

## Parkinsonism Induced by Chronic Manganese Intoxication— An Experience in Taiwan

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Excessive manganese exposure may induce a neurological syndrome called manganism, which is similar to Parkinson's disease (PD). However, close observation of patients with manganism reveals a clinical disease entity different from PD, not only in the clinical manifestations, but also in therapeutic responses, in neuroimaging studies such as magnetic resonance imaging, positron emission tomography and dopamine transporter images, and in the neuropathological findings. Furthermore, after long-term follow-up studies, patients with manganism showed prominent deterioration in the parkinsonian symptoms during the initial 5-10 years, followed by a plateau during the following 10 years, which is also different from the clinical course of patients with PD. Although typical patients with manganism are different from patients with PD, the potential risk of inhaling welding fumes, which may accelerate the onset of PD or even induce PD, has been raised during recent years. This controversial topic requires further investigation. (*Chang Gung Med J* 2007;30:385-95)



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Manganese (Mn), an abundant element in the Earth's crust, was first found by the Swedish chemist Scheele in 1771. Manganese dioxide is the most common form of Mn-rich ore, and manganese compounds are commonly used in the production of ferromanganese alloys and other industrial products, such as dry-cell batteries, paints, glazes, electronic parts, and chemicals for coloring glasses and tiles.<sup>(1-8)</sup> An important application for Mn is methylcyclopentadienyl manganese tricarbonyl (MMT), which is an organic compound used as an octane booster and antiknock agent in gasoline.<sup>(9,10)</sup> In addition, potassium permanganate is used as a powerful oxidizing

agent in purifying drinking water, treating waste water, removing waste odor, and as an agricultural fungicidal and bactericidal agent.<sup>(3-5)</sup> Mn is also a natural component of many foods, particularly of nuts, grains, and tea, and an essential trace element used by humans in metabolism.

Excessive exposure to Mn, mainly via occupational inhalation, may cause central nervous system (CNS) symptoms known as manganism. Chronic manganese poisoning was first reported in a manganese ore-crushing plant in France.<sup>(11)</sup> Subsequently, many cases of chronic Mn poisoning have been reported in industrial workers at dry-cell battery fac-

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ories<sup>(12)</sup> as well as among smelters<sup>(13)</sup> and welders.<sup>(14)</sup> Health risks due to exposure to Mn have been found in agricultural workers who were exposed to organic Mn-containing pesticides, such as Mn ethylene-bis-dithiocarbamate (Maneb).<sup>(15)</sup> Mn is also found in the street drug called 'Bazooka', a cocaine-based drug contaminated with manganese carbonate.<sup>(16)</sup> In addition, a significant concern has been raised about airborne Mn exposure from the fuel additive MMT.<sup>(17,18)</sup> Mn has been used as a contrast agent in medical diagnostics, although there have been no reported cases of Mn intoxication. However, some cases have also been reported in patients receiving long-term parenteral nutrition<sup>(19)</sup> and in those ingesting contaminated water.<sup>(20)</sup>

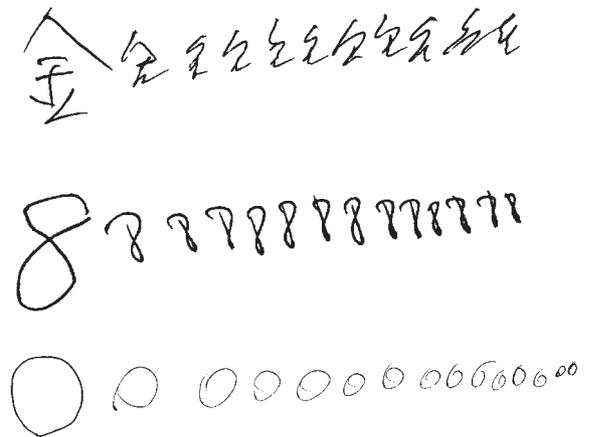
**Manganese neurotoxicity**

Chronic manganese poisoning was not recognized until 1837 when Couper reported five patients who worked in a manganese ore-crushing plant and had whispered speech, salivation, muscle weakness, limb tremors, and a bent posture.<sup>(11)</sup> His observations were almost ignored until the studies by Embden<sup>(21)</sup> and von Jaksch<sup>(22)</sup> in Germany. These researchers reported a peculiar "cock-walk gait". Edsall et al.<sup>(23)</sup> established a relationship among the epidemiological, clinical and pathologic effects of Mn on the CNS. Manganese neurotoxicity was subsequently reported in miners,<sup>(24)</sup> smelters,<sup>(25,26)</sup> welders<sup>(27,28)</sup> and workers involved in the manufacture of dry batteries.<sup>(12)</sup> The clinical features included psychiatric symptoms, parkinsonism, and dystonia.<sup>(29-34)</sup> Patients were reported to have hallucinations and psychoses, referred to as "manganese madness", and extrapyramidal features, including masked facies, postural instability, bradykinesia, rigidity, micrographia, and speech disturbances. Tremors were less common and tended to be postural or actional. Dystonia consisted of facial grimacing, hand dystonia and/or plantar flexion of the foot.

**Outbreak of manganism in Taiwan**

In 1985, a 44-year-old man working in a ferromanganese alloy factory developed manganese-induced parkinsonism.<sup>(13)</sup> Clinical investigations in this factory revealed that six patients disclosed bradykinesia, rigidity, masked face, diminished blinking, impaired dexterity, gait abnormalities, hypophonia and micrographia (Fig. 1).<sup>(35)</sup> The most

characteristic clinical feature was "cock-walk gait", consisting of a high-stepping gait, strutting on the toes with flexed elbows, and an erect spine (Fig. 2).<sup>(36)</sup> This peculiar walking difficulty can be unilateral or bilateral, is considered a form of dystonia, and generally becomes prominent after walking a short distance. Tremors were not prominent, usually they were rapids low-grade postural, and not resting. The



**Fig. 1** Micrographia in a patient with chronic manganese intoxication.



**Fig. 2** Cock-walk gait in a patient with chronic manganese intoxication.

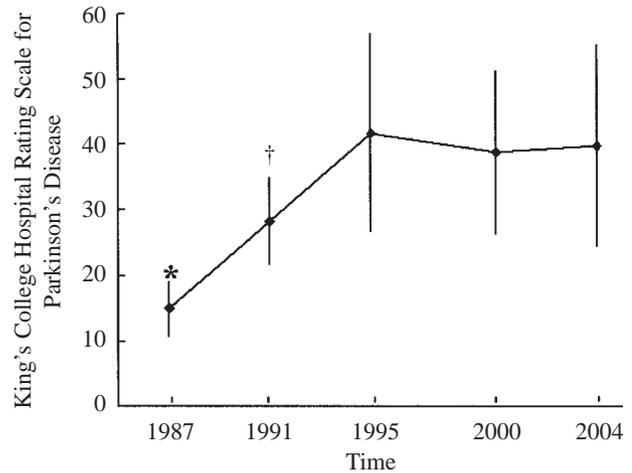
tremors may involve the hands and sometimes the tongue. Manganese concentrations in the blood, urine, scalp hair, and pubic hair were all high, ranging from three to 300 times the reference ranges in all six cases.<sup>(13)</sup> Environmental investigation results showed an increased manganese concentration above 28 mg/m<sup>3</sup> in the air (threshold limited value, 1 mg/m<sup>3</sup>) due to the delayed installation of a ventilation system.<sup>(35)</sup> From review of the reports in the literature, detailed field studies have rarely been reported for documented chronic manganese patients.<sup>(1,7,15,24,30,33,34)</sup>

#### Long-term follow-up studies

There have been no long-term follow-up studies of previous chronic manganese intoxication patients. A longitudinal follow-up study of our patients was conducted every 5 years following the cessation of manganese exposure.<sup>(37-39)</sup> Five years after the cessation of manganese exposure we compared the results with those of the previous study. Their parkinsonian symptoms showed prominent progression in gait disturbances, such as freezing during turning (gait en bloc) and walking backward with retropulsion. Slight deterioration was also found in writing, stability, posture, speed and rigidity. Ten years after the cessation of manganese exposure, the deterioration was still observed, particularly in the gait, rigidity, speed of foot tapping, and writing.<sup>(38)</sup> In addition, the concentrations of Mn in the blood, urine, scalp hair and public hair returned to reference ranges. The follow-up brain MRI did not show high signal intensity on the T1-weighted images. Serial follow-up studies of these patients were conducted continuously for 20 years.<sup>(39)</sup> The serial scores measured using the same scoring system as the King's College Hospital Rating Scale for Parkinson's disease showed rapid progression during the initial 10 years, followed by a plateau during the following 10 years (Fig. 3). The data infer that the causal event of manganese intoxication may destroy some cells and damage others, and that the damaged cells may undergo delayed premature death.

#### Treatment of manganese

Previously researchers revealed inconsistent results; some patients had good responses, some had limited responses and the others had poor responses after administering various dosages of lev-



**Fig. 3** The long-term clinical course study showing a rapid deterioration in the initial 10 years, followed by a plateau in the following 10 years. The serial scores measured with the King's College Hospital Rating Scale for Parkinson's Disease. (\*:  $p < 0.0001$ , the score in 1987 vs. the scores in 1991, 1995, 2000, and 2004; and †:  $p < 0.001$ , the score in 1991 vs. the scores in 1995, 2000, and 2004).

odopa.<sup>(1,30,34,35)</sup> Initially, our patients appeared to respond to levodopa in an open trial, but the benefits were not sustained.<sup>(13)</sup> A double-blind, short-term, placebo-controlled, cross-over study of levodopa was conducted in these patients and showed that their parkinsonism and dystonia failed to respond to levodopa.<sup>(40)</sup> Other antiparkinsonian drugs such as bromocriptine, selegiline, amantadine and trihexylphenidyl were also ineffective (unpublished data).

Previous chelation therapy with CaNa<sub>2</sub>EDTA showed that the Mn excretion in the urine increased and the Mn concentration in the blood decreased.<sup>(13,41)</sup> However the clinical symptoms did not improve.<sup>(13)</sup> In addition, para-amino-salicylic acid (PAS) therapy was reported to be effective in a few patients,<sup>(42)</sup> but the therapeutic responses should be investigated further.

#### Neuropsychological study

The earliest signs of chronic Mn intoxication are subtle, and include behavior changes, fatigue, mood changes, irritability, lack of sociability, and sleep disturbance.<sup>(43-45)</sup> Onset can be insidious or gradual, and the illness can develop after weeks, months, or years

of exposure. The early symptoms may be reversible and neuropsychological test may detect deficits, particularly in mood disturbance, sexual dysfunction as well as memory and intellectual impairment. In our study, comprehensive examinations of neurobehavioral functions were performed in two groups of workers with chronic exposure to manganese, and two control groups.<sup>(46)</sup> The neuropsychological battery consisted of tests of orientation, intelligence, learning and memory, language and communication, visuospatial and visual perception, visual attention, manual dexterity, and information processing speed. There were impaired general intelligence, visuoperceptive impairment and defective manual dexterity, and a slowdown in the response speed in the patients with manganism, while no evidence of neurobehavioral impairment was noted in the non-parkinsonian workers.

#### **Autonomic study**

Autonomic dysfunctions, including sialorrhea, seborrhea, profuse sweating, diminished libido and impotence have been reported in patients with manganism.<sup>(1,5,12,33)</sup> However the frequencies of occurrence varied considerably. The autonomic functions in our patients with manganism was investigated using sympathetic skin responses (SSR) and RR interval variations (RRIV), and the results were compared with 10 stage-matched patients with PD and 10 age-matched healthy control subjects.<sup>(47)</sup> Autonomic symptoms were noted in patients with manganism, but were less common than in those with PD. For the SSR, the latency was prolonged in patients with PD and manganism, while the amplitude was reduced only in patients with PD. The RRIV was decreased in patients with PD and manganism, but the reduction in RRIV was more severe in patients with PD than in patients with manganism. The data indicated that autonomic disturbances may occur in patients with manganism, but were less frequent and less severe when compared with patients with PD.

#### **Neuroimaging studies**

##### **Brain magnetic resonance images (MRI)**

Because Mn has a paramagnetic quality and a shortening of the proton T1-relaxation time, signal intensities are increased symmetrically in the globus pallidus (GP) and midbrain, particularly the substantia nigra pars reticularis (SNr) on T1-weighted brain

MRI in patients with manganism and in non-human primates with experimental Mn poisoning.<sup>(48-50)</sup> Signals on the brain MRI are commonly increased, with a frequency of 41.6% in Mn-exposed workers.<sup>(51)</sup> In addition, the hyperintensity lesions may resolve 6 months to 1 year after cessation of Mn exposure.<sup>(52)</sup> A similar MRI pattern was observed in patients with cirrhosis of the liver and portal systemic shunting.<sup>(53-55)</sup> Many workers who do not have any clinical symptoms may have hyperintensities in the brain MRI. Therefore, increased signal intensities on T1-weighted images may reflect exposure to Mn or accumulation of Mn, but not necessarily manganism.<sup>(52)</sup> The pallidum index (PI) was defined as the ratio of the signal intensity of GP to frontal subcortical white matter multiplied by 100.<sup>(56)</sup> In Mn-exposed workers, blood Mn concentrations were highly correlated with PI. The Mn-exposed workers also had higher PI than the non-exposed workers.<sup>(56,57)</sup>

##### **Positron emission tomography (PET) study**

Brain PET with 6-fluorodopa (6F-Dopa) can be used to study the integrity of the nigrostriatal dopaminergic projection.<sup>(58-60)</sup> Previously, there were no PET studies in patients with chronic manganism. We employed 6F-Dopa PET in our patients with manganism in 1988, and a normal uptake of 6F-Dopa was noted.<sup>(61)</sup> However, brain PET scanning with fluorodeoxyglucose showed decreased cortical glucose metabolism. These findings suggest that in patients with manganism, damage may occur in the pathways of the postsynaptic to the nigrostriatal system, probably involving the striatum or pallidal neurons. Raclopride is a PET marker for dopamine receptors.<sup>(62)</sup> In early untreated PD, the uptake of raclopride is increased, indicating an upregulation of the dopamine receptors. In patients with advanced PD with levodopa therapy, the uptake of raclopride was reduced.<sup>(63)</sup> In 1995, we further performed PET on our patients with manganism; presynaptic and postsynaptic dopaminergic functions were measured using 6F-Dopa and [<sup>11</sup>C]raclopride (RAC).<sup>(64)</sup> Influx constants (K<sub>i</sub>) of 6F-Dopa were within reference ranges in the caudate and putamen. RAC binding was mildly reduced in the caudate and within reference ranges in the putamen. Nigrostriatal dopaminergic dysfunction was further confirmed to be not responsible for chronic Mn-induced parkinsonism.

**Brain single photon emission computed tomography (SPECT) study**

Dopamine transporter (DAT) SPECT is easily accessible and less expensive than 6F-Dopa.<sup>(65)</sup> Various ligands binding to DAT, such as [<sup>123</sup>I]-β-CIT, [<sup>123</sup>I]-fluoropropyl-CIT, and <sup>99m</sup>Tc-TRODAT-1, can be used in SPECT studies.<sup>(66-68)</sup> <sup>99m</sup>Tc-TRODAT-1 is a cocaine analogue that can bind to the DAT site, reflecting the function of presynaptic dopaminergic terminals.<sup>(69,70)</sup> There have been no previous reports dealing with <sup>99m</sup>Tc-TRODAT-1 SPECT studies in patients with chronic manganese intoxication. Brain <sup>99m</sup>Tc-TRODAT-1 SPECT was performed in our patients with manganism.<sup>(71)</sup> Twelve patients with PD and 12 healthy volunteers served as unhealthy and healthy control subjects, respectively. The DAT SPECT showed only slight decreases in the putamen of patients with manganism, as compared with those of the healthy controls, and the DAT results clearly differentiated between the patients with manganism and PD (Fig. 4). In addition, the DAT images provided a reliable, convenient and less expensive alternative in studying the function of the nigrostriatal dopamine neuron terminals.

**Pathologic findings and experimental studies**

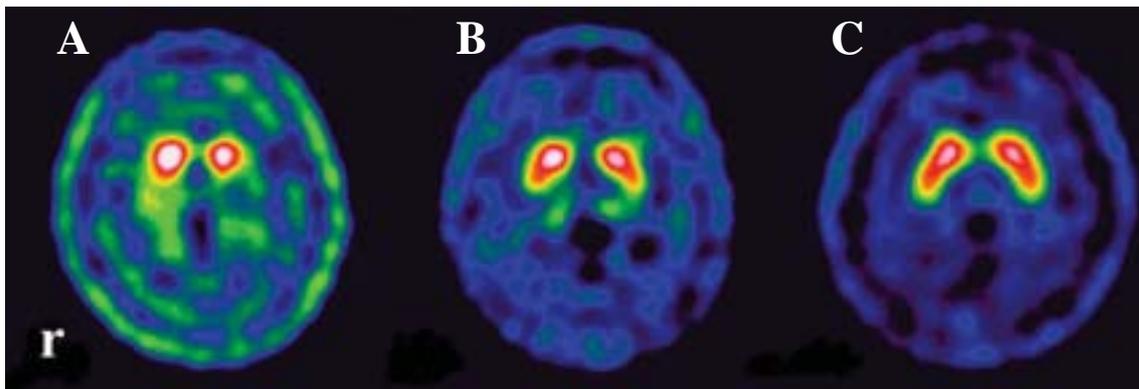
There have been only a few pathologic studies on patients or experimental animals concerning chronic manganese intoxication.<sup>(72-76)</sup> Degeneration of the basal ganglion is primarily confined to the medial segment of the GP and SNr. The putamen and the caudate are affected to a lesser degree, while the substantia nigra pars compacta (SNc) is only rarely

involved. Other areas of the brain, including the cerebral cortex, thalamus, subthalamus, hypothalamus, and red nucleus may be inconsistently involved.

Experimental studies with rhesus monkeys were conducted after intravenous (IV) injections of manganese chloride were given for 2-3 months at 1-week intervals.<sup>(77)</sup> Serial clinical examinations were evaluated and neuropathologic, neurochemical, and laser microprobe mass analysis (LAMMA) were studied. These monkeys developed a parkinsonian syndrome characterized by bradykinesia, rigidity, and facial dystonia, but no tremors. These monkeys did not respond to levodopa. Autopsy demonstrated that the gliosis was confined to the GP and the SNr. Mineral deposits in the perivascular region were found in the GP and SNr. The mineral deposits were comprised of iron and aluminum using the LAMMA studies. These studies demonstrated that manganese primarily damaged the GP and SNr, and relatively spared the nigrostriatal dopaminergic system.<sup>(77,78)</sup> In patients with PD and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism, the primary lesions are localized to the SNc. The results suggest that Mn-induced parkinsonism can be differentiated from PD and MPTP-induced parkinsonism. The accumulation of iron and aluminum may induce oxidants that contribute to the damage of the GP and SNr.

**Differential diagnosis between patients with manganism and PD**

It is becoming clear that manganism and PD are



**Fig. 4** The uptakes of <sup>99m</sup>Tc-TRODAT-1 brain SPECT were decreased in the corpus striatum particularly in the left side in one patient with PD (A), and nearly normal in patient 4 with chronic manganism (B), and one normal healthy subject (C).

distinct clinical entities that can be differentiated based on their clinical manifestations and long-term course, as well as the pharmacological, neuroimaging and neuropathologic features.<sup>(79,80)</sup> The similarities of clinical manifestations between patients with manganism and PD include the presence of bradykinesia, rigidity, masked facies, micrographia, and loss of postural reflex. Manganism differs from PD in the less frequent incidence of resting tremors, more frequent incidences of dystonia, easily falling backward, and characteristic cock-walk gait. Regarding the long-term course, patients with PD may deteriorate continuously while patients with manganism may show rapid progression during the initial 5-10 years, followed by a plateau during the following 10 years.<sup>(39)</sup> With respect to the therapeutic responses, failure to achieve sustained responses was noted in patients with manganism.<sup>(40)</sup> In contrast, patients with PD who had degeneration of dopaminergic neurons in the SNc, and preservation of dopamine receptors on the striatal neurons were capable of responding to levodopa.<sup>(79)</sup> Pathologically, patients with PD were associated with neuronal loss in the locus ceruleus, nucleus basalis of Meynert and dorsal motor nucleus of the vagus, as well as the loss of dopaminergic neurons within the SNc, whereas in manganism gliosis, neuronal loss was limited to the SNr and the medial segment of GP, which is linked to the degeneration of GABA minergic neurons within the GP in pathways postsynaptic to the nigrostriatal system. In addition, the presence of Lewy bodies in the SN and other regions of the brain was noted in patients with PD, but not in patients with manganism.<sup>(80,81)</sup>

The results of neuroimaging procedures have been used to distinguish patients with manganism from patients with PD, including MRI, PET, and DAT-SPECT.<sup>(52)</sup> Manganism is generally associated with hyperintense signal abnormalities in the GP, striatum, and SNr bilaterally on MRI, whereas the MRI results are normal in patients with PD. PET and DAT-SPECT provide means of discrimination between patients with PD and manganism.<sup>(61,64,65)</sup> In patients with PD, there is a reduced uptake of 6F-Dopa in the striatum, whereas the results of PET and DAT-SPECT are generally normal or minimally abnormal in patients with manganism. Neuroimaging is very important in the differential diagnosis of Parkinsonism, particularly in patients with PD with incidental exposure to Mn. When patients have high

T1 signals in the brain MRI, with a Mn exposure history, and the brain PET or DAT-SPECT shows a prominently decreased uptake, the patients can be considered as PD with coincidental Mn exposure.<sup>(52)</sup> Table 1 shows the differences between patients with chronic manganism and PD.

***Symmetry should not be considered a differential clue***

The pattern of focal asymmetry has been investigated during the course of PD, and revealed persistent asymmetry.<sup>(82,83)</sup> In patients with manganism, a high degree of symmetry was suggested to be a differential clue between patients with PD and manganism.<sup>(80,81)</sup> However asymmetrical cock gait and asymmetric dystonia were reported in patients with chronic manganism.<sup>(84)</sup> In our study, asymmetry was noted during the early stage of manganism, and persisted during the long-term follow-up course, which was very similar to that found in patients with PD.<sup>(38)</sup> Therefore, symmetry should be not considered as a differential clue between patients with PD and manganism.

***Manganism, PD and welding***

Chronic occupational exposure to high concentrations of Mn dust and fumes in mining and some industrial settings has been associated with an increased risk of “manganism”. Based on the above findings, patients with typical manganism differ from PD. However, during recent years, questions have been raised regarding a possible causal association between neurological effects and welding.<sup>(28,85-89)</sup> Although there is insufficient evidence to support the existence of such a relationship, welding has been suggested to be a risk factor for PD.

**Conclusion**

Chronic manganese poisoning can induce parkinsonism after absorption through the body circulation and transport to the CNS. Typically, manganese-induced parkinsonism differs from idiopathic PD according to the clinical features, and therapeutic responses, as well as from the results of neuroimaging studies, including MRI, 6F-Dopa PET, and DAT SPECT, and neuropathologic studies. In long-term follow-up studies, patients with PD usually present with continuous deterioration while patients with manganism presents with rapid progression during

**Table 1.** Differences between Manganism and Parkinson's Disease

Features	Manganism	Parkinson's disease
Clinical		
Symmetricity	Asymmetry or symmetry	Asymmetry
Tremor	Less frequent, rapid postural, hands, or tongue	Usually frequent, resting, pill rolling usually hands
Dystonia	Usually prominent in face (grimace) and limbs	Sometimes
Gait disturbance	More frequent, cock-walk gait, sometimes wide-base gait, gait en bloc	Festinating gait, small step gait
Long term course	Rapid deterioration in initial 5-10 years, a plateau in the following 10 years	Continuous deterioration
Therapeutic response		
to levodopa	No response	Excellent response
to other antiparkinsonian drugs	No response	Good response
Autonomic involvement	Less common	More common
Brain MRI (T1-weighted images)	Hyperintensity in initial 6 months to 1 year	Normal
Brain PET with 6F-Dopa scan	Normal	Markedly decreased
Brain PET with RAC	Mildly reduced	Increased initially, but reduced in an advanced stage
Brain DAT-SPECT	Normal or mildly decreased	Markedly decreased
Pathologic findings	Degeneration in the GP and SNr, less degree in the putamen and caudate, absence of Lewy bodies	Loss of neurons in the SNc, and LC, presence of Lewy bodies

**Abbreviations:** MRI: magnetic resonance images; PET: positron emission tomography; RAC: raclopride; DAT-SPECT: dopamine transporter- single photon emission computed tomography; GP: globus pallidus; SNr: substantia nigra pars reticularis; SNc: substantia nigra pars compacta; LC: locus ceruleus.

the initial 5-10 years, followed by a plateau during the following 10 years. It has also been hypothesized that manganese-containing welding fumes pose a hazard that may induce neurotoxicity. However, further investigations are warranted to determine the validity of this hypothesis.

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## 慢性錳中毒導致巴金森氏症候群——台灣經驗

黃錦章

過量的錳暴露可導致神經症候群，類似巴金森氏病俗稱錳症。但是仔細的觀察錳症病患，發現錳症有別於巴金森氏病，是一個臨床的特殊疾病。其區別不僅在於臨床表現，而且也在於治療效果，神經影像學如磁振掃瞄、正子掃瞄和多巴胺傳送影像和神經病理學結果。此外，經過長期追蹤研究發現，錳症病人在開始前5-10年有明顯的退步現象，接著的10年則呈現穩定狀態，此種特殊現象與巴金森氏症病患具有明顯的差別。雖然典型的錳症有別於巴金森氏病，但最近有人提出吸入過多錳的焊接粉塵，可能會加速或引起巴金森氏病，此種論點仍需進一步的探討。(長庚醫誌 2007;30:385-95)

**關鍵詞：**錳症，巴金森氏症，焊接，神經影像學，神經病理學

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