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Progressive Parkinsonism in a Young Experimental Physicist Following Long-Term Exposure to Methanol

Yoram Finkelstein*, Jacob V...di

Department of Neurology, Shaare Zedek Medical Center and Faculty of Health Sciences, Ben-Gurion University, Jerusalem 91031, Israel

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Abstract

A case is described of an experimental physicist who developed parkinsonism, apparently as delayed toxic effect of long exposure to vapors of methanol in the laboratory. Clinical and magnetic resonance imaging (MRI) supported the diagnosis, after exclusion of hereditary diseases and primary degenerative diseases. Screening for heavy metals in urine and plasma ceruloplasmin was negative. This case illustrates the neurotoxic delayed effect of long-term exposure to methanol with no episodes of acute intoxication. The setting of a research laboratory with prolonged exposure to mixed single crystals and inhalation of methanol vapors may exist in other academic and hi-tech environments, and pose the risk of similar delayed toxic influences.

Keywords: Parkinsonism; Methanol; Methyl bromide; Long-term exposure; Delayed toxicity

INTRODUCTION

Parkinson's disease (PD) in its classical form is referred to as "idiopathic" whenever causative or hereditary etiologies remain unestablished. During the recent decade extensive studies have been undertaken to investigate environmental agents which might cause dysfunction of the basal ganglia, possibly via oxidative-mediated degeneration (Jenner et al., 1992). The incidence of PD increases with age. It affects about 1% of the population over 65-years-old and 0.4% of those over 40-years-old. The mean age of onset is about 57 years (The Merck Manual, 1999).

PD and parkinsonism in a young person require diagnostic considerations which emerge from the routine list of differential diagnosis of idiopathic PD. After exclusion of hereditary etiologies, the suggested diagnosis of young parkinsonian patients often remains within the scope of environmental or toxic etiologies.

Parkinsonism and defects of praxis have been described as delayed neurological sequelae of acute methanol poisoning (Mozaz et al., 1991). However, it is unclear whether such a clinical picture could be manifested after chronic exposure to methanol. The delayed neurological sequelae of methanol poisoning show marked clinical variation (Ellenhorn and Barceloux, 1988). Methanol is widely used in the setting of research laboratory of mixed single crystals, and inhalation of methanol vapors may exist in both academic and high-tech institutions. The workers in these settings are usually exposed not only to different organic solvents but also to many other chemicals. We report here on a patient who presented with delayed parkinsonism and dyspraxia following prolonged occupational exposure to methanol as a solvent of bromine.

This case illustrates a neurotoxic delayed effect of long-term exposure to methanol with no episode of acute intoxication.

* Corresponding author. Tel.: +972-2-678-1781; fax: +972-2-678-1781.
E-mail address: yfinkel@md2.huji.ac.il (Y. Finkelstein).

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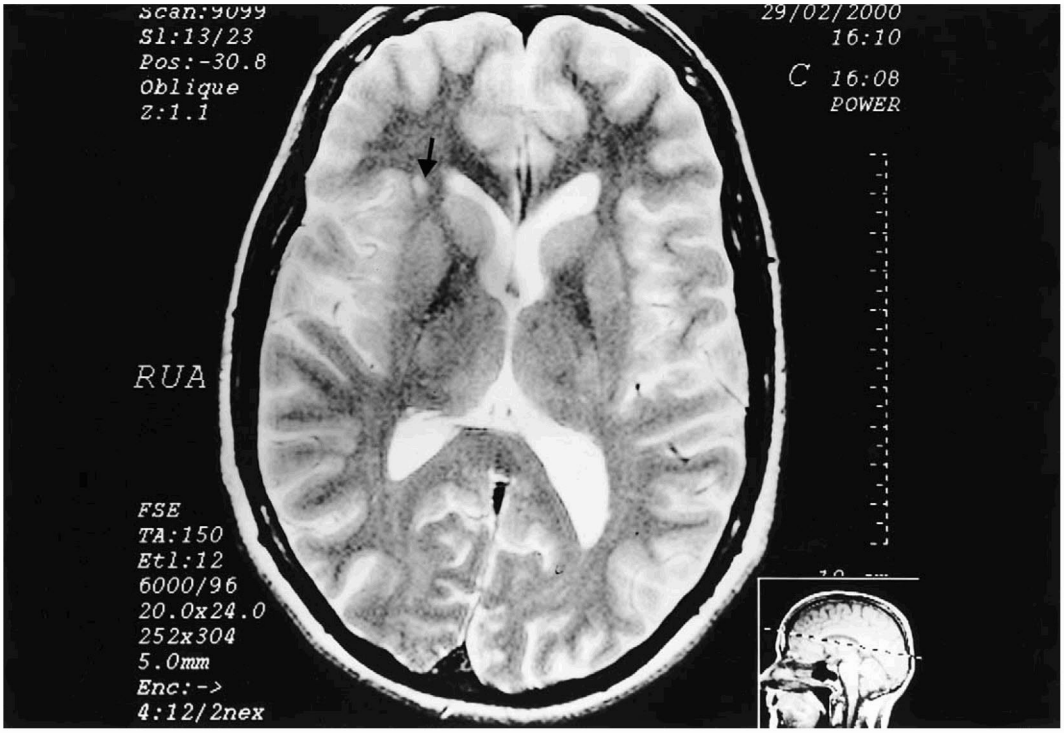

Fig. 1. Magnetic resonance imaging (MRI) of brain showed the focus of a bright T2 signal in the subcortical white matter near the left basal ganglia.

CASE HISTORY

A 40-year-old female experimental physicist noted a right hand tremor during writing. Her past medical history was insignificant and there was no relevant family history. Six years earlier she completed her Ph.D. thesis on the optical properties of mixed single crystals of II–VI compounds, working for 5 years extensively with CdS_xSe_{1-x}, CdS, $Zn_xCd_{1-x}Se$ crystals that she thinned by etching with bromine diluted in methanol. According to the detailed description by the patient, she conducted all these activities with insufficient protective measures, and the ventilation and hygiene of the laboratory were poor.

The disease progressed relentlessly. Initially the disease was diagnosed as right hemiparkinsonism. Levodopa and dopaminergic medications exerted their effect only partially beneficial, with minor improvement of rigidity. Two years after onset of the clinical signs, dystonic features were noted with "peak-dose dystonia", drug-induced chorea and end-of-dose augmentation of tremor and rigidity. Four years after onset, the disease was manifested bilaterally, including bradykinesia with further reduction of agility and further limitation of the intervals of alleviated symptoms achieved by the medications. Clinical long tract signs were noted with bilateral hyperriflexia and Hofmann's sign. Ideomotor dyspraxia was observed as the patient herself reported difficulty in initiating movements and executing planned and well-directed actions with her right hand. Magnetic resonance imaging (MRI) of brain showed bilateral foci of bright T2 signals in the subcortical white matter (Figs. 1 and 2); an increase in the number of these foci was noted in MRI scans repeated over the following years. The differential diagnosis included hereditary diseases and primary (idiopathic) degenerative diseases such as multiple system atrophy and progressive supranuclear palsy. These diagnoses were excluded in view of only scarce signs of dysautonomia and the absence of any sensory, cerebellar, bulbar and ocular signs. Screening for heavy metals in urine and plasma ceruloplasmin was negative.

DISCUSSION

Only rarely is it possible to clearly demonstrate a specific agent as the causative agent of PD in a specific case. In the present case, methanol could be presumed to be the causative agent of PD in the young patient. Methanol is a volatile colorless gas with a typical odor, and is well absorbed by inhalation via the respiratory system. Its toxicity rating is 3—moderately toxic

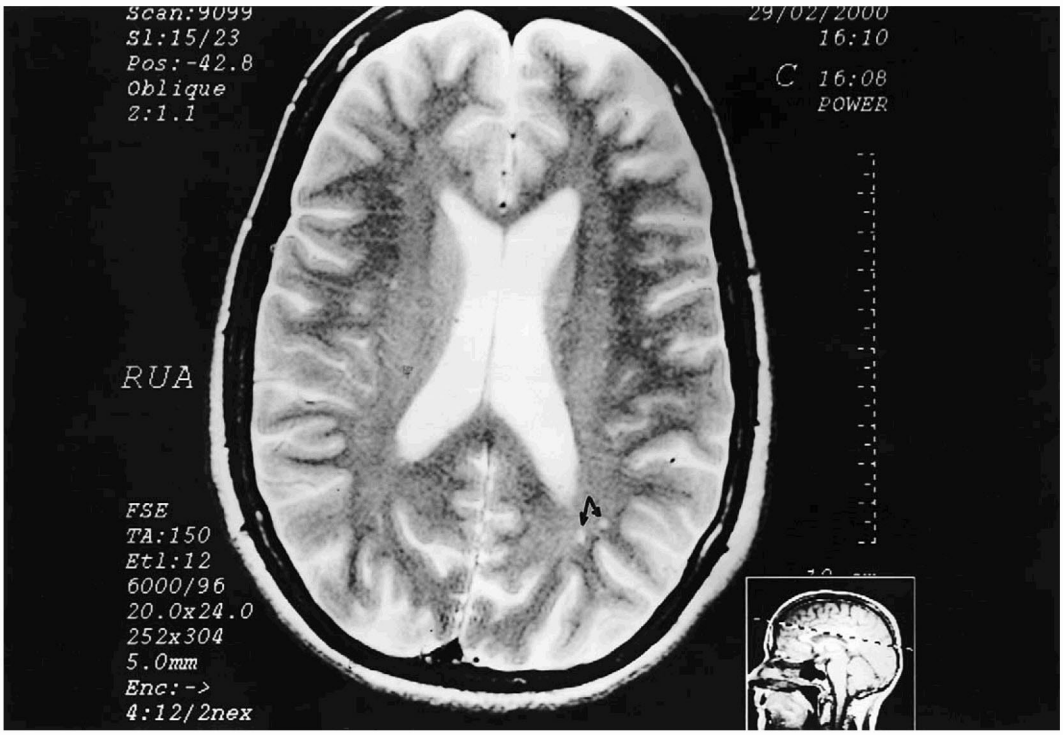

Fig. 2. Magnetic resonance imaging (MRI) of brain showed foci of bright T2 signals in the subcortical white matter in the right occipital region.

(Gosselin et al., 1985). It might injure the central nervous system (CNS) causing usually well defined permanent lesions in the basal ganglia with putaminal necrosis. Consequently, parkinsonism might be the permanent clinical sequel of methanol poisoning (Ellenhorn and Barceloux, 1988). Cases of acute methanol poisoning with delayed parkinsonism have been reported, and the delayed parkinsonian signs and symptoms were manifested several weeks after the acute phase of poisoning (Guggenheim et al., 1971; McLean et al., 1980).

The first clinical reports were published before the computerized tomography (CT) era, describing patients with extrapyramidal rigidity and bradykinesia that had been partially relieved by levodopa treatment. In later clinical reports, with the routine use of CT and MRI brain scans, typical basal ganglia lesions were demonstrated in several cases, and these radiological findings were compatible with the clinical signs and provided an unequivocal etiological clue. However, in a case of a 47-year-old male poisoned with methanol, MRI showed scattered lesions in the basal ganglia (including caudate nuclei and putamina), and also in the hypothalamus and subcortical white matter (Anderson et al., 1997). Another report described a patient with diffuse necrotic lesions in the caudate nucleus, putamen and white matter. The clinical picture in that case included both pyramidal and extrapyramidal signs with dystonia (Davis and Adair, 1999), similar to the present case. In another patient with parkinsonian syndrome after acute methanol poisoning, brain lesions were radiologically observed in the lenticulocapsular region (Ley and Gali, 1983). All these reported cases indicate the propensity of acute methanol poisoning to cause CNS lesions, first and foremost in different sites within the basal ganglia but also in the adjacent white matter, inferring damage to the extrapyramidal system including the basal ganglia and their pathways. Methanol, like other organic solvents, can be expected to harm the white matter in addition to its specific damage to the basal ganglia. In the present case, both clinical and imaging findings indicated white matter involvement: clinical long tract signs alongside MRI evidence of mild brain atrophy and bright T2 subcortical foci.

Pyramidal signs may be observed in 10–15% of the cases of idiopathic PD (Mozaz et al., 1991). However, in the present case there was a plethora of additional neurological signs including dyspraxia, an evident cognitive sign. Thus many clues in the medical history, clinical signs and subsequent clinical course indicated "atypical" PD. This clinical complex undoubtedly differs from that of PD in its classical idiopathic form. Moreover, the occupational exposure to methanol in

this case is evident. This corroborates the diagnosis of parkinsonism which could not be referred to as "idiopathic" PD.

The assessment of higher cognitive functions plays a role in establishing the diagnosis. The patients with solvent-induced parkinsonism are prone to be impaired in attention–executive functions (Chang and Dyer, 1994), as indeed observed in the present patient who had impaired executive motor skills.

Although some of the atypical parkinsonian syndromes are clinically less likely in the present case, the possibility of corticobasal degeneration was considered in light of the combination of parkinsonism, upper-motor neuron signs and apraxia. However, the apraxia was present in the dominant arm, it did not spread, over several years, to the other limbs, and it was not followed with additional signs of frontal and parietal cortical dysfunction such as sensory loss and frontal lobe release phenomena. This, and the absence of cortical atrophy by MRI failed to support such diagnosis.

Delayed-onset parkinsonism might follow an episode of acute exposure to methanol even in cases in which the typical immediate onset of blindness was not manifested. Two patients developed parkinsonism several weeks after methanol poisoning. Brain imaging demonstrated putaminal lesions in both patients, but in neither of them did blindness occur during the acute phase of exposure to methanol (Indakoetxea et al., 1990). Formic acid, the product of methanol oxidation, is presumably responsible for the immediate clinical outcome of blindness, and was also indicated to be involved in the pathophysiology of delayed basal ganglia lesions (Faris et al., 2000). Some authors proposed that mitochondrial dysfunction or dopaminergic presynaptic impairment underlies the basal ganglia damage in these cases (Indakoetxea et al., 1990). Decreased levels of methionine–methenkephalin and increased enzymatic activity of dopamine-β-hydroxylase were measured in the cerebrospinal fluid of a parkinsonian patient following acute methanol poisoning (Verslegers et al., 1988). The patient reported in that case had putaminal lesions demonstrated by brain imaging by both CT and MRI. These findings may provide evidence for the involvement of both noradrenergic and opiate CNS systems.

In the present case, rapid progression of the disease was evidenced. There were remarkable fluctuations in the clinical response to medication, with prominent appearance of dyskinetic movements shortly after commencing L-dopa treatment. In patients with idiopathic PD, the natural history of disease is much slower and medical treatment is much more effective than in the presented patient. Similarly, the onset of dyskinesia was much earlier than could be expected in a case of idiopathic PD.

The clinical cases reported in the medical literature referred to delayed and permanent signs of parkinsonism following acute methanol poisoning. The effects of the chronic methanol poisoning were manifested in our patient after a long delay.

Several possible mechanisms could be proposed to explain this time gap between end of exposure and the beginning of clinical manifestations. It is well accepted that any population of neurons has a normal rate of cell loss over life. The neurodegenerative process is clinically manifested when the slope of cell loss crosses the symptomatic threshold. Long-term low-level exposure to a neurotoxic substance accelerates the normal rate of neuronal cell loss. After the termination of toxic exposure of a young individual the normal rate of cell loss resumes, still above the symptomatic threshold. This threshold is crossed several years later after the period of exposure, but still earlier than expected by the natural "programmed" rate of cell loss. Consequently, symptoms of neurodegeneration might emerge in a relatively young individual (Rosenberg, 1995).

The exposure of this patient to methanol occurred under the unique circumstances of exposure to two solvents only—methanol and methyl bromide, while workers in research laboratories are almost always exposed to multiple solvents and mixtures. In this case, the methanol alone had been extensively used for a research purpose. The only other solvent to which this patient was exposed might have been methyl bromide (bromomethane). Methyl bromide is highly volatile: chronic exposure to it could contribute to the demyelinating damage in subcortical white matter.

Indeed the clinical course of organic solvent-induced neural disorders might be progressive even after discontinuation of the chronic exposure to solvents (Hageman et al., 1999). Similarly, drug-induced parkinsonism might persist and progress after discontinuation of neuroleptic medications (Melamed et al., 1991).

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