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 malignant 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]

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...
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.
pschomotor 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/mm³) 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 6h 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;
diethylidithiocarbamate, 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
Kumar, et al.: Malignant catatonia and disulfiram overdose

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 Spannungsirrese 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.

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Conflicts of interest
There are no conflicts of interest.

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