Manganese Toxicity

*Distinguishing Parkinson’s Disease from Manganese Exposure*

Parkinson’s disease (PD) is a neurodegenerative disease caused by deficiency of dopamine production in the substantia nigra region of the brain. Characteristic features of PD include resting tremor, rigidity, bradykinesia and postural instability. Interestingly, a very similar syndrome in its clinical presentation can be produced by exposure to the metal manganese (manganism), often through inhaling welding fumes.

Clinical features of manganism, in contrast to PD, include:
- Gait ataxia plus other neurologic findings (ataxia-plus)
- Cognitive impairment with psychiatric features.
- Liver failure.

Manganese toxicity is primarily thought to affect two regions of the basal ganglia, in contrast to PD: the striatum and globus pallidus. Because the two syndromes overlap in clinical features, it is important to have a strong identification of causation when evaluating these patients/clients. Although there may be significant overlap, recent studies show that these two etiologically distinct syndromes may be distinguished by:
  - The clinical presentation,
  - Therapeutic response to levodopa,
  - Biological Markers, including blood and urine Mn levels.

Recently, several publications in the peer-reviewed medical literature have pointed to the potential use of Magnetic Resonance Imaging (MRI) as a tool to distinguish these two syndromes. Specifically, the radiologic literature indicates that the T1 (spin lattice relaxation) signal in the basal ganglia on MRI can distinguish Mn-induced Parkinson’s-like disease (manganism) from dopamine-deficient PD. (Josephs 2005). This technique has the potential to allow a more definitive answer to the essential question of differentiating patients with Parkinsonism due to manganese intoxication from patients with idiopathic PD who have incidental manganese exposure. This typically involves an analysis of the clinical syndrome, the patient’s response to levodopa and pathologic features. Incorporating MRI studies in the diagnostic workup can be highly beneficial in ruling out spontaneous PD or a toxic-metabolic encephalopathy from liver disease.

By using MRI, one can specifically look for the differentiating component of PD vs. MN. Remembering that a manganese-induced movement disorder primarily affects two regions of the basal ganglia — the striatum and globus pallidus, One can select this area
as a region of interest (ROI) on MRI. Racette, et al (2005) has shown that the globus pallidum interna had increased signal on T1-weighted MRI images. In practice, a sagittal T1-weighted MRI is taken over that ROI. A Pallidal Index (PI) can then be calculated as the ratio of the signal intensity of the globus pallidus to the subcortical frontal white matter in sagittal T1-weighted MRI planes (Kodua 2004). This PI may serve as a semi-quantitative indicator of brain manganese concentration in vivo, and may functionally represent the target organ (brain) dose of occupational manganese exposure (Kim 2006).

Cognitive Impairment

Because neurocognitive loss can occur in either syndrome (PD or MN), significant impairment of activities of daily living can occur. In addition to patient reports of symptoms on eliciting the medical history, a documented measure of the degree of neurocognitive loss needs to be made. This typically encompasses a battery of written tests administered by a trained professional. The difficulty is that these test results may not correlate well with the reported symptoms and deficits, and are difficult to quantify in absolute or comparative terms. Recently, MR Spectroscopy (MRS) has come into use as a method to identify and actually measure brain areas damaged in syndromes of neurocognitive loss. The methodology involves the identification of compounds, for example N-acetylaspartate (NAA) in the brain that are associated with damaged, dying or dead neurons and nerve tracts.

Ultimately, in practice, a clinical differentiation of idiopathic PD from manganism is a clinical determination which must include determination of:
  - Complete review of the medical records,
  - Occupational History/exposure to Mn,
  - A complete physical and neurologic exam, including a hepatologic evaluation,
  - Evaluation by a testifying neurologist,
  - Targeted neuro-psychiatric testing
  - MRI,
  - Generation of an expert report on the etiology of symptoms, which incorporates the principles of causation and scientific evidence.

Conclusion

When implemented, a practical clinical program can determine with medical probability whether the extrapyramidal condition being analyzed is caused by manganese toxicity or due to a neurodegenerative process. This protocol uses valid scientific principles and refers to medical and radiologic studies published in peer-reviewed journals.

References


Seppi K and Schocke MFH. An update on conventional and advanced magnetic resonance imaging techniques in the differential diagnosis of neurodegenerative parkinsonism. *Current Opinion in Neuro*