Reversible, Late-Onset Disulfiram-Induced Neuropathy and Encephalopathy

D. Borrett, MD,* P. Ashby, MD,*† J. Bilbao, MD,‡ and P. Carlen, MD*†§

Disulfiram toxicity is a well-recognized cause of peripheral neuropathy and encephalopathy, usually developing within a few months of the start of therapy. We describe a patient who insidiously developed a peripheral neuropathy and encephalopathy after thirty years of disulfiram ingestion. Both complications partially resolved after the medication was stopped.

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Toxic peripheral neuropathies and encephalopathies represent remediable neurological conditions and require consideration in any patient with neurological complaints receiving medication. Drug-induced complications often are dose related and may be reversible if the offending agent is removed early. This report describes a partially reversible neuropathy and encephalopathy developing after thirty years of disulfiram use.

Case Report

A 67-year-old man complained of recent memory impairment and difficulty in walking in May 1978, four years prior to admission. He had had an alcohol abuse problem thirty years prior to admission and at that time had been started on a regimen of disulfiram, 250 mg daily. He had then lost contact with his physicians but had continued to take disulfiram for the subsequent thirty years. He had stopped the medication and used alcohol for 1 to 2 days on two occasions during this period, the second being three years prior to admission. He had no other medical problems and had taken no other medications. In 1967 he had obtained a supervised IQ test score of 143, administered by Mensa.

Neuropsychological testing in May 1978 revealed a mild memory disturbance and impairment of higher cognitive function consistent with an early dementia (Table). Neurological examination revealed absent ankle jerks and mild impairment of pinprick, temperature, and vibration sensation distally in the legs. He was unsteady when attempting to walk heel to toe. A computed tomographic scan showed mild, generalized cerebral atrophy, and an electroencephalogram (EEG) was reported as normal. He continued to take disulfiram and to work actively at his job.

His condition progressively deteriorated and by January 1982 he was disoriented to time, with impairment of attention, recent memory, constructional ability, and abstraction. A severe sensorimotor neuropathy was evident, with distal wasting, weakness, and sensory impairment, most marked in the legs. He had an ataxic steppage gait. Quantitative sensory assessment showed that vibration threshold at 128 cps in the fingers was 16 μ (normal, 0.5 μ).

Psychometric testing documented the progressive cognitive deterioration (see the Table). The EEG showed excess theta activity and occasional bitemporal delta components. The computed tomographic findings were unchanged. Motor nerve conduction could not be measured in the peroneal or posterior tibial nerves, because no responses could be recorded from the extensor digitorum brevis or abductor hallucis muscles. Conduction velocity was slowed in the motor fibers of the median (39 m/s) and ulnar (36 m/s) nerves (normal, greater than 50 m/s). Distal latencies were within normal limits, but the amplitudes of the negative peaks of the compound muscle action potentials were at the lower limit of normal at 5 mV (normal lower limit, more than 4 mV; mean, 11 mV). No sensory action potentials could be recorded from the sural nerves. Low-amplitude sensory action potentials were recorded from the median nerves. Fibrillation potentials were present in extensor digitorum brevis and first dorsal interosseous muscles (trace). Long-duration polyphasic potentials were present in the tibialis anterior and first dorsal interosseous muscles. There were no motor units under voluntary control in the extensor digitorum brevis. A sural nerve biopsy was taken in January 1982.

Disulfiram administration was discontinued. At the first reassessment in April 1982, the patient was more appropriate in his behavior, with improved verbal and memory function (see the Table). The EEG was now normal. The peripheral neuropathy was clinically and electrophysiologically unchanged. By August 1982, there was improvement in concentration and behavioral control, but learning capacity remained impaired. The computed tomographic scan remained unchanged. Weakness in the arms was now restricted to the interosseous muscles. Vibration threshold in the fingers had fallen to 2.5 μ. There was improvement in the motor conduction velocities in the median (45 m/s) and ulnar (41 m/s) nerves. The sensory action potentials recorded from the median and ulnar nerves were larger, and their distal latencies had decreased. The electrophysiological findings in the legs were unchanged, although the patient claimed he could walk farther and he showed less ataxia.

Sural Nerve Biopsy Findings

Light microscopic examination of thick sections revealed a preferential reduction in the number of large myelinated fibers and frequent axonal clusters (Fig 1). Electron microscopy showed occasional axonal de-

From the Departments of *Medicine (Neurology) and §Pathology, University of Toronto, the †Playfair Neuroscience Unit, Toronto Western Hospital, ‡St. Michael's Hospital, and the §Addiction Research Foundation Clinical Institute, Toronto, Ontario, Canada.

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Address reprint requests to Dr Ashby, 25 Leonard Ave, Toronto, Ontario, Canada M5T 2R2.

Psychological and Electrophysiological Findings

Date	Memory Quotient	Intelligence Quotient			Median Sensory Palm to Wrist		Median Motor		
		Verbal	Performance	Total	Latency (ms) (N < 1.5)	Amplitude (mV) (N > 14 μV)	Conduction Velocity (m/s) (N > 50)	Distal Latency (ms) (N < 4.1)	Amplitude (mV) (N > 4)
May 1978	100	130	114	124	...	...	...	...	...
Apr 1981	100	123	89	109	...	...	...	...	...
Jan 1982	93	113	80	94	1.5	8	39	4.1	5
DISULFIRAM DISCONTINUED									
Apr 1982	120	119	82	...	1.3	14	45	4.3	4
Aug 1982	119	...	92	...	1.3	25	45	3.9	5
Feb 1983	140	126	99	...	...	...	...	...	...
Mar 1983	...	...	...	...	1.3	30	45	3.4	6
Oct 1983	124	124	103	...	1.4	10	48	3.4	8

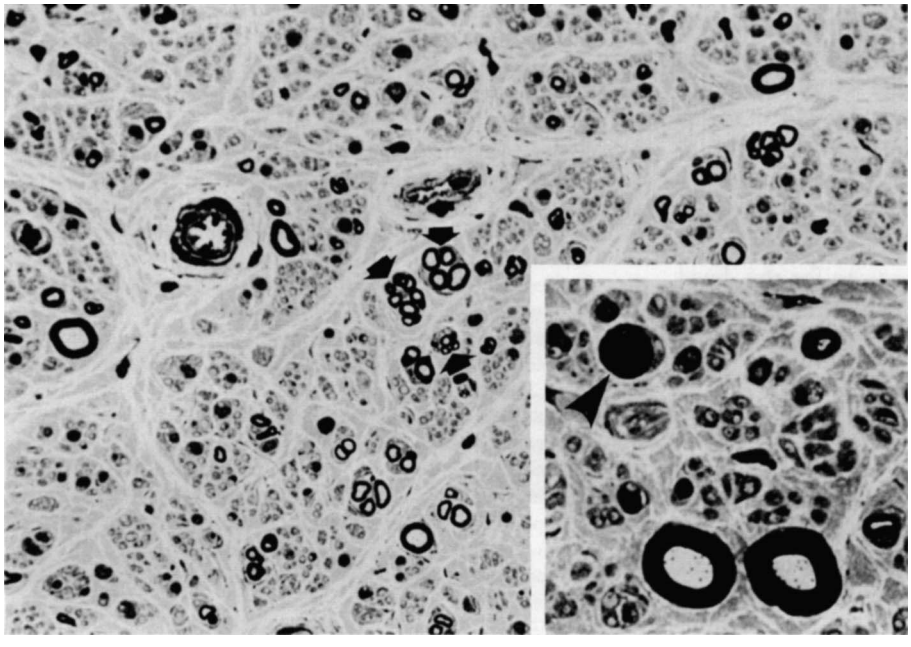
N = normal.

generative changes, varying from acute disintegration of the axoplasm to the formation of denervated bands of Schwann cells. Some medium-sized myelinated fibers exhibited swollen axons (Fig 1, inset) containing membranolamellar bodies, mitochondria, and bundles of neurofilaments (Fig 2). Quantitative changes included a total myelinated fiber density of 2,495 per square millimeter (normal, 7,710 ± 1,210) and a shift of their caliber spectrum toward thinner diameters.

Fig 1. Transverse thin section of sural nerve, showing a paucity of large myelinated fibers. Many axons are present as components of "regenerating units" (arrows). *(×80 before 25% reduction.) (Inset) Note swollen axon in medium-sized myelinated fiber* (arrowhead). *(Toluidine blue; ×128 before 25% reduction.)*

Discussion

Peripheral neuropathy secondary to disulfiram treatment is well known [1–3, 6, 7, 14–16, 19, 21]. A sensorimotor neuropathy may develop ten days to eighteen months after initiation of therapy and can occur with doses of 250 mg a day [1, 7]. Electrophysiological studies demonstrate denervation in distal muscles with normal or slightly reduced conduction velocities, indicative of an axonal form of neuropathy. Pathologically, loss of large myelinated nerve fibers is



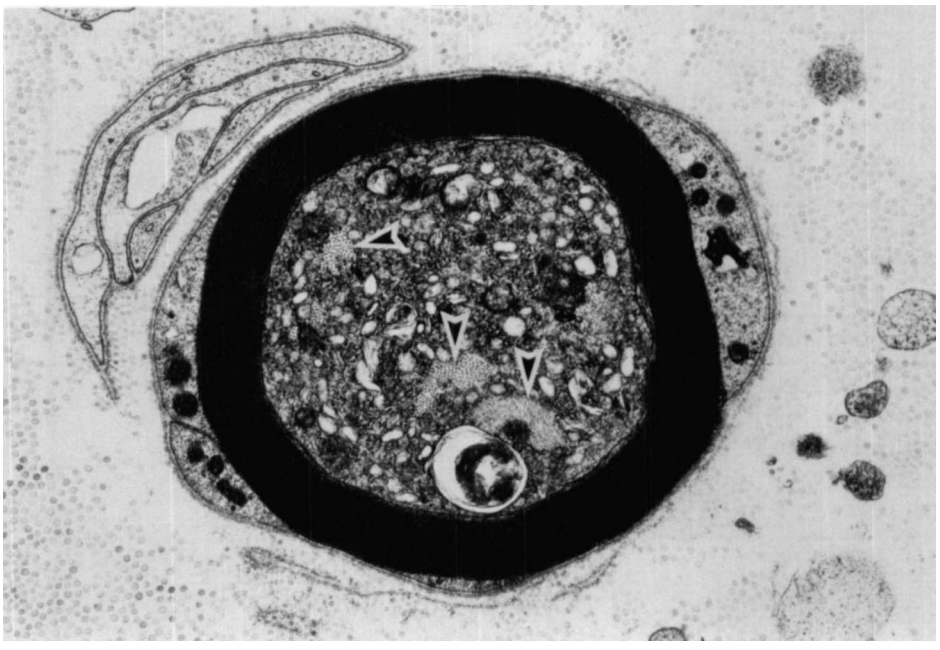


Fig 2. Electron photomicrograph showing an axon that contains mitochondria, membranolamellar structures, and bundles of neurofilaments (arrowheads). *(×22,300 before 25% reduction.)*

conspicuous. Fibers appear to undergo axonal degeneration characterized in early stages by dissolution of organelles and precipitation of electron-dense amorphous material in the axoplasm [14, 15, 20].

A number of central effects of disulfiram have been described, including optic neuritis, an extrapyramidal syndrome, and encephalopathy [9–11, 13, 17, 18]. The encephalopathy usually arises days to months after the medication regimen is instituted. EEG findings during disulfiram therapy consist of mild, diffuse slowing or accentuation of preexisting abnormalities [4].

The mechanism by which disulfiram causes peripheral neuropathy or encephalopathy is not known. Disulfiram is catabolized to diethyldithiocarbamate, which is further metabolized to diethylamine and carbon disulfide [5]. Disulfiram and its metabolite diethyldithiocarbamate inhibit both aldehyde dehydrogenase and dopamine beta hydroxylase [8, 12]. Inhibition of these enzyme systems has been implicated as a cause of the neuropathy, whereas elevation in brain dopamine levels secondary to inhibition of dopamine beta hydroxylase may be a prerequisite for the development of encephalopathy [17, 19]. Alternately, carbon disulfide has been implicated in the development of the neurological side effects. In the experimental animal treated with carbon disulfide, the neuropathy is characterized by accumulation of 10 nm neurofilaments in axonal swellings [19]. This pathological abnormality has recently been described in a human disulfiram-induced neuropathy [1].

All previously reported cases of disulfiram-induced neuropathy or encephalopathy have occurred within months after initiation of therapy. This case indicates that these complications may develop insidiously over a long period and that recovery may occur with cessation of drug intake.

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Infantile Cerebellar Atrophy

J. M. Furman, MD, PhD,* R. W. Baloh, MD,*
H. Chugani, MD,* V. Waluch, MD, PhD,†
and W. G. Bradley, MD, PhD‡

We describe a family whose members have a dominantly inherited, early-onset, nonprogressive syndrome that includes spontaneous upbeating nystagmus and mild gait ataxia. Magnetic resonance imaging showed localized atrophy of the cerebellar vermis. Several families described in the literature resemble our family but differ in mode of inheritance, age at onset, rate of progression, or clinical findings. We believe this family represents a unique type of inherited early-onset atrophy of the cerebellar vermis.

Furman JM, Baloh RW, Chugani H, Waluch V, Bradley WG: Infantile cerebellar atrophy. Ann Neurol 17:399–402, 1985

Familial ataxia syndromes presenting in childhood are uncommon. Friedreich's ataxia and ataxia–telangiectasia are both progressive disorders associated with multiple neurological abnormalities. Less common syndromes include a sex-linked progressive cerebellar ataxia associated with myoclonic epilepsy [1], Refsum's disease, and cerebellar ataxia associated with severe mental deficiency [2, 5, 9, 10]. We report on a family whose members have a dominantly inherited, nonprogressive cerebellar ataxia syndrome with onset in infancy.

From the *Department of Neurology, UCLA School of Medicine, Los Angeles, CA 90024, and †Huntington Medical Research Institute and ‡Huntington Memorial Hospital, Pasadena, CA 91105.

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Address reprint requests to Dr Baloh.

Case Reports

Proband

A 32-year-old, right-handed woman was first evaluated at age 24 for "dizziness." She complained of visual blurring and oscillopsia, along with nausea and occasional vomiting upon physical exertion. She was clumsy as a child, a trait that became more noticeable in adolescence in association with increased physical activity during her high school years. She was an average student. Her symptoms remained stable since their onset, without exacerbations or remissions. On neurological examination she was noted to have a normal mental status; cranial nerve examination showed no abnormalities except primary-position upbeating nystagmus, which increased in amplitude with upward gaze and decreased with downward gaze. There was horizontal gaze-evoked nystagmus bilaterally. Saccade peak velocity measured with electro-oculography was normal. Motor system examination revealed normal strength, symmetrical deep tendon reflexes, and flexor plantar responses. Coordination testing revealed mild dysdiadochokinesia and mild dysmetria on finger-to-nose and heel-to-shin testing. Sensory examination findings were normal. The patient's gait was mildly wide based and ataxic, and she was unable to perform tandem gait. The patient was followed for 8 years by one of the authors (R. W. B.), during which time there was no marked change in her neurological signs. Magnetic resonance imaging (MRI) (Figs 1A and 2) revealed focal atrophy of the cerebellar vermis, especially of the anterior vermis.

Children

In addition to the mother, two children were clinically affected (Fig 3). Patient 2, an 8-year-old daughter, was first evaluated at age 4 years for ataxia and developmental delay. She had crawled at age 7 months, first talked at age 1½ years, had a diminished intelligence quotient of 81, and was not yet toilet trained at age 8 years. Her mother related that her balance and coordination had been poor since birth and that the clinical course had been stable, without exacerbations or remissions. Patient 3, a 4-year-old daughter, had crawled at age 7 months, talked at 1 year, was toilet trained at 1 year, had normal intelligence, and since birth had had mild unsteadiness and incoordination, which had not changed in severity. Patient 4, a 9-year-old son, was asymptomatic, having crawled at 6 months, talked at 1 year, and been toilet trained at 1 year, although he related that he was always the last child selected for competitive sports.

On neurological examination Patients 2 and 3 demonstrated primary-position upbeating nystagmus, which increased on upward gaze and decreased on downward gaze. Both had horizontal gaze-evoked nystagmus bilaterally. Patient 4 had upbeating nystagmus on upward gaze only. All