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Neurotoxicity of Manganism: An Emerging Issue

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Toxicity from Manganese (Mn) is most commonly observed in the occupational environment. However, there have been reports of health effects from this element as a result of environmental exposures. Poisoning from this element is referred to as manganism [1,2]. This naturally occurring element primarily exists in an oxidized form usually represented as MnO_2 (manganese dioxide) or Mn_3O_4 (manganese tetroxide). It also exists in organic forms particularly as an additive to fertilizers and fuels [1]. This element is essential for normal biochemical and physiological functions and serves as a co-factor for a number of enzymes [1,3]. The suggested dietary intake of Mn is 2-5 mg/day [3]. Organ systems most affected are the liver, heart and nervous system. Absorption of this metal is usually through inhalation and ingestion. Occupationally workers are at greatest risk who are employed in welding, mining and steel production; although, those in other industries have been impacted. The frequently cited health effect from occupational exposure is the occurrence of Parkinson-associated disease events; although, such disease states have been reported in intravenous drug infusions from those abusing different types of drugs [4,5]. Other reported health effects have been associated with neurobehavioral issues, respiratory system, reproductive tracts and developmental impairments [1,5]. Inflammation of the respiratory system has been noted as an important consequence of inhaling Mn.

The first report of Parkinson-related disease associated with Mn was in 1837 by Couper. This report involved workers grinding "black oxide', resulting in high levels of exposure to Mn and the subsequent occurrence of Parkinson-like symptoms [2]. Neurotoxicity from this element is becoming of greater concern in certain occupations (e.g., welders), especially as related to the medical-legal environment [6]. However, there are difficulties in determining idiopathic Parkinson's disease (PD) from that induced by industrial activities where chronic exposure to Mn has occurred. Epidemiological studies have shown a relationship with long-term inhalation of Mn and PD [7]. Investigations [6,8] have suggested that Mn is not the only proposed metal or substance (e.g., other metals, endotoxin) responsible for causation of PD, particularity as related to long-term occupational exposure. Various sections of the brain (e.g., substantia nigra, globus pallidus, putamen, and thalamus) appear to also be affected by this and other metals/substances [6]. It is possible, there may be a synergistic or co-impaction relationship with several substances in causation of harm by Mn including occurrence of PD. It is possible that combined interactions may be contributing to various disease states as has been suggested with a leaky blood brain barrier (BBB) and endotoxin [8]. Variations of susceptibility have been suggested regarding Mn and PD [5,9]. It is likely there are numerous genetic factors influencing outcome regarding exposure to Mn along with interaction of other substances [10].

Studies [5,6] have suggested Mn-related PD is a result of dysfunction of the dopamine neurotransmission system associated with the substantia nigra. Mn may also be acting as a "trigger" for increasing the risk of idiopathic PD. It has been suggested that those with Mn-induced PD are not responsive to levodopa and has been indicated to be a determinative factor distinguishing idiopathic PD from manganism [1]. However, manganism does appear to be a variant of PD. Evaluation of Mn exposed workers with those not exposed support these findings in that Mn appears to result in pre-synaptic damage and loss of dopamine responsiveness [1]. However, with the suggestion that damage to the BBB may also be impacting susceptibility to PD these events may only be secondary to the primary insult allowing entry of neurotoxins [8]. Alternatively, Mn has been shown to affect GABAergic neurons. This could cause a disruption in the GABA homeostasis with a change in neurotransmission resulting in damage to the globus pallidus and other related systems. It has also been suggested Mn impacts glutamate regulation and

its toxicity may prevent removal of biochemical metabolites resulting in damage to the neuro-system. Mn has been shown to cause impaired biochemical functions in transporting glutamate in astrocytes resulting in defective cell signaling [11]. This dysfunction may eventually lead to an inoperable

GABA system resulting in manganism [12]. The underlying metabolic "toxicity" to astrocytes may eventually lead to the ineffectiveness of dopamine response resulting the Mn-caused PD. Manganism maybe a result of impacts from oxidative stress by Mn to different systems resulting in a Parkinson state [10].

Neurotoxicity, as related to manganism, from Mn does not appear to reversible with standard chelation therapy (CaNaEDTA) [5]. However, chelation does reduce the body burden level of Mn. A new therapy employing para-aminosalicylic acid, an anti-tuberculosis drug, has shown promise in preventing neuronal injury. Differences exist between PD and manganism, but separating these diseases clinically is difficult and in most cases impossible [6]. With improved understanding of molecular medicine distinguishing these similar diseases can be accomplished. Better information on the causes and contributing factors of manganism will allow development of novel treatments.

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