Disulfiram intoxication: diffuse anoxic leukoencephalopathy

Hugo Corte-Real*, Margarida Silva**, Teresa Matias***

Abstract

Disulfiram can be used as adjuvant therapeutic in the management of some selected cases of chronic alcoholism dependency, causing extreme discomfort in the course of drinking alcoholic beverages.

The authors present a case report of leukoencephalopathy, peripheral neuropathy and hyponatraemia in an alcoholic patient discussing the relations between those adverse reactions and the intoxication with disulfiram and its metabolite, carbon disulphide.

Keywords: disulfiram, intoxication, diffuse anoxic leukoencephalopathy, carbon disulphide.

Introduction

Disulfiram is used as adjuvant therapy to treat selected cases of chronic alcoholism due to the discomfort that provokes with alcohol intake.[1, 2]

Both nervous central system[3,4] and the peripheral one[8,11] associated to the intoxication with disulfiram are rare and very few cases are published in the literature.

The authors present a case of local encephalopathy, peripheral polyneuropathy and hyponatraemia in a subject with marked alcoholic habits and discuss the association of changes referred to the intoxication by carbon disulfiram, a disulfiram metabolite.[3,4,8,11]

Case Report

F.D.P.G, 56 years old, Caucasian, a sawyer, unmedicated hypertensive patient, with a usual consumption of 300g ethanol a day, since he was 30 years old, self-medicated with disulfiram for eight consecutive days after nine days of alcohol withdrawal.

On the first day he ingested 1500 mg and on the seven following days 1000 mg a day (when the therapeutic dose should not exceed 500 mg a day).

Around the fifth day of self-medication he started feeling sick, frequent food vomiting, frontal headache and reduced strength on his left hemibody.

On the 8th day, he drank 250 cc of beer, becoming confused, and being admitted in the emergency services.

On admission he was not cooperative, very prostrated, marked confusional status, space and time disorientation, auditory hallucinations and psychomotor restlessness.

The blood pressure was 180 – 100 mmHg, axillary temperature of 37° Celsius, skin and mucosa with good colour, non-cyanotic, the cardiorespiratory and abdominal exams were normal and there were no stigma of chronic hepatic disease.

Eye pupil isochoric and iso-reactive with 3 mm of diameter, eye-cephalic reflexes presenting ipsilateral simultaneous rotation of the head and eyes, corneal reflexes were present and symmetric, with exam of eye fundus did not show any changes.

There were a flaccid left hemiparesis with homolateral cutaneous-plantar reflex in extension presenting also nuke stiffness.

The diagnosis complementary exams on admission highlighted haemoglobin of 14.8 g/dL, mean corpuscular volume of 86.2 fl, leukocytosis 14.4 x 10.09/l with 80.8% of neutrophils and prothrombin time 14 seconds.

Sodium was 114 mEq/l, gamma-glutamyl-transpeptidase 60 U/L and VDRL and hemocultures were negative. The gasometry, ECG and Thorax X-Ray were normal.

On the second day of admission, started a febrile condition with axillary temperature of 38–39°C and convulsive seizures located on the left hemibody .

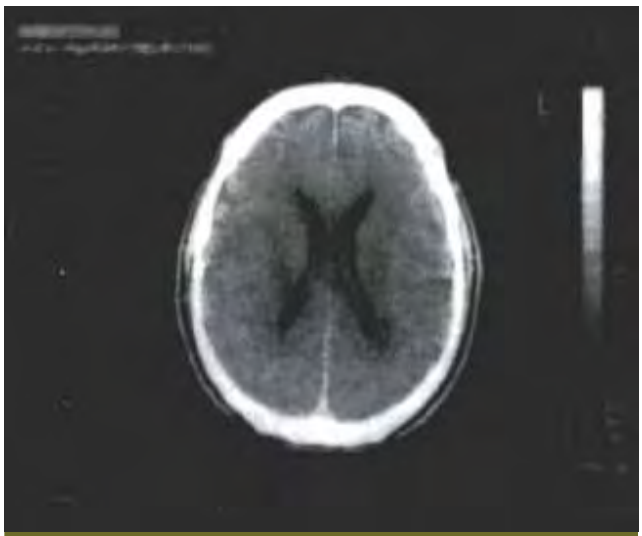
A cranial-encephalic CT has revealed small subcortical hypodense parietal images on the left (*Fig. 1*).

*Resident of the Supplementary Internal Medicine Internship

**Neurology Hospital Assistant

***Internal Medicine Hospital Assistant

Medicine Service of Hospital S. José, Lisbon



Cranio-encephalic CT – left small subcortical parietal lacunar images.

FIG. 1

Lumbar puncture showed a rock crystal fluid, CSF glucose 64 mg/dL, LDH 40 U/l, protein 53.9 mg/dl and a number of cells of 2.4 mm^3. The bacterial study, mycology as well as the CSF BK was negative.

Nuclear magnetic resonance (NMR) has shown multiple widespread lesions, involving predominantly the deep white matter, and some peripheral and involving the corpus callosum radiations, a central-protuberance region of irregular limits and punctiform foci discreetly hypertensive in the head and body of the caudal and lenticular nucleus and white matter (*Fig. 2*).

The patient was medicated with tiapride, haloperidol, thiamin, oxazepam, captopril and diltiazem and it was made the correction of hyponatraemia with isotonic serum in four days.

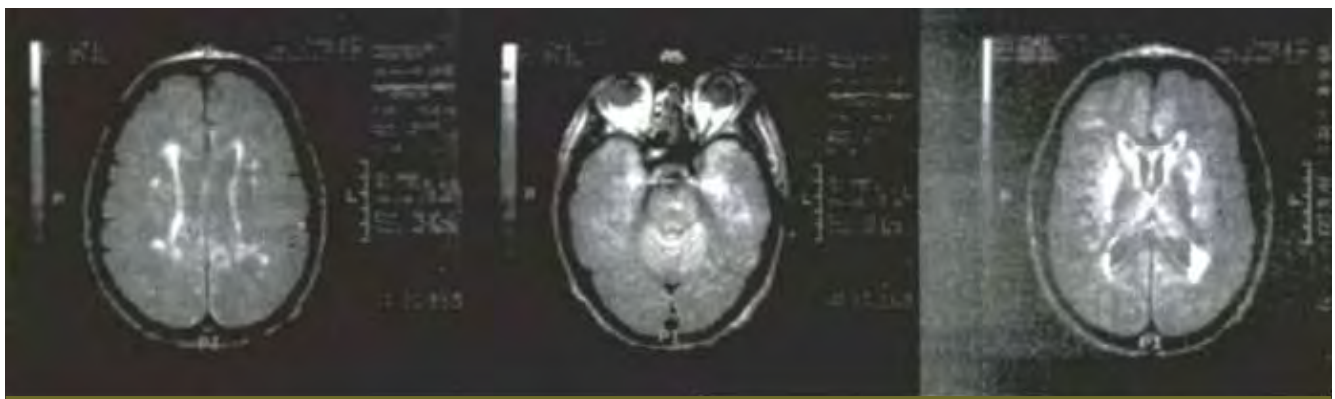
On the sixth day of admission all the changed assessed values began to go back to normal and on the ninth day (15 days after the first intake of disulfiram) the patient presented a return to normal of the level and content of awareness, the assessed signs disappeared on the left hemibody and blood pressure returned to normal.

On the 12th day of admission an EEG was performed showing awake state trace with a slow base activity (due to an increase on the diffuse theta rhythm), interfered by outbreaks of variable duration of short waves of the Delta bands, sinusoidal, with a projection also diffuse and symmetric, particularly abundant in the sleeping periods (frequent) and reactive to sound stimulation, such study was compatible with diffuse encephalic suffering (*Fig. 3*).

A new lumbar puncture was performed with a protein immunoelectrophoretic study, showing a slightly transudate profile and a virologic study for EBV and HSV which were negative.

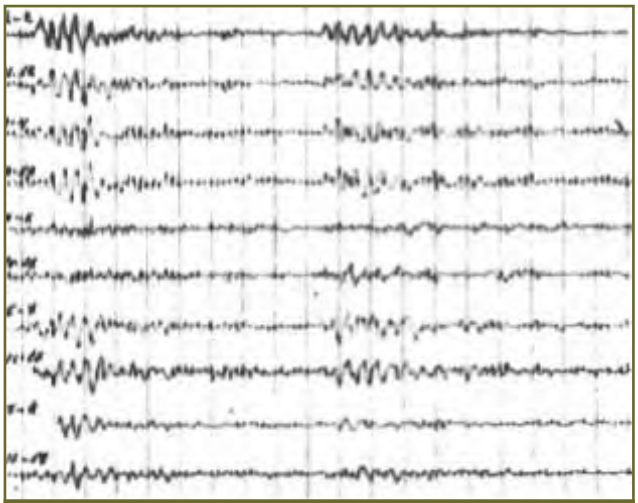
Somatosensitive evoked potentials were studied (posterior and median tibial) (*Fig. 4*) and auditory (*Fig. 5*). The former were compatible with peripheral polyneuropathy and the second with protuberance lesion.

On the 16th of admission, the NMR was repeated showing a similar study to the previous one and the



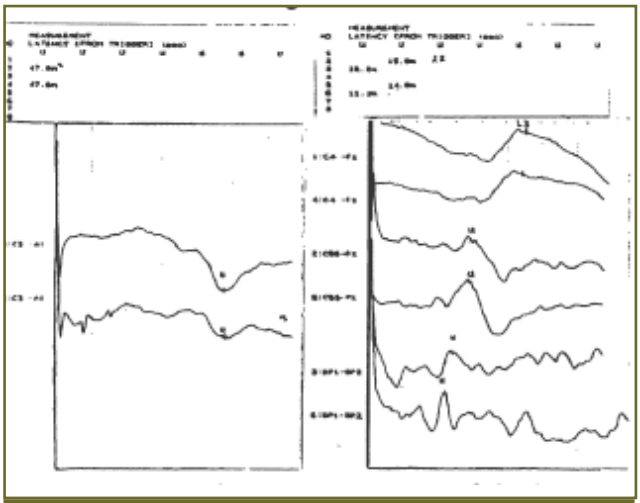
Nuclear magnetic resonance – multiple disseminated lesions (see text)

FIG. 2



Compatible study with diffuse encephalic suffering (see text)

FIG. 3



Somatosensitive evoked potential (posterior and median tibial) – Study compatible with peripheral polyneuropathy

FIG. 4

somatosensitive, auditory and now, also the visual evoked potentials. The study of somatosensitive was similar to the previous one, with a normalisation of the auditory and visual which were also normal.

He was discharged without any symptoms on the 17th day, medicated only with anti-hypertensive therapy, being referred to the Outpatient Clinic where he has been monitored.

Discussion

Alcohol is metabolised into acetaldehyde by 2 paths: by the alcohol dehydrogenase enzyme in the hepatocyte cytosol, during moderate intake of alcohol and by the microsomal system located in the mitochondria, during a chronic and marked alcohol intake.[1,2]

Acetaldehyde is then oxidized into acetate through the dehydrogenase aldehyde.[1,2]

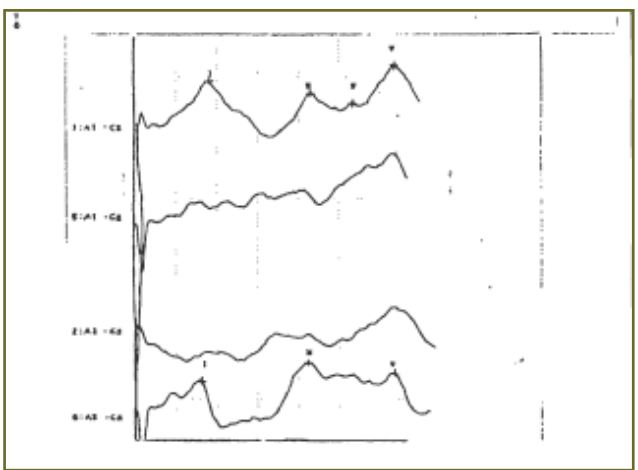
The chronic alcoholic intake reduces the dehydrogenase aldehyde, although the enzyme was not affected.[1]

Disulfiram (tetraethylthiuram disulphide), a widely used antioxidant in the rubber industry, causes extreme discomfort to those drinking alcohol.[1] It acts inhibiting the dehydrogenase aldehyde enzyme, in an apparently irreversible way,[2] accumulating aldehyde.

Disulfiram is metabolised and eliminated very slowly (1 to 2 weeks) by the liver. Therefore it acts for several days.[2]

The symptoms triggered result some from the accumulation of acetaldehyde in toxic levels, others when a quaternary ammonium toxic compound is formed, others due to its metabolite carbon disulphide, others by the action of diethyilthiocarbamate and other metabolites.[2,6,7,9,10]

Disulfiram secondary effects go from headache, nausea, electrolytic changes, confusional state, optical polyneuropathy up to respiratory depression, seizures, coma, arrhythmias, cardiorespiratory arrest and death.[2]



Auditory evoked potential – Study compatible with protuberance lesion.

FIG. 5

The intake of disulfiram has triggered in the patient a change in his awareness state and signs of deficient foci.

The concomitant consumption of alcohol along with the ingestion of a total of 8.5 g of disulfiram, with a half life probably increased by an altered hepatic metabolism, has caused toxic levels of acetaldehyde and disulfiram metabolism.

Disulfiram action at the central nervous system and at the peripheral nervous system level is made through its metabolite intermediary, carbon disulphide, provoking respectively a lesion preferably in the white matter and basal ganglia (anoxic leukoencephalitis, occurring predominantly in the depth of the semi-oval centre disseminating along the circumvolutions axis, tending to save the subcortical arcuate fibres, having even, sometimes a complete demyelinization of the corpus callosum and the anterior commissure) and peripheral polyneuropathy.[3,4]

The effects triggered by carbon disulphide can explain the changes in the images detected in the NMR and the resulting clinical condition.

Neurological changes can be worsened by the electrolytic changes (hyponatraemia).[4] However this slow correction of hyponatraemia, the regularly character of the pontine lesion,[4] the predominant presence of multi-focal lesions of the white matter and the concomitant attainment of the basal nuclei is suggestive of a dominant causality by carbon disulphide.[3,4]

The pathophysiological mechanism is described as an induction of the enzyme blockage, leading to a reduced capacity to eradicate the oxygen free radicals (cell anoxia),[5] what will trigger a cell tumefaction and subsequent vasogenic oedema.[4]

Through this process – accumulation of extra cellular fluids – the outcome would be tumefaction at encephalic level what on its turn can lead to the compression of veins and eventually arteries. Such compression would increase anoxic (now of stagnating type) and vasogenic oedema, appearing then a vicious cycle.[4]

As the white matter is more resistance to anoxia then the grey matter (oxygen consumption in the white matter is five times less than grey matter) how come that in this case the reverse occurs? It is because in the white matter, parallel fibres bundles has weak interconnections, what allows the easy movement of fluid, what does not happen in the grey matter where the big number of synapses among nervous cells and the cell junction among the astrocytes and several components of the grey matter make up a very cohesive tissue.[4]

The peripheral polyneuropathy – neurofilament distal axonopathy (sensorial motor)[11] – can occur from 10 days to 8 months after starting the intake (it can occur just with doses of 250 mg a day)[8] – it is described as resulting of the toxic action of carbon disulphide.[8,11]

The other disulfiram metabolite, the diethyldithiocarbamate, inhibiting the B-dopamine enzyme through the copper chelation, inhibiting the synthesis of noradrenaline from dopamine, a mechanism thought to be responsible for the psychotic frame (due to the excess of dopamine).[6,7,9,10]

The described psychotic frame in our patient can be explained by the dominating action of diethyldithiocarbamate. ■

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