

Disulfiram-induced delirium: diagnostic dilemma

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Abstract : *Disulfiram, a useful medication to deter the relapse of alcohol dependence, has been associated with a number of neuropsychiatric adverse effects. Disulfiram induced delirium is rare in the absence of an ongoing psychosis or a disulfiram-ethanol reaction. We present the case of an alcohol dependent patient who had a past history of both an alcohol-induced psychotic episode (which had resolved completely) and alcohol withdrawal seizure. Following inpatient detoxification and induction on disulfiram, to which he was compliant and maintaining totally abstinent, he developed an acute delirious state 6 weeks after disulfiram. It was characterized by fluctuating disorientation, marked inattention, affective lability, increased psychomotor activity, irrelevant speech, social disinhibition, at times staring, talking to self and gesturing in air, and sleep-wake cycle reversal with evening worsening of symptoms. He was re-hospitalized and symptoms subsided by 72 hours after stopping disulfiram. The diagnostic dilemma associated with such a presentation is discussed, along with the putative mechanisms and clinical pointers.*

Keywords: Disulfiram, Alcohol dependence, Delirium, Psychosis

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INTRODUCTION

After the quick realization by two Danish physicians, who became ill at a cocktail party after ingestion of disulfiram taken in the course of an investigation of its potential anthelmintic efficacy (that the compound had altered their responses to alcohol), a series of pharmacological and clinical studies provided the basis for the use of disulfiram as an adjunct in the treatment of chronic alcoholism. Among the various side effects, including the neuropsychiatric ones, delirium alone is very rare in absence of an ongoing psychotic process or disulfiram-ethanol reaction; and more so in current scenario when disulfiram is used in lower (deterrent) doses than the higher (aversive) doses used earlier. To the best of our knowledge, a case of disulfiram induced delirium at current deterrent doses in absence of ongoing psychosis and

disulfiram ethanol reaction is very rare and hence can cause a diagnostic dilemma.

CASE

Mr. R.S, 35 years old matriculate, farmer from rural Punjab, who was drinking country made liquor in dependent pattern for last 7 years (meeting both ICD-10 and DSM IV-TR criteria), had a past psychiatric history of alcohol induced psychotic episode with predominantly paranoid features 6 years back. However, the psychosis resolved completely with abstinence from alcohol and treatment with antipsychotic within 4 weeks. He also had history of alcohol withdrawal induced generalized tonic clonic seizure 1 year back, gout and essential hypertension for last 4 years. With this background, he was treated as an inpatient in August 2008. Detoxification and relapse prevention counseling was done and patient was

discharged on Tab disulfiram 250 mg OD, Tab amlodipine 5mg OD and Tab ramipril 5mg OD.

While he was compliant with his medications and with strict alcohol abstinence (corroborated by family members), 6 weeks after his hospital discharge the patient was again brought by his family members with a 3-day history of acute onset cognitive-behavioral disturbance characterized by fluctuating disorientation, marked inattention, affective lability, increased psychomotor activity, irrelevant speech, social disinhibition, at times staring, talking to self and gesturing in air, and sleep-wake cycle reversal with evening worsening of symptoms. There was no history of alcohol consumption in any form during that whole month after being discharged from hospital.

Physical examination and investigations including complete blood count, urea, creatinine, serum electrolytes sodium, potassium, chloride, hepatic transaminases, blood sugar, urinalysis, thyroid function and uric acid levels were all within normal limits. Tab disulfiram was stopped and Tab haloperidol 1 mg/day was given along with behavioral management of delirium.

He recovered completely in 72 hours and thereafter Tab haloperidol was tapered and stopped over the period of 1 week. Motivation enhancement and relapse prevention counseling was done. Tab disulfiram was excluded from further treatment option and patient and family members did not accept any other medication with view of fair motivation and regular follow ups at our de-addiction center.

DISCUSSION

Neuropsychiatric adverse effects of disulfiram accounts for 4-13% of total adverse drug reactions.¹ Amongst these anxiety, impaired memory, decreased concentration, depression, delusion (paranoia), sleep disorder, acute organic brain syndrome, psychotic reactions, catatonia,

ataxia, dysarthria and frontal release signs such as snout and grasp reflex are reported to occur in decreasing order of frequency which may appear as a direct result of the drug itself.^{2,3} Basal ganglia are one of the major targets of disulfiram neurotoxicity which may involve carbon disulfide metabolite.⁴

The most important toxic metabolites are diethyldithiocarbamate (DDC) and its metabolite carbon disulfide (CS₂). DDC chelates copper, thus impairing the activity of dopamine beta-hydroxylase, an enzyme that catalyzes the metabolism of dopamine to norepinephrine. In this way, DDC causes depletion of presynaptic norepinephrine and accumulation of dopamine, so increasing the levels of dopamine and reducing those of norepinephrine in the mesolimbic region.⁴⁻⁶ In addition, one study found that disulfiram and DDC increase the release of glutamate from striato-cortical synaptic vesicles, both in vitro and in rats, suggesting yet another possible mechanism for DDC-mediated neuronal damage.^{3,7} Acute exposure to carbon disulfide (CS₂) causes rapid onset of headache, confusion, nausea, hallucinations, delirium, seizures, coma, and potentially death.^{3,6,8,9}

Disulfiram associated encephalopathy, although uncommon, typically occurs within first few months of therapy.¹⁰ Although delirium usually accompanies psychotic reactions, psychosis in clear consciousness has also been known to occur.^{3,7,11-15} But delirium alone without psychosis, disulfiram ethanol reaction and other medical complications is very rare.¹¹⁻¹⁶ In our knowledge disulfiram induced delirium without other contributing factors has been reported in only two case reports^{10,17} similarly disulfiram induced psychosis without other contributing factors has been reported in another case report.¹² For disulfiram induced encephalopathy, the risk is increased when: excessive amounts of the drug are ingested, the patient is already suffering from

a major psychiatric illness, has anatomical brain lesions. In all cases observed, the toxic effects appeared in the first weeks and were reversed after suspension of the drug.¹⁸ Hence, the above-mentioned risk factors should be evaluated before prescribing disulfiram to any individual.

In the index patient, delirium occurred within 8 weeks of starting disulfiram. He had past history of alcohol induced psychotic disorder and withdrawal seizure; hence the diagnostic dilemma. However, his delirium resolved within 3 days of stopping the disulfiram and no other psychiatric or physical cause or disulfiram ethanol reaction could be identified.

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