Case Report
DOI: 10.5455/amaj.2017.02.034

Differential Diagnosis of Psychotic Disorder with High Creatine Kinase and Subfebrile Fever: A Case Report

Mehmet Hamdi Orum, MD[1]
Helin Yilmaz, MD[2]
Tezan Bildik, MD[2]
Mahmut Zabit Kara, MD[3]
Ali Saffet Gonul, MD[4]
Serpil Erermis, MD[2]
Meryem Dalkilic, PhD[2]

[1] Adiyaman University, Faculty of Medicine, Department of Psychiatry, Adiyaman, Turkey.

[2] Ege University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Izmir, Turkey.

[3] Adiyaman Training and Research Hospital, Child and Adolescent Psychiatry, Adiyaman, Turkey.

[4] Ege University, Faculty of Medicine, Department of Psychiatry, Izmir, Turkey.

Correspondence:
Mehmet Hamdi Orum, MD,
Adiyaman University, Faculty of Medicine, Department of Psychiatry, Adiyaman, Turkey.
email: mhorum@hotmail.com

Catatonia is a syndrome, comprised of symptoms such as excessive motor activity, extreme negativism, motor immobility, and stereotyped movements. The malignant form of catatonia (MC) is considered to be a fatal and rapidly progressive subtype. It is a rare condition that pres¬ents subtle signs and symptoms and different etiologies, and is therefore underdiagnosed. Neuroleptic malignant syndrome (NMS) is an uncommon but potentially fatal idiosyncratic reaction to neuroleptics and characterized by a distinctive clinical syndrome of mental status change, rigidity, fever, and dysautonomia. MC resembles NMS in many ways but was described long before the introduction of neuroleptics. Cotard and capgras delusions may be associated with MC and NMS. The present case report demonstrates the difficulty of correctly diagnosing MC, NMS and emphasizes the importance of symptom chronology while going to take a diagnosis.

Keywords: Cotard syndrome, capgras syndrome, malignant catatonia, neuroleptic malignant syndrome, subfebrile fever.

Introduction

Catatonia is a neuropsychiatric syndrome characterized by psychomotor abnormalities which may appear due to neurological and other medical causes in addition to psychiatric causes [1]. Malign catatonia (MC) is a less common but fatal variant of catatonia. With additional symptoms such as hyperthermia, tachypnea, tachycardia, hypertension or unstable blood pressure, diaphoresis, and stupor, MC is a clinical condition which has many common characteristics with neuroleptic malign syndrome (NMS) but was defined before neuroleptic use [2]. NMS is an emergency which may generally occur after potent psychotropic drug use. With a pathophysiology which cannot be explained exactly, it is a syndrome observed in 0.2% of psychiatry patients and can be fatal despite treatment. Altered mental status, muscle rigidity, tremor, tachycardia, hyperpyrexia, leucocytosis, and increased serum creatine phosphokinase (CPK) level can be observed in patients [3, 4].

NMS and MC are conditions which are rare, difficult to diagnose, and may have a fatal course, and thus early diagnosis is important. In this case presentation, the chronological order of events was examined in an adolescent patient with coexisting lethal catatonic symptoms, infection, and NMS symptoms. The relation between psychosocial stress factor, catatonic symptoms, afebrile NMS findings, and respiratory tract infection were discussed in the light of literature.

Case report

A 15-year-old male patient was admitted to Ege University Medical School Hospital because of a change in mental status and mutism. Four months prior to admission, he was irritable, dysphoric, and showed tremendous lability of mood. He had no prior history of psychotic symptoms. Weird and blocked talking, aimless wandering in the dormitory, school non-attendance, refusal to eat and physical inactivity were added to the clinical presentations. The

boy was admitted to an adult psychiatric outpatient clinic of a local general hospital with catatonic symptoms, treated with olanzapine 5 mg/day, and fluoxetine 20 mg/day. His catatonic symptoms exacerbated on the days he was going to return to the school and the patient had decreased need for sleep on the following days. The members of his family stated that he said "Burn me, cut me" and "I'm the devil", he was afraid of mirrors and couldn't sleep during that period. Gradually stopping other drugs, the patient was managed by amisulpride 400 mg/day and antibiotics due to upper respiratory tract infection. His catatonic symptoms recurred, body temperature was 37.1°C, and he had urinary incontinence twice. Lumbar puncture, head computed tomography scan, and diffusion-weighted magnetic resonance imaging results made were all negative. He was subsequently transferred to Ege University Medical School for further evaluation and treatment.

On admission to the emergency service of Ege University Medical School, he was confused and not following commands. His evaluation consisted of a detailed psychiatric, medical, substance abuse, and psychosocial history as well as relevant laboratory studies. Family history revealed a paternal aunt had psychotic features. Vital signs included blood pressure 120/80 mmHg, heart rate 97 beats/minute with regular rhythm, and temperature of 36.7°C. Neurological examination was significant for diffuse muscular rigidity, catatonic excitement, catatonic posturing, hypertonia of limbs, and trunk, tremor, mutism, diaphoresis, and urinary incontinence. Results of standard blood tests (electrolytes, creatinine, urea, thyroid, and liver function) and urinalysis were within normal limits. His serum CPK was 3710 U/L (normal range 24 to 170 U/L) and white blood cell (WBC) count was 10,500/mm^3 (normal range 3,500 to 10,000/mm^3) (Table 1). Also, his thyroid stimulating hormone and electrocardiogram were normal.

Based on his clinical symptoms, laboratory results, and a history of neuroleptic use, a diagnosis of NMS without hyperthermia was postulated with a differential diagnosis of MC and encephalitis. The patient was treated with 2.5 mg/day of bromocriptine and 5 mg/day of diazepam twice daily. During the next ten days, the serum CPK level declined to 56 U/L, the WBC count declined to 5,760/mm^3 (Table 1).

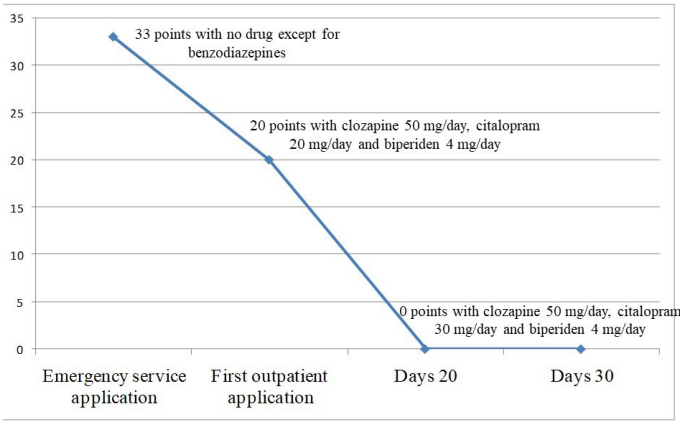

Figure 1.
Pediatric Catatonia Rating Scale (PCRS) Scores.

The symptoms such as "being dead and other people replacing the patient's mother and father" were observed during hospitalization. Due to bradycardic course and pulse rate not exceeding 55 with atropine, the anaesthesia department decided that this was not suitable for electroconvulsive therapy, and clozapine 12.5 mg/day was started. With clozapine 50 mg/day, citalopram 20 mg/day, and biperiden 4 mg/day, discharge and outpatient follow-up were decided for the patient upon the request of his family. The patient had 20 points in PCRS applied (Figure 1) in subsequent psychiatric interview. Drug therapy was rearranged as clozapine 50 mg/day, citalopram 30 mg/day, and Biperiden 4 mg/day, and an appointment was arranged for the following week. In the next interview, it was learned that the catatonic symptoms of the patient recovered dramatically and 'schizoaffective disorder' accompanied by Cotard and Capgras delusions was observed in 'Kiddie-Sads-Present and Lifetime Version (K-SADS-PL)' applied in the fourth month of the disease while the present treatment was continued [5].

Discussion

Catatonia is a syndrome, comprised of symptoms such as motor immobility, excessive motor activity, extreme negativism, and stereotyped movements [6]. Presented as a subtype of schizophrenia in DSM-IV-TR and thus having a limited area of diagnosis, catatonia was covered under a separate title in DSM-V and other conditions it accompanies other than schizophrenia were also mentioned (Table 2). Malign catatonia (MC) is a less common but fatal variant of catatonia. Aside from catatonic hyperactivity and stupor, the clinical features of MC described in literature are hyperthermia, altered consciousness, tachypnea, tachycardia, hypertension, unstable blood pressure, and varying degrees of cyanosis. MC resembles NMS in many ways. The diagnostic criteria for NMS are not universally agreed upon. In general, most sets of diagnostic criteria include altered mental status, hyperthermia, muscular rigidity, and autonomic instability, with many associated features (e.g., elevated CPK levels, and leukocytosis). Although hyperthermia is generally considered a major criterion for the definitive diagnosis of NMS, there are case reports of NMS without hyperthermia in the literature. These reports of supposed atypical NMS give credence to the idea proposed by many authors that NMS represents a spectrum of pathological processes [7].

Our patient developed altered mental status, diffuse muscular rigidity, mutism, catatonic excitement, catatonic posturing, tremor, diaphoresis, and incontinence following the introduction of therapy with antipsychotics. Results of laboratory tests showed elevated CPK levels, and leucocytosis. Emotional stress may prepare the background for the catatonic symptoms as in our patient. In some catatonic conditions, it was reported that patients had periods of opening, and closing regardless of the treatment [8]. Results acquired from lumbar puncture and imaging methods provided us to exclude encephalitis and other organic brain syndromes. Altered mental status, waxy flexibility, mutism, negativism, refusal to eat, muscle rigidity, urinary

Table 1. Laboratory data during the treatment course.

Items	1st 10:00pm	2nd 00:50am	2nd 02:00am	2nd 03:00am	2nd 06:40am	3rd	4th	6th	9th	13th
Serum CPK (U/L)		4566	4215	3809	3710	3270	3100	2500	357	56
AST (U/L)	82		69	65	69	43	48	35		14
CRP (mg/dL)	3.5		3.87		3.87	3.4	3.94	3.15		
Urea (mg/dL)	40.5		44.7	44.1	44.7	31	19	17		13
Creatinine (mg/dL)	0.79		0.92	0.86	0.82	0.5	0.48	0.42		0.54
Uric acid (mg/dL)	8.5		9	9	8.9	5.4	4	4.5		6.6
WBC (K/mm^3)	12.9				10.5	10.7	12.6	8.99		5.76

CPK - Creatine Phosphokinase, CRP - C-Reactive Protein, WBC - White Blood Cell.

incontinence, diaphoresis, instable blood pressure occurring together with high CPK, and hyperthermia occurring both after a drug change, and respiratory tract infection made diagnosis harder.

Studies emphasized that MC and NMS have similar clinical characteristics and their clinical and laboratory differentiation is difficult. A study on MC cases showed that it was not possible to clinically distinguish NMS and MC in 20% of the cases. Some studies have revealed that NMS occurred after MC. Again, some studies pointed out that NMS and catatonia may occur together. Some authors stated that NMS and MC are medical disorders in the same spectrum [9]. Mathews and Aderibigbe [10] stated that NMS is a severe subtype of catatonia. Castillo et al. [11] stated that extreme psychotic excitation is related to MC and extreme muscle rigidity is related to NMS. Mann et al. [12] emphasized that MC could occur due to NMS. Bristow and Kohen [13] stated that catatonia is a risk factor for NMS development. Another study stated that symptoms such as diaphoresis, muscle rigidity, fever, CPK increase, and leukocytosis increased significantly in NMS, and symptoms such as negativism, catatonic posturing, waxy flexibility, and stupor increased significantly in catatonia. Although none of these symptoms are specific to these diseases, it is considered that the rigidity is intermittent in MC, continuous in NMS, prodrome period is shorter in NMS, agitation is more severe in MC, and the related destructive way of behaviour is more frequent [14]. In our study, it was considered that the throat infection which started a few weeks after these symptoms induced MC. Apathy, ambivalence, agitation, and catatonic excitation in the probable prodromal period (15 days before urinary incontinence) allow us to interpret the initial situation as MC. Subsequently, MC, insufficient oral intake, and dehydration have triggered NMS. The lead pipe rigidity occurred at this period was a symptom of NMS. In the final situation, it is thought that there were comorbid syndromes including NMS and MC.

It is important to be aware that early recognition of the prodromal signs and identification of the relevant risk factors may help abort early cases. In other words, detecting cases before the full syndrome becomes manifest and active treatment may lead to a lower mortality [15]. Consistent with this, a review of the NMS literature demonstrated that the mortality rate was 44% (4/9) in case reports from 1973 to 1980; it was 5.5% (1/19) in those from 1981 to 1990; and there was no mortality those from 1991 to 1998 [16].

Table 2. The Catatonia Diagnosis in DSM-V.

1. Catatonic disorder due to a general medical condition

2. Specifier "with Catatonia" for
   a. Schizophrenia
   b. Schizoaffective disorder
   c. Schizophreniform disorder
   d. Brief psychotic disorder
   e. Substance-induced psychotic disorder

3. Specifier "with Catatonia" for current or most recent major depressive episode or manic episode in
   a. Major depressive disorder,
   b. Bipolar I disorder
   c. Bipolar II disorder

4. Catatonic disorder not otherwise specified

The elevation of CPK levels is often seen in NMS and MC secondary to skeletal muscle damage. Nearly 94% of children with NMS demonstrate elevations in CPK levels [17]. CPK may also be elevated by the use of intramuscular injections or physical restraints but usually at lower levels (below 600 U/L) than in NMS [18]. The initial treatment of NMS and MC is aimed at discontinuation of the offending agent and supportive therapy that includes careful attention to electrolyte balance, urine output, and renal functions. After the discontinuation of the inciting agent, the recovery typically occurs within two weeks. In our case, as in others, bromocriptine and diazepam were the drugs of choice. Bromocriptine is recommended as a

first-line treatment, while the benefits of using dantrolene are unproven. Bromocriptine is a strong dopamine D2-receptor agonist and partial dopamine D1-receptor agonist that enhances the dopaminergic transmission [17].

Conclusion

As it can be understood from the examples above, a consensus has not yet been compromised on MC and NMS differentiation. In our case, emotional stress experienced before catatonia development was evaluated as a risk factor. It was considered that symptoms occurred two weeks ago such as apathy, ambivalence, agitation and psychotic excitation were prodromal symptoms of MC. Again, it was considered that the respiratory tract infection which started a few weeks after these symptoms induced MC and the lead pipe rigidity occurred after these symptoms during this period was a symptom of NMS.

NMS and MC are conditions which are clinically difficult to distinguish or which sometimes cannot be distinguished at all. It should not be forgotten that NMS and MC can be seen comorbidly. This study is important for indicating chronological order of symptoms in diagnosis. MC may have triggered NMS and NMS may have been added on MC symptoms. In our study, it was also observed that catatonic symptoms recovered quickly with clozapine treatment without ECT. It shouldn't be forgotten that NMS can occur as atypical cases with an afebrile or subfebrile course.

Finally, additional research is needed to elucidate the differential diagnosis of NMS and MC.

References

1. Jaimes-Albornoz W, Serra-Mestres J. Catatonia in the emergency department. Emerg Med J. 2012 Jan 1; 29: 863–7.
2. Entrambasaguas M, Sánchez JL, Schonewille W. Catatonia maligna. Rev Neurol. 2000;30(2):132-8.
3. Stübner S, Rustenbeck E, Grohmann R, Wagner G, Engel R, Neundörfer G, Möller HJ, Hippius H, Rüther E. Severe and uncommon involuntary movement disorders due to psychotropic drugs. Pharmacopsychiatry. 2004 Mar;37(S 1):54-64.
4. Erermis S, Bildik T, Tamar M, Gockay A, Karasoy H, Ercan ES. Zuclopenthixol-induced neuroleptic malignant syndrome in an adolescent girl. Clinical Toxicology. 2007 Jan 1;45(3):277-80.
5. Gökler B, Ünal F, Pehlivantürk B, Kültür EÇ, Akdemir D, Taner Y. Reliability and validity of schedule for affective disorders and schizophrenia for school age children-present and lifetime version-Turkish version (K-SADS-PL-T). Turkish Journal of Child and Adolescent Mental Health. 2004;11(3):109-16.
6. Taylor MA, Fink M. Catatonia in psychiatric classification: a home of its own. American Journal of Psychiatry. 2003 Jul 1;160(7):1233-41.
7. Lev R, Clark RF. Neuroleptic malignant syndrome presenting without fever: case report and review of the literature. The Journal of emergency medicine. 1994 Jan 1;12(1):49-55.
8. Vırıt O, Kokaçya MH, Kalenderoğlu A, Altındağ A, Savaş HA. Karmaşık Bir Katatoni Olgusu. Klinik Psikiyatri Dergisi. 2009 Jan 1;12(1).
9. Tsai JH, Yang P, Yen JY, Chen CC, Yang MJ. Zotepine-Induced Catatonia as a Precursor in the Progression to Neuroleptic Malignant Syndrome. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2005 Aug 1;25(8):1156-9.
10. Mathews T, Aderibigbe YA. Proposed research diagnostic criteria for neuroleptic malignant syndrome. The The International Journal of Neuropsychopharmacology. 1999 Jun;2(2):129-44.
11. Castillo E, Rubin RT, Holsboer-Trachsler E. Clinical differentiation between lethal catatonia and neuroleptic malignant syndrome. The American journal of psychiatry. 1989 Mar 1;146(3):324.
12. Mann SC, Caroff SN, Bleier HR, Welz WK, Kling MA, Hayashida M. Lethal catatonia. Am J Psychiatry. 1986 Nov 1;143(11):1374-81.
13. Bristow MF, Kohen D. Neuroleptic malignant syndrome. British journal of hospital medicine. 1996;55(8):517-20.
14. Lang FU, Lang S, Becker T, Jäger M. Neuroleptic malignant syndrome or catatonia? Trying to solve the catatonic dilemma. Psychopharmacology. 2015 Jan 1;232(1):1-5.
15. Velamoor VR, Fernando ML, Williamson P. Incipient neuroleptic malignant syndrome?. The British Journal of Psychiatry. 1990 Apr.; 156:581–584.
16. Ty EB, Rothner AD. Topical Review: Neuroleptic Malignant Syndrome in Children and Adolescents. Journal of child neurology. 2001 Mar;16(3):157-63.
17. Silva RR, Munoz DM, Alpert M, Perlmutter IR, Diaz J. Neuroleptic malignant syndrome in children and adolescents. Journal of the American Academy of Child & Adolescent Psychiatry. 1999 Feb 1;38(2):187-94.
18. Pelonero AL, Levenson JL, Pandurangi AK. Neuroleptic malignant syndrome: a review. Psychiatric Services. 1998 Sep;49(9):1163-72.