Toxin Induced Parkinsonism

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Patients with Parkinson's disease admitted to the hospital have unique presentations. This unique subset of patients requires a multidisciplinary approach with a knowledge-based care team that can demonstrate awareness of complications specific to Parkinson's disease to reduce critical care admissions, morbidity, and mortality. Early recognition of toxic exposures, medication withdrawals, or medication-induced symptoms can reduce morbidity and mortality.

Parkinson's disease toxins Parkinsonism

1. Introduction

Parkinson's disease (PD) remains the second- fastest growing movement disorder, with 7–10 million cases worldwide generating a financial burden of nearly $52 billion per year in the United States [1]. In a 2012 review, 45% of PD patients visit the emergency room (ER) annually, with 28% of these patients subsequently being admitted, making PD patients 1.4–1.5 times more likely to be hospitalized than age- and sex-matched controls [2][3]. Greater than 50% of the patients admitted are considered advanced-stage PD [4][5]. Based on a 2020 meta-analysis of 7162 admissions, the most common etiologies are infection (22%), worsening PD motor features (19%), falls/fractures (18%), cardiovascular comorbidities (13%), neuropsychiatric complications (8%), and gastrointestinal dysfunction (7%) [3]. A 2016 epidemiologic review of PD inpatient stays demonstrated the median age of patients admitted from 2002 to 2011 was 89.9 years, with a disposition to home (32.6%), facility (62.9%), or death (3.9%) [6]. Patients with PD also experience more perioperative complications, with PD being an independent risk factor for increased length of stay and morbidity when undergoing elective surgery, such as Deep Brain Stimulation (DBS) [2].

2. Toxins Induced Parkinsonism Presenting to the Emergency Room

2.1. Carbon Monoxide

Carbon monoxide (CO) is a gas that is rarely perceived by human senses. Inhalation, however, results in 40,000 annual ER visits and between 5000 and 6000 deaths [7]. It is estimated that 40% of patients who suffer from carbon monoxide poisoning will subsequently develop neurologic dysfunction [7]. A population-based cohort study (n = 9012) of patients exposed to carbon monoxide without comorbidities was at a 15.8-fold risk of developing PD [7]. A separate study of 242 patients demonstrated that 23 (9.5%) patients with carbon monoxide poisoning developed Parkinsonism within 2–26 (median = 4) weeks of exposure.

2.1.1. Pathophysiology

CO binds to hemoglobin (Hb) with a 250-fold greater affinity than oxygen [8]. CO binding results in decreased oxygen-carrying capacity of red blood cells, subsequently reducing oxygen delivery to the tissues [8]. CO subsequently inhibits mitochondrial respiration, halting oxidative phosphorylation, and decreasing Adenosine Triphosphate (ATP) production, which is most prominent in cerebral and cardiac tissue [8]. In the absence of ATP production, the electron transport chain (ETC) generates superoxide, resulting in cellular and tissue damage [8]. CO will also displace nitrous oxide (NO) from platelets, which binds with superoxide to produce peroxynitrite, resulting in additional mitochondrial inhibition and increased platelet activation [8]. Myeloperoxidase (MPO) and reactive oxygen species (ROS) are formed, which impact myelin basic protein, triggering a lymphocytic response and microglial activation [8]. Reduced cerebral oxygenation and increased mitochondrial inhibition result in anoxic brain injury, which is often delayed but can be rapid, resulting in death hours after CO poisoning [8]. Parkinsonism in the setting of CO poisoning is attributed to bilateral globus pallidus involvement [9]. While the exact pathogenesis of Parkinson's induction from CO intoxication remains unclear, recent studies suggest it is a result of oxidative stress from structural damage, whether from reperfusion injury or prolonged ischemia [10].

2.1.2. Clinical Presentation and Diagnosis

Acute presentation of CO poisoning manifests itself as headache, fatigue, nausea, emesis, cognitive impairment, chest discomfort, shortness of breath, lightheadedness, and potentially loss of consciousness [8]. Chronic exposure can result in fatigue, vertigo, paresthesia, abdominal pain, diarrhea, and polycythemia [8]. While acute presentations, with emergency medical services identifying exposure upon arrival, may be overtly diagnosed, chronic exposures may pose a diagnostic challenge. Given that conventional pulse oximetry may not identify COHb, clinical suspicion is necessary to accurately identify the presence of CO [8]. Non-specific neurologic manifestations of CO toxicity include changes in mood (anxiety, depression), cognitive dysfunction (memory), disequilibrium (vertigo), and motor deficits [8]. MRI of the brain may demonstrate bilateral globus pallidus T2 hyperintensities, in addition to diffuse atrophy with increased ventricular size and sulcal widening [11]. In severe exposures, the corpus collosum, internal capsule, external capsule, and subcortical white matter may also be affected [11].

Patients with CO exposure may present after 2–26 (median = 4) weeks with Parkinsonism and encephalopathy [9]. Parkinsonism manifestations include bradykinesia, masked faces, rigidity, and retropulsion with associated frontal release signs such as the grasp reflex or glabella sign [9]. While an intention tremor and disequilibrium are typically seen, a resting tremor is typically absent [9].

2.1.3. Treatment

The standard of care is 100% normobaric oxygenation, though hyperbaric therapy has been utilized, and limited data exist to support hyperbaric over normobaric oxygen therapy [9]. Pharmacologic therapy is currently under investigation and may have pre-hospital applications, though none are currently Food and Drug Administration

(FDA) approved therapies [9]. In the clinical experience, complete recovery can be achieved, though the prognosis is often dependent on exposure time and time to treatment.

2.2. Manganese

Occupational history is a salient aspect of manganese toxicity evaluation, as exposure is common for intravenous (IV) drug abusers, welders, miners, steel workers, battery manufacturers, and fungicide production (Maneb) [12]. Grain, dried fruit, vegetables, nuts, and tea are the primary nutritional sources of manganese and may also be seen in patients on long-term parenteral nutrition [11]. Oral ingestion of food sources rarely causes toxicity, except in the setting of liver failure, which results in reduced excretion [11].

2.2.1. Pathophysiology

Trivalent manganese is the reactive form that results in PD [11]. Trivalent manganese has a high affinity for neuromelanin, which can be found in high concentrations in the pars reticulata of the substantia nigra and basal ganglia, key anatomical aspects of PD [11]. Mitochondrial uptake inhibits oxidative phosphorylation and results in calcium accumulation [11]. Manganese also exhibits functional impairment of glutamate transport, increasing glutamate accumulation with subsequent apoptosis [11]. Autoregulation of dopamine release, in addition to the depletion of cerebral dopamine, results in amplified dopamine synthesis and release. Chronic sequelae result in neurotoxicity of the globus pallidus [11].

2.2.2. Clinic Presentation and Diagnosis

At presentation, acute psychosis is often noted, with associated headache, vomiting, and hepatic dysfunction [11]. Psychosis will begin to resolve with the emergence of Parkinsonism, which will include steppage gait with dystonic features, imbalance, ataxia, and kinetic tremor [11]. The gait will be an important feature, as idiopathic PD presents with a shuffling gait [11]. Recognition of phenomenology and target occupational and exposure questioning are keys to early identification of manganese toxicity. Laboratory analysis and radiographic investigation may demonstrate elevated manganese in urine, serum, and whole blood [11][13]. MRI of the brain may demonstrate T1 hyperintensity in the caudate, putamen, and globus pallidus [11][13].

2.2.3. Treatment

Removal of exposure is critical in the treatment of acute manganese toxicity [13]. Chelation therapy utilizing intravenous ethylenediaminetetraacetic acid (EDTA) increases manganese excretion, but has not demonstrated significant clinical improvement [12]. Patients may respond to dopaminergic therapy, though reports suggest it is less prominent when compared to idiopathic PD [12]. In the experience, prolonged manganese exposure results in persistent Parkinsonism that is not as responsive to medical therapy.

2.3. MPTP

1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), formed as a byproduct of 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP) is a meperidine analogue known to induce Parkinsonism in humans [14]. MPTP, sold under the guise of “Synthetic Heroin,” was originally identified in IV drug abusers [14]. No other sources of MPTP have been identified.

2.3.1. Pathophysiology

MPTP induces a neurotoxic effect in the substantia nigra pars compacta because of Monoamine oxidase B (MOA-B) activity, generating 1-methyl-4-phenyl pyridine, inciting free radicals and oxidative stress [12]. 1-methyl-4-phenyl pyridine targets intracellular dopaminergic neurons by inhibiting Complex I of the ETC, resulting in endoplasmic reticulum stress and apoptosis [12]. MPTP is also a rare cause of Parkinsonism.

2.3.2. Clinical Presentation and Diagnosis

Patients will present with rapid onset Parkinsonism manifesting as bradykinesia, and rigidity with a resting tremor in the setting of recent IV drug use. Clinical diagnosis is key, as there are no known biomarkers [12].

2.3.3. Treatment

Acute onset MPTP Parkinson’s disease is a neurologic emergency requiring astute identification and rapid removal of the offending agent to minimize neuronal damage. Non-selective Monoamine Oxidase Inhibitor (selegeline) has been used to reduce neurotoxicity ameliorating clinical symptoms [14][15]. Symptomatic relief may be achieved with dopaminergic therapy [12]. This change is typically permanent in terms of developing PD-like symptoms, as documented clinically in past exposures [11].

2.4. Rotenone

Rotenone was discovered following exploration for a functional analogue of MPTP. Rotenone is primarily utilized as an agricultural insecticide and as an ingredient in home and pet products [16]. The naturally occurring plant species (timbo, barbasco, cub, haiari, and nekoe) have been employed as pesticides by indigenous groups [16]. As with MPTP, rotenone is a rare cause of PD; however, both serve as a reminder to consider exposures when hospitalizing patients with PD.

2.4.1. Pathophysiology

Rotenone inhibits Complex I of the ETC, causing mitochondrial toxicity in the same pathway as MPTP, though microtubule destabilization has also been proposed as a mechanism [16]. Selective injury to the nigral dopaminergic neurons, in addition to cytoplasmic α-synuclein accumulation, induces motor and non-motor features of Parkinsonism [16]. Rotenone has a short half-life, without bioaccumulation, though animal models have demonstrated that brief exposures can result in progressive Parkinsonism.

2.4.2. Clinical Presentation and Diagnosis

The diagnosis is based on clinical evaluation and exposure history. Human data is sparse, but based on rat models, repeated exposures are necessary to induce structural changes that result in the clinical manifestations of Parkinson's disease [16][17]. Patients exposed to rotenone toxicity often present with conjunctivitis, dermatitis, pharyngitis, congestion, and vomiting when ingested [12]. Tachypnea may be present if the substance is inhaled [12]. Continued exposure will result in Parkinsonism with bradykinesia, postural instability, and rigidity [12]. No specific biomarkers are commercially available [12].

2.4.3. Treatment

The offending agent should be promptly removed. Symptomatic management may be achieved with dopaminergic agents and an adenosine receptor agonist [12]. While not FDA approved, dietary phytocannabinoid has been shown to decrease neurotoxicity in rat models [12]. Clinically, Rotenone results in permanent PD-like symptoms that are minimally responsive to drug therapy.

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