Multiple System Atrophy

The Putative Causative Role of Environmental Toxins

Philip A. Hanna, MD; Joseph Jankovic, MD; Joel B. Kirkpatrick, MD

Background: Whereas a number of studies have investigated the putative role of environmental toxins in the pathogenesis of idiopathic Parkinson disease, the possibility of such a role in multiple system atrophy has received little attention.

Design and Setting: Review of records of patients examined in the Parkinson’s Disease Center and Movement Disorder Clinic, Baylor College of Medicine, Houston, Tex, from July 1, 1977, to February 4, 1998.

Patients: We reviewed 100 consecutive medical records of patients who satisfied the diagnostic criteria for multiple system atrophy formulated by the Consensus Committee of the American Autonomic Society and the American Academy of Neurology.

Intervention: The type and amount of toxin exposure were verified by history and examination of records whenever possible. Severity of parkinsonism was assessed by clinical rating scales.

Main Outcome Measure: Development of multiple system atrophy after environmental toxin exposure.

Results: Eleven patients had a notable history of heavy exposure to environmental toxins. One patient with multiple system atrophy confirmed by postmortem evaluation was exposed to high concentrations of malathion, diazinon, and formaldehyde, while the other patients with multiple system atrophy had well-documented high exposures to agents including n-hexane, benzene, methyl isobutyl ketone, and pesticides. The case studied pathologically demonstrated extensive advanced glial changes, including glial cytoplasmic inclusions in deep cerebellar white matter, brainstem, cortex (superior frontal, insula) and putamen, with notable cell loss and depigmentation of the substantia nigra and locus ceruleus.

Conclusion: While many studies report a possible role of environmental toxins in Parkinson disease, such a role is even more likely in multiple system atrophy, as this is a sporadic disease.

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A number of studies have evaluated the possibility of a causative role of environmental toxins in Parkinson disease (PD), but the possible role of these toxins in the etiology of multiple system atrophy (MSA) has not been investigated. Multiple system atrophy is a sporadic, progressive, adult-onset disorder with overlapping features of Shy-Drager syndrome, striatonigral degeneration, and olivopontocerebellar atrophy, and may be designated MSA-A (Shy-Drager syndrome–predominant autonomic dysfunction), MSA-P (striatonigral degeneration–predominant parkinsonism), and MSA-C (olivopontocerebellar atrophy–predominant cerebellar ataxia). The 3 disorders are linked by the presence of a recently discovered histological marker, the glial cytoplasmic inclusion.

Of the 100 patients with MSA, there were 11 cases with a notable history of heavy exposure to environmental toxins (Table). Three illustrative cases are presented below in more detail.

Although we routinely query all patients about possible toxic exposure, we found that only 1 of the 100 patients with PD had potential exposure. He had lived on a farm all his life with reported exposure to herbicides and pesticides, but the degree and type of exposure were unknown to the patient.

Case 1

A mushroom farmer was referred to our clinic in January 1991, at age 46 years, with a 3½-year history of decreased dexterity and rest tremor of the right upper extremity along with progressive freezing of gait and falling. Further symptoms included moderate depression, severe snoring, prominent dysarthria, and frequent episodes of postural lightheadedness with occasional syncopal episodes.
SUBJECTS AND METHODS

We reviewed 100 consecutive medical records of patients examined in the Parkinson’s Disease Center and Movement Disorder Clinic, Baylor College of Medicine, Houston, Tex, from July 1, 1977, to February 4, 1998, who satisfied the diagnostic criteria for MSA formulated by the Consensus Committee of the American Autonomic Society and the American Academy of Neurology. In addition, consecutive medical records of 100 patients with PD were reviewed.

The patient reported having worked for 2 years (approximately 4 years before the examination) in a mushroom factory, where he was exposed to high concentrations of the organophosphorous pesticides malathion and diazinon, and to formaldehyde. His task was to sterilize a 7.5 × 7.5-m room (which had only 1 ventilator) by spraying these chemicals within the room (including on the ceiling). This exposure was for at least 2 hours every night, during which the patient was drenched with these chemicals, as he did not wear any protective clothing or mask. One other worker in the same plant allegedly developed PD. The onset of the foregoing symptoms occurred nearly 6 months after the patient stopped working in the mushroom factory.

The patient had been taking carbidopa-levodopa for 2 years before the clinic visit, with only mild improvement in his symptoms for nearly 1 1/2 years. The levodopa therapy was, however, complicated by severe dyskinesias manifested by choreiform movements of the head and extremities. Medications included clonazepam, 0.5 mg orally every night, and carbidopa-levodopa 25/100, 2 tablets 3 times a day. Family history was noncontributory except for a lifelong history of tremor of the right arm in the patient’s father. There was no reported intravenous illicit drug use or neuroleptic exposure.

Initial examination disclosed intact speech, language, and cognitive functioning. There was mild limitation of upgaze, but the extraocular movements were otherwise normal. The patient had action-induced myoclonus involving the pectoral muscles as well as the 4 extremities. A 6- to 7-Hz flexion-extension tremor at rest and during posture holding was seen in the right arm and both legs. There was also dystonic posturing of the right arm. Rigidity was 3+ (0-4 scale) in the neck and right arm, 2+ in the left arm, and 4+ bilaterally in the lower extremities, and body bradykinesia was rated 4+. He was unable to rise from a chair without assistance and had markedly stooped posture with prominent freezing and severe difficulty with gait initiation. Deep-tendon reflexes were symmetrical, with flexor plantar responses. Results of a sensory examination were unremarkable.

An electroencephalogram was normal, and there was no electroencephalographic correlate associated with the myoclonus. Electromyography and nerve conduction studies showed normal motor and sensory conduction studies in the right arm and leg. A polyelectrolymographic study showed a 5- to 7-Hz tremor with random brief electromyographic bursts consistent with myoclonus. Magnetic resonance imaging of the brain demonstrated diffuse cortical atrophy. The results of cerebrospinal fluid examination were normal. These studies were obtained during a hospital admission, shortly after the clinic visit, that was remarkable for aspiration pneumonia with near–respiratory arrest that required temporary ventilator support. A tracheotomy was later performed secondary to severe obstruction and central sleep apnea. In addition, the patient demonstrated marked orthostatic hypotension with decreases in blood pressure of more than 30 mm Hg from supine to standing.

The patient’s condition declined steadily, and he died of respiratory complications. The autopsy, performed on November 3, 1992, showed findings consistent with MSA. Extensive advanced glial changes including glial cytoplasmic inclusions were seen particularly in the deep cerebellar white matter (Figure 1), brainstem, cortex (superior frontal, insula, and hippocampus), and putamen by Bielschowsky and ubiquitin stains (Figure 2). There was prominent involvement (cell loss with depigmentation) of the substantia nigra and locus ceruleus. In addition, there was widespread cortical neuronal loss, particularly in the frontal and temporal regions (with relatively sparing of the hippocampus) with neurofibrillary tangles and neurontil threads, without senile plaques. Sections of the midbrain show a moderate loss of substantia nigra neurons, pigment extravasation into the surrounding neuropil, neuronophagia, and occasional Lewy bodies. Occasional Lewy body inclusions were also seen in the cortical areas (superior frontal in particular) and rarely in the thalamus, putamen, and globus pallidus. In addition, neuronal cytoplasmic inclusion bodies were present in the tegmentum of the pons. An incidental vascular malformation was seen in the midbrain tectum near the inferior colliculus.

CASE 7

A 50-year-old fireman was examined in December 1997 with a 2-year history of dysarthria and stuttering, decreased upper-limb dexterity most prominent on the left, anterocollis, a shuffling gait, and a 3-month history of dysphagia, urinary incontinence, postural lightheadedness, heavy snoring, and decreased sexual function. He had previously worked in pest control for 10 years, with extensive exposure to various pesticides including diazinon and chlorodane. He primarily sprayed against roaches and termites for 8 to 9 hours a day, most commonly while crawling under homes or working in attics with poor ventilation, and typically without wearing a protective mask or clothing. He had no response to carbidopa-levodopa while taking a maximum of 1 g of levodopa per day. His father reportedly was alcoholic with upper-extremity tremor.

The patient complained of postural lightheadedness, but orthostatic blood pressure changes could not be documented on examination. He had severe stuttering, lateral oscillating head tremor, and facial tremor, with anterocollis and hypomimia. There was mild 4-extremity tremor at rest. Rigidity and bradykinesia were of moderate degree and worse on the left side. Gait testing showed decreased left-
arm swing but was otherwise unremarkable. A T$_2$-weighted magnetic resonance image of the brain displayed hypointensity of the globus pallidus bilaterally, extending into the putamen, with hyperintensity in a linear fashion along the lateral border of the putamen, consistent with findings seen in patients with MSA.

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Clinical Features</th>
<th>Occupation</th>
<th>Toxic Exposure History</th>
<th>Coworkers With Parkinsonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/46</td>
<td>Parkinsonism, dysautonomia, poor levodopa response</td>
<td>Mushroom farm worker</td>
<td>2-y history of spraying malathion, diazinon, and formaldehyde in poorly ventilated room</td>
<td>1</td>
</tr>
<tr>
<td>2/M/56</td>
<td>Parkinsonism, anarthria, blepharospasm, anterocollis, dysautonomia, levodopa nonresponsive</td>
<td>Communication engineer</td>
<td>15-y history of installing communications systems with exposure to pesticides, cyanide gas, wood-cleaning solution containing hydrocarbons</td>
<td>0</td>
</tr>
<tr>
<td>3/M/59</td>
<td>Parkinsonism, spastic gait with extensor plantar responses, anterocollis with no tremor, dysautonomia, nonsustained response to levodopa</td>
<td>Chemical plant supervisor</td>
<td>20-y history of direct daily exposure to benzene, n-hexane, methyl isobutyl ketone, naphtha, phosgene, epichlorhydrin, sulfuric acid, formaldehyde, and carbon disulfide</td>
<td>1</td>
</tr>
<tr>
<td>4/M/72</td>
<td>Parkinsonism with predominant gait and postural impairment, anterocollis, dysautonomia, levodopa nonresponsive</td>
<td>Entomologist</td>
<td>30-y history of examining cotton plants in the fields for 8-9 h/d shortly after they were sprayed with pesticides (primarily malathion and diazinon)</td>
<td>2</td>
</tr>
<tr>
<td>5/M/74</td>
<td>Parkinsonism, dysautonomia, levodopa nonresponsive</td>
<td>Laboratory technician at chemical plant</td>
<td>15-y exposure to bismuth, cobalt, iron, nickel, chromium, silica, and acrylonitrile; urine examination showed elevated nickel and zinc levels</td>
<td>3</td>
</tr>
<tr>
<td>6/M/60</td>
<td>Parkinsonism, dysautonomia, levodopa nonresponsive</td>
<td>Chemical engineer</td>
<td>Worked in same oil refinery for 30 y, exposed to fumes (particularly benzene)</td>
<td>≥3</td>
</tr>
<tr>
<td>7/M/50</td>
<td>Parkinsonism, severe dysarthria and dysphagia, dysautonomia, anterocollis, levodopa nonresponsive</td>
<td>Fireman, pest control</td>
<td>From 1975 to 1984, worked in pest control, spraying insecticides (primarily diazinon and chlordane) for 8-9 h/d</td>
<td>0</td>
</tr>
<tr>
<td>8/M/47</td>
<td>Parkinsonism, dysautonomia, sleep apnea, nonsustained mild response to levodopa</td>
<td>Industrial plant worker</td>
<td>Approximately 5-y history of exposure to benzene and other hydrocarbons</td>
<td>2</td>
</tr>
<tr>
<td>9/F/60</td>
<td>Parkinsonism; anterocollis; dysautonomia; mild, nonsustained response to levodopa</td>
<td>Homemaker</td>
<td>Lived immediately adjacent to melon fields for nearly 30 y, sprayed weekly by plane with pesticides; her car was covered by thick film after each session</td>
<td>Aware of 8 people in her immediate vicinity with “Parkinson disease”</td>
</tr>
<tr>
<td>10/M/70</td>
<td>Parkinsonism, severe dysarthria, dysphagia, anterocollis, dysautonomia, levodopa unresponsive</td>
<td>Aeronautical worker</td>
<td>26-y history of inspecting airplane engines typically in enclosed environment with constant exposure to large amounts of kerosene fumes</td>
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</tr>
<tr>
<td>11/M/65</td>
<td>Parkinsonism, urine incontinence, orthostasis, sexual dysfunction</td>
<td>Horticulturist</td>
<td>25-y history of spraying pesticides including malathion, diazinon, and trichlorophenoxyacetic acid</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 1. Numerous glial cytoplasmic inclusions (arrows) within glial cells located in the deep cerebellar white matter adjacent to the fourth ventricle (Bielschowsky stain, original magnification ×400).

Figure 2. A glial cytoplasmic inclusion (arrow) taken from a section of the putamen (ubiquitin, original magnification ×400).
CASE 11

A 65-year-old horticulturist was examined in our clinic in February 1998 with a 1 1/2-year history of a slowly progressive akinetic-rigid syndrome with a slow, shuffling gait and decreased dexterity of his upper limbs; sexual dysfunction; orthostatic hypotension with supine blood pressure of 108/50 mm Hg dropping to 70/50 mm Hg when he was upright; and snoring with reported apnea and daytime sighing. He had recently begun taking carbidopa-levodopa, with mild benefit. He had worked for 25 years as a horticulturist, having retired 1 year before the onset of symptoms. This work included the near-daily spraying of pesticides, most commonly malathion, diazinon, and trichlorophenoxycetic acid, for at least 1 to 2 hours per day. He “almost never” wore a mask, gloves, or other protective gear while spraying these agents.

Examination disclosed moderate hypomimia, mild bilateral upper-extremity kinetic tremor, moderate 4-extremity rigidity, and bradykinesia, worse in the legs. Gait testing displayed decreased arm swing with marked postural instability. Magnetic resonance imaging of the brain demonstrated marked signal hypointensity on T2-weighted images in the globus pallidus bilaterally, extending into the putamen, with hyperintensity in a linear fashion along the lateral border of the putamen.

The common link among the patients described herein, all of whom had the clinical features of MSA, was an unusually heavy exposure to occupational toxins. As this is not an epidemiological study, we cannot prove that the toxic exposures caused the development of MSA in these patients. Certain of the toxins, however, such as n-hexane, pesticides, cyanide, and formaldehyde, have been linked to the development of parkinsonism. Further support of the causative role of these toxins in these cases is that the majority of our patients had colleagues with a parkinsonian disorder, who had a history of exposure similar to that of the patients, suggesting the possibility of a “cluster.”

Theories of environmental toxin exposure having a role in parkinsonian disorders have drawn more attention from the scientific community since the discovery of parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and the evidence of a possible environmental cause of the amyotrophic lateral sclerosis–parkinsonism–dementia complex of Guam. MPTP produces selective degeneration of the substantia nigra and locus ceruleus, and eosinophilic intraneuronal inclusions similar to Lewy bodies. MPTP is a lipophilic protoxin, requiring conversion into 1-methyl-4-phenylpyridinium ion by monoamine oxidase B in glia. 1-Methyl-4-phenylpyridinium ion is then taken up into dopaminergic neurons and blocks complex I of the electron transport chain, which ultimately leads to free radical formation and subsequent cell death.

A number of epidemiological studies have suggested the possible role of environmental toxins in the development of PD, but similar data are lacking in parkinson-plus disorders, such as MSA. Although intriguing, these studies have failed to establish a clear link between environmental toxins and PD. Since MSA is a sporadic disorder, without strong evidence of genetic cause, the hypothesis of toxin-induced MSA may be more plausible than that of toxin-induced PD. Furthermore, in addition to our cases, MSA-like disorders have been reported as a result of exposure to certain toxins. For example, manganese intoxication, reported in manganese miners, in those manufacturing dry batteries, and in those with long-term ingestion of potassium permanganate, can produce clinical, neuroimaging, and pathological findings that may overlap with those of MSA. Pezzoli et al described a woman who developed parkinsonian symptoms at age 45 years after a 20-year exposure to glues that contained n-hexane. Although her condition initially responded to levodopa, it later deteriorated and she developed autonomic dysfunction, axonal neuropathy, and anemia caused by bone marrow suppression. Pathological examination of the brain showed severe dopaminergic neuronal loss with marked gliosis in the substantia nigra, with nearly complete loss of tyrosine hydroxylase immunostaining in the striatum. Neuronal loss was also present in the locus ceruleus, pedunculopontine nucleus, and periaqueductal gray matter. Other toxins that have been documented to cause MSA-like parkinsonian disorders include inorganic mercury, methyl, carbon tetrachloride, carbon disulfide, and cyanide.

The role of environmental toxins in the pathogenesis of PD has been emphasized in the past, but the recent discovery of a mutation in the gene on chromosome 4 that codes for α-synuclein suggests that perhaps genetic factors alone are sufficient to cause the disease. In contrast, there is no evidence of genetic predisposition in MSA, and, therefore, the possibility of environmental causes seems more likely. While a toxin-induced model of MSA, similar to the MPTP model of PD, is still lacking, there are toxins that can cause an MSA-like disorder in experimental animals. For example, intrastriatal injection of 3-nitropropionic acid (a mitochondrial toxin) into experimental rats produces degeneration of intrinsic striatal neurons, the transverse fiber bundles of the internal capsule in the striatum as well as the nigrostrial dopamine system. The behavioral and pathological features led the authors to conclude that this may serve as a model of MSA. Deutch et al reported that intraperitoneal injection of 3-acyethylpyridine in rats produces neurochemical and histological changes consistent with olivopontocerebellar atrophy. In addition to causing degeneration of the nigrostriatal dopaminergic pathway, this neurotoxin also causes degeneration of the climbing fibers that normally originate in the inferior olive and terminate in the cerebellum.

Although a variety of toxins have been implicated in the pathogenesis of MSA in our cases, organic solvents appear to be particularly common. Organic solvents also have been reported to contribute to the development of another parkinson-plus disorder, progressive supranuclear palsy. That report described 4 such cases: a housewife with extensive exposure to liquid insecticides, 2 lithographers with daily exposure to “solvents,” and a banker who was an avid horticulturist and was exposed to “insecticides with organic solvent bases.” Exposure to organic solvents (benzene, n-hexane, methyl isobutyl ketone, and epichlorohydrin) and pesticides (malathion, diazinon, and chlor dane) was prominently noted in our patients. Toxic exposure to organic solvents may result in a variety of behavioral, sensory, and motor deficits.
Although MSA has not been previously attributed to this class of toxins,30 Methyl isobutyl ketone is an industrial and pharmaceutical solvent. Peripheral neuropathy has been reported after occupational exposure to methyl butyl ketone.31 Pesticides include the organochlorines, organophosphates (diazinon, malathion), carbamates, pyrethrins, and rotenone. Long-term exposure to these agents may cause peripheral as well as central nervous system abnormalities,32 but despite the implication of pesticides in the development of parkinsonism in various epidemiological studies,17,15 pesticides-induced MSA has not been documented.

Our case 1 demonstrates the typical histological features of MSA: a wide distribution of glial cytoplasmic inclusions, as well as neuronal cytoplasmic inclusions, and neuropil threads.3-11 In addition, similar to other reported cases of MSA,33 this patient had marked degeneration in the substantia nigra and locus ceruleus. The relative sparing of the striatum, in contrast to the typical, pathologically proved, sporadic cases of MSA, suggests that the toxin(s) preferentially damaged the most vulnerable areas, namely the substantia nigra and locus ceruleus.

We recognize that objective evidence proving a causative relationship between the toxin exposure and the development of MSA in our patients is lacking. Nevertheless, the striking and prolonged exposure of the toxins, the suggestion of clusters in some cases, and the absence of alternative explanations for the occurrence of the disorders support the possibility of toxin-induced neurodegeneration. Such cases may have an atypical course. Although we do not suggest that all cases of MSA have an antecedent toxic exposure, we believe that the findings of our study provide support for future population-based study of environmental factors in MSA.

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Reprints: Joseph Jankovic, MD, Department of Neurology, Parkinson’s Disease Center and Movement Disorders Clinic, Baylor College of Medicine, 6550 Fannin St #1801, Houston, Texas 77030.