Case Report

Malignant Catatonia and Neuroleptic Malignant Syndrome in Relation to Disulfiram Overdose

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ABSTRACT

Disulfiram is a widely used drug in the management of alcohol dependence syndrome as an aversive agent. Although a drug of high efficacy, it has a large number of side effects. Disulfiram-induced catatonia is a known rare side effect of the drug and herein we report a case of what appeared to be the sequential development of malignant catatonia and neuroleptic malignant syndrome in a patient with a diagnosis of alcohol dependence syndrome and co-morbid paranoid schizophrenia following disulfiram overdose. Clinicians need to be vigilant on the emergence of such rare side effects.

Key words: *Disulfiram, malignant catatonia, neuroleptic malignat syndrome*

INTRODUCTION

Disulfiram (tetraethylthiuram) is used in the treatment of alcohol dependence for more than 50 years. It inhibits the metabolism of ethyl alcohol by inhibiting the enzyme aldehyde dehydrogenase leading to accumulation of acetaldehyde which causes strong aversive behavior because of associated physiological reaction. Numerous side effects of disulfiram has been reported in literature, including disulfiram-induced catatonia.[1,2]

Catatonia is a neuropsychiatric syndrome most commonly characterized by mutism, stupor, refusal to eat or drink, posturing, and excitement or hypokinesis.[3] Catatonia with escalating fever and autonomic instability is known as "lethal" or "malignant" catatonia.[3]

Access this article online	
Website: www.ijpm.info	**Quick Response Code**
DOI: 10.4103/0253-7176.185944	

Malignant catatonia (MC) resembles neuroleptic malignant syndrome (NMS) in many ways, but was described long before the introduction of neuroleptics.

NMS, first described nearly five decades ago, is an idiosyncratic, life-threatening complication of treatment with antipsychotic drugs that is characterized by fever, severe muscle rigidity, leukocytosis, raised creatinine phosphokinase and autonomic and mental status changes.[4]

The relationship between catatonia and NMS remains a moot point. There is considerable overlap in symptomatology between NMS and lethal (malignant) catatonia. It has been argued that NMS is a malignant variant of catatonia. Various authors have described

How to cite this article: Kumar KK, Bondade S, Sattar FA, Singh N. Malignant catatonia and neuroleptic malignant syndrome in relation to disulfiram overdose. Indian J Psychol Med 2016;38:344-7.

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the conversion of antecedent catatonia, particularly the malignant type, into NMS following exposure to neuroleptics.[5,6]

CASE REPORT

A 28-year-old unmarried male patient hailing from low socioeconomic status and rural background with positive family history of paranoid schizophrenia in elder brother and a diagnosed case of alcohol dependence syndrome for the past 5 years with multiple failed attempts of abstinence, currently abstinent on aversive agents and with a co-morbid diagnosis of paranoid schizophrenia for the past 3 years and on antipsychotics presented to Department of Psychiatry with history of disulfiram overdose (2500 mg of disulfiram) allegedly due to persistent, third person auditory hallucinations with derogatory content.

At the time of admission, patient was receiving tablet risperidone 3 mg, trihexyphenidyl 2 mg, nitrazepam 10 mg, chlordiazepoxide 20 mg, and disulfiram 250 mg from a private psychiatrist, which he was continuing from the past 6 months with good tolerability but persistent second and third person auditory hallucinations and delusion of persecution. He was abstinent from the use of alcohol for the past 6 months and currently had no signs suggestive of alcohol use and subsequent ethanol-disulfiram reaction.

Patient was attended to in the emergency medicine department for disulfiram overdose and was revived following gastric lavage, use of activated charcoal and supportive management. After about 36 h (2nd day of hospitalization) it was noted that patient developed following signs and symptoms of catatonia viz. psychomotor retardation, vacant staring look, mutism, posturing/catalepsy, stereotypy, and mild autonomic abnormality in the form of tachycardia. Patient was treated with injection. lorazepam 4 mg intravenous, to which the patient responded positively with reduction in catatonic signs and symptoms for about 4 h but later persisted to have catatonic symptoms and auditory hallucinations. The following day that is, 3rd day of hospitalization patient continued to have catatonic signs and was febrile (100°F) with autonomic instability; his biochemical, immunological and hematological parameters were within normal limits and computed tomography brain showed no evidence of intracranial pathology. Patient was continued on risperidone 3 mg and trihexyphenidyl 2 mg along with lorazepam 6 mg in divided doses and supportive measures for hydration and adequate oral intake instituted. On the 4th day of admission, it was noted that along with worsening catatonic symptoms (Bush-Francis catatonia rating scale score: 20) patient also developed asymmetrical cog-wheel rigidity (more in the left upper limbs), confusion, high grade fever (103°F), labile blood pressure (180/120 mmHg), and tachycardia (120/min) along with deranged laboratory parameters in the form of leukocytosis (total count: 11,400 cells/mm^3) and raised creatine phosphokinase (CPK) levels (557 g/dL).

A diagnosis of NMS was made and neuroleptics were stopped and patient was shifted to Medical Intensive Care Unit (MICU) on the 5th day for further management. In the MICU, patient had persistent symptoms with gradually raising CPK titers, reaching 2913 g/dL on the 6th day along with raised serum myoglobin values (376.8 mg/L) and leukocytosis. Patient was started on tablet bromocriptine 2.5 mg po 6th hourly and supportive treatment along with measures to reduce fever and to maintain water and electrolyte balance was ensured. On the 7th day, he was also started on capsules dantrolene 25 mg po tid after confirming normal baseline LFT reports. Following specific and supportive measures patient started to improve with clinical features of catatonia, confusion and autonomic instability returning to normal. Patient was apparently normal on the 13th day and bromocriptine and dantrolene was tapered and stopped. Patient was continued on lorazepam 2 mg HS. Currently, patient continues to have active psychotic symptoms and the need for re-challenge with safer atypical antipsychotics or electro convulsive therapy needs to be discussed with patient and his care takers.

DISCUSSION

Disulfiram is an agent used in the treatment of alcohol addiction or abuse due to its alcohol-aversive effect. This agent may cause the accumulation of acetaldehyde metabolized from alcohol in toxic amounts, by inhibiting the acetaldehyde dehydrogenase enzyme. Disulfiram also acts on the dopaminergic system; diethyldithiocarbamate, the breakdown product of disulfiram, blocks the dopamine β-hydroxylase enzyme and inhibits the conversion of dopamine into noradrenalin and may cause neuropsychiatric side effects such as delirium, paranoid conditions, lack of concentration, memory impairment, depression, ataxia, and dysarthria. In addition to these side effects, cases of catatonia induced by disulfiram have been reported, though rarely.[1,7,8] In the present case, though the patient was a known case of Paranoid schizophrenia with a strong family history of schizophrenic psychosis, he had never exhibited catatonic signs or symptoms and there was no other clinical parameters that predisposed the individual to

catatonia other than disulfiram overdose in a temporal cause effect relationship.

Credit for defining catatonia as a motor syndrome in patients with behavior disorders is usually given to the German psychopathologist Karl Kahlbaum who published Die Katatonie oder das Spannungsirresein in 1874. Catatonia is now recognized as a syndrome that may be encountered in a wide range of conditions including primary psychiatric disorders, metabolic disorders, neurologic disorders and brain injury, and drug-induced disorders.[9] The core features of catatonia are stupor, motoric immobility, mutism, negativism, excitement, catalepsy, and posturing. The core features are the same regardless of whether the condition occurs in the context of a mood, psychotic, or medical state.[9] However, in our case though the initial presentation was the classical catatonic signs, gradually we noted the development of high grade fever and autonomic instability with no "dramatic" response to lorazepam.

This pernicious or lethal or malignant form of catatonia was first termed "tödliche Katatonie" (fatal catatonia) (Stauder 1934). Other authors have labeled the syndrome Bell's mania, manic delirium, delirious mania, acute or fulminating psychosis, and oneirophrenia.[10] More recently, Philbrick and Rummans (1994), stressing that not all cases prove fatal, have promulgated the term MC,[11] which we use here as a generic term for this disorder. Aside from catatonic hyperactivity and stupor, the clinical features of MC described in literature are hyperthermia, altered consciousness, and autonomic instability as manifested by diaphoresis, tachycardia, labile or elevated blood pressure, and varying degrees of cyanosis. Catatonic signs aside from stupor and excitement continue to be noted.[11] Almost all of the signs mentioned except for catatonic excitement and cyanosis were demonstrated in the reported patient.

MC resembles NMS in many ways but was described long before the introduction of neuroleptics. NMS is an idiosyncratic response to dopamine receptor antagonist medications. The incidence of NMS is estimated at 0.01-0.02% of patients treated with neuroleptic medications.[3] In the present case, it is interesting to note that the patient was on neuroleptic drug (risperidone 3 mg) since the past 6 months and had tolerated the drug without any extrapyramidal adverse effects. The drug was continued until the occurrence of signs and symptoms suggestive of NMS in the hospital.

The relationship between these two conditions that is MC and NMS has been conceptualized in three ways. Castillo *et al*. argued that MC and NMS can be distinguished by clinical features, especially lead pipe rigidity.[12] Mann *et al*. state that MC is a syndrome that may have many causes, one of which is NMS.[13] Bristow and Kohen (1996) regard catatonia as a risk factor for the development of NMS and MC being identical to NMS.[14] There is evidence that the NMS may be related to a central dopamine deficiency, predominantly in the basal ganglia, and anterior hypothalamus. Reduced dopaminergic transmission in the diencephalon and other brain areas has also been postulated to explain the hyperthermia and catatonic signs described in lethal catatonia.[13] It would be logical to suppose that the already deficient dopaminergic activity in the brain of catatonics would be aggravated by the dopamine blockade produced by neuroleptics. The result of this situation may be the precipitation of the NMS has exhibited in this case.

To summarize, in our case the patient had predisposing factors in the form of a young adult male, current schizophrenic illness with genetic predisposition, substance abuse, and on atypical antipsychotics. However, what pushed the stabilized patient into an acute emergency state was disulfiram overdose leading to hypothesized MC due to alterations in dopaminergic activity and then the occurrence of NMS in the back drop of continued neuroleptic agent and considering MC as a harbinger of NMS. A final diagnosis of NMS was arrived at and the patient was successfully treated. Hence, treating psychiatrist should consider such rare side effects when the patient is on disulfiram therapy, particularly with co-morbid psychiatric illness.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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