

Catatonia is Hidden in Plain Sight Among Different Pediatric Disorders: A Review Article

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Over the past two decades, catatonia has been better demarcated in adult psychiatry as a unique syndrome that consists of specific motor signs with a characteristic response to benzodiazepines and electroconvulsive therapy. Pediatric catatonia is considered rare, but may be underdiagnosed, and hence undertreated. Discussed here are the current diagnostic criteria of catatonia in individual cases of children and adolescents diagnosed with childhood disintegrative disorder, Kleine-Levin syndrome, Prader-Willi syndrome, tic disorder, and autoimmune encephalitis, and the effects of benzodiazepines and electroconvulsive therapy. In these cases, catatonia resolved safely once it was recognized and treated properly. Children and adolescents presenting with these disorders should be systematically assessed for catatonia; when the presence of catatonia is confirmed, the use of benzodiazepines and electroconvulsive therapy should be considered. The occurrence of catatonia in such a wide range of child and adolescent disorders supports the view that pediatric catatonia is not so rare, that there are shared elements in the etiology, psychopathology, and pathophysiology of these disorders, and that catatonia is best classified as a unique neurobiologic syndrome. © 2010 by Elsevier Inc. All rights reserved.

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Introduction

Catatonia was originally described in 1874 by Kahlbaum [1] as a unique clinical presentation of motor, vocal and behavioral abnormalities. It was incorporated as a type of dementia praecox by Kraepelin [2] in 1896, but further

recognized nearly a century later as a prominent feature of affective disorders [3,4]. Various neurologic, medical, and drug-related etiologies are also found in adult patients with catatonia [5]. Indeed, catatonia is currently best conceptualized as an independent syndrome, one deserving “a home of its own” for purposes of accurate diagnosis and prompt implementation of appropriate anticatatonic treatments [6]. This position is under active review in the development of the upcoming fifth edition of the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5).

Accepted catatonia rating scales list specific symptoms, such as rigidity, posturing, waxy flexibility, stupor, unresponsiveness, negativism, echopraxia, echolalia, verbigeration, mutism, stereotypic and repetitive movements, physical agitation and aggressive behaviors, and autonomic and thermoregulatory instability, as well as multiple unique symptoms such as mitgehen, gegenhalten, ambitendency, and automatic obedience. In detail, these symptoms of catatonia can be defined as follows:

Excitement: Extreme hyperactivity, constant motor unrest, which is apparently nonpurposeful.

Immobility/stupor: Extreme hypoactivity, immobility. Minimally responsive to stimuli.

Mutism: Verbally unresponsive or minimally responsive.

Staring: Fixed gaze, little or no visual scanning of environment, decreased blinking.

Posturing/catalepsy: Maintains posture(s), including mundane (e.g., sitting or standing for hours without reacting).

Grimacing: Maintenance of odd facial expressions.

Echopraxia/echolalia: Mimics of examiner’s movements/speech.

Stereotypy: Repetitive, non-goal-directed motor activity (e.g., finger-play, repeatedly touching, patting, or rubbing self).

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Mannerisms: Odd, purposeful movements (hopping or walking tiptoe, saluting passersby, exaggerated caricatures of mundane movements).

Verbigeration: Repetition of phrases or sentences.

Rigidity: Maintenance of a rigid posture despite efforts to be moved.

Negativism: Apparently motiveless resistance to instructions or to attempts to move/examine the patient. Contrary behavior, does the opposite of the instruction.

Waxy flexibility: During repositioning of the patient, offers initial resistance before allowing himself to be repositioned (similar to that of bending a warm candle).

Withdrawal: Refusal to eat, drink, or make eye contact.

Impulsivity: The patient suddenly engages in inappropriate behavior (e.g., runs down the hallway, starts screaming, or takes off clothes) without provocation. Afterwards, cannot explain.

Automatic obedience: Exaggerated cooperation with examiner's request, or repeated movements that are requested once.

Passive obedience (*mitgehen*): Raising arm in response to light pressure of finger, despite instructions to the contrary.

Negativism (*gegenhalten*): Resistance to passive movement that is proportional to strength of the stimulus; response seems automatic rather than willful.

Ambitendency: Appears stuck in indecisive, hesitant motor movements.

Grasp reflex: Striking the patient's open palm with two extended fingers of the examiner's hand results in automatic closure of the patient's hand.

Perseveration: Repeatedly returns to the same topic or persists with the same movements.

Combativeness: Belligerence or aggression, usually in an undirected manner, without explanation.

Autonomic abnormality: Abnormality of body temperature (fever), blood pressure, pulse rate, respiratory rate, inappropriate sweating.

Criteria require that a patient exhibit at least two of these symptoms for at least 1 hour [7-9]. Catatonia responds to anticonvulsants, particularly benzodiazepines, and to electroconvulsive therapy [8,9]. Despite the availability of effective treatments, catatonia often remains underdiagnosed [10] and probably undertreated, with risk of significant patient morbidity and even mortality. The pathophysiology of this syndrome is unknown.

The earliest report of pediatric catatonia dates to 1903 [11]. In the 1950s, Leonhard [12] characterized early childhood catatonia in children with developmental delays who exhibited high rates of stereotypies, impulsive aggressive, self-injurious and disruptive behaviors, lack of expression, negativism, excitement, ambivalence, countergrasping, mannerisms, and peculiar speech patterns (including echolalia and neologisms). Today, most of these children would likely be diagnosed as suffering from an autism spectrum disorder. Modern studies of catatonia in children and

adolescents are few, but demonstrate catatonia in this age group occurring in psychotic, affective, autistic, developmental, drug-induced, and neurologic-medical disorders [13-16].

A few studies suggest that pediatric catatonia is not so rare. In one study, although catatonia was not formally assessed, more than one third of children with schizophrenia exhibited catatonic signs [17]. Findings in child and adolescent psychiatric outpatients revealed a 5% prevalence of catatonia and 17% prevalence in the subgroup with psychotic disorders [18]. Catatonia has been increasingly recognized as a comorbid syndrome of autism, at a rate of 12-17% in adolescents and young adults with autism spectrum disorders [19,20], sometimes occurring in patients with other neurodevelopmental disabilities [14,21].

Is catatonia underdiagnosed in children and adolescents, as it is in adults? In the early 1980s, catatonia in adults was thought to be almost extinct [22]. Recent reports, however, indicate prevalence rates of catatonia ranging from 7% to 17% in acute adult psychiatric inpatients, supporting the evidence that catatonia is underdiagnosed and undertreated in adults with affective and psychotic disorders [7,23,24]. Underdiagnosis of catatonia in children and adolescents may have many antecedents, including the historic decision to classify catatonia as a type of schizophrenia, the separation of autism from the childhood psychoses [25], diagnostic overshadowing in autism and developmental disorders (i.e., falsely attributing psychiatric symptoms as part of the developmental disorder), the segregation of children and adolescents with autism and developmental disorders in long-term facilities, poor recognition of the catatonic syndrome in nonpsychiatric settings, the perceived lack of anticatatonic treatments, and stigmatization of benzodiazepine treatment and electroconvulsive therapy (especially in pediatric patients), as well as the lack of modern systematic studies.

Evaluation, Diagnosis, Differential Diagnosis, and Treatment of Pediatric Catatonia

From case reports and case series, it is gathered that the evaluation, diagnosis, and treatment of catatonia in children and adolescents are straightforward and similar to those in adults [8,15,26]. The diagnosis is directly based on the presence of specific symptoms of catatonia according to accepted catatonia rating scales (e.g., as detailed in the Introduction).

Acute onset of myriad infectious, metabolic, endocrine, neurologic, toxic, and autoimmune conditions are frequently associated with catatonia. Recreational drugs (phencyclidine, mescaline, psilocybin, cocaine, ecstasy, opiates, and opioids), disulfiram, steroids, antibiotic agents (ciprofloxacin), baclofen, and bupropion have also been associated in case reports with the emergence of catatonia. Withdrawal of benzodiazepines, gabapentin, and dopaminergic drugs, especially if done rapidly, has sometimes precipitated catatonia [8].

A thorough clinical, laboratory, and imaging evaluation and drug screen are mandatory, and prescribed medications should be evaluated for their potential to precipitate catatonic symptoms. Antipsychotic medications should be discontinued, because of their potential to worsen catatonia or to cause frank neuroleptic malignant syndrome [8,9]. Lahutte et al. [27] recommend a comprehensive interdisciplinary approach in the evaluation and diagnosis of catatonic symptomatology, in order to adequately address the wide differential diagnosis in the acute catatonic presentation, including organic causes. Proposed basic paraclinical investigations include a complete blood count and metabolic panel, erythrocyte sedimentation rate, magnetic resonance imaging, electroencephalography, cerebrospinal fluid analysis, antinuclear antibodies, and urine and organic metabolic testing, with further testing dependent on clinical findings [27].

Malignant catatonia (also known as lethal catatonia) is a severe form of catatonia, acute in onset, systematically devastating, and associated with fever and autonomic instability [8,9,28,29]. The patients appear to have an infectious disease, particularly an infectious encephalopathy, but usually no specific infectious process is found. Some are considered to suffer from a coma of unknown etiology. In such instances, prompt diagnosis and treatment is warranted, to avoid dehydration, exhaustion, thrombosis, renal failure, respiratory arrest, and death. Whereas untreated malignant catatonia is associated with a 10-20% lethality rate, electroconvulsive therapy has an 80-100% efficacy rate in resolution of catatonia [8,9,30,31]. Malignant catatonia should feature prominently in the differential diagnosis of the acute pediatric encephalopathies as a treatable syndrome in children and adolescents with acute onset of unresponsiveness, muteness, echolalia, echopraxia, and other psychomotor abnormalities, along with fever and signs of autonomic instability [26,32]. Malignant catatonia is similar to malignant hyperthermia, in that both share muscular rigidity and hypermetabolic and hyperthermic states, but the latter is uniquely associated with either succinylcholine usage or a genetic response to inhaled anesthetics [8,9].

A detailed history, clinical examination, and application of diagnostic criteria must differentiate catatonia from other well-recognized conditions, syndromes, or disorders featuring psychomotor abnormalities that may overlap with the manifestations of catatonia. Making an adequate differential diagnosis of catatonia is complicated by the fact that there is no biologic marker diagnostic of catatonia. The differential diagnosis of catatonia among hyperkinetic disorders includes:

1. Acute dystonia
2. Tardive dyskinesia
3. Akathisia
4. Withdrawal-emergent dyskinesias
5. Tics and Gilles de la Tourette syndrome
6. Selective mutism

7. Conversion disorder
8. Compulsions (in obsessive-compulsive disorder)
9. Epilepsy
10. Delirium

Among hypokinetic disorders, the differential diagnosis of catatonia includes:

1. Parkinsonism and Parkinson disease
2. Malignant hyperthermia
3. Neuroleptic malignant syndrome
4. Serotonergic syndrome
5. Epilepsy
6. Status epilepticus
7. Delirium
8. Coma

Among the hyperkinetic states, acute dystonia, tardive dyskinesia, withdrawal-emergent dyskinesia, and akathisia are medication-induced conditions that may be mistaken for catatonia. Typical antipsychotics are the medications usually associated with these movement disorders, but atypical antipsychotics, tricyclic and tetracyclic antidepressants, selective serotonin-uptake inhibitors, monoamine oxidase inhibitors, antiemetics, calcium antagonists, anticonvulsants, stimulants, and a variety of other psychotropic agents have also been implicated through alterations in central dopamine metabolism [33]. As already mentioned, antipsychotics may additionally be a risk factor for the development of catatonia itself. Tic disorder, Gilles de la Tourette syndrome, elective mutism, conversion disorder, and compulsions in obsessive-compulsive disorder may also overlap with catatonia [34-36].

Among the hypokinetic states, both morbus Parkinson and its medication-induced form, parkinsonism, resemble catatonia. Typical antipsychotics are especially prone to cause parkinsonism in dose-dependent fashion, usually within the first month of administration [37].

Malignant hyperthermia, neuroleptic malignant syndrome, toxic serotonin syndrome, and delirium constitute another group of disorders characterized by varying levels of hypokinesia and muscle stiffness, in combination with altered levels of consciousness, that should be included in the differential diagnosis. For example, there is discussion in the literature as to whether neuroleptic malignant syndrome and toxic serotonin syndrome truly differ in key aspects from catatonia, or alternatively, whether they should be regarded as medication-induced forms of catatonia [38,39]. The fact that neuroleptic malignant syndrome and toxic serotonin syndrome seem to respond to the same treatments as catatonia strengthens the argument for relatedness.

Diagnostic rules in the current edition of the *Diagnostic and Statistic Manual*, DSM-IV, state that catatonia should not be diagnosed if occurring exclusively during the course of a delirium, but acknowledge that similar medical conditions of infectious, metabolic, endocrine and neurologic etiologies are associated with both catatonia and delirium [40].

The validity of this provision is uncertain, given the lack of studies in the literature that have assessed the importance of catatonia during delirium. The issue has crucial therapeutic consequences, as anticatatonic and antidelirium treatments are different, albeit with overlap. Whereas delirium is typically treated with antipsychotics (typical or atypical), the emergence of catatonia in delirium may caution against the use of antipsychotic medications, because of the aforementioned risk of worsening catatonia with antipsychotic medications [39].

Another unresolved classification issue is whether catatonia should be included in the differential diagnosis in patients with coma (complete unresponsiveness) [41], and, in a similar vein, whether stupor or profound unresponsiveness can be the sole presenting symptom of catatonia [41-43]. According to recent case reports, patients with levels of unresponsiveness similar to those in coma, and without other catatonic symptoms (except resistance to eye-opening) have responded to electroconvulsive therapy [44] and intravenous benzodiazepines [43].

A benzodiazepine challenge test of 1 or 2 mg of lorazepam can be used to verify the catatonia diagnosis, and is indeed a widely accepted diagnostic intervention in the assessment of potential catatonia [8,9,23]. Underutilization of lorazepam in pediatric catatonia has nonetheless been reported [27]. Use of the γ -aminobutyric acid A receptor modulator zolpidem has also been developed as an alternative catatonia challenge test and is implemented particularly in Europe [45]. When a single dose of lorazepam improves catatonia, lorazepam can be prescribed at regular intervals to maintain improvement. Many catatonic patients require relatively high doses of lorazepam, up to 24 mg daily, for symptom resolution [8,9,23]. In our experience, pediatric catatonic patients also require high doses of lorazepam, and tolerate such without inducing sedation or respiratory compromise.

Electroconvulsive therapy is indicated when increased dosages of lorazepam do not bring rapid relief, or when acute patient morbidity requires immediate treatment. Electroconvulsive therapy involves use of modified electrical current delivered through unilateral or bilateral electrodes placed at given positions on the head to induce a generalized tonic-clonic seizure. During the entire procedure, the patient is under complete anesthesia and neuromuscular blockade, with continuous oxygenation and comprehensive cardiorespiratory, electroencephalographic, and often electromyographic monitoring. Electroconvulsive therapy as delivered in modern medical facilities is an extremely safe procedure, with an estimated mortality less than that of normal childbirth in a healthy mother and fetus. Risks consist largely of time-limited anterograde and retrograde memory loss, acute confusion, headache, muscle soreness, and nausea after treatment, as well as the risks associated with the use of general anesthesia [46,47].

The relief of catatonia requires more frequent induction of seizures than the relief of major depression, especially in patients with malignant catatonia, who often require daily

en bloc treatments or two electrical stimuli in a single session (and sometimes both approaches). The number of sessions needed for substantial improvement or remission varies greatly. Continuation treatment after an effective electroconvulsive therapy course with lorazepam or maintenance electroconvulsive therapy is often essential, because relapse after short courses of treatment is common [8,9].

Materials and Methods

Presented here as examples for discussion are three pediatric cases with catatonia from the authors' previous reports, cases that were concomitantly diagnosed with childhood disintegrative disorder [48], Prader-Willi syndrome [14], and tic disorder [49], along with a new report of case of catatonia in an adolescent diagnosed with Kleine-Levin syndrome. In each case, catatonia resolved safely once it was recognized and treated properly. Two pediatric cases of catatonia in autoimmune encephalitis reported by others [50,51] are also discussed.

Case 1: Severe Regression and Malignant Catatonia in a Prepubertal Boy

A 9-year-old boy with normal development, but high familial loading of psychosis, was admitted for agitation, anxiety, perplexity, negativism, and psychomotor slowing. Stupor, mutism, fever, and facial flushing developed over the next 2 weeks. Extensive medical and neurologic examinations were uninformative. Cranial magnetic resonance imaging revealed normal brain structures. Electroencephalographic recordings consistently indicated generalized slowing but no epileptic spikes. The symptoms satisfied criteria for childhood disintegrative disorder, a type of late-onset autism that is characterized by acute and severe regression, with loss of language, social skills, adaptive behavior, play, bladder or bowel control, and motor skills. Childhood disintegrative disorder is considered to be very rare and refractory to treatment, similar to a neurodegenerative process. This child's symptoms additionally met criteria for the malignant variant of catatonia, in which fever and autonomic symptoms such as abnormal blood pressure, profuse sweating, and flushing are found in addition to the motor signs of catatonia.

Beneficial treatment options do exist for malignant catatonia, in contrast to childhood disintegrative disorder. After 4 weeks of failed trials with anticonvulsants, antiviral medications, and high-dose benzodiazepines, bilateral electroconvulsive therapy was started after obtaining consent of the mother. Stupor, mutism, and refusal to eat and drink resolved rapidly during the first course of seven treatments, but agitation, stereotypies, repetitive speech, and poor level of function remained. Electroconvulsive therapy was stopped and lithium and clozapine were started, because these medications also are considered beneficial in some cases of catatonia [52,53]. Nonetheless, the patient relapsed within 1 week into stupor and immobility. A second electroconvulsive therapy course of nine treatments was given. Again, the most severe catatonic symptoms dissipated, but the patient remained impaired. The patient was discharged and continued with outpatient electroconvulsive therapy (once every week or biweekly) for the next 5 months. No psychotropic medications were prescribed during that time.

The patient did not experience any adverse effects of electroconvulsive therapy, and during the 5 months of ongoing outpatient electroconvulsive therapy, he slowly returned to baseline function. As of writing, there had been no relapses for 5 years. The child attends regular classes, lives at home, and is completely free of psychotic or catatonic symptoms. This outcome is markedly superior to that generally expected in childhood disintegrative disorder.

Comment

Electroconvulsive therapy is infrequently used in prepubertal children [54], but proved life-saving in resolving malignant catatonia in this case,

in which the alternative consideration was childhood disintegrative disorder. The child's condition was prone to relapse and required intensive maintenance treatments for months. The experience reflects the necessity of maintenance electroconvulsive therapy in some adult patients with catatonia [8] and in some adolescents with autism who developed catatonia [55,56]. Indeed, electroconvulsive therapy is a treatment rather than a cure for catatonia. Since the early 1990s, catatonia has been recognized in an increasing number of patients with established autistic disorder [57-70], and electroconvulsive therapy resolved catatonia in several of these patients without altering the baseline autistic pathology [59,62,66,69,70].

This case illustrates how early recognition and effective treatment of acute catatonia in some children with otherwise suspected childhood disintegrative disorder, an autistic variant, offer the opportunity to prevent further deterioration and possibly provide reversal of an otherwise intractable and severely-impairing condition. We propose that catatonia should be assessed in children with suspected childhood disintegrative disorder, and treated accordingly with lorazepam and electroconvulsive therapy if criteria are met [48]. Successful trials of electroconvulsive therapy in the regressive stages of childhood disintegrative disorder offer support for this type of late-onset autism being an early type of idiopathic catatonia that, if left untreated, progresses into an irreversible autistic state with profound patient incapacitation [71,72].

Case 2: Catatonia and Use of Lorazepam in an Adolescent Diagnosed With Kleine-Levin Syndrome

A 13-year-old boy with normal development and without personal or family psychiatric history was brought to the emergency department with a 3-month history of altered behavior and responsiveness after a flu-like illness. The mother reported the occurrence of 10-day episodes of bizarre behavior, decreased speech and eating, confusion, and mild aggression and agitation, as well as episodes of hypersomnolence lasting up to 24 hours. Although the boy was not incontinent, he would urinate in unusual places. After each 10-day episode, the patient resumed normal function and remembered little of his behavior, other than feeling "odd."

The patient was admitted to the pediatric hospital for a neurologic evaluation, including comprehensive laboratory studies and cranial magnetic resonance imaging. The findings were within normal limits, and he also had a normal awake and sleep electroencephalogram. He was diagnosed with Kleine-Levin syndrome. After failed trials of anticonvulsants and stimulants, a psychiatric consult was requested. On examination, the patient was unresponsive to verbal commands and displayed echolalia and stereotypies. Because criteria for catatonia were met, a test dose of 1 mg of lorazepam was administered by mouth. Within the next few hours, the patient began to speak normally and regained normal behaviors and cognition. He was discharged from the hospital the next day. Three relapses over the next 6 months were aborted with administration of 1 mg of lorazepam two or three times per day.

Comment

Kleine-Levin syndrome is currently classified as a sleep disorder. The syndrome is characterized by recurrent episodes of excessive sleep, lasting days to weeks. During episodes, when awake, cognition is abnormal, with feelings of unreality or confusion, and behavioral abnormalities such as megaphagia or hypersexuality may occur. Patients have normal alertness, cognitive functioning, and behavior between the episodes. The disorder seems to be a genuine disease entity based on its consistent description in terms of clinical presentation, demographics (70% male, adolescent), evolution (eventually disappears), and therapeutic response (almost nothing is effective) [73]. Kleine-Levin syndrome should not be mistaken for depression or psychosis, and should not be treated as such.

The overlap between symptoms of catatonia and Kleine-Levin syndrome suggests that the latter may be an adolescent form of catatonia. Hypersomnolence in Kleine-Levin syndrome may be a manifestation of catatonic unresponsiveness and stupor, rather than a symptom of a sleep

disorder. The response to lorazepam in this case offers support for this notion, and also provided a treatment option in a condition with typically poor therapeutic response. Patients with Kleine-Levin syndrome could benefit from assessment for catatonia, and, if criteria are met, a trial of benzodiazepines is best considered. If benzodiazepines are not effective, electroconvulsive therapy may be another treatment option. Use of electroconvulsive therapy has been reported in an adolescent with Kleine-Levin syndrome, although it was not specified whether this patient also met criteria for catatonia [74].

Further trials of lorazepam in Kleine-Levin syndrome are warranted, and, if successful, would support that Kleine-Levin syndrome may be an adolescent form of catatonia. Prompt initiation of anticatatonic treatments may significantly reduce patient morbidity and facilitate rapid return to baseline functioning.

Case 3: Catatonia in an Adolescent With Prader-Willi Syndrome

A 17-year-old adolescent with Prader-Willi syndrome was admitted to the children's hospital because of acute onset of catatonia with stupor, staring, incontinence, mutism, rigidity, waxy flexibility, posturing, refusal to eat and drink, and severe disruption of the sleep-wake cycle. His symptoms developed a few hours after a severe argument with his mother regarding school. He was sent to his room. When he came back, he was very anxious, talked incoherently about Jesus, and made vague references to visual hallucinations. Within hours, he became catatonic and was brought to the hospital. Previously, he had functioned well at home and at school, despite mild mental retardation and the presence of the stigmata of Prader-Willi syndrome (short stature, hypogonadism, and mild obesity).

Examination indicated a neurologically intact patient. Electroencephalography indicated mild, nonspecific slowing in the prefrontal areas. Routine laboratory testing was uninformative. A trial of haloperidol was ineffective. He remained bedridden, mute, and withdrawn. On the 10th day of admission, a test dose of 1 mg of lorazepam was given orally. He improved over the next few hours, started walking and eating again the next day. He became more verbal and answered simple questions adequately. He also started making delusional statements that his parents had died, and reported visual hallucinations of his grandparents and Santa Claus. Lorazepam was increased to 4 mg daily over the course of a few days. Stupor gave way to motor restlessness, short attention span, impulsiveness, stereotypies, echolalia, echopraxia, automatic obedience, active resistance to movement, ambivalence, and negativism. Risperidone was started for delusions in addition to lorazepam, and titrated to 6 mg daily. Catatonia and delusions resolved during the next 2 weeks.

The patient was discharged from the hospital and returned back to baseline functioning. Risperidone and lorazepam were discontinued 2 months after discharge. There were no relapses of catatonic or psychotic symptoms, and the patient, now in his mid-20s, continues to live with his family. He is employed in a sheltered workshop, where he enjoys his work and social contacts.

Comment

Catatonia responded promptly to benzodiazepines in an adolescent with a developmental disorder of genetic origin. Once catatonic symptoms were resolved, antipsychotic medication relieved emerging delusions and hallucinations.

Systematic studies of catatonia in patients with specific developmental disorders, including Prader-Willi syndrome, are lacking, although in several case reports catatonia was present in patients with Prader-Willi syndrome [14,21,75-77]. The literature also contains one case of a 9-year-old boy with Prader-Willi who developed two episodes of hyperphagia, pica, irritability, stereotyped speech, memory impairment, and bizarre behaviors (writing on clothes, on himself, and on others) lasting for 10 days. The authors did not conduct a formal assessment of catatonia, but concluded that these episodes were compatible with Kleine-Levin syndrome. The episodes resolved spontaneously [78].

Prader-Willi syndrome is a genetic disorder arising from the lack of expression of genes on the paternally derived chromosome segment 15q11~q13, and is characterized by hypotonia at birth, small hands and feet, almond-shaped eyes, hypogonadism, short stature, and diabetes. Most patients exhibit mild to moderate mental retardation and obesity. The prevalence is estimated at 1 in 16,000-25,000 live births [79,80].

Prader-Willi patients seem particularly prone to develop psychosis [81-83]. This suggests that an abnormal pattern of expression of sex-specific imprinted genes on 15q11~q13 is a risk factor for psychosis in Prader-Willi syndrome. Genes in the same or nearby chromosomal region have independently been implicated in catatonic schizophrenia [84] and autism [85], suggesting overlap of genetic risk factors among catatonia, autism, and Prader-Willi syndrome [86,87]. Further studies of catatonia in Prader-Willi syndrome are warranted to assess whether specific genes on 15q11~q13 are associated with catatonia, thereby illuminating the validity of Prader-Willi syndrome as a genetic model of catatonia.

Case 4: Tics and Catatonia in an Adolescent

A 17-year-old adolescent with normal development was brought to the emergency department because of gradual onset of tic-like spitting, facial tics and grimacing, repetitive hand washing, lip smacking, face slapping, head banging, and repetitive finger flexing. These symptoms had worsened over the course of 4 months. On examination, he was withdrawn, with depressed mood; he answered questions in a whispering voice, and expressed suicidal ideas. Affect was restricted, and eye contact was poor. His thought process was ruminative and obsessive. The patient was admitted to the general hospital, where findings from medical evaluation and cranial computerized tomography were normal. He was transferred to the psychiatric inpatient unit of a university hospital; there, after trials of antipsychotics combined with antidepressants failed, electroconvulsive therapy was started. Full resolution of most affective and psychomotor symptoms, including tics and self-injurious behavior, occurred after two bilateral electroconvulsive therapy treatments. Before stopping acute electroconvulsive therapy, the patient was started on haloperidol 5 mg daily, benzotropine 1 mg twice daily, bupropion 100 mg daily, and modafinil 100 mg daily. The patient was then discharged home, but continued to receive electroconvulsive therapy on an outpatient basis first every 2 weeks, and later once a month, over a period of 1½ years. The patient dropped out of treatment for 5 months, but relapsed with reappearance of tics and depressed mood, despite compliance with haloperidol, bupropion, and modafinil. Outpatient electroconvulsive therapy was restarted with resolution of symptoms.

To date, he has received 33 bilateral treatments since the start of his illness. He attends school and is free of psychiatric symptoms. He continues with maintenance treatments every 2 weeks in combination with the above-mentioned medications for relapse prevention.

Comment

A remarkable feature in this case is that tics emerged together with classic catatonic symptoms, such as psychomotor retardation, stereotypies, and grimacing. Motor and vocal tics are often accompanied by self-injurious behavior and emerge prominently in some young patients with catatonia and underlying affective, psychotic, or autistic disorders [25]. Support that tics are signs of catatonia comes from a study that examined the phenomenologic expression and significance of catatonic signs in a nonpsychotic patient group with Tourette's syndrome [88]. Standardized rating scales were used to assess the presence and severity of catatonic signs, motor and vocal tics, and comorbid psychopathologies. Of the patients with Tourette's syndrome, 87% expressed catatonic signs sufficient to warrant the diagnosis of catatonia. The most common symptoms were echophenomena, perseveration, and excitement. These findings indicate that catatonia and tic disorders overlap and are related, which in turn suggests that, in some cases, tics (with or without self-injurious behavior) may be signs of catatonia.

In this case, all symptoms including tics and self-injurious behavior responded to electroconvulsive therapy. Patients with tics, Tourette's syndrome, or intractable self-injury [89,90] warrant assessment for catatonia.

If catatonia is present, electroconvulsive therapy provides a safe alternative to pharmacotherapy, psychosurgery, or invasive brain stimulation in the treatment of severely disabling and at times life-threatening tics or self-injury.

Cases 5 and 6: Malignant Catatonia in Two Children Diagnosed With Autoimmune Encephalitis

Lee et al. [50] presented the case of an 11-year-old girl who, after an upper respiratory tract infection, became uncooperative, confused, and agitated with slurred speech and hallucinations. She was admitted to the hospital with a diagnosis of acute psychosis and was prescribed a low dose of risperidone, with little effect. After administration of chlorpromazine for agitation, she became febrile, tachycardic, and rigid. Creatine phosphokinase was elevated, and neuroleptic malignant syndrome was diagnosed. Trials of antibiotics, acyclovir, diphenhydramine, low-dose lorazepam, and bromocriptine were ineffective, and the patient's condition worsened. She was unable to drink or eat, required nasogastric tube feeding, and was mute and cataleptic. An exhaustive evaluation for infectious, hematologic, metabolic, and endocrine disorders yielded negative findings. Neuroimaging studies of the brain revealed no abnormalities. Malignant catatonia was diagnosed on clinical grounds, and permission from the court to start electroconvulsive therapy was sought (as required by the local state laws for minors) and obtained. A course of eight bilateral treatments during 2 weeks resolved all symptoms, and the patient resumed normal function. After the second treatment, she no longer required tube feeding. Ongoing abdominal complaints prompted ultrasound and an abdominal computed tomography scan, which revealed an ovarian tumor. The mass was removed surgically and found to be a cystic teratoma. Surgical removal of the ovarian teratoma may have contributed to the full recovery of the patient. Absent controlled studies, however, proof for this supposition is lacking, because the patient had already achieved near remission after the intensive 2-week course of electroconvulsive therapy.

Schimmel et al. [51] presented the case of a 12-year-old girl who was admitted to the hospital with major psychiatric symptoms and autonomic instability. Neurologic, metabolic, and genetic evaluations were uninformative. Malignant catatonia was diagnosed and she was transferred to the intensive care unit. The patient was treated with prednisolone for possible autoimmunologic pathogenesis. Six weeks after admission, cerebrospinal fluid immunoglobulin G antibody reactivity with hippocampal neuropil was detected, as well as serum antibodies to the anti-N-methyl-D-aspartate receptor. Plasmapheresis was started with eight sessions over 13 days, with improvements after 2 sessions. Almost full recovery was seen after 1 month, and she was transferred to rehabilitation for 1 month. She exhibited only minimal dysfunction of short-term memory. Repeated imaging studies did not reveal any teratoma or other malignancy.

Comment

Autoimmune encephalitis is a nonviral, immune-mediated type of encephalitis that is associated with a number of known and unknown cerebral antibodies. Examples of autoimmune encephalitis associated with known antibodies are the antiphospholipid syndrome [91] and lupus cerebritis [92]. Catatonia has been associated with both these syndromes [91,93], as well as with other autoimmune disorders [94], and has responded to benzodiazepines [95] and electroconvulsive therapy [96,97].

Until the mid-1990s, most cases of nonviral encephalitis were considered paraneoplastic. Since then, however, an increasing number of reports have documented the absence of underlying cancers in many such patients. A new type of autoimmune encephalitis involving anti-N-methyl-D-aspartate receptor has been described as a novel autoimmune entity defined by specific clinical features, including presence of ovarian teratoma in young females, and positive serum and cerebrospinal fluid antibodies [98]. The neuropsychiatric presentation of children and adolescents with autoimmune encephalitis is compatible with catatonia [51,99,100], but catatonia is usually neither formally assessed nor treated. Recovery with immunotherapy is described as slow, frequently lasting months. A

further caveat is that the use of steroids has been described as both a cause [8,101] and a treatment [102] of catatonia.

Future studies on autoimmune encephalitis should include systematic assessments of catatonia. Confirming catatonia in such patients opens the possibility of comparing the efficacy, safety, and outcome of traditional antecatatonic treatments with immunotherapies. This is particularly pertinent for younger patients, in whom usually neither tumors nor teratomas are found and sluggish responses to immunotherapies are observed. Benzodiazepines and electroconvulsive therapy may provide faster and more lasting relief in severely impaired children and adolescents with catatonia associated with autoimmune encephalitis, compared with immunotherapies. Antecatatonic treatments may reduce the need for costly immune therapies, which also expose the pediatric patient to a blood-derived product. Absent controlled studies, however, the comparative benefits in autoimmune encephalitis of lorazepam and electroconvulsive therapy versus immune therapies remain unknown. Studies should also assess autoimmune parameters, including cerebral antibodies, in patients diagnosed with catatonia.

Discussion

Catatonia was diagnosed and resolved with specific treatments in individual cases presenting with childhood disintegrative disorder, Kleine-Levin syndrome, Prader-Willi syndrome, tic disorder, and autoimmune encephalitis. Considering and then confirming catatonia offered the availability of a safe and effective treatment and favorable prognosis with more rapid return to baseline functioning. The treatments used were specific, consisting of benzodiazepines and electroconvulsive therapy, and were safe and well tolerated by the patients. We propose that children and adolescents presenting with these disorders should be systematically assessed for catatonia, and that, when the presence of catatonia is confirmed, the use of benzodiazepines and electroconvulsive therapy should be considered. Malignant catatonia warrants even greater priority in assessment, because rapid recognition can ensure prompt treatment of life-threatening complications.

A new research agenda may be supported with focus on shared elements in the etiology, psychopathology, and pathophysiology of the wide range of pediatric and adult disorders in which catatonia occurs [25,71,87,103-105]. An appropriate focus is the area of stereotypic or repetitive movement abnormalities, which are considered cardinal symptoms of several different disorders, including catatonia, autism, stereotypic movement disorder, and tic disorders (when tics are viewed as sudden and nonrhythmic variants of stereotypy). Recent analyses of clinical data and animal models indicate that motor stereotypy constitutes a separate domain, with increasing evidence of a neurobiologic mechanism involving neuroadaptations in corticobasal ganglia pathways arising from the interplay of genetic and experiential factors [106-108].

The uniform response of catatonia to specific treatments across different disorders supports a unique biologic substrate without rigid ties to any specific disorder. Although a comprehensive biochemical theory of catatonia has so far proven elusive [8,9], a γ -aminobutyric acid theory of catatonia [105,109] has been proposed; this theory is supported by the often dramatic response to treatment

with benzodiazepines (i.e., positive modulators of the benzodiazepine- γ -aminobutyric acid_A receptor complex) [23,110]. Other effective treatments for catatonia, including barbiturates and electroconvulsive therapy, also enhance γ -aminobutyric acid function [111,112]. Empirical evidence for γ -aminobutyric acid dysfunction in catatonia comes from a receptor imaging study [113], in which a decreased density of γ -aminobutyric acid_A receptors in the left sensorimotor cortex was found. In a study of patients with neuroleptic malignant syndrome, the antipsychotic-induced variant of catatonia [114], cerebrospinal fluid levels of γ -aminobutyric acid were also decreased. Studies of γ -aminobutyric acid function in catatonia are warranted in patients with different underlying disorders.

The overlap between catatonia and autoimmune encephalitis suggests that autoimmunity and cerebral antibodies should be further investigated in patients with catatonia. Another research area concerns the search for common genetic risk factors among various disorders in which catatonia is a feature. Prader-Willi syndrome is of special interest as a candidate clinical genetic model of catatonia.

The implications for classification of catatonia are far reaching if further research supports that implication that seemingly disparate syndromes such as childhood disintegrative disorder and Kleine-Levin syndrome are in fact different expressions of catatonia (i.e., early-onset catatonia in the case of childhood disintegrative disorder and periodic, self-limiting, adolescent catatonia in the case of Kleine-Levin syndrome). The occurrence of catatonia in patients with autism, Prader-Willi syndrome, and tic disorders is an important finding that further loosens the historical link between catatonia and psychosis [26,115] and supports the view that catatonia should be more independent in psychiatric and medical classification, and indeed features best as a separate category. Most important, perhaps, consideration of the catatonia diagnosis and implementation of specific treatments in these disparate pediatric conditions may offer significant reduction in illness morbidity for many conditions in which the prognosis may otherwise be guarded.

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