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Follow-up of patients affected by manganese-induced Parkinsonism after treatment with CaNa2EDTA[☆]

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Abstract

In the period of 1998–2004, seven workers affected by manganese-induced Parkinsonism were diagnosed, studied and treated with CaNa2EDTA at our Occupational Health Ward. Biological markers, as well as magnetic resonance imaging and clinical examinations, were used to assess the disease trend. Those workers still employed were immediately removed from exposure. Our results seem to confirm that very good clinical, biological and neuroradiological results can be obtained by timely removal from exposure and chelating treatment, and that amelioration can persist in time. Manganism is, however, a severe condition that can also progress independent of further exposure. Therefore, chelating treatment can be a great aid in overt manganism, but particular attention must be paid to primary prevention, as this disease should now be totally preventable and definitely merits eradication.
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1. Introduction

Manganese intoxication has long been described, mainly in its chronic form as it persists among workers exposed to dust or fumes. Manganese (Mn) selectively targets the central nervous system, causing a syndrome resembling Parkinson's disease. The neurotoxic effects of Mn mainly affect the extrapyramidal system, causing dystonic rigidity and intention tremor. Neuropsychological symptoms have also been reported (see Lee, 2000; Levy and Nassetta, 2003 for a review).

Chelating agents are chemical substances that stably bind metal ions and promote their excretion. Therefore, these drugs are the treatment of choice for acute and chronic metal poisoning. Many biological substances and synthetic drugs possess chelating properties. Among these, ethylenediaminetetraacetic acid (EDTA) is a synthetic polyaminocarboxylic acid widely used in detergents and as a preservative in food and pharmaceutical solutions. It is also an effective drug for the treatment of heavy metal poisoning, as it binds divalent and trivalent metal ions (Levine, 1975), forming a stable chelate that is then excreted in urine. Its calcium disodium salt (CaNa2EDTA, calcium disodium edetate) does not induce hypocalcemia, a potentially dangerous effect induced by its parent compound.

As early as the 1950s and 1960s, the effectiveness of this drug was demonstrated in experimental animals, in which it protected against lethal $MnCl_2$ dosages (Rodier et al., 1954; Tandon and Khandelwal, 1982) and considerably lowered Mn concentrations in the liver and brain of intoxicated rats (Kosai and Boyle, 1956). The drug was also used with success in cases of human manganese poisoning (Peñalver, 1957; Ritter and Marti Feced, 1960; Wynter, 1962). The first treatments for manganism with CaNa2EDTA were administered to miners exposed to elevated concentrations of airborne Mn oxide. Peñalver obtained an impressive regression of an extremely

severe neurological syndrome in a 32-year-old miner (Peñalver, 1956, 1957). Mn mobilization in urine after $CaNa_2EDTA$ injection has also been studied in Mn ore crushing (Cook et al., 1974) and gun metal foundry workers (Sata et al., 1998).

Other chelating drugs, such as sodium para-aminosalicylic acid, have also been occasionally reported to be effective in chronic manganism (Ky et al., 1992).

More recently, our group successfully used $CaNa_2EDTA$ in the treatment of a welder (Case # 1 of our series, Discalzi et al., 2000), and a foundry worker affected by Mn-induced Parkinsonism (Case # 3 of our series, Herrero Hernandez et al., 2002); positive findings were also reported in a young welder showing Mn-induced myoclonic involuntary movements (Ono et al., 2002) and in a child accidentally poisoned by Mn showing a severe epileptic syndrome (Herrero Hernandez et al., 2003).

On the basis of medical literature data and direct experience with $CaNa_2EDTA$ in previous cases of accidental and occupational lead poisoning, we decided to apply the same treatment to our patients affected by chronic manganese poisoning. The present study describes our findings and their follow up.

2. Subjects and methods

In the period 1998–2004, seven patients affected by manganese-induced Parkinsonism were admitted, diagnosed and treated at our Occupational Health Ward. In addition, a 37-year-old welder exposed to Mn from October 2001 to February 2004 (Case # 8) showing early-stage symptoms (headaches) and a healthy volunteer control aged 31 were studied before and after challenge with 2 g of $CaNa_2EDTA$ administered intravenously.

Informed consent was obtained from all subjects. For every subject, lifetime occupational history was collected by an Occupational Health Physician, and the patients underwent a series of neurological examinations. The same neurologist evaluated our more recently observed patients, using the Unified Parkinson's Disease Rating Scale (Parts I–III) (Fahn and Elton, 1987) to derive an index of severity and objectively assess the temporal trend of the disease. Routine blood tests including renal and liver function assessment were carried out upon admittance and repeated periodically; serum prolactin was measured on admittance. Whole blood Mn, iron and copper in serum and urinary manganese were analyzed by atomic absorption spectrophotometry with graphite furnace (GF-AAS with Zeeman background correction, Perkin-Elmer 4100ZL), and serum zinc was analyzed by flame atomic absorption

spectrophotometry (FAAS, Perkin-Elmer 5100PC) in basal conditions and during chelating treatments.

Magnetic resonance imaging was used to detect and follow-up manganese deposits characterized by hyperintense signal in basal ganglia on T1-weighted images. Calculation of the pallidal index (Krieger et al., 1995) enables a semi-quantitative assessment of the manganese content in the globi pallidi. The MRI examinations were performed with a 1.0 T magnetic resonance imager (Signa Horizon LX, GE Medical Systems, Milwaukee, WI, USA) employing Spin Echo pulse sequences to obtain sagittal and axial T1-weighted images (TR 500 ms, TE 14 ms, 5/1 mm thickness/spacing, 2 Nex, acquisition matrix 256/224). Sagittal T1-weighted images were also obtained with Magnetization Transfer (MT) technique (saturation pulse 1200 Hz off resonance frequency). Pallidal index (PI) was calculated by measuring the signal intensity of a region of interest (ROI) sized 10 mm^2 in area, located in the globus pallidus (R1) and in frontal white matter (R0) on sagittal T1-weighted images, using the following formula: $PI = R1/R0 \times 100$.

SPECT with I 123 IBZM, a ligand for D_2 receptors, was performed in Cases # 4 and 6 to help the differential diagnosis with Parkinson's disease. The patients completed eye-hand coordination tests to discriminate resting versus intention tremor, and underwent the Mini Mental Scale Examination (Folstein et al., 1975) to quantitatively measure their cognitive status. Chelating treatment with $CaNa_2EDTA$ was administered intravenously (2 g $CaNa_2EDTA$ in 500 ml of physiologic solution infused in 4 h, followed by an additional 500 ml of physiologic solution).

3. Results

The patients' age, gender and occupational data are listed in Table 1, while Fig. 1 shows the temporal trend of the clinical phases in relation to the periods of exposure.

The main symptoms and signs observed in our patients, their clinical outcome, biological and neuroradiological findings and antiparkinsonian medication are summarized in Table 2.

In four patients (Table 2: Cases # 1, 2, 3, 5), a marked regression of the disease occurred after chelation with $CaNa_2EDTA$. Only one subject in this group required additional antiparkinsonian treatment (Case # 1).

Another patient experienced a mild improvement of tremor (Table 2: Case # 4).

Table 1
Patients' demographic and occupational data

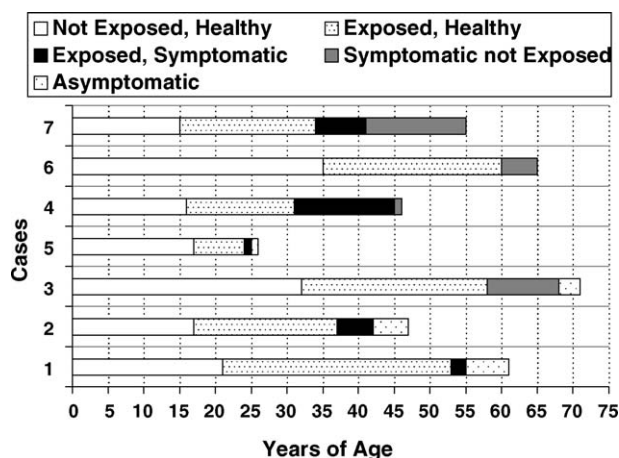| Case #	Year of birth	Age at onset	Age at observation	Occupation	Years of exposure
1	1943	53	55	Welder	31
2	1957	37	42	Welder	25
3	1933	58	68	Foundry worker (iron, aluminum)	26, indirect exposure
4	1958	32	45	Welder	28
5	1978	24	25	Welder	8
6	1939	63	64	Foundry worker (iron)	25
7	1949	33	54	Welder in foundry (steel)	26

Fig. 1. Temporal trend of the clinical phases in relation to Mn occupational exposure.

Changes were not considered significant in two patients (Table 2: Cases # 6 and 7). Of these, Case # 7 showed a marked change in gait and pronation–supination of upper limbs, with reduction of bradykinesia and rigidity after chelation. This subject was affected by very severe juvenile onset Parkinsonism, and underwent only one chelating course because of difficulties in travelling from his city of residence to our hospital. Case # 6 showed asymmetric resting tremor.

Antiparkinsonian drugs were globally ineffective in our Mn-induced Parkinsonism patients.

Blood and urinary Mn levels, pallidal indexes and neurological scores are showed in Fig. 2. Data from our early manganism welder (Case # 8) and healthy control (Control) are also included in Fig. 2 to allow comparison with overt cases.

Figs. 3 and 4 show MRI T1-weighted images in Case # 2 before and after chelation. Figs. 5 and 6 show MRI T1-weighted images without and with Magnetization Transfer in Case # 8 (early-stage patient).

SPECT with IBZM showed normal, symmetric ligand distribution in both examined patients.

No adverse or side effects, or depletion of essential metals (Fe, Cu, and Zn) were observed after chelating treatment.

Serum prolactin was measured in patients # 2, 4, 5, 6 and 7. The first four subjects had results within the normal range (3–17 ng/ml), while Case # 7 had levels below 0.5 ng/ml, but this patient was on levodopa treatment.

Individual risk factors were detected in three patients: viral hepatitis C, elevation of gamma glutamyl transpeptidase (γGT), and chronic iron deficiency (Fig. 2).

To date, no statistically significant correlation between blood Mn levels and pallidal indexes emerges from our series.

4. Discussion

CaNa$_2$EDTA has long been used for treating acute and chronic lead poisoning, and this contributed to its negative fame as a nephrotoxicant. Although this drug has long been considered intrinsically nephrotoxic, especially by old reports,

Table 2
Biological and neuroradiological data, clinical pattern and pharmacological treatment

| Case #	First Mn-blood (μg/L) and pallidal index	Last Mn-blood (μg/L) and pallidal index	CaNa$_2$EDTA total dose (g)	Main symptoms	Clinical outcome	Other drugs
1	14.4, 111 (1998)	5.2, 106 (2004)	16	Parkinsonism: postural-intentional tremor, muscle rigidity, bradykinesia, mask-like face, gait disturbances Headache, apathy	Very good	Levodopa, Pramipexol
2	19, 114 (1999)	8.7, 104 (2004)	52	Parkinsonism: postural-intentional tremor, muscle rigidity Headache, vertigo	Excellent	
3	20.1, 114 (2001)	14.8, 107 (2002)	50	Parkinsonism: postural-intentional tremor, muscle rigidity Impaired memory	Excellent	
5	9.4, 119 (2003)	11.2	20	Parkinsonism: postural-intentional tremor	Excellent	
4	8.4, 105 (2003)	7.3, 99 (2003)	40	Parkinsonism: postural-intentional tremor, muscle rigidity, mask-like face Headache	Mild improvement	Propanolol not effective
6	4, 105 (2003)	5.4, 98 (2003)	20	Parkinsonism: resting tremor, bradykinesia, mask-like face	No changes	Levodopa, Orfenadrine, Pramipexol, Gabapentin, Alprazolam: not effective
7	11.2, 107 (2003)	9.6	10	Severe Parkinsonism: postural-intentional tremor, muscle rigidity, bradykinesia, mask-like face, gait disturbances Apathy, impaired memory, speech disturbances, emotional liability	No changes	Orfenadrine, Amantadine, Levodopa, Bromocriptine, Gabapentin: not effective
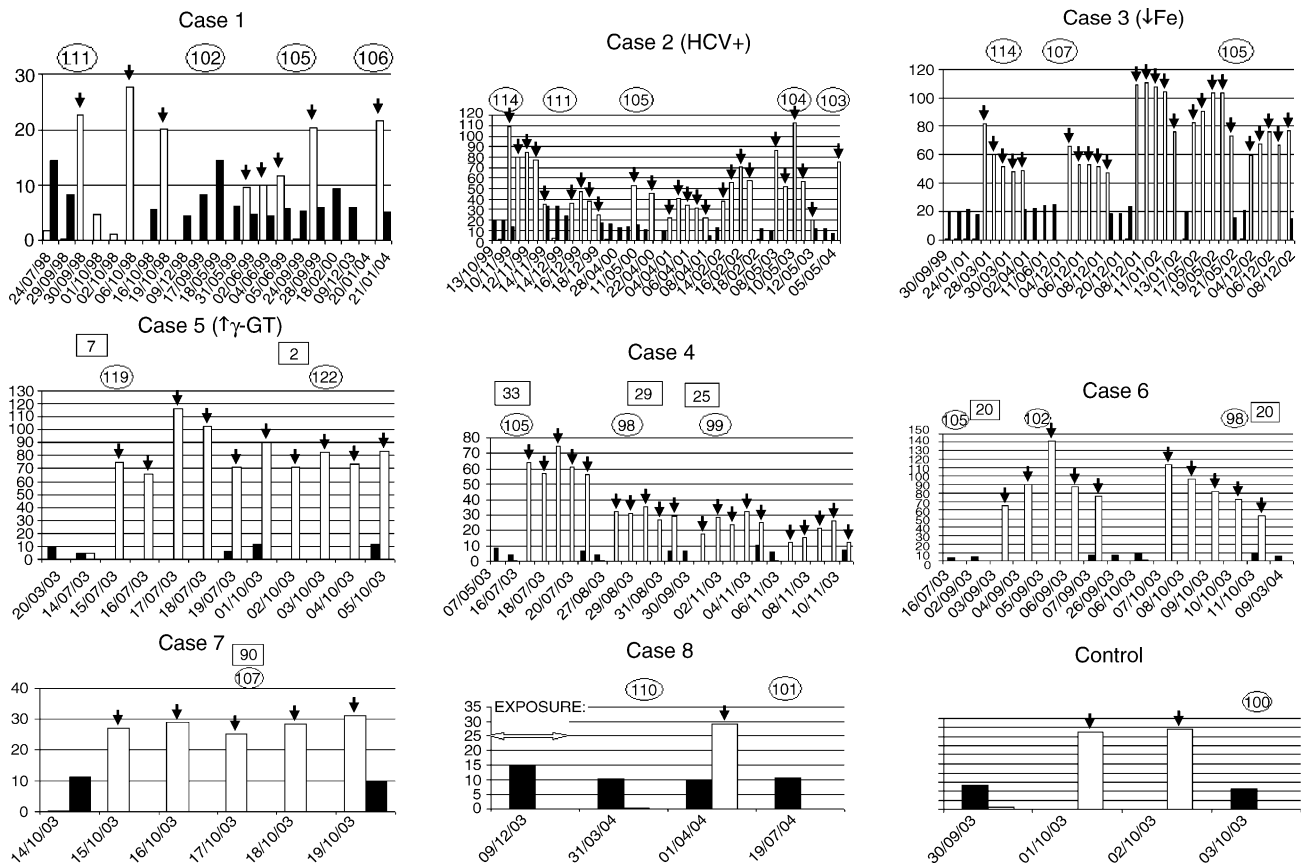
Fig. 2. Blood and urinary Mn levels, pallidal indexes and neurological scores. Black columns: Mn-blood expressed as μg/L (normal values <10 μg/L); white columns: daily urinary Mn expressed as μg Mn/24 h (normal urinary Mn 0.12–1.9 μg/L). High urinary levels correspond to chelation treatments; X-axis: time; Y-axis: μg Mn. Pallidal indexes values are indicated in circles, UPDRS I–II–III scores in rectangles (range 0–176). Arrows indicate chelation therapy timing.

lead itself is nephrotoxic, and the remarkable lead levels mobilized by this chelator and successively excreted through the renal system could account for toxic effects in this site. Cautious use of this drug also allowed detection of lead poisoning in patients with preexistent renal disease, and a review of older literature revealed that nephrotoxicity probably occurred due to inappropriate dosage and dose rate (Wedeen et al., 1983). Nevertheless, potential nephrotoxicity is still a matter of concern. Recent clinical research suggests that this aspect should be reconsidered. The drug, when repeatedly administered to renal failure patients, seems to improve their renal function and slow the progression of kidney impairment (Lin et al., 2003), and this beneficial effect is possibly attributable to lead chelation.

CaNa$_2$EDTA is a fairly safe drug, provided it is used by trained personnel on a hospital basis, together with careful assessment of the patients and cautious management of the administration dosage, schedule and procedures. Chelating drugs have a rational indication for the causal treatment of acute and chronic metal poisoning, and therefore their use in Mn-induced Parkinsonism should be further investigated on large groups to validate their effectiveness. Chelating treatment with CaNa$_2$EDTA seems to be very helpful in the treatment of overt manganese poisoning. An interesting inhibiting action of CaNa$_2$EDTA on serum dopamine-beta-hydroxylase has also been described in humans (De Paris and Caroldi, 1994) and this

pharmacological effect, as well as the in vitro observation of a decrease of Mn-triggered dopamine autoxidation by EDTA (Nachtman et al., 1987), both deserve further attention. It would also be very interesting to test and compare the effectiveness of different chelating agents, as well as to develop new drugs with chelating properties to treat Mn poisoning.

An accurate lifetime occupational history should always be collected, as it is particularly important in order to detect Mn-induced Parkinsonism. Manganism prevalence is probably underestimated and many cases of "atypical Parkinsonism" could in fact be due to chronic exposure to this metal. Postural or intention tremor and muscular rigidity are common in manganism and seem to be the most reversible signs. These signs are typically symmetric in manganism, but hemisyn-dromes have been sporadically reported (Marchand, 1960), and this rare presentation was also observed in our limited series (Case # 6). It appears unwise to rely only on clinical signs to achieve a good differential diagnosis with idiopathic Parkin-son's disease, and this has been clearly stressed in a recent study (Racette et al., 2001). The final diagnosis of Mn-induced Parkinsonism needs to be clarified by putting together occupational, clinical, biological and neuroradiological data.

To date, no significant correlation between blood Mn levels and pallidal indexes has been observed in our series. Nevertheless, the increasing number of observations seems to show a trend towards such a correlation. These findings differ
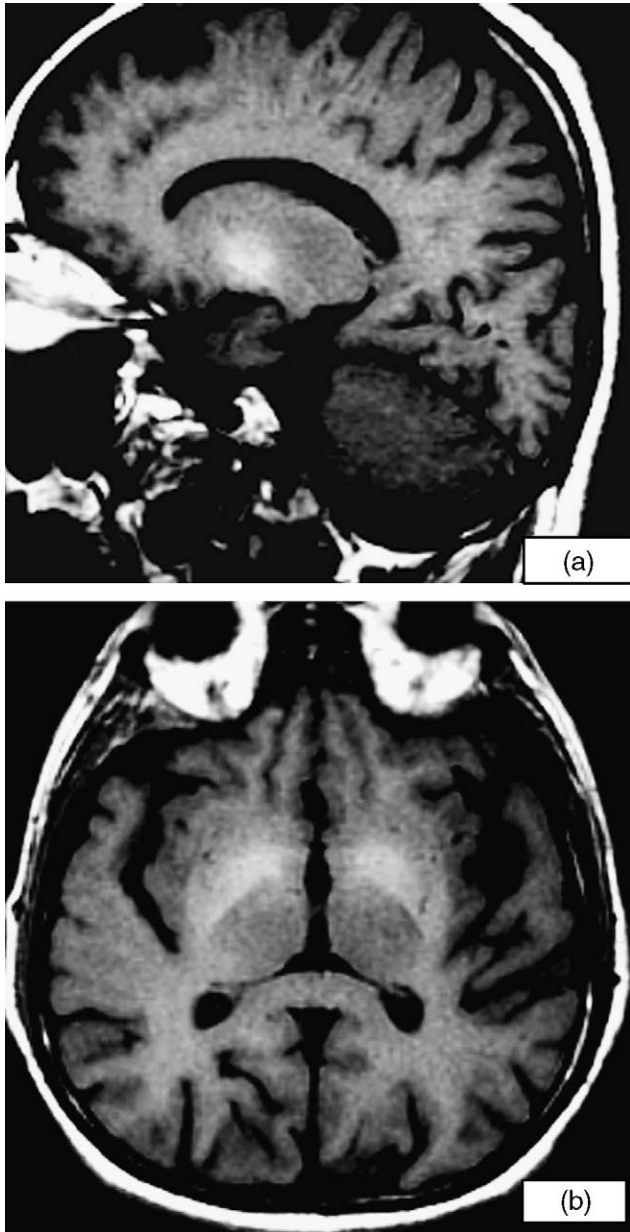
Fig. 3. Case # 2 before chelation (November 1999): pallidal index (right/left) 115/114. Brain MRI, sagittal (a) and axial (b) T1-weighted sequences showing a definite hyper signal of globi pallidi.
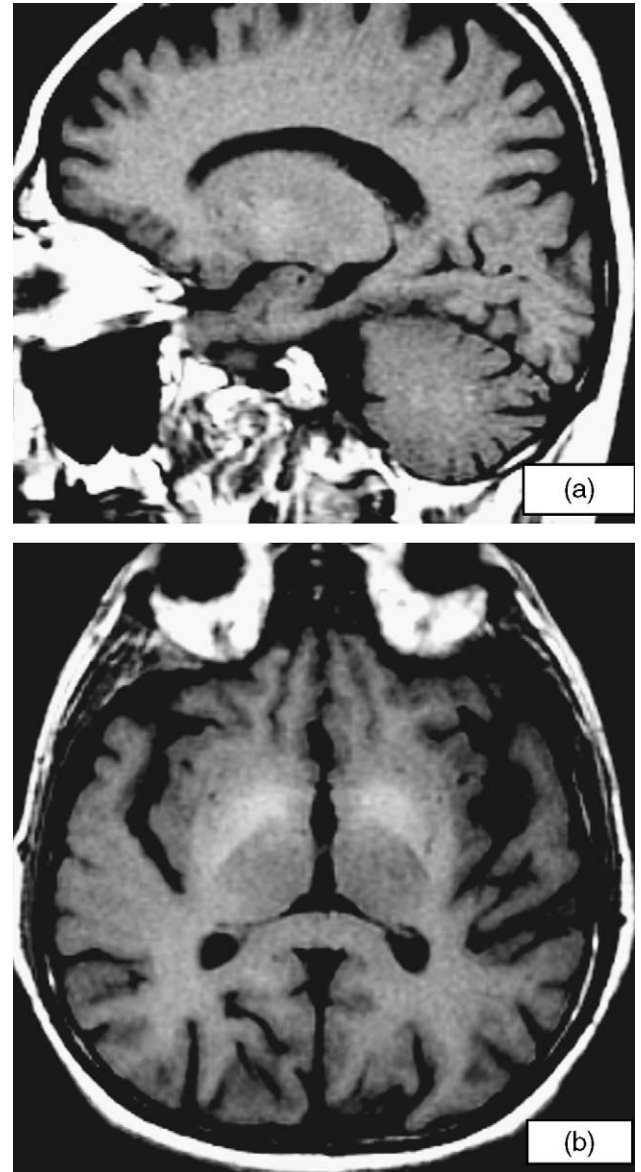

Fig. 4. Case # 2, last MRI after the whole chelation treatment (May 2004): pallidal index (right/left) 101/103. Brain MRI, sagittal (a) and axial (b) T1-weighted sequences showing a decreased hyper signal of globi pallidi.

from previous studies in which a significant correlation has been found (for a review on this subject see Lucchini et al., 2000), and such a difference can likely be explained by our very limited sample, as well as by differences in the cases studied. The larger studies were conducted in asymptomatic Mn-exposed workers (Kim et al., 1999) and cirrhotic patients (Park et al., 2003), the latter showing extremely high values of both parameters. As pallidal index probably reflects recent exposure to Mn (Kim et al., 1999), the time elapsed from exposure to diagnosis could be responsible for this apparent discrepancy.

Our patients did not respond to traditional antiparkinsonian drugs (Table 2). The effectiveness of levodopa in Mn-induced Parkinsonism is still debated, but a recent double-blind, randomized and placebo-controlled study showed that this drug is not effective for the management of Mn-induced Parkinsonism (Koller et al., 2004), and our results agree with this statement. This is probably justified by the involvement of different brain areas. As opposed to Parkinson's disease, Mn targets mainly the globi pallidi. However, in some cases of Mn-induced Parkinsonism, MRI detects Mn deposits also in substantia nigra. Levodopa could probably be useful in these cases, but it would be wise to administer it after the normalization of basal ganglia abnormal signal. It is known that Mn promotes dopamine autoxidation (Nachtman et al., 1987); therefore, in the presence of Mn overload, levodopa could increase cell damage.

Clinical amelioration seems to occur concomitantly with neuroradiological and biological normalization. Presently, Mn-
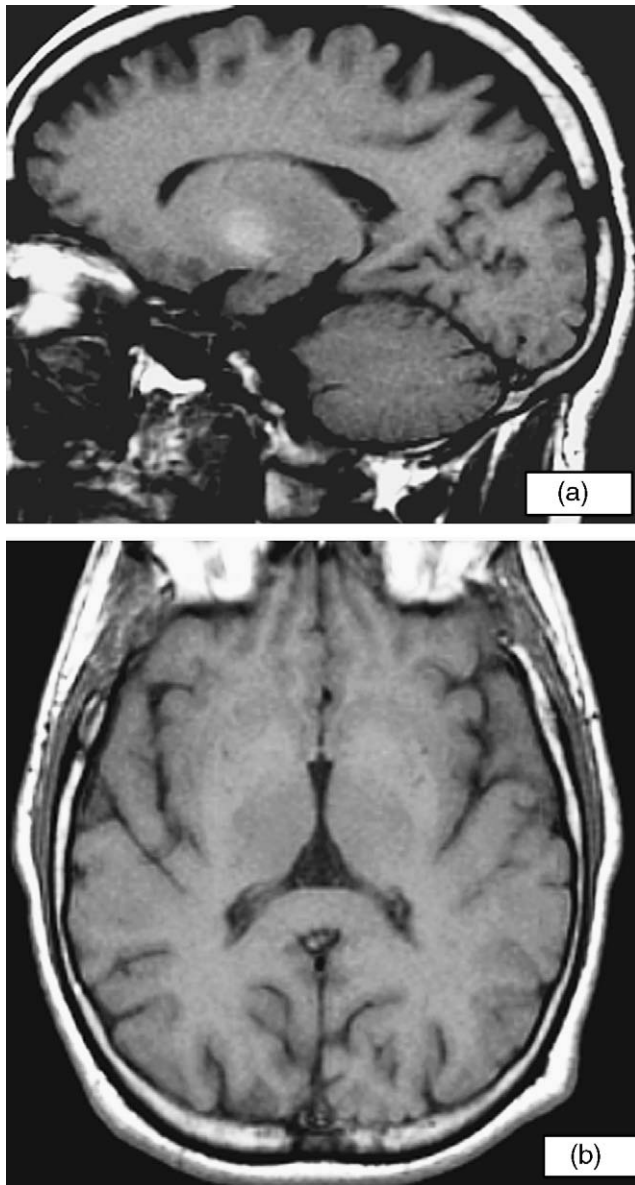
Fig. 5. Case # 8: welder affected by early symptoms of manganese poisoning. Brain MRI, sagittal (a) and axial (b) showing a faint hyper signal of globi pallidi.
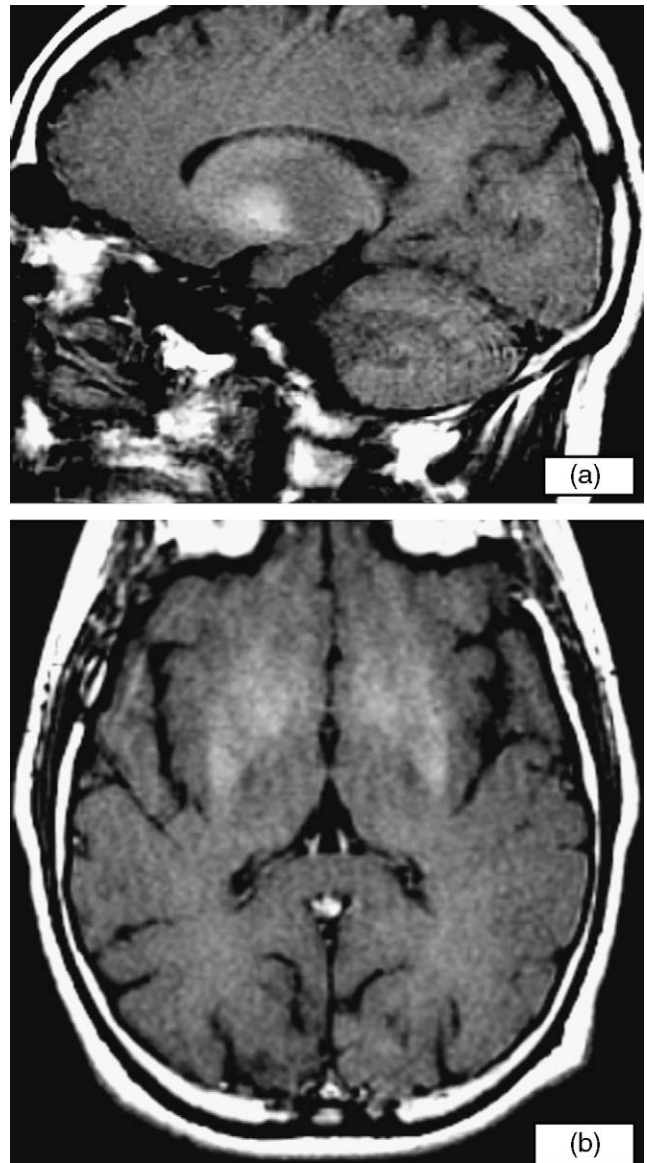

Fig. 6. Same case of Fig. 5. Brain MRI, sagittal (a) and axial (b) T1-weighted sequences with Magnetization Transfer (MT) technique showing a more pronounced hyper signal of globi pallidi.

induced Parkinsonism in healthy workers seems to appear after long exposure periods, but individual risk factors such as liver disease and iron deficiency can promote the development of the disease after only a few years of exposure. When symptoms arise, cessation of exposure is mandatory. Chelation can be effective if promptly and correctly administered and should probably precede other pharmacological treatments. Some cases are irreversible, apparently those characterized by a longer symptomatic period and low blood Mn and pallidal indexes (a probable expression of remote exposures that caused established neuronal damage). Others can be reversible if they are diagnosed early, removed from exposure, and causally treated.

MRI is also a helpful, sensitive and non-invasive tool for detection and follow up of brain Mn deposits in pre-clinical or very early stages. Magnetization Transfer images allow for easy detection of Mn deposits even in early stages. We believe that Magnetization Transfer technique (Van Buchem, 1999) improves the sensitivity of MRI in detecting the hyperintense signal in globi pallidi.

The availability of a pharmacological treatment that can be effective in some patients must not constitute in any sense an excuse to omit industrial hygiene preventive measures. Every effort must be made to prevent Mn-induced neurologic syndromes, as they can lead patients to invalidity. To achieve this goal, technical prevention at the source must be applied. Workers should be extensively informed and trained about risks posed by Mn use and their health status should be carefully monitored. More than one century and a half after Couper's first description of Mn poisoning (Couper, 1837), and by now the disease should be eradicated. Peñalver reported a pertinent statement by Johnstone from the 1954 Ramazzini Oration:

"*Depending on a pill for prevention rather than upon the proved measures prescribed by our hygienists is to be deplored*" (Peñalver, 1955). In this case especially, Johnstone's statement fully maintains its validity and should be food for thought.

Acknowledgements

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