Multiple Sclerosis Disease Progression and Paradichlorobenzene: A Tale of Mothballs and Toilet Cleaner

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The following case report illustrates how the diagnosis of paradichlorobenzene (PDCB) neurotoxicity can be challenging, especially in patients with an existing neurological diagnosis. A thorough history of PDCB exposure or ingestion is critical. In suspected cases, family members should be questioned so that exposure can be ceased and potentially beneficial interventions initiated.

Report of a Case

An African American woman in her late 30s with a history of relapsing-remitting multiple sclerosis was admitted with 3 weeks of fatigue, worsening lower extremity weakness, and an ichthyosiform rash that symmetrically involved her legs, arms, and trunk. During a workup for injuries related to a motor vehicle collision 5 years earlier, several white matter lesions were found on brain magnetic resonance imaging (MRI) and a cerebrospinal fluid study was positive for oligoclonal bands. Though she had no neurological symptoms prior to this, following the collision she reported intermittent blurred vision, right leg paresthesias, and short-term memory problems. A diagnosis of relapsing-remitting multiple sclerosis was made, and she began interferon beta-1b treatment. She experienced no significant change in symptoms with this therapy. The patient’s medical history was also significant for iron-deficiency anemia, sickle cell trait, and a single episode of depression.

At her first visit to our clinic, her only multiple sclerosis (MS) symptom was left circumferential thigh paresthesias. Over the next 3 months, she developed bilateral intranuclear ophthalmoplegia and began to experience impaired vision and a constant opsoclonus. During the next 3 years, she had several exacerbations of these symptoms. In addition, her gait became wide based, and she began to require the use of a walker for ambulation. A brain MRI obtained during an exacerbation showed 2 new lesions compared with a study from 4 years earlier: a single nonenhancing focus of T2 hyperintensity in her right temporal lobe and an enhancing lesion in the left parietal lobe. An MRI of the cervical spine at the time showed an area of T2 hyperintensity in the left posterior lateral cord. The patient was treated with high-dose intravenous steroids for an acute attack, and natalizumab therapy was initiated at the end of the episode.

Since then, the patient received 31 doses of natalizumab, with a 3-month interruption in therapy because of false-positive neuromyelitis optica-IgG test results. Despite natalizumab treatment, the patient continued to have visual symp-
toms, left leg weakness, and a wide-based gait that contributed to a decline in her ability to walk.

First Hospital Admission
At presentation, the patient complained of generalized fatigue. In addition, she reported worsening lower extremity weakness. She had previously been able to walk within her home unassisted, whereas now she was unable to rise from a seated position, stand upright, or walk without assistance from caretakers. Shortly after the onset of fatigue and weakness, a rash appeared, first on both of her feet and legs, then on her trunk and arms. It spared the face and scalp. The patient denied any associated pain, itching, redness, or warmth.

Further questioning brought to attention the patient’s long-standing history of chewing on toilet bowl deodorizing cakes. The main ingredient in this product is 99.9% PDCB, which is also used in mothballs. The patient described taking a single bite out of the toilet bowl deodorizer, chewing for several seconds, and spitting it out. She took only 1 bite per day but had done this on and off several times a week for more than 15 years. Her use had been regular for the past 5 years, averaging 1 bite per day, 3 or 4 days per week. According to the patient, the practice did not produce euphoria; rather, it provided a sense of calm that helped reduce anxiety. She denied changing her pattern of use at any point over the past 5 years or in the month prior to hospital admission.

On entering the patient’s room, there was a strong odor of PDCB. Pertinent findings on her examination included no orientation to time, slowed responses to questions and commands, a bilateral intranuclear ophthalmoplegia and nystagmus in all planes, and diminished strength with left-sided hip flexion, knee flexion, and extension, as well as brisk upper extremity reflexes with spreading to the triceps on the left side, downgoing plantar reflexes, and 3 to 4 beats of left ankle clonus. Newly identified deficits included upper extremity dysmetria on finger to nose, as well as truncal ataxia.

Perhaps the most concerning finding was the patient’s rapid cognitive decline over the short period since her last office visit. She exhibited marked deficits on neurocognitive testing, including impairment of orientation, attention, and recall, as well as impaired visuospatial and executive function.

Her skin rash was ichthyosiform in appearance, with prominent scaling (Figure 1). It involved her upper and lower limbs, hands, feet, and trunk up to her neckline.

Initial MRI scans of the brain and cervical and thoracic cord revealed decreased prominence of several white matter lesions compared with scans obtained 3 and 4 years earlier and no new or enhancing lesions. Periventricular lesions and lesions within the corpus callosum were consistent with a diagnosis of MS (Figure 2).

Nerve conduction studies of the left peroneal, tibial, and sural nerves, including F-wave latencies, and an electromyogram of the left lower extremity muscles were essentially normal. An electroencephalogram performed at the time was also normal.

Laboratory findings were unremarkable: a basic metabolic panel and levels of vitamin B₁₂, folate, thyrotropin, and free T₄ were all within normal limits. Test results for JC virus, human immunodeficiency virus 1, and human immunodeficiency virus 2 antibodies were negative. Results of rapid plasma reagin were nonreactive, as were assay findings for anti-N-methyl-D-aspartate receptor antibodies, anti-thyroid peroxidase, anti-thyroglobulin antibodies, and ferritin. Cerebrospinal fluid analysis demonstrated more than 2 oligoclonal bands by isoelectric focusing, clear fluid with less than 1000 white blood cells per milliliter, and normal protein and glucose levels and was absent of organisms. Her PDCB blood level was 18 μg/mL.
The diagnoses MS exacerbation and PDCB-induced encephalopathy were entertained. The patient was treated with 5 days of intravenous methylprednisolone, 1 g daily. Fluoxetine was initiated at a dose of 60 mg daily, and it was decided to continue therapy with natalizumab. Through the course she remained alert, awake, and able to follow commands. At discharge, she was able to walk with a walker. She was sent home, where she was no longer supposed to have access to PDCB.

**Second Hospital Admission**

Within days of discharge, the patient’s mother contacted the MS clinic to inform her physicians that the patient was disoriented, incontinent of urine and bowels, not eating, and no longer able to walk without assistance. She was readmitted to the hospital 2 weeks after her last discharge. On examination, she was afebrile, and her vital signs were within normal limits. She was alert and oriented to self and place, but not time. Her affect was flat, and her responses were slowed. Her neurological examination was essentially unchanged.

The patient was found to have a white blood cell count of 24,600/mm³, which subsequently increased to as high as 33,000/mm³. Based on the results of a chest radiograph, the patient was diagnosed with aspiration pneumonia. This diagnosis was consistent with a swallowing evaluation showing limited oral range of motion and weakness.

Repeated lumbar puncture again showed normal blood cell count, glucose and protein levels, no organisms, and more than 2 oligoclonal bands. Serological results for JC virus were negative. The PDCB blood level had fallen to 1.8 μg/mL. An electroencephalogram was read as normal with a 9- to 10-Hz alpha rhythm.

The results of neuropsychological testing were consistent with major depression; however, she reported having a difficult time seeing visual stimuli secondary to her MS, resulting in reduced testing. Her performance on verbal measures was significantly impaired, though there were concerns for variable effort secondary to depression.

Repeated brain MRI compared with the study obtained during her initial admission showed interval development of diffuse white matter hyperintensities involving the corona radiata and centrum semiovale bilaterally as well as the cerebral peduncles/corticospinal tracts (Figure 3). They did not enhance with intravenous gadolinium.

Over the next week, the patient’s level of alertness progressively decreased and she became stuporous and unable to protect her airway. On examination she was lethargic but able to follow simple commands, grip with her right hand, and move the right toes. Her gaze was dysconjugate. She was tachycardic and tachypneic. Repeated electroencephalogram was disorganized with diffusely slow background frequencies in the delta and theta range. Then, 16 days after the start of her second admission, the patient developed respiratory failure and was intubated and mechanically ventilated.

There was no clinical improvement. The patient remained ventilator dependent and minimally responsive, occasionally squeezing with her right hand on command or moving her right foot. Eyes were open at times and gaze remained dysconjugate. Her PDCB level was 1.1 μg/mL. She was discharged to a long-term care facility 8 weeks after her initial hospital admission. After admission to this facility, her clinical condition continued to worsen. She had spontaneous eye movements but did not follow commands and had no spontaneous movements. Ventilatory and nutrition support were continued. Two months later, she remained in the hospital and awake, followed some commands, and required oxygen via tracheostomy but did not require mechanical ventilator support. Her family declined to continue treatment of her MS.

**Discussion**

We describe the case of a woman in her late 30s with relapsing-remitting multiple sclerosis receiving natalizumab therapy who had rapid cognitive decline, fatigue, progressive
Gait impairment, and an ichthyosiform skin rash in the setting of long-term PDCB ingestion. In the absence of other significant laboratory findings, and a lack of response to natalizumab, we propose that the patient’s neurological decline and skin rash are explained by leukoencephalopathy due to long-term PDCB exposure.

We were alerted to a secondary cause of the patient’s concerns by her precipitous neurological deterioration in the absence of increased disease activity on MRI. We conclude that PDCB ingestion over many years, which eventually may have surpassed a threshold toxic for neurons and glial cells, was the cause of the patient’s rapid neurological deterioration and encephalopathy.

Aromatic hydrocarbons are known to cause leukoencephalopathy in toxic concentrations. For instance, toluene leukoencephalopathy is a well-characterized demyelinating disorder that spares the axons and afflicts central nervous system–producing neurobehavioral deficits. The precise mechanism is unknown. Paradichlorobenzene is a chlorinated aromatic hydrocarbon, C₆H₄Cl₂, and is the principal ingredient in the toilet deodorizer this patient consumed. It is highly volatile with a strong distinctive odor. It is well absorbed via oral, inhaled, and subcutaneous routes. Paradichlorobenzene rapidly distributes in tissues, accumulates in adipose tissue, and is primarily eliminated by the kidneys after conversion to its major metabolite 2,5 dichlorphenol. This conversion occurs in the liver primarily by cytochrome P450 CYP2E1.

Our patient had elevated levels of blood PDCB at the time of presentation, consistent with her history of long-term mothball ingestion. In many affected individuals, toxic effects persist and clinical deterioration occurs despite discontinuation of exposure to the toxin, a phenomenon known as “coasting,” consistent with this patient’s clinical course. Again, the mechanisms underlying coasting are unknown.

Data on PDCB-induced neurotoxic reactions in humans are based on 11 published case reports. A neurotoxic reaction occurred after intentional misuse via inhalation and/or ingestion of PDCB-containing products. While isolated peripheral neurotoxic reactions may occur, central neurotoxic reactions with alteration in mental status are more common. They are often associated with gait disturbance due to weakness and/or ataxia, tremor, extraocular movement abnormalities, spasticity, hyperreflexia or hyporeflexia, and speech impairment.

Cerebellar and extrapyramidal signs and symptoms were reported in the majority of cases with limb spasticity, bradykinesia, dysmetria, ataxia, and tremor. Speech is often affected; deficits range from slow spastic hypophonic dysarthric, bradyphrenic, abulic, or dyskinetic speech to complete mutism. Skin findings are a distinctive feature and scaling, ichthyotic lesions and/or hyperpigmented areas accompanied by neurological signs should raise suspicion for PDCB toxic reaction.

Our patient presented with concerns of depressed mood and fatigue. Though she also had concerns of worsening weakness over the month prior to admission, motor deficits on neurological examination were stable compared with past visits. These findings parallel several case reports describing depressed mood and fatigue as the presenting symptom of PDCB intoxication. In many of these cases, patients exhibited measurable deficits on objective cognitive assessments, particularly in short- and long-term memory and visuospatial and executive function. Our patient had a similar pattern of deficits on neuropsychological testing.

Brain imaging in cases of PDCB intoxication demonstrates diffuse lesions, particularly in the periventricular white matter and splenium of the corpus callosum, as well as the internal capsules and brainstem. This is consistent with the abnormalities seen on our patient’s second brain MRI. The patient’s ichthyosiform skin rash involving the upper and lower...
limbs and trunk is also strikingly similar to changes described in other reports of PDCB intoxication.

Our position that the patient’s neurological worsening is attributable to PDCB toxic reaction alone is confounded by the fact that all of her neurological signs and symptoms are also commonly seen in patients with MS. In this regard, it is highly relevant that this patient was being treated with natalizumab, and a dramatic neurological deterioration under this agent is unusual. A substantial worsening of the neurological status due to MS during natalizumab treatment is therefore a cause of concern and may be due to progressive multifocal encephalomyelitis, an infection of the brain with the human polyoma virus JC. However, serological results were negative for JC virus during both admissions and numerous times previously. The patient had also tested negative for anti-idiotypic antibodies against natalizumab, another possible cause for neurological deterioration associated with this therapy. On discharge from our hospital, we recommended the continuation of natalizumab therapy to avoid a reactivation of MS disease activity.

The patient was encouraged to discontinue the ingestion of PDCB. In a majority of reports, patients demonstrate significant improvement in cognitive and motor deficits with cessation of PDCB use. Because of the behavior of PDCB and the “coasting” phenomenon, initially there may be continued deterioration and improvements may take up to 9 months. Treatment is supportive. Unfortunately, there are currently insufficient data to predict our patient’s neurological outcome. Development of aspiration pneumonia during this same period also complicated her clinical picture.

Conclusions
This case illustrates that environmental causes for neurological deterioration should be investigated in patients with MS who display a rapidly progressive disease course and in whom potent pharmacotherapies fail. One possible cause is the ingestion of PDCB-containing mothballs and toilet cleaners.

Conflict of Interest Disclosures: None reported.

REFERENCES
6. Krupp L. Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. Mult Scler. 2006;12(4):367-368.