## A Case of Wernicke Encephalopathy Combined With Disulfiram Intoxication

Elena Tartara, MD, Simona Fanucchi, MD, Ignazio D'Errico, MD, Lisa M. Farina, MD, Francesca Casoni, MD, Elena Sinforiani, MD, Giuseppe Micieli, MD, and Alfredo Costa, MD

Abstract: There have been several reports of disulfiram intoxication, but little evidence of neurologic conditions resulting from disulfiram-induced brain damage combined with Wernicke encephalopathy-associated lesions. We report a rare patient with both Wernicke encephalopathy and disulfiram intoxication. This 50-year-old woman, who was taking disulfiram for chronic alcohol abuse, presented with an acute confusional state, dysarthria, nystagmus, supranuclear ophthalmoplegia, and paraparesis. Biochemical serum and cerebrospinal fluid analyses were normal. An electromyogram detected a motor polyneuropathy. Cognitive assessment revealed severe impairment of memory, attention, and logical and executive abilities. Magnetic resonance imaging with gadolinium enhancement showed brain lesions consistent with Wernicke encephalopathy, but also symmetric hyperintensities on T2-weighted images in the globus pallidus. Stopping the disulfiram and treating with hydration, high-dose thiamine supplements, and benzodiazepines significantly improved the patient's consciousness and oculomotor function. A magnetic resonance imaging scan after 1 month of treatment showed complete disappearance of the brain lesions and the hyperintensities in the globus pallidus. After a further month of intensive neurorehabilitation, the patient was able to interact with the medical staff, and her neuropsychological tests showed only mild memory impairment. Patients with alcoholism who present at emergency departments are at high risk for misdiagnosis, especially because there is no specific routine laboratory test for detecting asymptomatic disulfiram intoxication. Although uncommon, the combination of Wernicke encephalopathy and disulfiram intoxication should be suspected in patients with alcoholism. The disorder can be detected through a careful history and prompt clinical evaluation, together with characteristic magnetic resonance imaging findings.

**Key Words:** Wernicke encephalopathy, alcohol, disulfiram intoxication, neurodegeneration, magnetic resonance imaging

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Carattere Scientifico C. Mondino, University of Pavia, Pavia, Italy. The authors declare no conflicts of interest.

Reprints: Alfredo Costa, MD, National Institute of Neurology, Istituto Di Ricovero e Cura a Carattere Scientifico C. Mondino, University

of Pavia, Pavia 27100, Italy (e-mail: alfredo.costa@mondino.it). Copyright © 2013 by Lippincott Williams & Wilkins **Reader Benefit:** Readers of this article should increase their suspicion that a patient with alcoholism and Wernicke encephalopathy may also have disulfiram intoxication, and they will be better prepared to diagnose and manage such a patient.

 $\mathbf{MRI}$  = magnetic resonance imaging.  $\mathbf{WE}$  = Wernicke encephalopathy.

Wernicke encephalopathy (WE), an acute neurologic disorder caused by thiamine (vitamin B1) deficiency, is one of the conditions resulting from alcohol-related brain damage (Zahr et al, 2011). Carl Wernicke defined the condition as "superior acute hemorrhagic polyencephalitis." In 1881, he described the first cases in 2 men with chronic alcoholism and a woman suffering from pyloric stenosis (Wernicke, 1881).

The classic triad of WE signs and symptoms, based on Wernicke's original description, is the abrupt onset of (1) a confusional state with impaired consciousness, (2) ataxia, and (3) the eye movement disorders nystagmus and ophthalmoplegia. Despite being labeled "classic," this triad is actually found in only 16% to 38% of all patients with WE. This explains why the condition is often misdiagnosed, for instance, as delirium or a stroke-like episode. Autopsy studies have consistently shown that WE can be diagnosed definitively only after death (Harper et al, 1986; Victor, 1976). Autopsy is crucial for patients with atypical clinical manifestations (Zuccoli et al, 2007). With the introduction of modern, noninvasive neuroimaging techniques, particularly magnetic resonance imaging (MRI), it is possible to detect the brain alterations of the acute and chronic phases of WE. The MRI findings often confirm the neuropathologic autopsy findings (Baker et al, 1999; Sullivan and Pfefferbaum, 2009).

Disulfiram (tetraethylthiuram disulfide) is a thiuram derivative long used in manufacturing rubber. In 1937, disulfiram was discovered to be a potential treatment for alcoholism, and the drug has been approved by the US Food and Drug Administration for the treatment for alcoholism since 1951. The primary pharmacologic action is the irreversible inhibition of acetaldehyde dehydrogenase, which, in the process of metabolizing alcohol, is responsible for converting acetaldehyde to acetic acid. After people drink alcohol, disulfiram raises their plasma levels of acetaldehyde.

Disulfiram is highly lipid-soluble. An oral dose has 80% bioavailability. About 5% to 20% is not

metabolized and is excreted unchanged in the feces. Any remainder is converted into toxic or nontoxic metabolites, such as carbon disulfide. Nontoxic carbon disulfide metabolites (eg, 2-thiothiazolidine-4-carboxylic acid [ITCA]) can be measured in the urine. Disulfiram and its metabolites are eliminated from the body very slowly over 1 to 2 weeks. Their accumulation produces unpleasant reactions to alcohol that deter the patient from drinking.

When people who are taking a therapeutic dose of disulfiram drink even a small amount of alcohol, they immediately develop facial flushing, sweating, and mild headache. If they drink heavily, they can develop nausea, tachycardia, palpitations, hyperventilation, hypotension, and dyspnea. Rare patients suffer respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, seizures, and even death.

Current treatment recommendations for disulfiram start with a dose of 800 to 1600 mg/day for the first 3 to 4 days, and then a daily maintenance dose of 250 mg for an average-sized person, with a range of 125 to 500 mg (Banys, 1988). After some weeks on the maintenance dose, most patients can be switched to a long-term dose of 600 to 800 mg twice a week, for a minimum of 1 year (Borup et al, 1992).

## CASE REPORT

A 50-year-old woman with arterial hypertension, high cholesterol levels, and a history of chronic alcohol abuse and depression was admitted to the Emergency Neurology Department of the San Matteo General Hospital (Policlinico San Matteo) in Pavia, Italy. On admission, she had an acute confusional state, dysarthria, nystagmus, supranuclear ophthalmoplegia, and paraparesis.

The patient had abused alcohol for about 20 years. During those years she had made several attempts to quit drinking, most recently about 2 years and 7 months before this admission. After about 2 years of abstinence, she had started drinking again, consuming about 2 liters of wine a day. Six months later, in a new attempt to help her stop, her neurologist prescribed disulfiram 400 mg/day. As soon as she started treatment, she was able to stop drinking. However, she erroneously doubled the disulfiram dose to 800 mg/day. After about 1 week she started experiencing psychomotor retardation, impaired consciousness, severe asthenia, short lapses of consciousness, and progressive gait difficulties. Then, over the next 2 days, she stopped eating, developed urinary incontinence, and began to confabulate. She was referred to our Emergency Department and, after a neurologic examination, was admitted. We immediately stopped her disulfiram.

On admission, the patient showed an acute confusional state, severe psychomotor retardation with difficult speech, mild dysarthria, nystagmus, conjugate gaze palsy, paraparesis with hypotonia, loss of deep tendon reflexes in both of her arms and legs, deep sensory loss, and urinary incontinence. No weight loss or episodes of vomiting were reported. Biochemical analyses performed on the day of admission did not show significant abnormalities. Notably, her ammonium levels and hepatic and renal function were normal, as were her nutritional status and body mass index. Her serum vitamin B1 level was slightly depressed. An electrocardiogram was normal. Cerebrospinal fluid analysis showed an intact blood-brain barrier and few cells.

Also on admission, an MRI brain scan with gadolinium enhancement revealed symmetric lesions in the dorsomedial thalami, cerebral peduncles, periacqueductal gray matter, quadrigeminal plate, superior and inferior cerebellar peduncles, and floor of the fourth ventricle (Fig. 1). T2-weighted images of the putamen also detected atrophy of the mammillary bodies as well as symmetric hyperintensities in the globus pallidus. All of these findings were strongly consistent with our clinical suspicion that the patient had WE and possible disulfiram intoxication.

We immediately started the patient on hydration, intramuscular thiamine supplements of 2000 mg/day, and benzodiazepines. She responded promptly with significant improvement in her consciousness and oculomotor function.

Two days later, an electroencephalogram revealed diffuse, symmetric slowed activity at 6 Hz, with poor reactivity to eye opening. An electromyogram showed axonal motor polyneuropathy. Neuropsychological tests performed on admission were reported as showing severe memory impairment with disorientation and fluctuating attention, consistent with delirium, as well as impaired logical and executive abilities. The same tests, repeated 1 week later, showed slow improvement of the patient's global attention and memory. An MRI scan of the spinal cord showed nothing more than degenerative arthrosis of the cervical and lumbar spine.

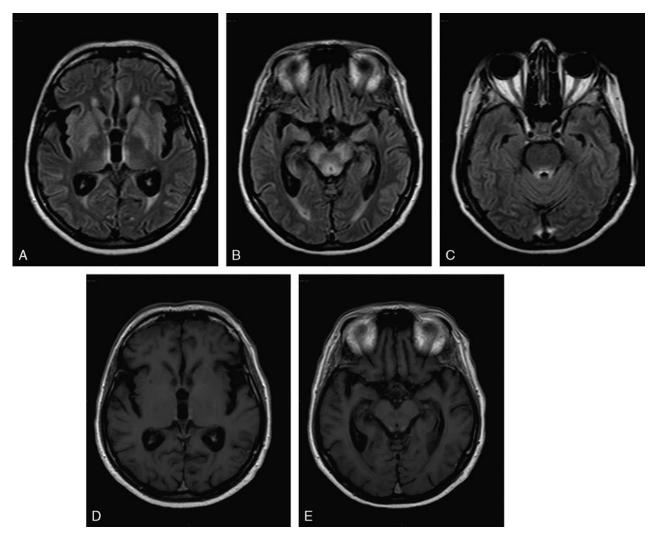
After a month of therapy, a second MRI scan of the brain revealed complete disappearance of the patient's lesions, including those in the basal ganglia (Fig. 2). The resolution of the lesions was accompanied by partial cognitive and motor clinical recovery.

The patient then underwent 1 month of intensive neurorehabilitation, after which she was discharged to a rehabilitation hospital. On discharge, she was able to interact properly with the medical staff, with normal vigilance and language. Neuropsychological tests performed on discharge showed only minor memory impairment. Her logical and executive function had improved markedly.

After a total of 3 months of neurorehabilitation, the patient could walk only with a walker, but she was able to return home. Neurologic reassessment 3 months later showed her to be almost completely independent, and to need assistance only in climbing stairs.

## DISCUSSION

A number of studies have focused on the clinical and neuroradiologic features of WE. However, to our



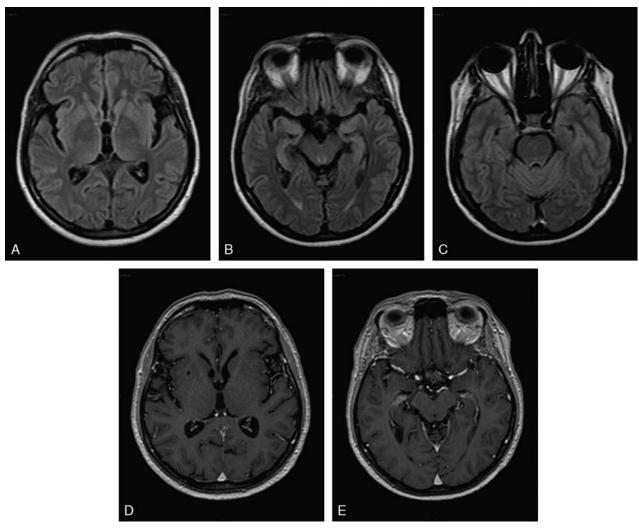
**FIGURE 1.** Magnetic resonance imaging scan performed at admission. A–C, Axial T2 FLAIR images show symmetric hyperintensities in the basal ganglia (globus pallidus), medial thalamus, and midbrain (cerebral peduncles, periacqueductal area, and tectal plate). D and E, Axial T1-weighted postcontrast images show enhancement in the medial thalami (adjacent to the third ventricle) and midbrain (tectal plate).

knowledge, the association of WE with acute disulfiram intoxication has to date been described in only 1 published case, by Charles et al (2006). Both Charles's patient and ours had delirium with ataxia and supranuclear ophthalmoplegia; unlike ours, Charles's patient had akinetorigid parkinsonism.

In view of the low diagnostic value of the classic clinical triad for WE and its poor prognosis—depending critically on the speedy start of thiamine supplements— neuroimaging has a crucial role to play in assessment. Our patient's clinical features correlated closely with the evolution of her MRI findings. Indeed, her dorsomedial thalamic and brainstem lesions were consistent with WE and mirrored the consequences of her thiamine deficiency. That deficiency leads to loss of osmotic gradients across cell membranes and to cytotoxic edema, first in astrocytes and then in neurons of selective, more vulnerable, brain regions (Hazell et al, 1998). Our patient

showed mental status changes consistent with an involvement of thalamic or mammillary bodies; nystagmus and conjugate gaze palsy, caused by lesions in the pontine tegmentum and in the abducens and oculomotor nuclei; and trunk ataxia and dysarthria, which can reflect cerebellar vermis involvement and vestibular dysfunction.

The mechanism underlying neuronal cell death and the tendency of certain brain structures to be affected in WE may be an increased permeability of the blood-brain barrier in the periacqueductal region, facilitating the passage of some systemic toxins. MRI studies have indeed shown an increased T2 and FLAIR signal, bilateral and symmetric, in the paraventricular regions of the thalamus, hypothalamus, mammillary bodies, periacqueductal region, floor of the fourth ventricle, and cerebellar vermis (Zuccoli et al, 2007). T1 images taken after gadolinium administration have shown enhancement in the same regions, caused by disruption of the blood-brain barrier (Lenz et al, 2002).



**FIGURE 2.** Magnetic resonance imaging scan performed after 1 month of treatment. A–C, Axial T2 FLAIR images show complete resolution of signal alterations in the medial thalamus, globus pallidus, and midbrain. D and E, Axial T1-weighted postcontrast images no longer show contrast enhancement in the medial thalami and midbrain.

Reversible symmetric involvement of the basal ganglia is found in some systemic, metabolic, vascular, and toxic diseases (Lim, 2009). On the basis of our patient's history and evaluations, we could exclude metabolic disorders (such as hypoglycemia, osmotic myelinolysis, and hemolytic uremic syndrome), vascular diseases (such as deep cerebral vein thrombosis), hypertensive crisis, cerebral thromboembolism, and viral encephalitis. Involvement of the basal ganglia has also been described in children with WE (Zuccoli et al, 2010) and in 2 adults with nonalcoholic WE (Zuccoli et al, 2011). The hypothesis of disulfiram-induced toxic damage to the basal ganglia has been shown to be highly compatible with MRI findings (Dietemann et al, 2004; Laplane et al, 1992; Mesiwala and Loeser, 2001; Thannberger et al, 2000). In 1 study (Mesiwala and Loeser, 2001), lesions affecting the basal ganglia may have represented old damage, and the reported imaging pattern was more likely related to an association of disulfiram with WE.

With respect to disulfiram toxicity, it has been reported that patients can develop acute intoxication at doses higher than 500 mg/day, and the drug can be lethal at doses of 10 to 30 g/day (Petersen, 1992). When our patient became intoxicated, she had been taking a high dose of 800 mg/day for 10 days.

The peripheral neurologic complications of disulfiram tend to arise from chronic use. One reported patient apparently developed a neuropathy after taking the drug at a stable therapeutic dose for as long as 30 years (Borrett et al, 1985). At the other extreme, acute nerve damage, in the form of vocal fold (or cord) palsy, has been described in a 49-year-old woman who took a single high dose in a suicide attempt (Bae, 2009).

The neurologic complications of disulfiram treatment are most often dose-related. The most common are peripheral neuropathy and encephalopathy. The peripheral neuropathy is an axonopathy resulting from neurofilamentous axonal swelling. It typically involves distal areas (legs more than arms), and is characterized by pain, paresthesia, pansensory loss, and, in rare patients, motor deficits and quadriplegia. Symptoms usually begin after > 2 weeks of treatment at a dose of at least 500 mg/day, which can be regarded as chronic high-dose exposure. The clinical pattern can be difficult to distinguish from that of alcoholic neuropathy, except for the fact that disulfiram neuropathy tends to improve when the disulfiram dose is reduced, while alcoholic neuropathy is essentially a chronic degenerative process (Bevilacqua et al, 2002; Dupuy et al, 1995).

Our patient showed paraparesis together with a neuropathy that could have been related to chronic alcohol exposure, disulfiram intoxication, or both. She had persisting paraparesis after 3 months of rehabilitation, despite the resolution of her brain lesions on MRI. Her peripheral nerve damage may have been induced by a combination of the alcohol and disulfiram (Bevilacqua et al, 2002; Dupuy et al, 1995).

Disulfiram toxicity can also present as encephalopathy. In many patients it is associated with severe optic neuritis and sensory and/or motor polyneuritis; a few patients develop quadriplegia. Most patients begin having symptoms within 2 months after they start taking disulfiram; the onset ranges from 15 days to 6 months into treatment. The main central nervous system manifestations are psychotic reactions, acute organic brain syndrome, and catatonia. The catatonia is caused by the effect of disulfiram and its metabolite carbon disulfide on dopaminergic pathways. One patient has been reported with an unusual presentation of posterior reversible encephalopathy syndrome (Coppens et al, 2011). Most patients with disulfiram-induced encephalopathy make a full recovery (Hotson and Langstone, 1976). The optic neuritis can regress spontaneously within 2 months after the patient stops the disulfiram.

In many patients with disulfiram intoxication, the cognitive and motor sequelae are associated with bilateral symmetric lesions of the basal ganglia, shown on brain computed tomography and MRI scans. One patient was reported to have parkinsonism, with akinesia and rigidity; a pseudobulbar-like syndrome; and a frontal lobe syndrome, with lesions in the basal ganglia revealed by computed tomography (Albin, 2000). The main hypothesis centered on carbon disulfide neurotoxicity, which has been shown to produce severe microangiopathic lesions of the globus pallidus and substantia nigra in animals (Chuang et al, 2007).

The reason for this selective vulnerability of the putamen and the pallidum is not understood. Further, many other toxins are known to damage the basal ganglia, including manganese, cyanide, hydrogen sulfide, carbon monoxide, and methanol; all can cause bilateral necrosis and hemorrhage (Hsieh et al, 1992). Another possible explanation is impairment to brain dopaminergic transmission and to removal of free radicals. The basal ganglia involvement described in the literature is characterized by bilateral symmetric lesions of the pallidum and putamen (only in 1 case were unilateral lesions reported). These lesions may develop after either acute or chronic disulfiram ingestion (De Mari et al, 1993). Some patients have been reported to experience transient movement disorders such as choreoathetoid hyperkinesias, transient akinesias, myorhythmias, and myokymias, although persistent movement disorders are extremely rare (Inoue, 1993). Krauss et al (1991) described a patient who developed a form of parkinsonism with early akinesia and late dystonia, an expression of persistent pallidal and putaminal lesions.

In our patient, the lesions in the globus pallidus were not associated with signs or symptoms of extrapyramidal impairment; moreover, the lesions disappeared within 1 month after the start of treatment. Like the earlier patient reported by Charles et al (2006) to have WE associated with disulfiram intoxication, our patient showed a clear frontal impairment, and she had a similar imaging pattern. Unlike Charles's patient, she did not have signs of akinetorigid parkinsonism. It is unclear whether this discrepant picture may be explained by a different disulfiram dose or a different duration of exposure to the drug. We must note here that our patient had been taking disulfiram for only 10 days. She may have had a peculiar sensitivity to the drug, leading to her brain lesions. Thus, high-dose disulfiram itself cannot be ruled out as having precipitated WE in a predisposed patient.

In conclusion, we have described a rare case of concomitant WE and disulfiram intoxication. Patients with alcoholism who present at emergency departments are at high risk for misdiagnosis. There is currently no specific routine laboratory test for detecting asymptomatic disulfiram intoxication. Measurement of blood thiamine concentrations shows poor specificity. Carbon disulfide metabolites (eg, ITCA) in the urine can be measured only by toxicology laboratories; their use should be restricted to patients in whom intoxication is very likely. However, the unusual association between WE and disulfiram intoxication *can* be diagnosed early on the basis of a careful medical history and prompt clinical evaluation, combined with characteristic brain MRI findings. MRI is considered the most useful diagnostic technique. Our patient's disulfiram intoxication would have been misdiagnosed if MRI had not revealed her atypical lesions.

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