Comunicações Curtas e Casos Clínicos

Toxic Optic Neuropathy caused by Disulfiram

José Alberto Lemos[1], Isabel Ribeiro[1], João Martins[2], Carlos Menezes[1], Rita Gonçalves[1], Pedro Coelho[1], Tiago Maio[1]

[1]Serviço de Oftalmologia do Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos (ULSM), Matosinhos, Portugal.

[2]Serviço de Neurologia (Departamento de Medicina) do Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos (ULSM), Matosinhos, Portugal.

RESUMO

Objetivos: O dissulfiram é utilizado no tratamento do alcoolismo crónico há mais de 50 anos. Este fármaco interfere no metabolismo do etanol e encoraja a abstinência por causar sintomas desagradáveis com a ingestão concomitante de álcool. Efeitos adversos incluem casos raros de neuropatia óptica bilateral. O objetivo deste artigo é descrever um caso clínico de neuropatia óptica tóxica causada por dissulfiram.
Métodos: Descrição do caso clínico e breve revisão bibliográfica.
Resultados: Reporta-se o caso de um homem de 56 anos, tratado nos últimos 7 anos com dissulfiram por alcoolismo crónico, que recorreu ao Serviço de Urgência de Oftalmologia por diminuição da acuidade visual bilateral severa com 2 meses de evolução, associada a uma neuropatia óptica. Extensa investigação etiológica revelou como causa provável uma neuropatia óptica tóxica causada pelo dissulfiram. A interrupção do dissulfiram resultou em rápida e significativa recuperação visual.
Conclusões: Na presença de uma neuropatia óptica com suspeita de toxicidade pelo dissulfiram, a cessação do fármaco é mandatória. O prognóstico visual é habitualmente bom, conforme ilustrado no nosso caso e descrito na literatura.

Palavras-chave
Neuropatia óptica; dissulfiram; alcoolismo; toxicidade; escotoma.

ABSTRACT

Objectives: Disulfiram is used to treat chronic alcoholism for over 50 years. This drug interferes with alcohol metabolism and encourages abstinence by causing painful symptoms with simultaneous alcohol ingestion. Adverse effects include rare cases of bilateral optic neuropathy. This article's main objective is to report a case of toxic optic neuropathy caused by disulfiram.
Methods: Case report and brief review of literature.
Results: Authors report the case of 56 years-old man, treated with disulfiram in the last 7 years due to chronic alcoholism that presented to the Ophthalmology Emergency Department with severe bilateral visual acuity loss with 2 months evolution, related to an optic neuropathy. Extensive etiologic work-up revealed that toxic optic neuropathy associated with disulfiram was the probable cause. Discontinuation of disulfiram resulted in rapid and important visual recovery.
Conclusions: In the presence of an optic neuropathy with suspicion of disulfiram toxicity,

drug interruption is mandatory. Visual prognosis is usually good, as illustrated by our case and other literature descriptions.

Keywords
Optic neuropathy; disulfiram; alcoholism; toxicity; scotoma

INTRODUCTION

Optic neuropathies (ON) are an heterogeneous group of optic nerve disorders, which may occur secondary to ischemia, genetic susceptibility, nutritional deficiencies, nerve compression or toxins, in this last case designated as a toxic optic neuropathy (TON). Further to a broad spectrum of visual field defects, ON are also characterized by a loss of visual acuity that may be slight or profound, and of gradual or sudden onset.

Disulfiram, sold in Portugal under the name Tetradin®, is a drug derivative from carbamate that has been used in the treatment of chronic alcoholism for over 55 years[7]. This substance was used since the nineteenth century in rubber industry and by accident it was discovered it usefulness in the treatment of alcoholism.[7] Disulfiram mechanism of action consists of partial irreversible inhibition of the enzyme acetaldehyde dehydrogenase (that converts acetaldehyde to acetate).[9] It's an unique drug because disulfiram main effect is to cause extremely unpleasant physiological and psychological reactions when combined with alcohol ingestion (secondary to the increase in the plasmatic concentration of acetaldehyde). Recent studies also showed disulfiram efficacy in cocaine dependence (through a distinct mechanism of action).[3]

The incidence of adverse drug reactions to disulfiram is low, however there are reports of dermatological, gastrointestinal, hematological and neurological reactions, including rare cases of TON (22 cases described in literature).[1,2,4-6,8,10-15]

Authors report a case of reversible TON in a man under chronic therapy with disulfiram.

CASE REPORT

We report the case of 56 years-old man that went to the Ophthalmology Emergency Department with a 2 month history of severe, bilateral and progressive visual loss. Patient denied ocular pain, headaches or dyschromatopsia.

Past medical history included type 2 diabetes, arterial hypertension, hyperlipidemia, obesity, smoking (20 cigarettes daily) and a past history of chronic alcoholism, from which he had abstained for the previous 7 years while on treatment with disulfiram (currently 250 mg/day). The remaining usual medication was: metformin, fluoxetin, alprazolam, candesartan, amlodipine, simvastatin and acetylsalicylic acid.

Best-corrected visual acuity (BCVA) was 1/20 in

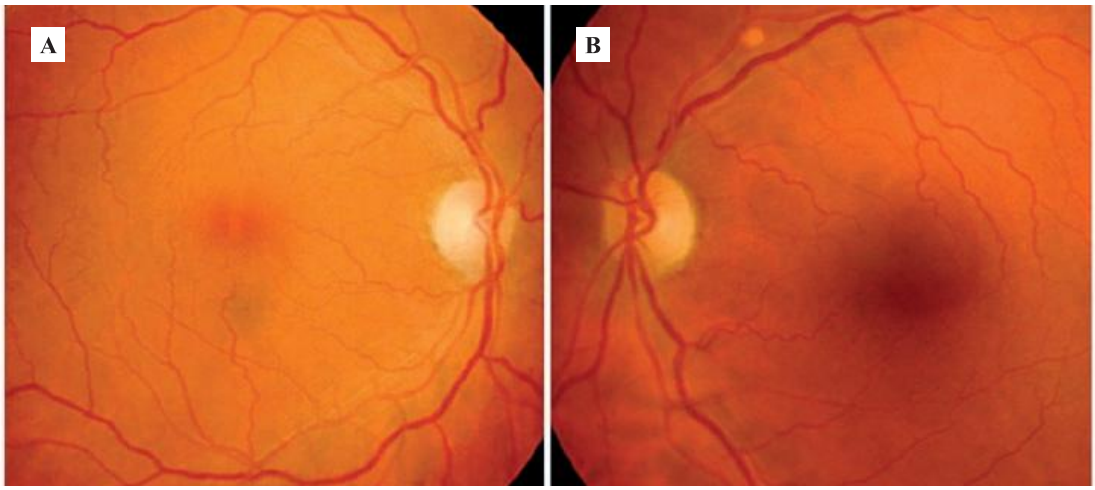

Fig. 1 | Right eye (**A**) and left eye (**B**) fundoscopy showing temporal optic disc pallor.

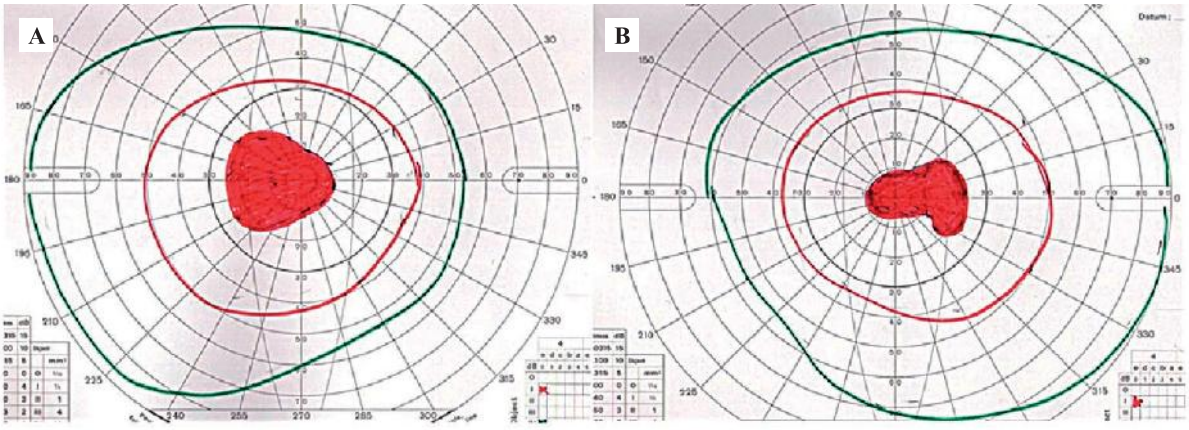

Fig. 2 | Goldmann visual field at presentation, revealing centrocaecal scotoma, which was more severe in the left eye (**A** - left eye; **B** - right eye).

right eye (RE) and left eye (LE). Relative afferent pupillary defect was absent. Slit-lamp examination showed bilateral incipient cataract. Fundoscopy revealed bilateral temporal optic disc pallor (Fig. 1).

Optical coherence tomography (SOCT Copernicus 3D®, Optopol Technology, Zawiercie, Poland) of the optic disc showed decrease of retinal nerve fiber layer (RNFL) thickness in temporal, superior and nasal quadrants in RE and decrease of RNFL thickness in 4 quadrants in LE. Goldmann visual field testing revealed bilateral centro-caecal scotoma, which was more severe in LE (Fig. 2). Remaining ophthalmological and neurological examination showed no relevant changes.

Patient was admitted for etiological investigation, including brain magnetic resonance imaging, fluorescein angiography and extensive laboratory workup that showed no changes suggestive of inflammatory, infectious, ischemic or infiltrative ON. Visual evoked potentials showed abnormally prolonged P100 peak latency bilaterally (119.2 ms RE and 140.0 ms LE, our laboratory upper limit of normal 112 ms).

Because of suspected toxicity caused by disulfiram, this drug was stopped on day two following admission, with gradual improvement of visual function. One week later, BCVA improved to 2/10 in RE and LE.

Color vision test (Farnsworth-Munsell 100 hue test) fulfilled after BCVA improvement (3 weeks after disulfiram suspension) revealed attenuation of color vision in the red-green axis bilaterally.

Upon follow-up 6 months after disulfiram suspension, BCVA had stabilized at 9/10 RE and LE. Repeated visual field testing showed a notable improvement in bilateral

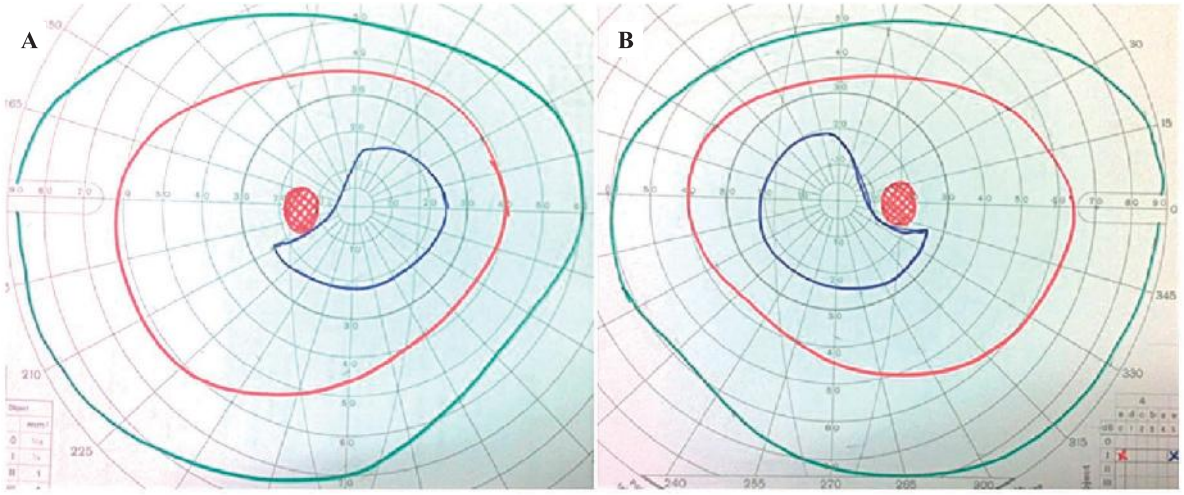

Fig. 3 | Goldmann visual field 5 months after suspension of disulfiram, showing significant bilateral improvement in sensitivity, bilaterally. (**A** - left eye; **B** - right eye).

sensitivity (Fig. 3), with disappearance of bilateral centrocaecal scotoma. We notified the adverse drug reaction to INFARMED.

DISCUSSION

Alcohol is metabolized in the liver to acetaldehyde, which in turn is oxidized to acetate by the enzyme aldehyde dehydrogenase (ALDH). Disulfiram irreversibly inhibits this oxidation, leading to increased serum levels of acetaldehyde and causing the unpleasant reaction associated with alcohol consumption, varying in severity from a mild reaction of facial flushing, excessive sweating and headaches to severe reactions like cardiac arrhythmias and respiratory failure.[11]

TON caused by disulfiram is a rare entity, as shown by the paucity of described cases. Reported cases usually show the insidious onset of an ON characterized by a centro-caecal scotoma, variable visual acuity loss and temporal optic disc pallor, findings that are present in our clinical case.[2] If this etiology is recognized, patient visual function can be improved with drug suspension.

The presence of an acquired centro-caecal scotoma requires a wide differential diagnosis with nutritional ON, optic neuritis, compressive and infiltrative ON and Leber ON. In our patient, absence of previous symptoms and significant improvement with drug suspension (as well as the exclusion of other possible causes) support a causal relationship between disulfiram and clinical manifestations.

TON caused by disulfiram arises unpredictably, idiosyncratic, being independent of treatment duration or dose.[2] The mechanism of disulfiram-induced ON has been attributed to a metabolite of this drug, known as carbon disulphide. Industrial exposure to carbon disulphide has been shown to cause ON as a result of axonal degeneration.[5]

TON caused by disulfiram typically has a significant visual recovery that occurs 1-6 months after drug suspension[2], as happened in our case. Previous studies showed no correlation between the recovery time and final visual acuity with disulfiram dose, treatment duration, symptoms duration or initial visual acuity.[2]

We report a case involving the subacute onset over 2 months of ON in a patient on long-term disulfiram therapy, with significant visual recovery after drug withdrawal, as described in literature. This case serves to emphasize the need to take a thorough inventory of all patient medications in cases of unexplained ON. Furthermore, it is probably prudent that patients on disulfiram therapy undergo annual ophthalmic assessments, and these assessments should include visual field and color vision testing.

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CONTACTO
José Alberto Lemos
Rua Nossa Senhora de Fátima, nº546
4775-266 Viatodos, Barcelos
Email: japm.lemos@gmail.com