 'end-state' response to feelings of imminent doom, originating in ancestral encounters with carnivores whose predatory instincts were triggered by movement. This response, of remaining still, is now expressed in a range of major psychiatric or medical conditions.

Conclusions

Catatonia is a not-uncommon and treatable condition that can have an acute or acute on chronic presentation in emergency medicine, in developmental and general paediatrics, and in child and adolescent psychiatry. The four subtypes include withdrawal, automatic, repetitive and agitated/ resistive. Assessment includes consideration of a range of serious medical and neuropsychiatric disorders, and lorazepam 1-3mg IM can help as a diagnostic test. Of psychiatric causes, mood disorders are more common than schizophrenia. Amongst the

difficult to diagnose and treat adolescent presentations in developmental psychiatry, we need to actively look for and provide the test treatment for catatonia. Does the frequency of catatonia in ASD reflect difficulty in communicating subjective mental phenomena and difficulty in diagnosing comorbidity? However, with the availability of SSRIs and greater sensitivity to identifying depression in ASD, I wonder whether we see catatonia less frequently than the literature might suggest?

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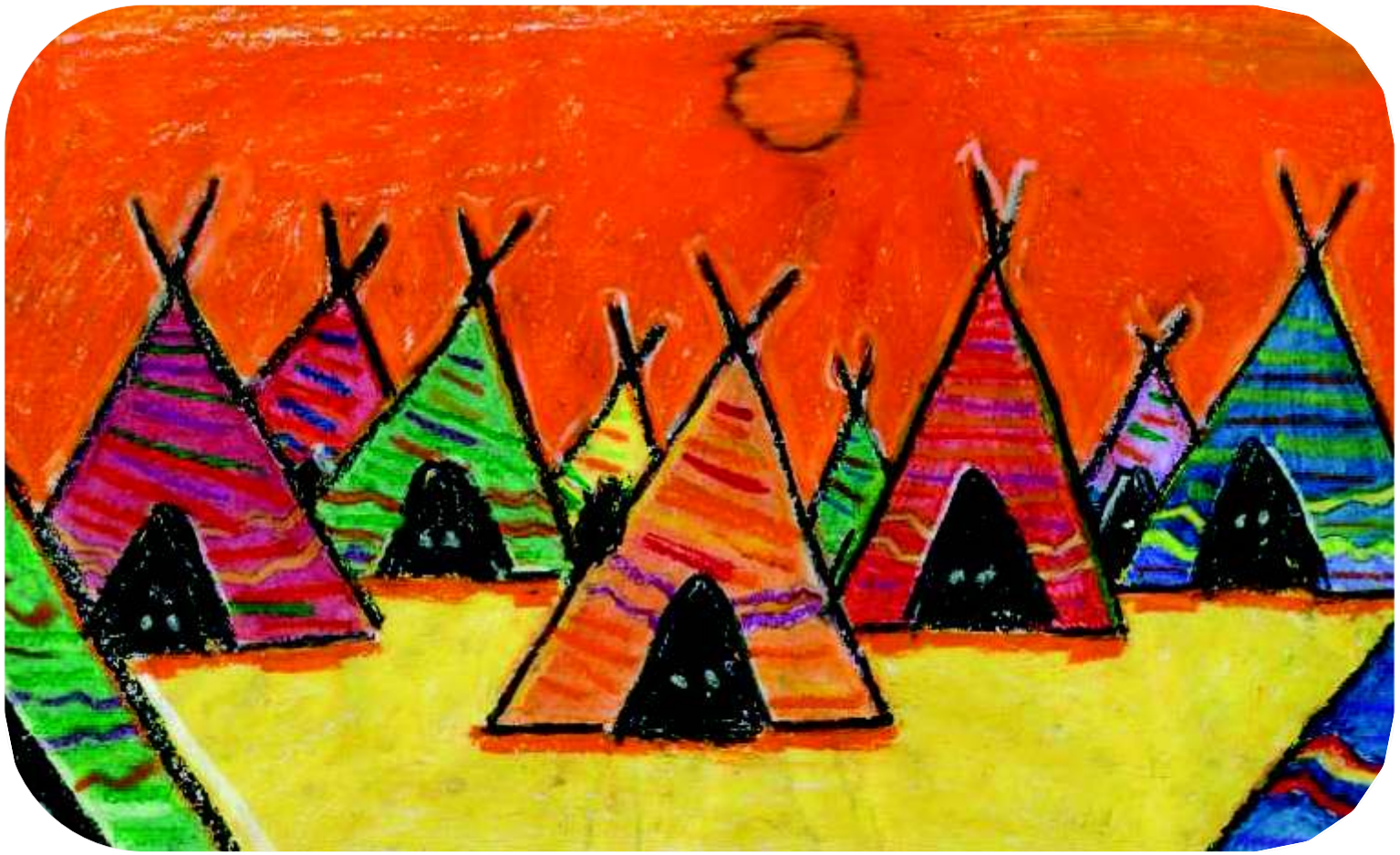

Glossary of Terms

Anhedonia [an″he-do´ne-ah]

inability to enjoy what is usually pleasurable.

Enuresis [en″u-re´sis]

a type of urinary incontinence, usually referring to involuntary discharge of urine during sleep at night (*nocturnal enuresis* or bed-wetting)

Echopraxia [ek″o-prak´se-ah]

stereotyped imitation of the movements of another person; seen sometimes in catatonic schizophrenia and Gilles de la Tourette's syndrome.

Echolalia [ek″o-la´le-ah]

stereotyped repetition of another person's words or phrases, seen in some cases of schizophrenia, particularly in catatonic schizophrenia, in Gilles de la Tourette's syndrome, and in neurological disorders such as transcortical aphasia.

Encephalopathy [en-sef″ah-lop´ah-the]

any degenerative disease of the brain.

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