Catatonia: A narrative review of its historical development, diagnosis, pathophysiology, and therapeutics

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Abstract

Catatonia was initially a clinical presentation of certain types of schizophrenia, but basic and epidemiological evidence has demonstrated its association with multiple somatic and psychiatric conditions. We describe and discuss current clinical, etiological, pathophysiological, and therapeutic concepts regarding catatonia. We conducted a broad narrative review of articles published in MEDLINE/PubMed. The diagnosis is clinical and can be supported by additional tests, but there are psychometric instruments with different clinical focus. The most validated subtypes are inhibited and excited catatonia. It is mostly associated with somatic, neurological, affective, psychotic, and autistic spectrum disorders. Genetic factors related to oligodendrocytes have been studied in its pathophysiology. Some findings point to an imbalance in neurotransmission and density of GABA and dopamine receptors, consistent with their function in motor pathways and therapeutic response with benzodiazepines. Likewise, glutamatergic activity has been analyzed from the pathophysiological model of autoimmune encephalitis. The cortico-cortical and cortico-subcortical pathways would have a central role, including structures such as the orbitofrontal and temporal cortex, basal nuclei, and brainstem, involved in decision-making, emotion regulation, storage, planning, and motor processing. The main therapeutic lines are benzodiazepines and electroconvulsive therapy. Other interventions studied are zolpidem, antipsychotics, mood stabilizers, glutamatergic modulators, and transcranial magnetic stimulation. New neurobiological findings challenge nosological and therapeutic precepts, renewing the cycle in the conceptualization of catatonia. We highlight the affective component of the psychomotor syndrome and the role of interventions aimed at its modulation.

Main messages

- Catatonia is a clinical entity formulated in the 19th century, which has undergone major nosological changes and renewed research interest over time.
- Its research is scarce, which may be explained by underdiagnosis or a decrease in its prevalence since the introduction of the most modern pharmacological agents.
- This article presents a theoretical review that addresses the formal and pragmatic changes that catatonia has manifested since its origin to avoid any potential errors in this field.

Introduction

Psychomotor activity is a dimension that involves the transposition of various elements, including planning, execution, and modulation of motor activities by will and affectivity [1]. One psychomotor syndrome that has presented great changes in its nosological, pathophysiological, and therapeutic conceptualization is catatonia, whose current conception points towards integrating the earlier phenomenological precepts with the new neurobiological findings. It comprises multiple psychomotor symptoms characterized by quantitative and qualitative alterations, including motivation and communication [2].

The syndrome involves a series of symptoms that vary according to the reference used for its diagnosis. Among them are the lack of psychomotor activity (stupor), the persistence of a given position of limbs and joints that is induced by the examiner with a slow release of its rigidity (waxy flexibility), the maintenance of fixed and awkward postures for prolonged times (catalepsy), resistance to body mobilization by the examiner (negativism), and the presence of repetitive movements without a clear objective (stereotypies) [3].

Since its original conceptualization during the second half of the 19th century, successive advances in basic and epidemiological research have led to reforming its diagnosis and therapeutics, going from the schizophrenic spectrum to its current link with affective and somatic disorders. For these reasons, it is necessary to have a theoretical review that addresses the formal and pragmatic changes that catatonia has presented since its origin since a decontextualized reading of the phenomenon can lead to theoretical confusion. This review describes and analyzes the current considerations on catatonia, starting with its clinical, etiological, pathophysiological, and therapeutic aspects and historical development.

Methods

A broad narrative review was conducted on the different aspects of catatonia. Publications available in the MEDLINE/PubMed and Scopus databases were selected, and the three authors participated in this process. "Catatonia" and "catatonic syndrome" were used as search terms. The reference list of each article was reviewed to select other relevant articles. There was no restriction by methodological design, language, or year of publication. This was due to the fact that the first definitions of catatonia come from 19th-century sources, and research on catatonia is scarce and mostly observational, cross-sectional, or retrospective. Primary studies were prioritized for the etiology, pathophysiology, and treatment sections.

Results

Historical aspects

Initially, it was described by Kahlbaum [4] as an independent psychomotor syndrome characterized by abnormalities in motor acts. His description included phenomena such as melancholia, mania, stupor, confusion, and seizures, with alternating forms of presentation [5]. The author pointed out that his conceptualization of catatonia had been predicted by *melancholia attonita*, characterized by immobile mutism, facial rigidity, lack of movement or reaction to the environment, and *flexibilitas cerea* [5]. This demonstrates the importance that Kahlbaum gave to the affective sphere in his initial proposal. Subsequently, and although initially endorsing Kahlbaum's notion of catatonia as a separate clinical category [6], Kraepelin presented his definition of *dementia praecox* as a unique entity separate from manic-depressive psychosis, incorporating catatonia in addition to hebephrenia, and paranoid dementia as forms of *dementia praecox*. This meant that the affective component took a back seat, emphasizing the motor and behavioral elements [7].

Later, Bleuler considered it an integral part of the recently formulated schizophrenia [8] but recognized that catatonic phenomena are accessory symptoms of the disease that can occur in other conditions [9].

Contemporary authors such as Hoch [10] rejected this view, categorizing catatonia as a form of benign stupor, which in turn was one of the presentations of manic-depressive disorder. However, the prevailing concept was that of Kraepelin. However, from the 1970s onwards [11], research showed that it was more frequently present in affective, somatic, and other psychiatric disorders [12]. In 1994, the fourth version of the Diagnostic and Statistical Manual of Mental Disorders

(DSM-IV) [12] transformed catatonia into a clinical specifier ("catatonic symptoms") that could accompany other psychiatric and somatic disorders, an idea that has been maintained until the current classification proposed by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) [13]. This manual proposes a definition based on fulfilling descriptive diagnostic criteria. For its part, the Royal College of Psychiatrists points out that it is a state in which a person is conscious but appears unresponsive to others and their environment, affecting movement, speech, and behavior in many different ways [14].

Regarding its presentation, a systematic review found an overall prevalence of 9% for catatonia. This figure was obtained from the meta-analysis of 74 studies that evaluated its prevalence in different contexts. The highest proportion was in somatic

Table 1. Inclusion of catatonic symptoms in the DSM-5-TR, the Bush-Francis Catatonia Rating Scale, and the Northoff Catatonia Rating Scale.

	DSM-5-TR	Bush-Francis Catatonia Rating Scale	Northoff Catatonia Rating Scale
Immobility/stupor	Included	Included	Included
Mutism		Included	Included
Staring		Included	Included
Abnormal posturing/catalepsy	Included	Included	Included
Grimacing	Included	Included	Included
Echopraxia/echolalia	Included	Included	Included
Stereotypy	Included	Included	Included
Mannerisms	Included	Included	Included
Rigidity		Included	Included
Negativism	Included	Included	Included
Waxy flexibility/*flexibilitas cerea*	Included	Included	Included
Autism/withdrawal/refusal to eat, drink or make eye contact		Included	Included
Hyperactivity or psychomotor excitement		Included	Included
Psychomotor agitation	Included		Included
Impulsivity		Included	Included
Automatic obedience		Included	Included
Passive obedience/*Mitgehen/Mitmachen*		Included	Included
Muscle resistance/*Gengenhalten*		Included	Included
Ambitendency/Ambivalence		Included	Included
Grasp reflex		Included	
Perseveration		Included	Included
Combativeness		Included	Included
Autonomic abnormality		Included	Included
Verbigeration		Included	Included
Akinesia			Included
Abnormal speech			Included
Dyskinesia/Parakinesia			Included
Festination/jerky movements			Included
Flaccidity/muscular hypotonus			Included
Affect-related behavior			Included
Affective latency			Included
Flat affect			Included
Anxiety			Included
Athetotic movements			Included
Compulsive behavior			Included
Compulsive emotions			Included
Emotional lability			Included
Compulsive speech			Included
Loss of initiative			Included
Sudden muscular tone alterations			Included

DSM-5-TR: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition, Text Revision.
Source: Prepared by the authors [13,24,26,27].

disorders (20.6%), bipolar disorders (20.2%), and puerperal psychosis (20%), followed by autism spectrum disorders (11%), and schizophrenia (9%) [15,16].

Although catatonia has been rarely linked to other psychiatric scenarios, such as obsessive-compulsive disorder and post-traumatic stress disorder [17], evidence suggests that its prevalence is higher in affective and psychotic disorders, specifically in bipolar disorders [15,17]. These figures are consistent with a later quantitative analysis of Kahlbaum's work, from which it appears that of the 26 cases of catatonia presented by the author (including patients with terminal tuberculosis, peritonitis, neurosyphilis, and affective illnesses), the two main groups were deliriums and depressive psychoses. This is consistent with Hoch's initial proposal and the current observation, which verifies that catatonia is more prevalent in somatic and affective disorders [5,15].

Clinical manifestations and diagnosis

It is diagnosed clinically through a thorough psychiatric evaluation and a physical examination focused on neurological function. Onset is usually acute (hours, days), although if associated with schizophrenia, it may be subacute. The clinical presentation may vary from interview to interview. The duration of symptoms is a matter of discussion, but if they persist for more than one hour or recur over time, this is sufficient [18]. Currently, more than 40 symptoms and signs of catatonia are listed [19], which include excessive, diminished, and abnormal psychomotor components [20]. Different studies have shown that immobility and mutism would be the most frequent phenomena [21,22]. The DSM-5-TR [13] does not distinguish diagnostic criteria between age groups. If the criteria are not met, or the etiology is unknown, catatonia is classified as unspecified. The International Statistical Classification of Diseases and Related Health Problems (ICD-11) [23] places catatonia as a specific nosological entity in the same hierarchy as the others. This differs from its previous version, where it was considered a symptomatic specifier.

Many authors suggest a psychometric diagnosis of catatonia [3,19] since clinical observation could be insufficient since affective and cognitive characteristics are not considered. The most commonly used scales are the Bush-Francis Catatonia Rating Scale [24], the Bräunig Catatonia Rating Scale [25], and the Northoff Catatonia Rating Scale [26]. Table 1 lists the catatonic symptoms considered by the DSM-5-TR and two psychometric instruments. The definition of each symptom may vary depending on the source.

Some authors classify catatonia by subtypes without losing sight that each form of presentation is neither exclusive nor excluding, being able to alternate and combine. The first and most frequent is hypokinetic, akinetic, delayed, stuporous, or inhibited catatonia, where mutism, immobility, and isolation predominate, with proper consciousness and attention capacity [19,28]. Indeed, the lack of intentional psychomotor responses should not be interpreted as a lack of awareness of the environment, a statement corroborated in the report of some patients who presented hypokinetic catatonia and later recalled what they experienced during the episode [11].

The second subtype is hyperkinetic or excited catatonia, characterized by purposeless impulsive movements and agitation, with a risk of self- and hetero-aggression [29]. This classification is supported by some factor analyses [30]. Another subtype identified is malignant catatonia, originally termed "lethal catatonia," [31] differentiated by autonomic and hemodynamic instability involving fever, tachycardia, palpitations, altered consciousness, changes in blood pressure, diaphoresis and tachypnea [32]. It has a rapid progression and potentially fatal outcomes, requiring a high suspicion index and immediate treatment [33].

Other entities that could be related through clinical and pathophysiological associations with the spectrum of "catatonic diseases" include malignant catatonia, neuroleptic malignant syndrome, malignant serotonergic syndrome, and forms of autoimmune encephalitis with catatonia. In all of them, a catatonic syndrome associated with autonomic instability and encephalopathy is observed [1,18]. Fink [34] suggests that based on the clinical and therapeutic response evidence, malignant catatonia and neuroleptic malignant syndrome should be considered a single entity, while other groups advocate that neuroleptic malignant syndrome is a form of drug-induced catatonia [35]. However, Walther et al. [1] argued about the nosological placement of malignant catatonia since autonomic and hemodynamic instability do not participate in the psychomotor syndrome and should be considered a separate diagnosis.

In different periods, authors such as Wernicke, Kleist, Gjessing, and Leonhard reported the existence of periodic catatonia [3,36]. It has progressive clinical features with alternating phases of total remission and psychotic symptomatology [2]. Its pathophysiology is less clear than the rest, so its treatment is not yet established, and the evidence is based on case reports [37].

Auxiliary tests

Within the usual tests, it is recommended to include a complete blood count and urea nitrogen, creatinine, liver and muscle enzymes, plasma electrolytes, thyroid tests, and glycemia determinations. Iron deficiency and higher D-dimer and creatine kinase values have been more frequently observed in malignant catatonia and neuroleptic malignant syndrome [38,39]. However, the latter could be associated with muscle fiber rupture caused by rigidity and agitation. If a significant elevation of creatine kinase and total leukocyte count is found, it is suggested to consider the diagnosis of neuroleptic malignant syndrome [3]. Due to the frequent association between catatonia and autoimmune encephalitis, it is advisable to evaluate anti-N-methyl-D-aspartate (NMDA) receptor immunoglobulin G levels [40] in high-suspicion scenarios, such as in pediatric patients with catatonic symptoms. Urine drug testing will be indicated in case of suspected substance use.

Etiologies

The main causes of catatonia have been studied in the middle-aged population and are as follows. However, etiologies may vary towards the extremes of life. In the pediatric population, its prevalence is lower and is usually associated with anti N-methyl-D-aspartate receptor encephalitis (more than one-third of cases) and with autism spectrum disorders (one-fifth of cases) [19,41]. In the elderly, it is associated with benzodiazepine withdrawal [42] and with dementia [19,42].

Psychiatric causes

Probably, due to the historical roots of the condition, it is the first group of suspected causes. Catatonia occurs most frequently in bipolar and psychotic disorders. Specifically, it is more prevalent in mood elevation phases of bipolar disorder than schizophrenia, contrary to historical belief. The higher the age, the probability of presenting catatonia in unipolar depression increases [3]. In middle-aged groups, cases of catatonia in autism spectrum disorders have increased [1,11].

Somatic causes

Medical diseases account for 20% of catatonia cases [43]; 70% are related to an intrinsic alteration of the central nervous system [19]. The most common are strokes, infectious diseases, neoplasms, autoimmune diseases, neurodegenerative disorders, and metabolic disorders [44]. A special place is held by encephalitis due to anti N-methyl-D-aspartate receptor antibodies, a condition that usually presents psychiatric symptoms with psychomotor involvement. Seventy percent of cases of catatonia of autoimmune origin are due to this type of encephalitis [45]. Its presentation may be confused with a psychotic episode in the context of schizophrenia or substance abuse [46].

Other causes

There is an elevated risk of catatonia following withdrawal of drugs such as benzodiazepines and clozapine ("withdrawal catatonia"). The hypothesis states that excitatory neurotransmission would be exacerbated after the withdrawal of molecules that stimulate GABA activity and dopaminergic signaling in the ventral tegmental area, increasing metabolism in the striatum and triggering catatonic symptoms [47]. As for clozapine, abrupt withdrawal would trigger rebound cholinergic and serotonergic hyperactivity. However, this observation should be corroborated in further studies [48]. Finally, cases of cocaine- and ecstasy-induced catatonia have been reported, but this group is less representative [3].

Differential diagnosis

The literature has pointed out several pictures in which the possibility of catatonia should be contemplated: akathisia, extrapyramidal syndrome (history of antidopaminergic use), neuroleptic malignant syndrome (history of antidopaminergic use), stiff person syndrome (presence of pain and absence of mutism), akinetic mutism, vegetative states (alterations in the electroencephalogram and preservation of the sleep-wake cycle), conversion disorders, dissociative disorders and non-convulsive status epilepticus (alterations in the electroencephalogram) which, when presenting catatonic symptoms, has been called "ictal catatonia" [3,11,19]. The distinction between catatonia and delirium deserves a special place since they are conditions that should not necessarily be differentiated but can coexist. In fact, it represents a typical presentation of catatonia of somatic etiology, malignant catatonia, and neuroleptic malignant syndrome. Vice versa, the finding of catatonic symptoms is frequent during delirium [42]. Despite this, the DSM-5-TR [13] rules out the possibility of diagnosing catatonia when a picture of delirium is present, a consideration frequently criticized by the published literature [49].

Pathophysiology

It has been suggested that catatonia is a response to extreme anxiety that presupposes a vital threat triggered by a predator [50]. This idea recalls the tonic immobility observed as an animal defense strategy in response to fear, represented by symptoms such as stupor, catalepsy, and mutism. In parallel, fight-flight-type reactions to an external threat would be found based on excited catatonia [42]. Some studies report higher levels of anxiety and hyperactivity in older patients during the catatonic episode [51]. Rasmussen et al. [11] reported experiences of catatonic patients who, previously and during the syndrome, indicated that they were about to die, had already died, or had to remain immobile to avoid environmental threats. However, many patients do not report significant anxiety levels; thus, the theory fails to explain the picture's complexity. In contrast, the prevailing pathophysiological view involves genetic input in an incipient manner and findings in neurotransmission and motor pathways.

Genetics

The heritability of catatonia is considerable: if a person has a first-degree relative affected with catatonia, the risk of suffering it will increase by 27% [2,52]. Some studies point to a certain familial aggregation for periodic catatonia [1], as is the case for some symptoms, such as mutism and rigidity [1]. At the preclinical level, genetic factors related to oligodendrocytes have been studied. In a knockout mouse model for the gene encoding cyclic nucleotide phosphodiesterase, relevant in the functioning of these cells, behaviors compatible with a catatonic phenotype (catalepsy, apathy, and social isolation) were found, mitigated by pharmacological cell inactivation [53]. In humans, variations in the expression of this gene have been reported more frequently in patients with catatonia [2].

Dopaminergic and GABA neurotransmission

The use of dopaminergic blockers in psychosis has been linked to an increased risk of catatonic symptoms and neuroleptic malignant syndrome. This action would increase the activity of GABA-B receptors, which affects the balance with GABA-A

signaling, manifesting as catatonic symptoms [54]. This phenomenon would also happen when using dopaminergic antagonists when a previous GABA/dopamine signaling imbalance is present [2]. Indeed, Osman and Khurasani [55] proposed massive and sudden dopamine blockade as a cause of catatonia.

The density of GABA-A receptors would be lower in the left sensorimotor cortex in persons with inhibited catatonia, which results in a subcortical dopaminergic hypoactivity in the striatal nucleus, explaining the hypokinetic picture [28]. Likewise, reduced GABA-A activity has been reported in the right posterior parietal and right lateral orbitofrontal cortex [28]. Thus, benzodiazepines, being positive allosteric modulators of GABA receptors, would decrease the hyperfunction of motor pathways involved in catatonia by activating inhibitory pathways.

Glutamatergic neurotransmission

N-methyl-D-aspartate receptor hyperactivity, highly present in the basal nuclei circuitry, has been implicated in catatonia. One pathophysiological model of catatonia comes from N-methyl-D-aspartate encephalitis, where autoantibodies alter N-methyl-D-aspartate receptor metabolism [56]. The interconnectedness of neurotransmitter pathways explains how alterations in glutamatergic (excitatory) activity lead to dysregulation of GABA-A neurotransmission [19,45].

Motor pathways

Northoff's hypothesis [57] on the neurobiology of catatonia consists of a model of top-down regulation of the basal nuclei from medial and lateral orbitofrontal, prefrontal, and posterior parietal dysfunction, whose essential mediators are dopamine [58] and GABA [59]. These results would be limited to patients with schizophrenia spectrum disorders and catatonia. Other authors argue that the "horizontal abnormalities" verified in cortico-cortical circuits are of greater importance [60]. Essentially, three motor pathways have been involved. The first is related to inhibition and activation of movements; it starts in the primary motor cortex, goes to the putamen, internal and external pallid nucleus, and thalamus, and returns to the primary motor cortex [1,61]. The second pathway, responsible for motor dynamics and temporality, involves the primary motor cortex, thalamus, cerebellum, and pontine nuclei [1,61]. The third is responsible for the motor organization and speed of movements. It involves the primary motor cortex, supplementary motor area, posterior parietal cortex, and medial prefrontal cortex [1,2,61]. Disruption of all three pathways involves an imbalance in the inhibition and excitation of movements, resulting in catatonic symptoms.

It has been shown that blood flow is increased in the primary motor cortex and the supplementary motor area, reflecting increased neuronal activity in cases of catatonia [2,62]. Functional imaging studies have corroborated decreased activity during voluntary movements in the primary and secondary motor cortex, supplementary motor area, inferior parietal cortex, and basal nuclei [1]. Specifically, in a pathophysiological model of inhibited catatonia, it has been proposed that increased activity in premotor and supplementary motor areas, whose function is inhibitory, results in the inhibition of cortico-cortical pathways (associated with connectivity to the inferior parietal lobe) or indirect/hyper direct pathways (associated with connectivity to the subthalamic nucleus) [1]. Other research has demonstrated differences in blood perfusion between patients with inhibited and excited catatonia in the supplementary motor area and regions of the parietal cortex. Parietal disturbances could be why many patients who experienced catatonia do not clearly remember the experience since disturbances in this area lead to dysfunction in motor attention [62].

Treatment

Before introducing pharmacological agents and electroconvulsive therapy, mortality associated with catatonia was quite high [1,63]. Today, the prognosis is usually favorable when interventions are early. Some factors predicting a better response are acute onset and younger age. In contrast, chronicity, which is more frequent in patients with schizophrenia, is associated with worse outcomes. Since most studies have included schizophrenia patients with chronic catatonia, the observation arises that catatonia in affective disorders has a better response to treatment than in psychotic disorders [17].

General aspects

Simultaneously, related complications (due to immobility, rejection of hydration and food intake, and autonomic dysfunction) [19], as well as the catatonic symptomatology itself, should be prevented and treated [19]. Patients with autonomic and hemodynamic instability are at high-risk for complications and mortality, requiring immediate treatment [33]. Among the most frequent complications are deep vein thrombosis, pulmonary thromboembolism, aspiration, rhabdomyolysis with potential renal damage, pressure ulcers, and muscle contractures [1,11]. If sustained immobility is found, prophylactic anticoagulant therapies can be used [64].

Benzodiazepines

They are the first line of treatment since they can restore GABA neurotransmission in the frontal cortex, with a response rate of 80% [17]. They should be administered with special caution in case of impaired consciousness [65], for which doses should be lower [2]. In this scenario, the most commonly used pharmacological treatment is antipsychotics since benzodiazepines can worsen the impaired consciousness, but, at the same time, antipsychotics could deepen the catatonic symptomatology [1,42].

Evidence indicates that a lorazepam test can be performed with diagnostic and therapeutic value. It consists of administering 0.5 to 6 milligrams of the drug intravenously, intramuscularly, sublingually, or orally to evaluate the clinical response within 10 to 30 minutes. Suppose a significant clinical improvement (50%

decrease measured with a standardized scale) [17]. In that case, the test is considered positive and can be continued with an identical dose every six to eight hours. If the outcome is negative, it can be repeated after 30 minutes and every three hours [11]. The dose of lorazepam can be increased to 12 or 16 milligrams per day for an undetermined time [17]. Lorazepam has been the most studied and used benzodiazepine; however, there are reports of successful responses with diazepam [66] and clonazepam [67]. In case of a lack of response on the fifth day, electroconvulsive therapy should be considered [68].

Electroconvulsive therapy

It is a highly effective intervention, both for catatonia in psychiatric and somatic pathologies [69], with a favorable response between 80 and 100% [70], especially when there is autonomic instability [2,70]. It is also considered a safe and effective intervention for children, adolescents, and the elderly [71]. It is considered when benzodiazepine treatment has failed since it is not available in every hospital and has potential temporary adverse effects related to the cognitive sphere [68]. However, it is the first-line treatment when there is a greater life risk, i.e., in malignant catatonia, neuroleptic malignant syndrome [19], or delirious catatonia [2]. Its mechanism of action would be related to an increase in blood flow to the orbitofrontal and parietal cortices, which would increase GABA activity [72]. Although some groups recommend the suspension of benzodiazepines in the case of electroconvulsive therapy, the appearance of catatonic symptoms after the suspension of benzodiazepines has been reported. In conjunction, some authors propose a synergistic effect between benzodiazepines and electroconvulsive therapy [73,74], so this indication is a matter of debate. Although the number of electroconvulsive therapy sessions is not determined, it is estimated that up to six sessions may be required. In a randomized clinical trial in patients with schizophrenia and catatonia, bifrontal stimulation showed superior clinical and cognitive outcomes compared to bitemporal stimulation [75]. It has also been proposed that stimulation with a stimulus substantially higher than the seizure threshold would be indicated in severely ill patients [76].

Other interventions

According to the literature, the following interventions would be reserved for cases in which treatment with benzodiazepines or electroconvulsive therapy is insufficient.

Zolpidem

Some studies have concluded favorable therapeutic responses following the use of zolpidem [77]. The zolpidem test [78], analogous to the lorazepam test, has been proposed. In this case, 10 milligrams of the drug are administered orally, and the patient is examined after 30 minutes.

Antipsychotics

They have been used in cases of catatonia associated with schizophrenia cautiously and under strict supervision. They are restricted to those agents with low affinity for the dopaminergic D2 receptor, such as clozapine, quetiapine, and olanzapine [2], or with partial agonist function, such as aripiprazole, considering the coadministration of benzodiazepines [72]. Second-generation antipsychotics exhibit weak GABA agonist activity and 5HT2 receptor antagonism, associated with increased prefrontal dopaminergic neurotransmission and an eventual decrease in catatonic symptoms [79].

Mood stabilizers

Their use has been tested in patients with bipolar disorders based on their GABA action. The use of carbamazepine, valproic acid, and topiramate has been published, but only at a descriptive level in case series [80].

N-methyl-D-aspartate receptor antagonists

Once the main therapeutic lines have failed or could worsen the clinical course, the use of amantadine (100 to 500 milligrams) and memantine (5 to 20 milligrams) has shown favorable results [17], possibly linked to their glutamatergic effect [2]. By blocking the N-methyl-D-aspartate receptor, the neurochemical balance favors GABA neurotransmission [3].

Transcranial magnetic stimulation

Transcranial magnetic stimulation has been proposed as a possible intervention, especially in cases requiring maintenance treatment. The targeted area will depend on the underlying psychiatric disorder. Some advantages over electroconvulsive therapy are that it does not require anesthesia and is not associated with cognitive alterations [81].

Discussion

Originally, catatonia was conceptualized as a presenting form of schizophrenia. Subsequently, it acquired independence as a clinical manifestation of psychiatric and somatic disorders. This has possibly renewed research interest, demonstrated by a significant increase in this condition in publications [19]. Even so, its research is scarce, perhaps because of a decrease in its prevalence after the introduction of the most modern pharmacological agents or due to underdiagnosis.

Most available evidence comes from expert opinion, case reports, and case series, mostly retrospective observational studies and clinical trials with small samples. However, on the other hand, understanding its neurobiology through animal models and functional neuroimaging studies in humans has clarified its pathophysiology and the underlying mechanisms of action of some pharmacological agents and neuromodulatory interventions. Some theoretical approaches point out that the affective component is central in catatonia, given the high frequency of symptoms of this sphere in this condition and the

excellent response achieved with benzodiazepine treatment. These modulate the functioning of the GABA system, which is highly involved in emotion regulation [61].

Although human studies using functional neuroimaging techniques have been able to characterize various circuits that would explain catatonic symptoms, no specific alterations of the basal nuclei have been identified. However, theoretical models agree on a common biological substrate, corresponding to subcortical structures dysfunction (i.e., basal nuclei, brainstem, cerebellum, and thalamus) leading to aberrant execution of stored motor plans [61].

Although some groups have emphasized the affective component of catatonia [7,61], no systematic associations between limbic system dysfunction and the clinic have been found. Nevertheless, some regions involved in emotion regulation, such as the temporal cortex, have shown altered functioning in catatonia, as well as the orbitofrontal cortex, which has important connectivity with limbic system structures such as the hippocampus, amygdala, and thalamus, and with cortical motor regions (cortico-cortical regulation).

Consequently, it could be hypothesized that alterations in the areas involved with decision-making and emotion regulation (orbitofrontal cortex) impact the planning and elaboration of movements (motor areas), which manifests as a psychomotor symptom within the catatonic constellation [82].

Current nosology indicates that it is a clinical syndrome associated with psychiatric and somatic pathologies, with a higher incidence of affective disorders, particularly those of the bipolar spectrum. Among somatic pathologies, the highest incidence is found in those directly involving the central nervous system, such as encephalitis, stroke, and neurodegenerative disorders.

Regarding therapy, there is a consensus on using high-dose benzodiazepines for a limited period of time as the first of treatment and electroconvulsive therapy as the second line, with high clinical response rates. The findings in autoimmune encephalitis and the upper motor systems support a new vision of the picture that discusses its nosological, pathophysiological, and therapeutic precepts, renewing the cycle in the conceptualization of catatonia. Therefore, it is a condition that should be of interest and knowledge to healthcare personnel in general and not only those circumscribed to psychiatry.

Conclusions

Current knowledge on the pathophysiological bases involved in catatonia should guide future research, whose main focus should be detecting pre-catatonic states by identifying patients at risk since the preventive approach in the field is still insufficient.

Notes

Contributor roles

All authors contributed to the planning and writing of the original manuscript. MA constructed Table 1. MA, AC, and UR jointly contributed to completing all manuscript sections.

Conflictos de intereses

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Catatonía: revisión narrativa de su desarrollo histórico, diagnóstico, fisiopatología y terapéutica

Resumen

Inicialmente la catatonía fue un componente clínico de algunas formas de esquizofrenia, pero la evidencia básica y epidemiológica demuestra su vinculación con múltiples cuadros somáticos y psiquiátricos. Se describen y analizan conceptos clínicos, etiológicos, fisiopatológicos y terapéuticos actuales respecto a la catatonía. Se realizó una revisión narrativa amplia de artículos publicados en MEDLINE/PubMed. El diagnóstico es clínico y puede apoyarse en exámenes complementarios, pero existen instrumentos psicométricos con distinto énfasis clínico. Los subtipos más validados son el inhibido y el excitado. Se asocia mayormente a patologías somáticas, neurológicas, afectivas, psicóticas y del espectro autista. En su fisiopatología se han estudiado factores genéticos relacionados con los oligodendrocitos. Algunos hallazgos señalan un desbalance en la neurotransmisión y densidad de receptores de GABA y dopamina, hecho concordante con su función en las vías motoras y la respuesta terapéutica con benzodiacepinas. Asimismo, se ha analizado la actividad glutamatérgica, desde el modelo fisiopatológico de la encefalitis autoinmune. Las vías córtico-corticales y córtico-subcorticales tendrían un rol central, incluyendo estructuras como las cortezas orbitofrontal y temporal, núcleos basales y tronco encefálico, involucradas en la toma de decisiones, regulación emocional, almacenamiento, planificación y elaboración motora. Las principales líneas terapéuticas son las benzodiacepinas y la terapia electroconvulsiva. Otras intervenciones estudiadas son el zolpidem, antipsicóticos, estabilizadores del ánimo, moduladores glutamatérgicos y estimulación magnética transcraneal. Los nuevos hallazgos neurobiológicos discuten los preceptos nosológicos y terapéuticos, renovando el ciclo en la conceptualización de la catatonía. Se destaca el componente afectivo del síndrome psicomotor y el rol de las intervenciones que apunten a su modulación.