Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry 2019; 11(3):257-270
doi: 10.18863/pgy.507214

Catatonia: Clinical Features and Treatment

Katatoni: Klinik Özellikler ve Tedavi

Ömer Asan [1]

Abstract

Catatonia was first introduced by Karl Kahlbaum in 1874 and it is a syndrome characterized by motor, cognitive, affective and autonomic symptoms. As first, it was linked with just schizophrenia for many years but it is currently known that this disorder may occur with many psychiatric disorders and other medical conditions. In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders that published in 2013, the subtypes of schizophrenia have been removed and the relationship between catatonia and schizophrenia which lasts over one hundred years ended. In this paper, we reviewed the literature about catatonia and aimed to look over its history, epidemiology, etiology, clinical features, prognosis and treatment through current knowledge.

Keywords: Etiology, malign catatonia, pathogenesis, schizophrenia, treatment

Öz

Katatoni ilk kez 1874 yılında Karl Kalbaum tarafından tanımlanmış, motor, bilişsel, affektif ve otonomik belirtilerle karakterize bir nöropsikiyatrik sendromdur. İlk başta sadece şizofreniyle ilişkilendirilirken günümüzde birçok psikiyatrik hastalık ve tıbbi durumla birlikte görüldüğü bilinmektedir. 2013 yılında yayınlanan DSM-5 (Diagnostic and Statistical Manual of Mental Disorders: Ruhsal bozuklukların tanısal ve sayımsal el kitabı)'te şizofreni'nin alttipleri kaldırılmış ve yüz yılı aşkın katatoni-şizofreni birlikteliği sona ermiştir. Bu yazıda katatoni ile ilgili literatür gözden geçirilmiş, tarihçesi, epidemiyolojisi, etiyolojisi, klinik belirtileri, prognoz ve tedavisi güncel bilgiler ışığında ele alınmıştır.

Anahtar sözcükler: Etiyoloji, katatoni, malign katatoni, patogenez, şizofreni, tedavi.

[1] Sakarya University Education and Research Hospital, Sakarya, Turkey

✉ Ömer Asan, Sakarya University Education and Research Hospital, Sakarya, Turkey
omerasan@hotmail.com

Geliş tarihi/Submission date: 02.01.2019 | Kabul tarihi/Accepted: 30.01.2019 | Çevrimiçi yayın/Online published: 12.02.2019

CATATONIA is a neuropsychiatric syndrome characterized by motor, cognitive, affective and autonomic symptoms. More than 40 symptoms associated with catatonia have been described in the literature; stupor, posturing, negativism and mutism are the most common symptoms among these. Catatonia is an important syndrome, it is potentially life-threatening and can dramatically improve with rapid diagnosis and treatment. Although it has been associated with only schizophrenia in the past, today, it is known that this disorder may occur with numerous psychiatric disorder and general medical conditions. In the fifth edition of DSM (Diagnostic and Statistical Manual of Mental Disorders) published in 2013, which is one of the most widely used classification systems worldwide, the association of schizophrenia and catatonia has been ended. Catatonia was reclassified under a separate heading in the chapter of "Schizophrenia Spectrum and Other Psychotic Disorders" (American Psychiatric Association 2013). In this review article, the literature on catatonia was reviewed and its history, epidemiology, etiology, clinical symptoms, prognosis and treatment were discussed through current information.

History

Catatonia was first described by Karl Kahlbaum in 1874. In Greek, it means "stretching tight". The term "catatonia" was described at a time when psychiatrists just began to associate psychiatric disorders with brain disfunction. In the article of "catatonia or tension insanity" published in 1874, Kahlbaum described catatonia as a degenerative brain disease with motor, cognitive and vegetative symptoms caused by birth trauma, alcoholism, or another brain disease. Kahlbaum stated that hebephrenia and catatonia were separate diseases, and that catatonia had a better prognosis despite lethal outcomes in some cases. However, as of 1877, numerous cases of chronic catatonia cases with residual symptoms and many cases of hebephrenia with motor symptoms similar to catatonia have been reported (Arndth 1902, Brosius 1877, Aschaffenburg 1898).

In the light of these developments, Kraepelin described hebephrenia and catatonia as the sub-groups of the same disease called "dementia praecox" in 1893. Kraepelin reported that catatonia arising with mood disorders was different from the clinical picture of catatonia with chronic psychotic disorder in terms of symptoms and prognosis and had a better prognosis. He differentiated melancholic and manic catatonia and chronic catatonia. Moreover, Kraepelin (1913) came up against the view of Kahlbaum suggesting that catatonia develops in association with organic causes, and argued that catatonia was a psychogenic disease caused by mental block. In 1911, Bleuler replaced the term of Kraepelin "dementia praecox" with the term "schizophrenia" and described catatonia as a subtype of schizophrenia. Bleuler refused the pathophysiological theories for the etiology of catatonia, indicated that the manifestation was of psychogenic origin and explained it psychoanalytically. According to Bleuler, catatonia is a psychogenic condition characterized by withdrawal under harmful environmental conditions. George Kirby separated the degenerative and non-degenerative types of catatonia in 1913 and suggested that it was more related to manic-depressive disorder rather than psychotic disorder, and argued that Kahlbaum and Bleuler had drawn the boundaries of schizophrenia too broadly. Kleist (1943) and Leonhard (1935) described cycloid psychosis characterized by increased and decreased motor activity and reported that this presentation was associated with manic-depressive disorder in the classification of Kraepelin.

Antipsychotics that were discovered in the 1950s made a breakthrough in the treatment of schizophrenia, other psychotic disorders and mood disorders, but added a new dimension to the controversy regarding catatonia. With the use of antipsychotic drugs, there was a significant decrease in the number of chronic catatonia cases presenting with schizophrenia, but this time, motor disorders secondary to drugs started to be observed. In the 1960s, drug-induced dyskinesia, its stereotype and mannerism cases were reported (Uhrband and Arild 1960, Rogers 1985). It has been reported that neuroleptic malignant syndrome (NMS), a life-threatening condition, which occurs as a side effect of antipsychotic drugs, is quite similar to catatonia and may even be a type of catatonia (Caroff 1980, Fink 1996).

DSM and Catatonia

Two commonly used classification systems in the world are the DSM and the ICD (International Statistical Classification of Diseases and Health Problems) classification systems. Catatonia was classified only as a subtype of schizophrenia until the DSM-4 published in 1994, despite numerous studies demonstrating that catatonia could be seen with many medical conditions, especially with mood disorders. Especially the studies by Fink and Taylor made a tremendous impact and catatonia was reclassified in three different forms in the DSM-4 as catatonic schizophrenia, catatonia secondary to mania or major depressive disorder and catatonia due to another medical condition (Fink and Taylor 1991). This revision is important in terms of revealing that catatonia is not only associated with schizophrenia but also may arise with other disorders. However, some researchers did not find this revision sufficient and argued that catatonia should be addressed as a completely separate heading in the DSM (Peralta et al. 1997, Taylor and Fink 2003).

The fact that catatonia may be seen with metabolic, toxic, neurological and various psychiatric disorders, rapidly improve with the ECT (electroconvulsive treatment) and benzodiazepines unlike schizophrenia, and does not respond well to antipsychotics that treat psychosis, and even antipsychotics may result in the emergence of catatonia-like conditions (neuroleptic malignant syndrome) has formed the basis of this view. Articles reporting that diseases such as Klein-Levine syndrome, autoimmune encephalitis, Prader-Willi syndrome and tic disorders, seen in children and adolescents, may be a clinical manifestation of catatonia (Dhossche and Wachtel 2010).

In light of all these findings, the subtypes of schizophrenia were removed from the DSM-5 published in 2013, and the relationship between schizophrenia and catatonia, which lasted for more than a hundred years, ended. In the DSM-5, catatonia was reclassified under a separate heading in the chapter of "Schizophrenia Spectrum and Other Psychotic Disorders" and under this heading, catatonia appears in three forms as “catatonia associated with another mental disorder”, “catatonic disorder due to another medical condition” and “unspecified catatonia”. Due to these revisions, patients diagnosed with catatonic schizophrenia in the DSM-4 also receive the diagnoses of "schizophrenia", as well as "catatonia associated with another mental disorder" in the DSM-5

Epidemiology

The studies to determine the estimated prevelance of catatonia usually include indivi-

duals with acute psychiatric disease. In the studies on catatonia, the prevelance rate ranges from 8% to 40% (Ungvari et al. 2009). The prevalence rate of catatonia has been reported to be about 10% in individuals with psychiatric disease; however, this rate ranges from 5% to 20% in studies conducted in different psychiatric clinics (Rosebush et al. 1990, Chalasani et al. 2005). This difference between the results probably depends on the type of study and how catatonia was diagnosed (the DSM-5 criteria, diagnostic scales). In clinical practice, there is an impression that catatonia is less common than in the past. It is a known fact that the number of severe chronic catatonia cases with dramatic symptoms such as posturing and waxy flexibility, especially seen in schizophrenia patients, decreased due to the widespread use of antipsychotics. However, the studies report that the diagnose of catatonia is frequently overlooked and the prevalence is higher than assumed. In a study included 139 acute psychotic patients in the Netherlands, it was reported that the researchers investigating the prevalence of catatonia determined the diagnosis of catatonia in 18% of the patients, but the team conducting the treatment of the patients diagnosed 2% of the patients with catatonia (van der Heijden et al. 2005).

It has been reported that catatonia can be most commonly seen with unipolar depression and bipolar disorder from psychiatric disorders. In a study included 106 patients admitted to the acute geriatric psychiatry unit, it was found that the prevalence of catatonia was 20.8% according to the DSM-5 diagnostic criteria and it was reported that it was most commonly seen in depression patients (48.6%) (Esteban et al. 2017). Apart from psychiatric disorders, catatonia can also be seen with numerous other medical conditions. In a meta-analysis of 73 studies included 110,559 patients, it was reported that the prevalence of catatonia was 20.6% in patients with another medical condition or neurological disease, 20.1% in bipolar disorder patients, 20% in post-partum psychosis patients, 11.1% in patients with the diagnosis of autism and 9.8% in schizophrenia patients (Solmi et al. 2017). In a study by Grover et al. investigating the prevalence of catatonia in 205 delirium patients consulted to the consultation-liaison psychiatry unit, they found catatonia in 12.2% of patients according to the DSM-5 diagnostic criteria and in 30.2% of the patients according to the Bush-Francis Catatonia Rating Scale (BFCRS). Excitation (72.7%), immobility/stupor (21.4%) and mutism (15.6%) were the most common symptoms in these patients (Denysenko et al. 2015).

Pathogenesis and Etiology

A psychodynamic view for the pathogenesis of catatonia is that it is a response to severe anxiety (Moskowitz 2004). Anxiety symptoms seen simultaneously with or before catatonic symptoms, the reports of the patients thinking that they should remain immobile against threats from others, the improving effects of benzodiazepines, which are an anxiolytic, on catatonic symptoms have been reported as the findings supporting this theory. Today, no catatonia-specific laboratory finding, no genetic or neurobiological pathology has yet been found; however, numerous studies are conducted on this issue. Some neurobiological findings associated with catatonia were identified, but it is not known exactly whether these are the causes of catatonia or arise in the course of catatonia. In some neurobiological studies, a hypothesis suggesting that catatonia may be the result of a pathology in the pathways connecting the basal ganglia to the cortex and thalamus has been proposed (Mann et al. 2005). In the literature, catatonia cases asso-

ciated with a single lesion in some regions (frontal lobe, basal ganglia, cerebellum, pons, corpus callosum) of the central nervous system (CNS) and due to frontal lobe degeneration and anterior cerebral artery aneurysm were reported (Fink and Taylor 2003, Arora and Praharaj 2007). However, there are more case reports and studies arguing the hypothesis that catatonia is a diffuse CNS pathology rather than a single CNS lesion. The post-mortem studies on cases of catatonia due to a medical condition did not reveal any definite CNS finding associated with catatonia (Carroll and Goforth 2004). Whereas, in some neuropathological studies conducted on patients with catatonic schizophrenia, it was found that there were some changes in the basal ganglia (nucleus caudatus, nucleus accumbens and globus pallidus) and thalamus (Northoff 2002). Also, functional anomalies of the prefrontal, orbitofrontal and parietal cortex were detected in patients with catatonia in neuroimaging studies (Northoff 2000). It has been reported that there is a link between lateral prefrontal cortex lesions and imitative behavior which may be associated with symptoms such as echolalia and echopraxia (Northoff et al. 1999, van der Heijden et al. 2005). Furthermore, it has been reported that dysfunction of the pathways between the prefrontal cortex and amygdala may be associated with extreme cowardice and timidity frequently described by catatonic patients. In neuropsychological tests carried out on catatonic patients, impaired visual-spatial ability indicating the right parietal cortex function has been reported.

The hypothesis most emphasized in neurotransmitter studies is the decreased GABA-A receptor activity. Recently, evidences suggest that NMDA antagonists were effective in the treatment of catatonia obtained, and accordingly, glutamate NMDA receptor hyperactivity has been suggested to also play a role in catatonic symptoms. It has been reported that NMDA hyperactivity inhibits GABA-A function, NMDA antagonists indirectly regulate GABA-A activity in the frontal lobes, but this effect is slower compared to GABA-A receptor agonists (Daniels 2009).

The role of dopamine in catatonia is quite complicated. The dopaminergic pathways along with other neurotransmitters and pathways play an important role in catatonia, malignant catatonia and NMS, but the role of dopamine is still not exactly known. According to Northoff, who conducted numerous studies in this field, the basic neurochemical disorder in catatonia is a cortical dysfunction caused by disruption of the GABA-A system in the thalamocortical pathways and subcortical area and subsequent dysregulation of the dopaminergic system (Northoff 2002). In addition, it was reported that catatonia and malignant catatonia may show up due to direct cortical dopamine antagonism (top-down) and NMS may show up as a result of subcortical dopaminergic dysregulation (bottom-up). In another study, it was reported that dopaminergic dysregulation in the corticothalamic pathway between the medial orbitofrontal cortex and the lateral hypothalamus may be responsible for autonomic symptoms in malignant catatonia and NMS (Mann et al. 2005).

Although genetic studies has found no catatonia-specific definitive finding to date, it is suggested that periodic catatonia may have a genetic basis. The studies reporting that the genes on the chromosomes 15 (15q15) and 22 (22q13) may be associated with periodic catatonia and the results of some family studies support this information (Meyer et al. 2001, Stöber 2001).

About a quarter of catatonia cases have been reported to be associated with other medical conditions (usually neurological) and drugs. Catatonia may occur in cases of

alcohol and other CNS depressant agents' intoxication or deprivation, benzodiazepine deprivation and lithium intoxication. The other drugs and agents reported to cause catatonia are corticosteroids, opiates, interferon, quinolones, levetiracetam, azithromycin, disulfiram, methylphenidate, cannabinoids, cocaine, amphetamines, mescaline and phencyclidine (Dubovsky and Dubovsky 2018). Antipsychotics used in the treatment of many psychiatric disorders, especially schizophrenia and bipolar disorder, may also lead to catatonia-like syndroms (NMS) and aggravate the existing catatonic disorder. Although there are publications reporting that second-generation antipsychotics can be used because of being effective in the treatment of comorbid psychosis and mood disorders in catatonia, all antipsychotics may exacerbate catatonia and clinicians should be careful while using these agents. The most common etiological factors in catatonia due to a medical condition are infections (encephalitis, sepsis), electrolyte imbalance (hyponatremia), autoimmune encephalopathy, paraneoplastic syndromes, neurodegenerative disorders, brain trauma, CNS tumors, vascular and hemorrhagic cerebrovascular events, wilson's disease and epilepsy (Denysenko et al. 2018). The most significant characteristic of catatonia due to a medical condition is the emergence during the course of comorbid medical condition and presence of evidence to suggest that catatonia is the direct result of the pathophysiology of another health condition in anamnesis, physical examination or laboratory findings. Although clinical symptoms are similar to catatonia secondary to psychiatric disorders, they may vary depending on the underlying medical condition. An important problem in cases of catatonia secondary to a medical condition is delirium. According to the DSM-5 diagnostic criteria, symptoms should not arise in the delirium period in order to diagnose comorbid catatonia in another medical condition. It has been reported that this is a diagnostic problem, and that delirium may also coexist in some cases of catatonia with another medical condition. The fact that the fluctuation in consciousness (delirium) is a diagnostic feature in malignant catatonia reveals this contradiction.

Although there is still no consensus on whether neuroleptic malignant syndrome is a subtype of catatonia or a separate disorder, there are numerous publications arguing that there is a catatonic syndrome secondary to neuroleptic use. This view is supported by the fact that NMS has similar motor symptoms with catatonia and both conditions are treated with electroconvulsive therapy (ECT) and benzodiazepines (Öncü et al. 1998).

Catatonic Symptoms

To date, more than 40 symptoms of catatonia have been described in the literature. In this section, catatonic symptoms are defined based on the DSM-5 diagnostic criteria.

According to the DSM-5 criteria, catatonia is diagnosed based on the presence of three or more of the following symptoms:

1. Stupor: Not actively relating to environment and/or absence of spontaneous movements and activity.
2. Catalepsy; is the temporary loss of contractions in the muscles. In some references, it is used to describe the same condition with waxy flexibility.
3. Waxy flexibility; is a plastic-like resistance similar to waxy flexibility against to change the strange posture of the patient.

4. Mutism; is no verbal response of the patient, although there is no structural anomaly.
5. Negativizm; The patient's resistance or counter action to commands. The patient resists to swallow the food put in the mouth, never responds to questions, does not carry out the instruction given, or does the exact opposite.
6. Posturing; is shaping the body in an unusual way, maintenance of an inappropriate or strange posture for a long time.
7. Mannerism; is the unusual repetition of an action that can be seen as goal-oriented.
8. Stereotypes (stereotyped behaviours); is the continuous repetition of certain physical movements and speeches in a non-goal oriented manner. The uniform repetition of words and sentences is called verbal stereotype or verbigeration.
9. Agitation; is a state of motor restlessness accompanied by severe anxiety which is not affected by external stimuli.
10. Grimacing; is strange gestures and facial expressions (such as grimace) usually arising on the face, around the mouth.
11. Echolalia ; is the patient's nonsensically repetition of the opposite person's speech, although not requested to do so, tends to be insistent and repetitive.
12. Echopraxia; is the patient's mimicking of the opposite person's movements or posture, although not requested to do so.

Rating Scales for the Diagnosis of Catatonia

Numerous scales have been developed to diagnose catatonia and to follow up the response to treatment. There are 14 to 40 symptoms in these scales. The most commonly used scales in clinical practice and literature are Bush-Francis Catatonia Rating Scale, Modified Rogers Scale, Northoff Catatonia Rating Scale, Brauning Catatonia Rating Scale, and Kanner Scale (Brendon et al. 2008).

The Bush-Francis catatonia rating scale (BCFRS), the most widely used scale in the world, was developed in 1996 and consists of 23 items. The first 14 items in this scale are used for screening. The Modified Rogers scale developed in 1991 is used for rating both extrapyramidal and catatonic symptoms. It allows a comprehensive, systematic neuropsychiatric motor examination and assessment includes 36 motor symptoms. The Northoff catatonia rating scale developed in 1999 is based on the catatonic symptoms described by Kahlbaum. It consists of 40 items classified as hypokinesia, hyperkinesia, affective symptoms, and behavior changes.

Subtypes of Catatonia

Numerous subtypes of catatonia have been described in the literature. These subtypes are usually defined based on the motor symptoms seen (Bush et al. 1996, Fink and Taylor 2001). A broad range of behavior and movement disorders from stupor to excitation can be seen in catatonia. The three most emphasized types of catatonia are retarded, excited and malignant catatonia. In a factor analysis study included 314 psychotic patients, it was reported that excited and retarded subtypes of catatonia were separated, and patients could simultaneously exhibit the characteristics of both subtypes (Peralta et

al. 2001). In other words, in a catatonia case, it is not necessary to have one of these subtypes fixedly, and patients may exhibit variation between the symptoms of retarded and excited catatonia. Moreover, retarded and excited catatonia manifestations may evolve in malignant catatonia. Periodic and late-onset catatonia are less mentioned forms in the literature.

Retarded Catatonia

The retarded form of catatonia is characterized by mutism, slowness of movements, posturing and negativism (Chalasani et al. 2005). Spontaneous speech and spontaneous motor movements are reduced. Response to sound and painful stimuli is decreased. In severe forms, the patient may stop eating and drinking, and incontinence may be seen.

Excited Catatonia

It is characterized by increased, purposeless motor activity (hyperkinesia) in the lower and upper limbs, restlessness, stereotype, impulsivity, enthusiasm and ill temper. Delirium-like fluctuations in consciousness may be seen in these patients, and the patient may harm himself/herself and his/her environment due to increased motor activity (Fink ve Taylor 2001).

Malignant Catatonia

It is a life-threatening picture in which symptoms such as feveri autonomic instability (sudden increase-decrease in blood pressure, tachycardia, tachypnea, sweating), fluctuation in consciousness, and rigidity may arise (Trigo et al. 2001, Özkul et al. 2010). It is a very rapidly progressive, fulminant disorder. Laboratory tests may reveal increased levels of leukocytosis and serum creatinine, and low serum iron levels (Northoff et al. 1996). The symptoms of malignant catatonia are quite similar to NMS. The emergence of NMS typically after initiating or increasing the dose of an antipsychotic drug is the most significant distinctive characteristic.

Periodical Catatonia

In 1908, Kahlbaum described periodic catatonia as a picture characterized by shifts between stupor and excitation. Today, periodic catatonia is defined as rapid-onset, repetitive, short hypokinetic and hyperkinetic episodes that last for 4-10 days, which may last for weeks and years (Carroll 2001). Some periodic catatonia cases have been shown to be familial with autosomal dominant inheritance associated with the chromosome 15q15 (Wijemanne and Jankovic 2015).

Late-onset Catatonia

In particular, it is extensively involved in the Japanese literature (Kocha ve ark. 2014). It is characterized by catatonic symptoms following a prodromal phase in which hypochondriac and depressive symptoms are seen during a stressful life event most commonly in women. In some patients, initial anxiety and hypochondriac symptoms may be accompanied by hallucinations, delusions, and excitatory behaviors. In the following phase, catatonic symptoms such as excitation, retardation, negativism, autonomic instability arise. It has been reported that it may be associated with late-onset schizophrenia and bipolar disorder.

Treatment and Prognosis

The treatment of catatonic patients is mainly based on the treatment of catatonic symptoms and underlying psychiatric disorders or other medical conditions. The goal of treatment is full remission. Although catatonia may be life-threatening, especially in severe cases, it can dramatically improve with rapid diagnosis and treatment. Today, benzodiazepines and ECT are the most commonly used and most effective methods in the treatment of catatonia. Amobarbital has been widely used in the treatment of catatonia since the 1930s. In a study included 20 catatonic patients, it was reported that 10% of the patients achieved an improvement rate of 56% in the symptoms with amobarbital treatment (McCall et al. 1992). When the literature is reviewed, numerous case reports and prospective studies conducted in the last 20 years reported an improvement rate of 60-80% in the symptoms within hours and days with the parenteral and oral use of benzodiazepines, such as lorazepam. In a study included 13 acute catatonic patients showed an improvement in catatonic symptoms by 60% within 10 minutes with 2 mg intravenous lorazepam treatment (Bush et al. 1996).

Catatonic patients are treated as inpatients in order to determine and treat the underlying psychiatric or other medical conditions, and to follow up complications that may arise due to catatonia such as aspiration pneumonia, venous thromboembolism, constipation and urinary retention (Zisselman and Jaffe 2010, Şahin et al. 2012). Especially the cases of malignant catatonia may be life-threatening and these patients require close follow-up and monitoring in terms of vital signs such as body temperature, blood pressure, and pulse. Some severe cases may require intensive care monitoring (Mann et al. 2005). Dehydration, malnutrition, deep vein thrombosis, pulmonary embolism, extremity contractures, excitation and impulsive behaviors are the medical conditions that should be followed up and prevented in catatonic patients.

In the treatment of catatonia, it is necessary to rapidly determine and treat the underlying medical condition. Catatonia is commonly seen in patients with mood disorders and psychotic depression hospitalized at psychiatric clinics. Catatonia may also be seen in patients with psychotic disorder and autism spectrum disorder (Mukaddes and Tanıdır 2015). Apart from psychiatric diseases, catatonia occurs due to numerous infectious, metabolic and neurological diseases (Fink and Taylor 2009, Daniels 2009). In such cases, the treatment of the underlying medical condition is of first priority. Dopamine antagonists should be used with caution in catatonic patients since they may aggravate the picture. The first-generation antipsychotics have not been shown to have a significant effect in the treatment of catatonia (Hawkins et al. 1995). Although there are studies reporting the efficacy of the second-generation antipsychotics in the treatment of catatonia, all antipsychotics may aggravate catatonia (Francis 2010, Erol et al. 2013). Clozapine is the most appropriate agent because of its lower dopaminergic antagonist effect. There are also publications reporting that olanzapine and aripiprazole, a dopamine partial agonist, can be effective (Beach et al. 2017). The use of antipsychotic drug in catatonic patients is a risk factor for the development of NMS. Especially in patients with a history of catatonia and dehydrated patients, the use of parenteral and high-dose antipsychotic poses a greater risk (Berardi et al. 2002). Antipsychotics are contraindicated in cases of malignant catatonia.

The first treatment option in patients with malignant catatonia is ECT (Falkai et al. 2006). In these cases, a benzodiazepine should immediately be initiated, and during

this process, consent for ECT should be obtained from the patient himself/herself or his/her relatives and required consultations should be performed immediately before the treatment. If there is no significant improvement in the picture within 24-48 hours, benzodiazepine treatment should be discontinued and ECT should immediately be initiated. The case reports published in the literature report that not initiating ECT in malignant catatonia within 5 days after the onset of symptoms increases mortality (Freudenreich et al. 2011). Again, the case reports published in the literature reported that 9 (89%) out of 11 malignant catatonia cases responded to ECT, and 2 (40%) out of 5 malignant catatonia cases responded to benzodiazepine treatment (Hawkins et al. 1995). Therefore, ECT is the gold standard in the treatment of malignant catatonia. In other cases, the choice of treatment should be based on the patient's clinical condition. According to the treatment algorithms of the American Psychiatric Association and the World Federation of Societies of Biological Psychiatry, benzodiazepine treatment or ECT may be preferred depending on the urgency of the patient's clinical condition. ECT should be preferred in cases of refusing to eat-drink, severe weight loss and dehydration, and benzodiazepine treatment should be preferred in milder pictures. Although it is not recommended by the treatment algorithms as a standard practice, numerous studies report that the combination of ECT and benzodiazepine treatment is also effective (Petrides et al. 1997, Espinola-Nadurille et al. 2007). However, it should be kept in mind that the antiepileptic effect of benzodiazepines may reduce the efficacy of ECT in this combination.

Among the benzodiazepines, the most commonly studied agent is lorazepam. There are also cases successfully treated with alprazolam, diazepam, clonazepam and midazolam (Delisle 1991, Benazzi 1991, Hung and Huang 2006, Bozkurt et al. 2016). In a study included 104 cases of catatonia, it was reported that benzodiazepine monotherapy exhibited improvement in 70% of the cases, while this rate was 79% with lorazepam (Hawkins et al. 1995). If a positive response is observed after the first dose of lorazepam, the chance of success for the treatment is higher (lorazepam challenge test). Patients with comorbid bipolar disorder and depression respond better to benzodiazepines than schizophrenia patients. In cases of chronic catatonia occurs with schizophrenia, response is obtained at higher doses (lorazepam> 6 mg/day). According to the clinical experience, response to benzodiazepines arises within a week in cases of excited and retarded catatonia. ECT should be considered in cases where response is not obtained within this period. It has been reported that 60% of patients who do not respond to benzodiazepine benefit from ECT. Another superiority of ECT is that it treats the underlying psychiatric disorders such as psychotic disorder, bipolar disorder and psychotic depression along with catatonic symptoms (Armstrong et al. 1999).

Alternative treatment modalities have been investigated for patients who do not respond to benzodiazepine or ECT or do not accept ECT. There are case reports reporting that valproate (Yoshida et al. 2005), memantine (Carpenter et al. 2006), amantadine (Babington and Spiegel 2007), topiramate (McDaniel et al. 2006), carbamazepine (Kritzinger and Jordaan 2001) and bromocriptine (Tang et al. 1995) are useful in catatonic symptoms. Clinicians should be careful with dopaminergic agents such as amantadine because of the risk of exacerbating the underlying psychotic symptoms. There are a limited number of publications reporting that transcranial magnetic stimulation may be an alternative treatment option (Hawkins et al. 1995). Glutamate

antagonists (amantadine, memantine) and an anticonvulsant may be used in cases where there is no response to benzodiazepine and ECT. As the last option, a combination of lorazepam and a second-generation antipsychotic agent such as olanzapine and clozapine, or aripiprazole, a partial agonist, should be tried. Dantrolene, a calcium channel blocker, was tried especially in the treatment of malignant catatonia and NMS but it was not found to be effective. Although there is no sufficient number of studies showing the long-term prognosis of catatonia, it is generally considered to have a good prognosis. The long-term prognosis of catatonia generally depends on the course and severity of the underlying psychiatric disorder or other medical conditions. The cases associated with mood disorders and toxic-metabolic causes usually improve by treating catatonic symptoms and underlying pathology. Catatonia may become chronic in some schizophrenia patients; however, cases of chronic catatonia are rare nowadays because of the widespread use of antipsychotic drugs. In cases of malignant catatonia, mortality rates up to 20% have been reported (Fink and Taylor 2003). Even if it does not result in death, these patients may develop permanent cognitive impairment, apathy syndrome and limb strictures. In cases of catatonia, the risk of recurrent catatonia increases. In a case series of 5 patients, it was reported that catatonia recurred within 5-20 months. In these cases, it was found that motor symptoms of the patients were similar in recurrent episodes and responded to the same treatments (Francis et al. 1997). Therefore, questioning the history of catatonia and treatment response may be a guide for treatment choice. In cases of periodic catatonia, maintenance ECT is an appropriate and effective method. In the literature, there is a case report in which the patient was successfully treated with 4-year maintenance ECT (Bulbul et al. 2013).

Conclusion

Catatonia is an independent neuropsychiatric syndrome that may occur with various medical conditions and psychiatric disorders. Despite numerous studies to date, no catatonia-specific genetic, structural, neurochemical etiology has been found. In neurotransmitter studies, a decrease in GABA-A and dopaminergic activity and an increase in glutamatergic activity were reported. The clinical manifestation is heterogeneous. Although there is a significant reduction in the incidence of chronic catatonia seen with schizophrenia due to the widespread use of antipsychotics today, the number of acute catatonia cases are more than assumed, and the diagnosis is frequently overlooked by clinicians. In cases of malignant catatonia with autonomic instability and changes in consciousness, mortality rates up to 20% may be seen. In cases of malignant catatonia, the most appropriate approach for the treatment is initiation of ECT without wasting time, and in other cases, the administration of benzodiazepine (especially lorazepam) and ECT depending on the severity of table. The first generation antipsychotics has not been shown to have any significant benefit in catatonia. It should even be kept in mind that these agents may aggravate catatonia and lead to NMS. Information on the use of second-generation antipsychotics is contradictory. Glutamate NMDA antagonists, antiepileptics and second-generation antipsychotic-lorazepam combination can be tried in cases when there is no response to lorazepam or ECT.

To date, numerous studies have been conducted on the nature, clinical characteristics, pathogenesis of catatonia and its place in classification systems. Catatonia was reclassified under a separate heading in the DSM-5 as a result of studies showing that

catatonia may occur with many medical conditions as well as psychiatric disorders. The reclassification of catatonia as a separate diagnostic class provides benefits in terms of understanding the nature of this syndrome, reducing the possibility of overlooking the diagnosis and being a guide for future studies. However, today, the contradictions and problems regarding catatonia have not been completely solved. The clinical symptoms may vary widely among patients diagnosed with catatonia. There is still no consensus on which symptoms are catatonic. The number of catatonic symptoms described in widely used classification systems such as the DSM, ICD, and in the scales developed for the diagnosis of catatonia varies substantially, and even there are differences in the definition of some basic symptoms such as rigidity, mannerism. As a consequence of all these, the prevalence of catatonia may vary to a great extent in epidemiological studies in the literature. There is still no definitive catatonia-specific laboratory, imaging finding or neurobiological disorder. Further studies are needed to solve important problems regarding catatonia such as conceptual clarity, neurobiology, diagnosis and pathogenesis.

References

American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV). Washington DC, American Psychiatric Association.

American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5). Washington DC, American Psychiatric Association.

Armstrong SC, Koek JR, Mervis JR, Boronow JJ (1999) Treatment-refractory catatonia, ECT and parenteral lorazepam. Am J Psychiatry, 156:160-161.

Arndt E (1902) Über die Geschichte der Katatonie. Centralblatt für Nervenheilkunde und Psychiatrie 25:81-121.

Arora M, Praharaj SK (2007) Butterfly glioma of corpus callosum presenting as catatonia. World J Biol Psychiatry, 8:54-55.

Aschaffenburg G (1898) Die Katatoniefrage. Allgemeine Zeitschrift für Psychiatrie. 65:1002-1026.

Babington PW, Spiegel DR (2007) Treatment of catatonia with olanzapine and amantadine. Psychosomatics, 48:534-536.

Beach SR, Gomez-Bernal F, Huffman JC, Fricchione GL (2017) Alternative treatment strategies for catatonia: a systematic review. Gen Hosp Psychiatry, 48:1-19

Benazzi F (1991) Parenteral clonazepam for catatonia. Can J Psychiatry, 36:312.

Berardi D, Dell'Atti M, Amore M, De Ronchi D, Ferrari G (2002) Clinical risk factors for neuroleptic malignant syndrome. Hum Psychopharmacol, 17:99-102.

Bleuler E (1911) Dementia Preacox oder Gruppe der Schizophrenien, in Handbuch der Psychiatrie. Spezieller Teil 4. Abteilung 1. Haelfte (Ed G Asschaffenburg):124-143. Leipzig, Deuticke.

Bozkurt H, Tabak S, Şahin S (2016) Ergen bir olguda diazepam ile düzelen katatoni. Journal of Contemporary Medicine, 6:80-83.

Brosius K (1877) Die katatonie. Allgemeine Zeitschrift für Psychiatrie. 33:770-802.

Bulbul F, Copoglu US, Sahin S, Alpak G, Altindag A, Virit O, Savas HA (2013) Successful treatment of idiopathic periodic catatonia with maintenance ECT. Klin Psikofarmakol Bulteni, 23:365-367.

Bush G, Fink M, Petrides G, Dowling F, Francis A (1996) Catatonia. II. Treatment with lorazepam and electroconvulsive therapy. Acta Psychiatr Scand, 93:137-143.

Caroff SN (1980) The Neuroleptic Malignant Syndrome. J Clin Psychiatry, 41:79-83.

Carpenter SS, Hatchett AT, Fuller MA (2006) Catatonic schizophrenia and the use of memantine. Ann Pharmacother, 40:344-346.

Carroll BT (2001) Kahlbaum's catatonia revisited. Psychiatry Clin Neurosci, 55:431-436.

Carroll BT, Goforth HW (2004) Medical catatonia. In Catatonia: From Psychopathology to Neurobiology. (Eds SN Caroff, SC Mann, A Francis):123-125. Washington DC, American Psychiatric Publishing.

Carroll BT, Kirkhart R, Ahuja N, Soovere I, Lauterbach EC, Dhossche D et al. (2008) Katatonia: a new conseptual understanding of catatonia and a new rating scale. Psychiatry (Edgmont), 5:42-50.

Chalasani P, Healy D, Morriss R (2005) Presentation and frequency of catatonia in new admissions to two acute psychiatric admission units in India and Wales. Psychol Med, 35:1667-1675.

Cuevas-Esteban J, Iglesias-Gonzalez M, Rubio-Valera M, Serra-Mestres J, Serrano-Blanco A, Baladon L (2017) Prevalance and

characteristics of catatonia on admission to an acute geriatric psychiatry ward. Progr Neuropsychopharmacol Biol Psychiatry, 78:27-33.
Daniels J (2009) Catatonia: Clinical aspects and neurobiological correlates. J Neuropsychiatr Clin Neurosci, 21:371-380.
Delisle JD (1991) Catatonia unexpectedly reversed by midazolam. Am J Psychiatry, 148:809-809.
Denysenko L, Freudenreich O, Philbrick K, Penders T, Zimbrean P, Nejad S et al. (2015) Catatonia in Medically Ill Patients An Evidence-Based Medicine (EBM) Monograph for Psychosomatic Medicine Practice. Nuremberg, Germany, European Association of Psychosomatic Medicine.
Denysenko L, Sica N, Penders TM, Philbrick KL, Walker A, Shaffer S et al. (2018) Catatonia in the medically ill: Etiology, diagnosis and treatment. Ann Clin Psychiatry, 30:140-155.
Dhossche DM, Wachtel LE (2010) Catatonia is Hidden in plain sight among different pediatric disorders: a review article. Pediatr Neurol, 43:307-315.
Dubovsky SL, Dubovsky AN (2018) Catatonia: How to identify and treat it. Curr Psychiatry, 17:16-26.
Erol A, Putgül G, Sert E, Mete L (2013) Klozapin kullanımına bağlı nöroleptik malign sendrom ve ardışık katatoni: Olgu sunumu. Turk Psikiyatri Derg, 24:140-144.
Espinola-Nadurille M, Ramirez-Bermudez J, Fricchione GL (2007) Pregnancy and malignant catatonia. Gen Hosp Psychiatry, 29:69-71.
Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, Möller HJ et al. (2005) World Federation of Societies of Biological Psychiatry (WFSBP) guidelines of biological treatment of schizophrenia, Part 1: acute treatment of schizophrenia. World J Biol Psychiatry, 6:132-191.
Fink M (1996) Neuroleptic malignant syndrome and catatonia: one entity or two? Biol Psychiatry, 39:1-4.
Fink M, Taylor MA (1991) Catatonia: a seperate category in DSM-IV? Integr Psychiatry, 7:2-10.
Fink M, Taylor MA (2001) The many varieties of catatonia. Eur Arch Psychiatry Clin Neurosci, 251: Suppl1:I8.
Fink M, Taylor MA (2003) Catatonia: A Clinician's Guide to Diagnosis and Treatment. New York, Cambridge University Press.
Fink M, Taylor MA (2009) The catatonia syndrome: forgotten but not gone. Arch Gen Psychiatry, 66:1173-1177.
Francis A (2010) Catatonia: Diagnosis, classification and treatment. Curr Psychiatry Rep, 12:180-185.
Francis A, Divadeenam KM, Bush G, Petrides G (1997) Consistency of symptoms in recurrent catatonia. Compr Psychiatry, 38:56-60.
Freudenreich O, Nejad SH, Francis A, Fricchione GL (2011) Psychosis, mania and catatonia.In Textbook of Psychosomatic Medicine: Psychiatric Care of the Medically Ill, Second Edition (Ed JL Levenson JL):219. Washington DC, American Psychiatric Publishing.
Grover S, Gosh A, Ghormode D (2014) Do patients of delirium have catatonic features? An exploratory study. Psychiatry Clin Neurosci, 68:644-651.
Hawkins JM, Archer KJ, Strakowski SM, Keck PE (1995) Somatic treatment of catatonia. Int J Psychiatry Med, 25:345-369.
Hung YY, Huang TL (2006) Lorazepam and diazepam rapidly relieve catatonic features in major depression. Clin Neuropharmacol, 29:144-147.
Kahlbaum K (1874) Catatonia, or tension insanity: a clinical form of psychic illness. Berlin, Verlag Aughust Hirschwald.
Kirby GH (1913) The catatonic syndrome and its relation to manic-depressive insanity. J Nerv Ment Dis, 40:694-704.
Kleist K (1943) Die katatonien. Nervenarzt, 16:1-10.
Kocha H, Moriguchi S, Mimura M (2014) Revisiting the consept of late catatonia. Compr Psychiatry, 55:1485-1490.
Krapelin E (1893) Psychiatrie: ein kurzes Lehrbuch für Studirende und Arzte. 4. Vollstaending umgearbeitete. Abel.
Krapelin E (1913) Dementia Preacox and Paraphrenia. Leipzig, Barth.
Kritzinger PR, Jordaan GP (2001) Catatonia: An open prospective series with carbamazepine. Int J Neuropsychopharmacol, 4:251-257.
Leonhard K (1935) Die den striaeren Erkrankungen am meisten verwandten zwei Formen katatoner Endzustaende und die Frageder Systemerkrankung bei Schizophrenie. Arch Psychiatr Nervenkr, 103:101-121.
Mann SC, Caroff SN, Bleier HR, Campbell EC (2005) Malignant catatonia. In Movement Disorder Emergencies (Ed SJ Frucht): 59-74. Totawa, Humana Press.
McCall WV, Shelp FE, McDonald WM (1992) Controlled investigation of the amobarbital interviewfor catatonic mutism. Am J Psychiatry, 149:202-206.
McDaniel WW, Spiegel DR, Sahota AK (2006) Topiramat effect on catatonia: a case series. J Neuropsychiatry Clin Neurosci, 18:234-238.
Meyer J, Huberth A, Ortega G, Syagailo YV, Jatzke S, Mossner R et al. (2001) A missense mutation in a novel gene encoding a putative cation channel is associated with catatonic schizophrenia in a large pedigree. Mol Psychiatry, 6:302-306.
Moskowitz AK (2004) "Scared stiff": catatonia as a evolutionary-based fear response. Psychol Rev, 111:984-1002.

Mukaddes NM, Tanıdır C (2015) Otizm spektrum bozukluklarında psikiyatrik komorbidite. Türkiye Klinikleri J Clin Psychiatry-Special Topics, 1:30-32.
Northoff G (2000) Brain imaging in catatonia: current findings and a patophysiologic model. CNS Spectr, 5:34-46.
Northoff G (2002) What catatonia tells us about "top down modulation": a neuropsychiatric hypothesis. Behav Brain Sci, 25:555-577.
Northoff G, Steinke R, Czcervenka C, Krause R, Ulrich S, Danos P et al. (1999) Decreased density of GABA-A receptor in the left sensorimotor cortexin akinetic catatonia: investigation of in vivo benzodiazepine receptor binding. J Neurol Neurosurg Psychiatry, 67:445-450.
Northoff G, Wenke J, Pflug B (1996) Increased of serum creatine phosphokinase in catatonia: an investigation of 32 acute catatonic patients. Psychol Med, 26:547-553.
Öncü F, Hariri A, Ceylan ME (1998) Nöroleptik malign sendrom. Dusunen Adam, 11:30-35.
Özkul A, Akyol A, Tamam Y (2010) Malign katatoni. Psikiyatride Güncel Yaklaşımlar, 2:595-608.
Peralta V, Cuesta MJ, Serrano JF, Martinez-Larrea JA (2001) Classification issues in catatonia. Eur Arch Psychiatry Clin Neurosci, 251: Suppl 1:I14-16.
Peralta V, Cuesta MJ, Serrano JF, Mata I (1997) The Kahlbaum syndrome: a study of clinical validity, nosological status, and relationthip with schizophrenia and mood disorder. Compr Psychiatry, 38:61-67.
Petrides G, Divadeenam KM, Bush G, Francis A (1997) Synergism of lorazepam and electroconvulsive therapy in the treatment of catatonia. Biol Psychiatry, 42:375-381.
Rogers D (1985) The motor disorders of severe psychiatric ıllness: a conflict of paradigms. Br J Psychiatry, 147:221-232.
Rosebush PI, Hildebrand AM, Furlong BG, Mazurek MF (1990) Catatonic syndrome in a general psychiatric inpatient population: frequency, clinical presentation, and response to lorazepam. J Clin Psychiatry, 51:357-362.
Solmi M, Pigato GG, Roiter B, Guaglianone A, Martini L, Fornaro M et al. (2017) Prevalance of catatoni and its moderators in clinical samples: results from a meta-analysis and meta-regression analysis. Schizophr Bull, 44:1133-1150.
Stöber G (2001) Genetic predisposition and environmental causes in periodic and systematic catatonia. Eur Arch Psychiatry Clin Neurosci, 251: Suppl1:I21-24.
Şahin Ş, Bülbül F, Ünal A, Bulut M, Vırıt O, Altındağ A, Savaş H (2012) Catatonia associated globe vesicale, Journal of Mood Disorders, 2:123-125.
Tang CP, Leung CM, Ungvari GS, Leung WK (1995) The syndrome of lethal catatonia. Singapore Med J, 36:400-402.
Taylor MA, Fink M (2003) Catatonia in psychiatric classification: A home of its own. Am J Psychiatry, 160:1233-1241.
Trigo MK, Crippa JAS, Wheat MK, Hallak JEC, Vale FAC, Sakamoto AC et al. (2001) The complexity of differantial diagnosis in psychiatry exemplified by a catatonic syndrome. Rev Psiquatr Clin, 28:144-147.
Uhrband L, Faurbye A (1960) Reversible and irreversible dyskinesia after treatment with perphenazine, chlorpromazine, reserpine and electroconvulsive therapy. Psychopharmacologia, 1:408-418.
Ungvari GS, Caroff SN, Gerevich J (2009) The catatonia conundrum: evidence of psychomotor phenomena as a symptom dimension in psychiatric disorders. Schizophr Bull, 36:231-238.
van der Heijden FM, Tuinier S, Arts NJM, Hoogendoom MLC, Kahn RS, Verhoeven WMA (2005) Catatonia disappeared or under-diagnosed? Psychopathology, 38:3-8.
Wijemanne S, Jankovic J (2015) Movement disorders in catatonia. J Neurol Neurosurg Psychiatry, 86:825-832.
Yoshida I, Monji A, Hashioka S, Ito M, Kanba S (2005) Prophylactic effect of valproate in the treatment of siblings with catatonia: a case report. J Clin Psychopharmacol, 25:504-505.
Zisselman MH, Jaffe RL (2010) ECT in treatment of a patient with catatonia consent and complications. Am J Psychiatry, 167:127-132.

Authors Contributions: All authors attest that each author has made an important scientific contribution to the study and has assisted with the drafting or revising of the manuscript.
Peer-review: Externally peer-reviewed.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study has received no financial support.