

Autonomic Dysfunction in Catatonia in Autism: Implications of a Vagal Theory

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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 [1,2] and with other intellectual disabilities [3,4]. Mutism, stereotypic speech, echolalia, stereotypic or repetitive behaviors, posturing, grimacing, rigidity, mannerisms and purposeless agitation are catatonic signs and feature prominently in autism. Some patients, often adolescents, experience a sharp increase of these symptoms and qualify for a diagnosis of catatonia [2,5,6].

Catatonia may be a feature of another major psychiatric syndrome such as depression [7], bipolar illness [8] or schizophrenia [9], yet many patients cannot be diagnosed with a clear mood or psychotic disorder due to the fact that these autistic patients are nonverbal and have severe cognitive impairments. Case-reports also describe catatonia in pediatric patients with Prader-Willi Syndrome [3] and Down Syndrome [10], genetic disorders that are characterized by varying degrees of developmental impairment, some autistic features, and medical and behavioral abnormalities that are specific to the genetic defect.

Most cases of catatonia in children and adolescents with autism are not associated with any underlying medical or psychiatric conditions. For example, in a sample of 58 children and adolescents with catatonia [11], 18 (31%) had a history of developmental disorder, i.e., autism spectrum disorder, intellectual disability or neurodevelopmental malformation. Only two of those had an identifiable underlying medical or psychiatric condition.

Benzodiazepines and ECT are the Treatments of Choice for Catatonia in Autism

Controlled trials of ECT for catatonia in autism are lacking. What we know about the management of catatonia in autism comes from case reports accumulated over the last 15 years and interventions in adults without developmental disorders.

Youngsters with catatonia and autism often suffer extreme physical compromise, including inability to move, eat or void, development of dangerous cardiovascular and thermoregulatory instability, as well as onset of repetitive, tic-like, self-injurious behaviors with prominent risk of extreme tissue and organ damage and often find significant symptom relief [12-26] by ECT for without altering underlying autistic pathology [14,17,21,24-26]. Milder and less advanced cases have benefitted from the use of lorazepam [23], and social, behavioral, and psychological interventions [22].

Prior to the recently reported cases, the only clinical passage on the benefits of prolonged courses of ECT in autistic adolescents to "avoid the rapid deterioration which tends to occur if such an acutely disturbed episode is prolonged" comes from O'Gorman's 1970 book [27]: "It appears that, in some hands, ECT is very often helpful, but the course of treatment will often have to be intensive and prolonged. Four or five treatments a week for four or even five weeks may be necessary. The present writer's practice is to employ this treatment only during acutely disturbed phases in older (adolescent) patients". The nature of the acute disturbances is left undefined; catatonia is not mentioned. This book dates from the 1970s at the nadir of public acceptance of ECT and peak of anti-psychiatric and anti-ECT movements [28]. This may explain why his insight into the use of continuation ECT in the medical management of autism was lost [14,17,21,25].

Recent reports that Maintenance-ECT (M-ECT) is often needed for sustained symptom remission [29] confirm O'Gorman's earlier experience. Ongoing ECT treatments are often imperative to prevent relapse similar as in non-autistic populations [30,31]. Studies during M-ECT in general psychiatric patients find no evidence of structural or histopathological changes [32,33], and demonstrate similar stability of cognitive measures [34-36].

Less information is available regarding M-ECT in autism. One case series [29] presents the M-ECT courses of three autistic catatonic patients who received up to 286 maintenance treatments with sustained remission of catatonia and without evidence of cognitive or adaptive skill decline. One patient was unable to access M-ECT for legal reasons and promptly relapsed into catatonia. While the number of M-ECT delivered to these patients appears high, this finding is considered within the context of a special patient population with frequent poor baseline response to psychotropics and overall treatment resistance.

In another report [37], an autistic 21-year-old male received 220 M-ECT for catatonia over two years, with remarkable recovery and return to baseline psychosocial and educational functioning after severe medical compromise. His global functioning was stable throughout M-ECT, and three batteries of comprehensive neuropsychological functioning done yearly showed consistent stability without any evidence of cognitive decline. These reports support stability of longitudinal neuropsychological testing in such patients. A further report presents an 18-year-old male with malignant catatonia in the context of congenital cerebellar dysgenesis in whom neuropsychological testing remained unchanged after two years following 61 maintenance ECT [38].

Mechanism of Catatonia in Autism

The etiology and pathophysiology of catatonia are unknown yet the overlap between autistic and catatonic symptoms and occurrence of frank catatonia in autism intimate new models of catatonia in addition to the available paradigms [39,40]. Historically, the field of experimental catatonia started in 1928 by de Jong and Baruk, who induced catatonia in animals by bulbocapnine [41].

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Experimental catatonia studies should expand into models of developmental impairment concerning a developmental frame where the occurrence of catatonia in young children causes, over time, irreversible psychopathology similar to autistic impairment [42,43]. Prenatal exposure to Valproic Acid (VPA) is such a promising animal model of early-onset catatonia that has also been studied as a model for autism [44]. Offspring of female rats injected with VPA on day 12.5 of gestation show brain abnormalities, including smaller cerebella with fewer Purkinje cells. The rats exhibit catatonic-like behaviors appearing before puberty that include lower sensitivity to pain, diminished acoustic prepulse inhibition, repetitive hyperactivity, unresponsiveness and withdrawal.

Another new model is a model of fear-induced catatonia based on the animal reflex of tonic immobility [45], supported by observations that catatonia can develop after severe traumatic events in children and adolescents with autism [46-48]. Shah and Wing [22] found that ongoing stressful experiences often precede the development of catatonia in autistic young adults. Life events, the loss of routine and structure, experiences of loss, conflicts with parents, caregivers, or peers, and discrepancies between the higher functioning autistic individual's capabilities and the expectations of parents, can precipitate catatonia. Observations that catatonia follows overwhelming anxiety due to trauma or perceived danger, the positive response of catatonia to anxiolytics such as benzodiazepines or barbiturates, and psychogenic theories of catatonia [49], are particularly applicable to people with autism due to their increased social, cognitive, and sensory vulnerabilities [50,51].

Autonomic Dysfunction in Catatonia

Catatonia is considered a motor syndrome characterized by mutism, stupor, catatonic excitement, posturing and grimacing yet autonomic symptoms including abnormalities of temperature, blood pressure, pulse rate, respiratory rate, and perspiration occur in about forty percent of catatonic patients [3,52]. Forty-five percent of pediatric cases show urinary-fecal incontinence [3], another feature of autonomous dysfunction. Some cases show bradycardia [53,54] and bronchorrhea [55], indicative of strong vagal activity. Autonomic dysfunction is the hallmark of malignant catatonia [52,56], its drug-induced variant Neuroleptic Malignant Syndrome [57], and aseptic encephalitis with catatonic symptoms, including the recently coined anti-NMDAR encephalitis [58-60]. Early studies support that there is autonomic dysfunction in catatonia [61,62] but recent studies are lacking.

Autonomic abnormalities in catatonia support the image that catatonia represents a common end state response to feelings of impending doom across a wide range of medical and psychiatric disorders, finding its evolutionary counterpart in tonic immobility [45]. Tonic immobility is a last-ditch animal defense strategy against entrapment by a predator within a sequence of freezing-flight-fighttonic immobility. Volchan et al. [63] found signs of tonic immobility, such as reduced body sway, increased heart rate, and diminished heart rate variability, in trauma-exposed patients with PTSD while listening to their autobiographical trauma, implying that tonic immobility is preserved in humans as an involuntary defensive strategy.

A Vagal Theory of Catatonia in Autism

Autonomic dysfunction in catatonia implies involvement of the autonomous nervous system that consists of the parasympathetic subsystem, mediated by the vagus nerve, and the sympathetic subsystem, medicated by sympathetio-adrenal circuits in the spinal cord. A useful framework is the Polyvagal Theory that was first formulated by Porges in 1995 [64,65].

The Polyvagal Theory poses that two different vagal branches control different behavioral responses to threat, and that a human immobility response with behavioral (stupor) and metabolic shutdown (increased sweating, hypoventilation, decreased peristalsis, urinary and fecal incontinence, and vasovagal responses) represents the most primitive response to perceived imminent danger when fight-flight reactions fail or are not available.

A separate set of unmyelinated vagal fibers projecting to the nucleus dorsalis of the vagal nerve is thought to mediate this response through efferent fibers to the diaphragm, heart, gastrointestinal tract, lungs, pancreas, and other visceral organs. This reflex is adaptive in reptiles but potentially lethal in humans. Catatonia resonates clearly in the description of the immobility response yet is not recognized or acknowledged in the Polyvagal Theory as its clinical manifestation.

A vagal theory of catatonia supports abnormalities in a wide range of functions, regulated by the efferent vagal nerve and associated with catatonia, encompassing brain electrical and motor circuitry function, neurotransmitters, neuroendocrine and immune function. Toxic and medical factors may also trigger catatonia through efferent vagal activation. It is an intriguing thought that the vagal nerve, whose fibers are eighty percent afferent, may also be involved in signaling, through its afferent pathways, information to be brain about "internal" (toxic, immune, infectious, metabolic) precipitants of catatonia. Studies support effects on vagal tone by benzodiazepines [66-68], zolpidem [69] (a non-benzodiazepine sedative that has been effectively used in catatonia) and ECT [70], the recommended first-line treatments for catatonia, as predicted and required by a vagal theory.

Implications of a Vagal Theory for Catatonia in Autism

Studies are warranted into various aspect of autonomic dysfunction of catatonia in autism. There is evidence that increased anxiety and arousal accompany the development of catatonia in people with autism [50]. These observations beg for more scrutiny, using modern techniques, along the lines of earlier studies [61,62].

A vagal theory intimates use of vagal nerve stimulatory techniques as novel treatments for catatonia. Intermittent stimulation of the left vagal nerve (Vagal Nerve Stimulation; VNS) was approved by the Food and Drug Administration in July 1997. Improvement in the control of seizures in children has been well documented with VNS. Nonepileptic benefits in the quality of life and changes in behavior have not been as well documented, except for the enhancement of short-term memory [71].

Reports of the use of VNS in catatonia are absent. There is only a case-series from 2000 supporting the use of VNS for behavioral abnormalities in children with autism [72]. In that report, six children and adolescents with medically refractory epilepsy secondary to hypothalamic hamartomas were treated with intermittent stimulation of the left vagal nerve. Three of the patients had remarkable improvements in seizure control. Four of these six patients had severe autistic behaviors. Striking improvements in aggression and self-injury and social behavior were observed in all four during treatment with intermittent stimulation. These behavioral improvements did not correlate with seizure control, showing that vagal nerve stimulation can control seizures and autistic behaviors in patients with hypothalamic hamartomas, but through different mechanisms. None of the patients were assessed for the presence of catatonia yet the levels of aggression, self-injury, and social withdrawal hint at the possibility of catatonia. Future studies using systematic assessments of catatonia are warranted.

Further studies need to assess if vagal nerve stimulation has any role in the treatment and relapse prevention of catatonia in autism. Several autistic adolescents require maintenance ECT for months and even years to avoid relapses into catatonia. Although maintenance ECT is safe and without neuropsychological sequelae in such patients, finding adjuvant or alternative preventive treatments would be very valuable.

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