Industrial Health 2003, **41**, 43–47

Case Report

Cerebellar Atrophy as a Delayed Manifestation of Chronic Carbon Disulfide Poisoning

Rodolfo FONTE[1], Alessia EDALLO[1] and Stefano M. CANDURA[1, 2]*

[1] Division of Occupational Medicine, "Salvatore Maugeri" Foundation, Work and Rehabilitation, IRCCS, Scientific Institute of Pavia, Via Ferrata 8, I-27100 Pavia, Italy

[2] Department of Preventive, Occupational and Community Medicine, University of Pavia, Italy

Received May 30, 2002 and accepted November 20, 2002

Abstract: A 70-year-old man developed a slowly progressive cerebellar syndrome after having been exposed to carbon disulfide (CS_2) in a viscose rayon plant for 27 years. Ataxia, dysmetria, dysarthria and adiadochokinesia appeared 7 years after retirement from work (at age 54), and were later accompanied by cognitive deterioration, dysmnesia, spatio-temporal disorientation, emotional lability, and paranoid-obsessive disturbances. Brain computed tomography (CT) and magnetic resonance imaging (MRI) showed advanced global cerebellar atrophy, and a picture of less severe cerebrocortical atrophy. The case illustrates the possibility of chronic toxic encephalopathy among patients with previous long-term exposure to CS_2. In such instances, cerebellar damage may develop as an exceptional, delayed manifestation of neurotoxicity: brain imaging techniques can significantly contribute to the diagnosis and follow-up, in addition to occupational anamnesis and neuropsychiatric evaluation. The patient presented also serves as a remainder that neurodegenerative disorders of apparently unknown origin sometimes derive from occupational toxic exposures suffered in the past. The clinical manifestations may appear several years after retirement from work, when the effects of toxic damage combine with age-related neuronal loss to overcome the brain functional reserve.

Key words: Carbon disulfide, Cerebellum, Neurotoxicity, Neuroimaging, Occupational disease, Viscose rayon

Carbon disulfide (CS_2) has been extensively employed as an industrial solvent and reagent since the early 19th century. Nowadays, the compound is utilised in the production of rayon and cellophane from wood pulp (viscose process) and, to a smaller extent, in the pesticide and chemical industries[1]. CS_2 is a systemic toxicant, and a wide range of adverse health effects (including neuropsychiatric, cardiovascular, ocular, gastrointestinal, endocrine, and reproductive disorders) has been observed in exposed workers[2–4].

The nervous system (both peripheral and central) represents the main target for CS_2 toxicity: clinical manifestations of occupational poisoning (resulting from chronic exposure) include polyneuropathy, cranial neuropathy, mental deterioration, pseudobulbar palsy, and movement disorders, both in the form of pyramidal (hemiplegia) and extrapyramidal (parkinsonism, choreoathetosis) syndromes[2–4]. Cerebellar involvement has been described in very few cases[5–8].

Thanks to the improvement of workplace hygienic conditions, overt CS_2 neurotoxicity is encountered exceptionally in the current clinical practice. As a consequence, CS_2-induced encephalopathy has been investigated only sporadically with modern neuroimaging diagnostic techniques, such as brain computed tomography (CT) and brain magnetic resonance imaging (MRI).

We report the clinical and neuroimaging findings of a case of occupational CS_2 poisoning evolving with severe cerebellar atrophy.

The patient is a 70-year-old man, who had been employed

*To whom correspondence should be addressed.

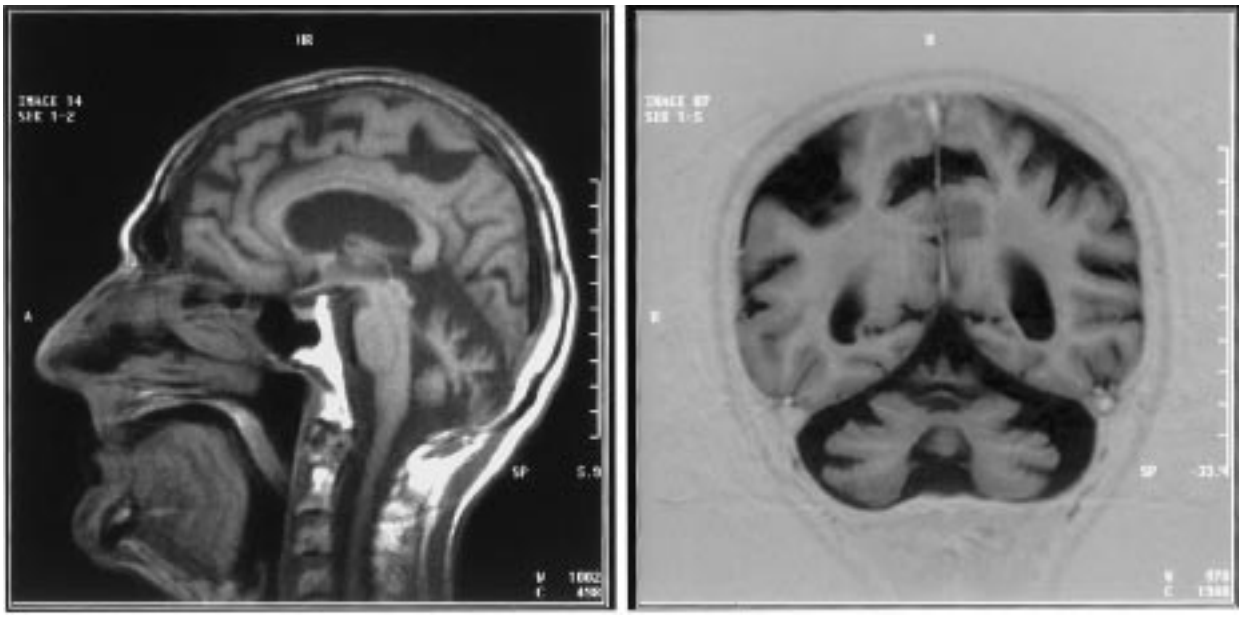

Fig. 1. Representative magnetic resonance scans showing diffuse atrophy of the cerebellum and, to a lesser extent, of the cerebral cortex.

in a viscose rayon plant from age 20 to age 47 (1951–1978). He had been occupied in the churn room (viscose preparation) for 5 years, and in the bleaching department for 13 years. During the last period of employment (9 years), he worked as a deliveryman. Most of the time, this job was also carried out in areas contaminated with CS_2. Personal exposure data are not available. During the '70s, measured CS_2 air levels from the factory ranged from 10 to 60 mg/m^3 (3–19 ppm)[9]. The patient occasionally abused of alcoholic beverages and was a lifelong smoker (10–20 cigarettes/day).

The subject was first hospitalized at age 44 with clinical and electromyographic findings indicative of mild peripheral polyneuropathy. He also presented cephalea, loss of libido, and gastroduodenitis. Chronic CS_2 poisoning was suspected, and the patient was referred to the Italian Institute for Insurance against Work Accidents (INAIL), which recognized the occupational origin of the disease. The peripheral neuropathy eventually recovered, however the patient returned to hospital at age 47 (the same year of retirement from work), due to the appearance of a mild and transitory right pyramidal syndrome, accompanied by vertigo, impotentia coeundi, and chronic dyspepsia.

A slowly progressive cerebellar syndrome (presenting with ataxia, dysmetria, dysarthria, and adiadochokinesia) developed starting from age 54. A brain CT (performed at age 55) revealed cerebellar atrophy with dilation of the fourth ventricle. The motor, balance and coordination disturbances worsened in the following years, and the patient developed a neurogenic bladder, complicated by an episode of acute urinary retention (age 63).

Currently (age 70), the patient is almost unable to walk and lives on a wheelchair continuosly assisted by his wife. Recent neuropsychiatric evaluation showed further worsening of the cerebellar syndrome, as well as cognitive deterioration (total MODA score: 53/100), severe dysmnesia, spatio-temporal disorientation, emotional lability, and paranoid-obsessive disturbances. Brain CT and MRI (Fig. 1) demonstrated advanced global cerebellar atrophy with marked dilation of the vermian and pericerebellar liquoral spaces, as well as a picture of less severe cerebrocortical atrophy. Echographic examination of the cardiovascular system was unremarkable, with the exception of a small (maximum diameter: 23 mm) aneurisma of the abdominal aorta.

In viscose rayon manufacturing, CS_2 reacts with alkali cellulose to form cellulose xanthate. Subsequent steps include filtration, spinning, washing, bleaching, drying, and packing. Workers may be exposed to CS_2 during all phases of the industrial process[1]. The subject described had been employed for several years in both viscose making and bleaching, that is in the departments which have been historically associated with the highest number of Italian occupational poisoning cases[2]. Most of his clinical features (i.e., cephalea, vertigo, peripheral neuropathy, hemiparesis, mental deterioration, digestive and genitourinary disturbances) are also consistent with previous reports[2–4]. Cerebellar damage, however, has

been observed very rarely. A decrease in cerebellar Purkinje cells had been documented in early pathological studies[10]. More recently, cerebellar signs (associated with atypical parkinsonism, hearing loss, and sensory changes) have been described in 21 grain storage workers exposed to CS_2 employed as a fumigant[5]. Ataxia was present in 8 of the 21 subjects. Aaserud *et al.*[6, 7] examined 16 workers who had been occupied in the spinning room of a viscose rayon factory for at least ten years. Coordination deficit (present in 8 individuals) was the most frequent finding at neurological examination, and two patients presented cerebellar atrophy on CT scans. Frumkin[8] documented a case of olivopontocerebellar atrophy in a viscose rayon worker following over 30 years of occupational CS_2 exposure.

The reasons for the development of cerebellar damage in a minority of patients only (and, more generally, for the clinical heterogeneity of chronic CS_2 encephalopathy) are elusive. A role might be played by the interaction among the genetic constitution of the individual, personal lifestyles, and environmental factors, such as the modality of CS_2 exposure and the contamination of the workplace with other chemicals (for example, viscose rayon workers may be co-exposed to H_2S[1]).

Cerebellar toxicity after CS_2 exposure is also unusual in animals. Ataxia and Purkinje cell degeneration have been reported in the dog and in the cat[10, 11]. Recently, dose-dependent gait abnormalities were observed in rodents as early manifestations of CS_2 toxicity, although they may have reflected peripheral nerve toxicity rather than central effects[12, 13].

The pathogenesis of CS_2-induced chronic encephalopathy is uncompletely elucidated and probably multifactorial. Some neurological deficits (e.g., hemiplegia) are compatible with brain ischemia. Vigliani[2] suggested that cerebral vasculopathy is the basic pathologic lesion in CS_2 poisoning, and indicated a direct effect of the compound on brain arterioles and precapillaries as the pathogenetic mechanism for central nervous system damage. Subsequent studies, however, demonstrated that CS_2 neurotoxicity is, at least in part, mediated by metabolic activation to hydrogen disulfide (H_2S) and dithiocarbamates, and that brain damage may partly depend on neurochemical mechanisms, such as interference with catecholamine and vitamin B_6 metabolism[14]. A direct neurotoxic effect of CS_2 (and/or its metabolites) is likely also in the case presented here. Indeed, the general cardiovascular conditions remained fairly good (in spite of lifelong smoking) even in the advanced stage of the disease, and neuroimaging excluded the presence of focal ischemic lesions.

Ethanol is notoriously neurotoxic, and both cerebral and cerebellar atrophy heve been documented in chronic alcoholics[15]. Experimental studies indicate that CS_2 and ethanol combined affect the nervous system to a greater extent than each of these compounds alone[16]. The subject described presents a history of occasional alcohol abuse. To which extent such drinking habit acted synergistically with the occupational exposure to CS_2, influencing the development of the encephalopathy and the predominance of cerebellar damage, is difficult to determine. A strong influence seems unlikely since, with the exception of the transitory polyneuropathy suffered at age 44, the patient did not develop other medical conditions possibly related to ethanol consumption (e.g., nutritional disorders, anemia, hepatopathy).

The clinical picture of chronic CS_2 poisoning may worsen after cessation of the exposure[2, 3]. Accordingly, both in the patient described by Frumkin[8] and in the present case, the cerebellar syndrome appeared after retirement from work and subsequently progressed. The subject followed by us also developed cerebrocortical atrophy and cognitive deterioration, configuring a picture of diffuse encephalic degeneration. This is noteworthy, since there is controversial evidence that occupational chemical exposure participate in the etiopathogenesis of some neurodegenerative disorders (e.g., Alzheimer's disease) which are usually labelled as "idiopathic"[17]. It has been postulated that some neurotoxic insults may not be reflected in any immediate clinical manifestation, and that this type of damage may deplete reserve capacity, making the brain more vulnerable to additional injury. Moreover, physiological loss of neurons with aging may be accelerated, resulting in functional changes several years after the toxic exposure has ceased[18]. It should also be noted that some individuals may be genetically predisposed to increased vulnerability to industrial chemicals[19].

In the patient described, both CT and MRI showed a picture of diffuse and progressive encephalic atrophy which was particularly pronounced in the cerebellum, according with the clinical picture. Focal or diffuse brain atrophy in CT scans following chronic CS_2 exposure was also documented in previous reports[6, 7, 20, 21]. A MRI study was performed by Peters *et al.*[5], who showed a pattern of central demyelinization in two out of four CS_2-poisoned patients. Huang *et al.*[21] described ten viscose rayon workers with polyneuropathy and neuropsychiatric disturbances: brain MRI abnormalities (mild cerebrocortical atrophy and/or multiple lesions of the basal ganglia and corona radiata) were present in seven of them. In the case reported by

Frumkin[8], MRI revealed advanced cerebellar atrophy and prominent atrophy in the posterior tracts and nuclei of the pons. Finally, Hageman *et al.*[22] reported the case of a painter who developed dementia and parkinsonism after over 40 years of exposure to CS_2 in a viscose rayon factory: brain MRI showed generalized cerebral atrophy and white matter hypodensity. On the basis of these observations, it appears that the neuroimaging findings of CS_2 encephalopathy are rather variable. Nevertheless, brain imaging can be useful (i) to exclude other brain diseases (e.g., neoplasms) that may show similar clinical features; (ii) to evaluate cerebellar damage, when present; and (iii) for follow-up observations.

In conclusion, although CS_2 poisoning is almost exclusively of historical importance, clinicians should be aware of the possibility of chronic toxic encephalopathy among patients with previous long-term exposure to this chemical. In such cases, cerebellar atrophy may develop as an unusual, delayed manifestation of neurotoxicity, in addition to the more common manifestations of the disease (e.g., mental deterioration): careful occupational anamnesis, serial neuropsychiatric evaluation, and brain imaging techniques (CT and MRI) can significantly contribute to the diagnosis and follow-up.

More generally, the case presented is a reminder that neurodegenerative disorders of apparently unknown origin might derive from occupational toxic exposures suffered in the past. The clinical manifestations may appear even decades after retirement from the job at risk, when the effects of toxic damage combine with age-related neuronal loss to overcome the brain functional reserve.

References

1) Candura F, Candura SM (1991) Principles of industrial technology for occupational medicine scholars' use. CELT, Piacenza (Italy) (in Italian).
2) Vigliani EC (1954) Carbon disulfide poisoning in viscose rayon factories. Br J Ind Med **11**, 235–44.
3) Seppäläinen AM, Haltia M (1980) Carbon disulfide. In: Experimental and clinical neurotoxicology. eds. by Spencer PS, Schaumburg HH, 356–73, Williams & Wilkins, Baltimore.
4) Beauchamp RO, Bus JS, Popp JA, Boreiko CJ, Goldberg L (1983) A critical review of the literature on carbon disulfide toxicity. CRC Crit Rev Toxicol **11**, 169–278.
5) Peters HA, Levine RL, Matthews CG, Chapman LJ (1988) Extrapyramidal and other neurologic manifestations associated with carbon disulfide fumigant exposure. Arch Neurol **45**, 537–9.
6) Aaserud O, Gjerstad L, Nakstad P, Nyberg-Hansen R, Hommeren OJ, Tvedt B, Russell D, Rootwell K (1988) Neurological examination, computerized tomography, cerebral blood flow and neuropsychological examination in workers with long-term exposure to carbon disulfide. Toxicology **49**, 277–82.
7) Aaserud O, Hommeren OJ, Tvedt B, Nakstad P, Mowé G, Efskind J, Russel D, Jörgensen EB, Nyberg-Hansen R, Rootwell K, Gjerstad L (1990) Carbon disulfide exposure and neurotoxic sequelae among viscose rayon workers. Am J Ind Med **18**, 25–37.
8) Frumkin H (1998) Multiple system atrophy following chronic carbon disulfide exposure. Environ Health Perspect **106**, 611–3.
9) Franco G, Malamani T (1976) Systolic time intervals as a measure of left ventricular function in viscose rayon workers exposed to carbon disulfide. Scand J Work Environ Health **2**, 107–14.
10) Alpers BJ, Lewey FH (1940) Changes in the nervous system following carbon disulfide poisoning in animals and in man. Arch Neurol Psychiatry **44**, 725–39.
11) Lewey FH, Alpers BJ, Bellet S, Creskoff AJ, Drabkin DL, Ehrich WE, Frank JH, Jonas L, McDonald R, Montgomery E, Reinhold JG (1941) Experimental chronic carbon disulfide poisoning in dogs. J Ind Hyg Toxicol **23**, 415–24.
12) Moser VC, Phillips PM, Morgan DL, Sills RC (1998) Carbon disulfide neurotoxicity in rats: VII. Behavioral evaluations using a functional observational battery. NeuroToxicology **19**, 147–57.
13) Sills RC, Valentine WM, Moser V, Graham DG, Morgan DL (2000) Characterization of carbon disulfide neurotoxicity in C57BL6 mice: behavioral, morphologic, and molecular effects. Toxicol Pathol **28**, 142–8.
14) Bus J (1985). The relationship of carbon disulfide metabolism to development of toxicity. NeuroToxicology **4**, 73–80.
15) Charness ME (1993) Brain lesions in alcoholics. Alcohol Clin Exp Res **17**, 2–11.
16) Opacka J, Opalska B, Kolakowski J, Wronska Nofer T (1986). Neurotoxic effects of the combined exposure to carbon disulphide and ethanol in rats. Toxicol Lett **32**, 9–18.
17) Candura SM, Manzo L, Costa LG (1998) Role of occupational neurotoxicants in psychiatric and neurodegenerative disorders. In: Occupational neurotoxicology. eds. by Costa LG, Manzo L, 131–67, CRC Press LLC, Boca Raton.

18) Reuhl KR (1991) Delayed expression of neurotoxicity: the problem of silent damage. NeuroToxicology **12**, 341–6.
19) Söderkvist P, Ahmadi A, Åkerbäck A, Axelson O, Flodin U (1996) Glutathione S-transferase M1 null genotype as a risk modifier for solvent-induced chronic toxic encephalopathy. Scand J Work Environ Health **22**, 360–3.
20) Sugimura K, Kabashima K, Tatetsu S, Inoue T, Oyama S, Harada M, Toya G, Hirata M (1979) Computerized tomography in chronic carbon disulfide poisoning. Brain Nerve (Tokyo) **31**, 1245–53.
21) Huang C-C, Chu C-C, Chen R-S, Lin S-K, Shih TS (1996) Chronic carbon disulfide encephalopathy. Eur Neurol **36**, 364–8.
22) Hageman G, van der Hoek J, van Hout M, van der Laan G, Jansen Steur E, de Bruin W, Herholz K (1999) Parkinsonism, pyramidal signs, polyneuropathy, and cognitive decline after long-term occupational solvent exposure. J Neurol **246**, 198–206.