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Current nosological status, pathomechanism and treatment of catatonia

Magdalena Julia Jabłońska[1], Katarzyna Lipa[1*], Patryk Kaczor[1], Kamil Leis[1], Krystian Kałużny[2], Przemysław Gałązka[3]

[1]Faculty of Medicine, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 85-067 Bydgoszcz, Poland

[2]Chair and Clinic of Rehabilitation, Faculty of Health Sciences, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 85-067 Bydgoszcz, Poland

[3]Department of General and Oncological Surgery for Children and Adolescents, Antoni Jurasz University Hospital No. 1 in Bydgoszcz, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 85-094 Bydgoszcz, Poland

* Corresponding author: Katarzyna Lipa ul. M. Curie Skłodowskiej 9 85-094 Bydgoszcz, Tel. 52/585 40 15, mail – kasialipa96@onet.pl

Abstract

Catatonia, otherwise known as catatonic syndrome is a frequent neuropsychiatric syndrome characterized mainly by motor disorders. There are many somatic and psychiatric dysfunctions, and the multitude of symptoms included in it make a problem

in diagnosis. Moreover, until now the mechanism of pathophysiology of catatonia has not been recognized. Among the hypotheses proposed, one may find theories concerning dysregulation of neurotransmission within the dopamineergic D2 or GABA-A-ergic receptors. For years, catatonia was closely related to schizophrenia, but with the publication of the 5th edition of the Diagnostic and Statistical Manual of Psychiatric Disorders - DSM-5, these disorders were separated, creating the hope that catatonia would be considered as a separate disease entity in the future. Pharmacotherapy involves the use of benzodiazepines in the first line, which are effective in most patients. An alternative is N-methyl-D-aspartic acid (NMDA) antagonists and atypical antipsychotic drugs, the use of which is controversial due to the high risk of neuroleptic malignant syndrome, which is a direct threat to life. In the case of catatonia resistant to benzodiazepines, electroconvulsive therapy (ECT) is effective. At the same time, in order to increase the effectiveness of treatment, electroconvulsive therapy and benzodiazepines are used in parallel, which brings satisfactory results.

Keywords: catatonia, neuroleptic malignant syndrome, benzodiazepines, electroconvulsive therapy, antagonists of N-methyl-D-aspartic acid, atypical antipsychotics

Introduction

Catatonia affects approximately 10% of patients treated psychiatrically and moreover, it coincides with many other somatic diseases [7,9]. Catatonia was described for the first time in 1874 by Karl Ludwig Kahlbaum. Disorders that occur within this syndrome include some systemic changes but mostly manifest themselves in the form of movement disorders. Nevertheless, catatonia does not only affect motor and sensory functions but also consists of a number of vegetative, mental and behavioral changes [2]. However majority of patients who suffer from it manifest reduced motor activity, there are cases in which the disorder takes hyperkinetic form. In addition these two subtypes of catatonia can coexist in a patient, smoothly passing from one another. For a long time catatonia had been identified as schizophrenia but nowadays the two are considered separate.

Differences in understanding of catatonia - recognition of the disease

Early diagnosis of catatonia and implementation of a treatment are crucial because of many grave consequences that might be provoked by an abandonment of these initial proceedings. Among them are noted: venous thromboembolism, urinary tract infection, respiratory tract infection (including aspiration pneumonia), electrolyte disturbances, eating disorders, increased risk of bedsores [5,6]. Kahlbaum suggested to consider catatonia a separate disease entity but his suggestion has not been welcomed by medical environment. Emil Kraeplin linked the occurrence of catatonia with dementia praecox, while Eugene Bleuler, following Kraeplin's idea, identified catatonia with schizophrenia, so that for many years it has been treated as a subtype of schizophrenia indeed [18]. All the same, this disorder occurs in many somatic and mental diseases, which urged researchers to revise their view. Catatonia co-occurs in approximately 43% of patients suffering from bipolar disorder, while in about 30% of those who suffer from schizophrenia [16]. It can occur likewise within post-traumatic stress syndrome, obsessive-compulsive disorder, after alcohol or benzodiazepines withdrawal, yet it can be observed in somatic diseases as: metabolic syndromes, infectious, neurological and endocrinological diseases [16]. The separation between catatonia and schizophrenia was due to the publication of 5th edition of "Diagnostic and statistical manual of mental disorders" (DSM-5) [19]. In order to diagnose catatonia, clinicians usually use Bush-Francis Catatonia Rating Scale (BFCRS) as well as DSM-5, which includes 12 criteria from which at least 3 must be met to diagnose catatonia. Here they are: muteness, echopraxia, echolalia, stereotypy, dementia, waxy flexibility, psychomotor agitation, negativism, catalepsy, posturing, mannerism [1,3,16,19]. BFCRS contains 23 criteria, among others some additional to those mentioned in DSM-5: the occurrence of a grasp reflex, automatic obedience, stiffness, repetitive motion. 6 out of the criteria are marked as either present (3 points) or absent (0 points), whereas to the rest of them a four-degree scale (from 0 to 3 points) is applied [3,20]. It should be remembered that there are many other rating scales used in descriptions of catatonia, e.g.: The Northoff Catatonia Rating Scale, but it is BFCRS that Carroll and collaborators considered the "golden mean" among other assessment methods, which happened to be the most common in use [20]. This is the major change which has been introduced to the new version of DSM-5 in comparison to the previous one, DSM-4: catatonia is grouped in four categories. Henceforth there are now being distinguished: (I) catatonia due to general medical conditions, (II) catatonia associated to other mental disorders, (III)

catatonic disorder related to another disease, (IV) unspecified catatonia [1,19,21,36]. Furthermore, criteria for diagnosis of catatonia have been standardized, which means that they are now equal regardless of primary causes of the disease. Afterwards, the notion of catatonic schizophrenia has been removed from the publication, at the time still present in the ICD-10 list. In addition, a new category of "unspecified catatonia - NOS" has been introduced successfully and it is intended for cases which cause problems to identify their psychiatric or somatic basis [6,21,17]. Thus it is possible to state that DSM-5, although not directly, allows to acknowledge catatonia a separate disease entity in future [6].

Pathomechanism of catatonia and NMS - neuroleptic malignant syndrome

Pathomechanism of catatonia remains unclear to the researchers, at the same time it causes nosological problems which impedes classification of catatonia to a syndrome provoked by many causes and which consists of many symptoms or to a clearly defined disease entity [14]. Moreover, a considerable number of its symptoms occur also within neuroleptic malignant syndrome (NMS) which generally constitutes a grave complication after antypsychotic-drug therapy. As a result, for a long time it had been stated that the two might be treated as a one and the same disorder. This statement turned out to be false because catatonia and NMS differ in terms of pathophysiology. Akinesia which is present in both cases is often explained as "motor-loop" damage, that is the path connecting motor cortex/pre-motor cortex with basal ganglia, but the mechanism of this loop dysregulation is distinct. NMS would be a consequence of blocking dopamine receptors in striatum. Plus, receptor D2 blockade in hypothalamus and, what follows, changes in dopamine concentration explain other vegetative symptoms that occur in NMS, that is: tachycardia, high fever, hyperhidrosis, high blood pressure [12,14,15]. It should be noted that NMS is a real threat to patient's life therefore an appropriate diagnosis and implementation of treatment have to be immediate. Catatonic disorders are usually the result of scattered degenerative changes which frequently affect such structures as frontal lobes, parietal lobes, basal ganglia or corpus callosum. A rupture of an aneurysm located in anterior cerebral artery [4] and damage in paths connecting basal ganglia and thalamus may provoke NMS. It proves that CNS damage is responsible for the occurrence of catatonia. A dysregulation of neurotransmission is commonly seen as the cause. 3 major hypothesis on the occurrence of catatonia have been presented so far: reduced activity of D2 receptors, reduced

activity of receptors for γ-aminobutyric acid (GABA) and increased glutamate signal [8,9,10,11]. Research done by using SPECT and flumazenil evidenced a reduced binding between neurotransmitter and GABA-A receptor in the right lateral orbitofrontal cortex and right posterior parietal cortex [10]. Another study, made also with SPECT, indicated a reduced blood flow in prefrontal and parietal cortex [11]. Neuroimaging techniques were able to zoom in the areas of the brain whose reduced activity may result in the onset of catatonia [13]. At the same time, an observation has been made that there is a certain connection between the occurrence of behavioral and affective disorders, which do not appear in NMS and the weakened linking of neurotransmitter and receptor GABA-A [11,12].

Subtypes of catatonia

There have been presented several methods how to distinguish different types of catatonia on the basis of character and severity of symptoms that occur. One of the most common and the easiest to observe in practice proposition of division is to classify catatonia as its: hyperkinetic (stimulated) form, hypokinetic (delayed) form, malignant form [4]. For the delayed form an inhibition of movement, staring at one point or muteness are typical. Patients usually stay vigilant but are unable to react to external stimuli or their reactions are minimal. Those who suffer from this particular form of catatonia tend to stay still without any movement as if they froze. There are cases in which they refuse to accept food and water, hence if the treatment was discontinued, it would lead to serious nutrition and eletrolyte problems. For the stimulated form of catatonia it is typical for the patients to show excessive physical activity without purpose. They tend to become aggressive and prone to violence, in the meantime posing a threat to themselves (self-mutilation) and to others. Their speech as well as their movements are disordered. Acute malignant catatonia was called acute fatal catatonia until 1986 because of a high patients' mortality rate that reached from 75% to even 100%. Whereas after 1986 the percentage decreased to 9% it is no longer called like that [4]. Typical traits of this form of catatonia, described for the first time in 1832 by Calmeil, are: high fever, persistent agitation after some days turning into a stupor, vegetative symptoms such as tachycardia, high blood pressure, respiratory disorders, electrolyte imbalance. Because of visible similarity, this form of catatonia should be distinguished from neuroleptic malignant syndrome since in both cases there is a real threat to life caused by multi-organ failure[18,22]. Another classification is based on a

division in two types: malignant and non-malignant, and then two subtypes: excited and delayed. Two subtypes of systematic and periodic division of catatonia can be treated as another, different type of classification [23].

Treatment

Despite the obscurity due to the not fully understood mechanism of catatonia, the methods of treatment applied to it happened to be effective. The therapy is based on the use of benzodiazepines and their derivatives. In case of ineffectiveness of pharmacological treatment, electroconvulsive therapy (ECT) is applied [2,4]. Along with the gradual exploring the nature of the disorder, the effectiveness of using N-methyl-D-aspartic acid antagonists (NMDA) or atypical antipsychotics such as clozapine has been revealed [4]. Within some cases of periodic catatonia, the usefulness of lithium in several patients has been demonstrated, but these reports are not confirmed by large clinical trials. However, the fact that those patients took lithium resulted in longer intervals between successive attacks or even prevented them from occurring again. Among medical methods, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have also been used [4,39]. It should be highlighted that a treatment of complications of catatonia and preventing them is an inseparable element of therapy. It is worth noting how important proper nursing care is for a catatonic patient, that is, especially, to prevent them from bedsores. Other medical procedures that are used in the case of catatonic patient are: bladder catheterization, administration of anticoagulants, establishment of percutaneous endoscopic gastrostomy or gastric lavage. It is also necessary that patients to undergo rehabilitation [16].

Benzodiazepines are the first line of catatonia treatment. The medicament works by its allosteric binding with GABA-A-ergic receptor. As a result of the combination, the affinity of GABA to the GABA-A receptor increases. In consequence, it leads to the opening of chloride channels to the interior of neurons causing their hyperpolarization. By extension, in relation to the treatment of catatonia, it can be concluded that the use of benzodiazepines enhances the inhibitory action of GABA, complementing its functional deficiency in the places responsible for the occurrence of catatonia (e.g. orbital cortex) [16,25]. The most common benzodiazepine, lorazepam is used as the first-line drug, achieving 79% of remission [28]. In the same time, lorazepam can be

also a diagnostic tool. Lorazepam Challenge Test consists in administering i.v. 1-2 mg of lorazepam, then after about 5 minutes the test is repeated. If there is no answer, the second dose is given. If a significant reduction (at least 50%) of catatonia symptoms is found using standardized scales, like BFCRS, the result of the test is considered positive, which confirms catatonia and gives the opportunity to implement therapy. It is possible to administer the medicine by other methods: per os or i.m. but in this case, a longer waiting time is required [16, 26].One of the research that confirms the efficacy of lorazepam catatonia treatment is the study conducted by Tibrewal et al. for 107 patients with diagnosed catatonia. They were given from 3 to 6 mg of the drug for 3 days in minimum. It was evidenced that in 32 of 99 patients, the disorders were completely gone and in 68 of 99 patients the symptoms were evidently reduced [27].The smaller number of patients with remission was explained by too low dose of the drug, proving at the same time that catatonia coexisting with schizophrenia is less responsive to benzodiazepine therapy [16].The currently recommended dose is approximately 8-24 mg per day. The introduction of the drug should start from 1-2 mg every 4-12 hours to avoid their sedation [16]. There is still a lack of credible reports on an optimum duration of treatment. There is a group of patients for who a discontinuation of the drug treatment results in recurrence of catatonia symptoms, which requires a long-term therapy [16,29]. Other benzodiazepines used in the treatment of catatonia include: diazepam or oxazepam [30,31]. There are known cases of catatonia induced by sudden discontinuation of clonazepam, which disappears completely after the re-implementation of benzodiazepines, and sudden recurrences of disorders can be understood as the effect of a rapid reduction of GABA-ergic transmission [32].

An alternative for those patients for whom benzodiazepines and electroshock were ineffective in the treatment of catatonia became zolpidem, belonging, which belongs to the imidazopyridine group. It is a selective agonist of the α1 subunit of the GABA-A receptor [33]. For the first time used in the treatment of catatonia resistant to available methods of treatment, occurring as a result of subcortical stroke in a 56-year-old woman. This and forthcoming successes with the use of zolpidem and the lack of any reports of grave side effects have encouraged more doctors to use it in a dose of 7.5-40 mg / 24h [16].

There is much controversy over the use of atypical antipsychotics in the treatment of catatonia. The mechanism of their action consists in blocking D2 dopamine receptors, simultaneously demonstrating small antagonistic effects on 5-HT2A receptors and hitherto unclear anticholinergic effects [4,34]. It has been proven that all atypical antipsychotics can lead to the occurrence of NMS, and the very presence of catatonia significantly increases the risk of this complication, which for many researchers is a clear choice to oppose the use of these drugs in the therapy of catatonia. However, in the literature one can find reports on the effectiveness of using medicaments from this group in the treatment of catatonia in patients with schizophrenia [4]. The first generation of antipsychotics, although effective in dealing with schizophrenia, often caused NMS and increased symptoms of catatonia - the occurrence of poneuroleptic catatonia, whereas in the case of second generation antipsychotics, they evidenced lower risk of worsening of symptoms [34]. The use of atypical antipsychotics in the treatment of catatonia should be considered case-by-case and with extreme caution due to life-threatening side-effects [16].

Another optional possibility for the treatment of catatonic disorders are antagonists of N-methyl-D-aspartic acid: amantadine and its derivative, memantine [16, 37]. The mechanism of action is to increase the release of dopamine in the striatum, which directly affects a relief of akinesia symptoms. One of the first studies using NMDA antagonists was carried out by Carroll et al. They gave 25 patients either amantadine in a dose of 200-500 mg p.os or i.v. or memantine in a dose of 5-20 mg p. os. [4,35]. Satisfactory reactions were obtained in all cases within 1 to 7 days. Although the action is slower than in therapy based on benzodiazepines, it is possible to achieve remission as early as 3 weeks after starting the therapy [4]. Positive reports make it possible to use NMDA antagonists as an alternative treatment option for the type of catatonia resistant to electroconvulsive therapy and first-line drugs, however, further studies confirming their usefulness are needed [35, 37].

Conventional electroshock therapy (ECT) is a regular method of treatment of catatonia. It is used when the first-line treatment fails (i.e. treatment with benzodiazepines) and when quick intervention is needed to save lives as in the case of malignant catatonia [16].It should be noted that the percentage of positive reaction to ECT is in the range of 59% -100%, demonstrating the high effectiveness of this method [36]. Moreover,

according to the Canadian Network for Mood and Anxiety Treatments, catatonia is one of the indications for the use of ECT [16]. For better results, it is possible to combine ECT and benzodiazepines therapy. In 2013, Unal and al. effectuated a retrospective medical examination of 57 patients with diagnosed catatonia. In 63,2% of them the basic disease was mood disorder, in 29% psychotic disorders, including schizophrenia; the most common symptom of catatonia, for more than 47% of people was muteness. The average number of ECT sessions was 9, and patients were simultaneously treated with benzodiazepines. In each patient the symptoms disappeared, which indicates the efficacy of the combination tested [24,38].

Summary

Catatonia consists of numerous psychomotor dysfunctions which occur at many mental and somatic disorders. To know it primary cause is a crucial step in choosing a proper therapy from many possibilities. Desistance of appropriate treatment might result in a serious threat to life. Catatonia, although is very common, still conceals some ambiguities. Not fully understood patophysiology of this disorder as well as a question of its nosological status urge clinicians and researchers to further research that would facilitate an understanding of the psycho-neurobiological nature of catatonia what is necessary to optimize treatment. The presented hypotheses regarding neurotransmission disorder seem to be reflected in pharmacotherapy

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