Case Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(3) 1–8

DOI: 10.1177/0300060521999756
journals.sagepub.com/home/imr
SAGE

Mercury as a cause of membranous nephropathy and Guillain–Barre syndrome: case report and literature review

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Abstract

Secondary renal involvement in chronic exposure to metallic mercury is well known. Mercury also causes central nervous system damage and demyelinating polyneuropathy. Here, we describe a case of a patient with daily exposure to mercury in skin lightening cream and hair dyes who was diagnosed with Guillain–Barre syndrome and then developed nephrotic syndrome because of membranous neuropathy. By reviewing the literature describing mercury-associated diseases, we found that mercury components have an immunomodulatory activity, which is also involved in both peripheral neuropathy and glomerulonephritis.

Keywords

Mercury, chronic poisoning, membranous nephropathy, Guillain–Barre syndrome, nervous system, nephrotic syndrome, cosmetic products

Date received: 31 January 2021; accepted: 9 February 2021

Introduction

Mercury can be absorbed into the human body by inhalation, ingestion, dermal absorption, or injection. It has toxic effects on the kidneys, lungs, nervous system, and gastrointestinal tract, causing acute and chronic poisoning. Some studies have reported cases of membranous neuropathy

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(MN) that were caused by mercury-containing preparations, such as skin lightening cream or hair dyes.[1] These types of cases have attracted the attention of nephrologists. Additionally, chronic or acute exposure to mercury has been reported to cause Guillain–Barre syndrome (GBS) in isolated cases.[2] Because multiple organs are involved in mercury poisoning, we reasonably presumed that MN and GBS were not coincidental concurrent illnesses that occurred after mercury exposure in our patient. Here, we describe a case of mercury toxicity complicated by peripheral neuropathy and nephrotic syndrome. The aims of this case report are to raise awareness of physicians and provide a better understanding of mercury poisoning in clinical practice.

Case Report

A 44-year-old woman was admitted to a local hospital with weakness of the legs and numbness of her fingertips and palms in March 2018. A neurological examination of the peripheral nervous system revealed that the muscles of the lower extremities were slightly weak, with a muscle force of approximately level 4 according to the Medical Research Council scale. The knee tendon reflexes were absent. A sensory examination showed no remarkable findings apart from fingertip and palm paresthesia. However, a nerve conduction examination was not performed at the local hospital. The patient was diagnosed with GBS, which was confirmed by albuminocytologic dissociation in the cerebrospinal fluid (which contained 4×10^6/L white blood cells and 803 mg/L protein). Her condition was well controlled with gamma globulin and steroid therapy. One year later, the patient presented with bilateral pedal edema. Investigations identified nephrotic-range proteinuria and microscopic hematuria. She denied arthralgia, rash, hair loss, fever, or gross hematuria and had no history suggestive of anemia. There was no family history of kidney disease. The patient worked as an officer and had no history or current use of medications or known allergies. She had a definite history of exposure to mercury-containing preparations, including hair dyes used five to six times per year for approximately 5 years and skin lightening cream used for 15 months.

On examination, her blood pressure was 106/71 mmHg. Findings from neurologic, cardiac, respiratory, and abdominal examinations were unremarkable. Low-grade peripheral edema was observed.

On evaluation, the patient was found to have proteinuria (3+) and microscopic hematuria (four to five red blood cells/high power field). The 24-hour urine collection results showed 7200 mg of protein. The urinary N-acetyl glucosaminidase enzyme level was 27.9 U per g of creatinine (reference range <16.5 U per g of creatinine). The urinary retinol-binding protein level was 0.32 mg/dL (reference range <0.5 mg/dL). The normal urinary osmolality was 382 mOsm/kg H_2O (reference range >800 mOsm/kg H_2O) after fasting.

The patient's complete blood count, electrolyte, calcium, phosphate, hemoglobin A1c, fasting glucose, and uric acid levels were normal. Her creatinine level was 0.63 mg/dL, serum urea nitrogen level was 8.8 mg/dL, and albumin level was 2.73 g/dL. Her quantitative immunoglobulin and C3 and C4 complement levels were normal. Peripheral blood lymphocyte subsets were measured, and the CD4+, CD8+, CD19+, and CD20+ counts were 620, 305, 38, and 39/μL, respectively. The serum protein electrophoresis; serologic tests for hepatitis B, hepatitis C, and human immunodeficiency virus; antineutrophil cytoplasmic antibody; antithyroid related antibody; and free light chain to rheumatoid factor results were negative.

The patient was seronegative for antibodies against phospholipase A2 receptor (PLA2R) (1.98 RU/mL, reference range <20 RU/mL). The antinuclear antibody results were positive (1:1024), but the antinuclear spectrum was negative, and no evidence of autoimmune disease was found. There was also no evidence of underlying malignancy.

A renal biopsy revealed 20 glomeruli with stiff glomerular peripheral capillary loops and a slightly thickened glomerular basement membrane under light microscopy (Figure 1a). Mild segmental mesangial expansion and matrix proliferation were observed. Slight interstitial injury, focal fibrosis, tubular atrophy, and partial loss of the tubular brush border were also observed. Subepithelial fuchsinophilic deposits were visible on periodic acid-Schiff and Masson staining (Figure 1b). Immunofluorescence showed diffuse granular deposits of IgG (2+), together with C3 (2+) and C1q (+) along the capillary loop, and deposits of IgG1, IgG2, and IgG4 (predominantly IgG4) were found. Immunofluorescence staining for PLA2R was negative. Electron microscopy showed subepithelial electron-dense deposits and small spikes that had formed around the deposits, as well as extensive (60%–70%) podocyte foot-process effacement (Figure 2).

These findings were consistent with MN. There was no evidence of underlying malignancy based on the examinations. Considering the exposure to mercury-containing preparations, we suspected that mercury poisoning had caused MN, which was confirmed by the presence of a very high level of mercury in the urine (122.5 μg/day, reference range <8 μg/day).

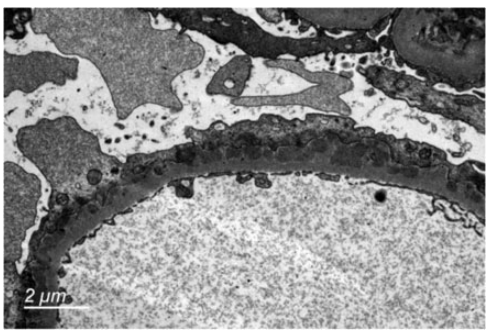

Figure 2. Electron microscopy findings in a case of mercury-induced membranous neuropathy. Subepithelial electron-dense deposits with formation of small spikes around the deposits and extensive (60%–70%) podocyte foot-process effacement were observed.

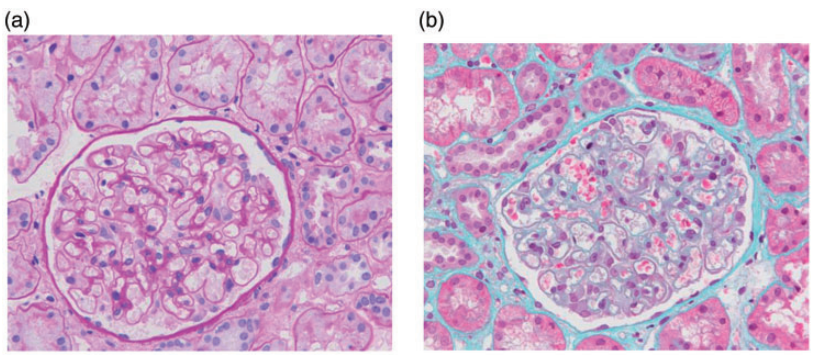

Figure 1. Pathologic findings in a case of mercury-induced membranous neuropathy. (a) Thickened glomerular basement membrane with mild segmental mesangial expansion and matrix proliferation (periodic acid-Schiff staining). (b) Subepithelial fuchsinophilic deposits along the epithelium (Masson staining).

Given the evidence of intoxication, chelation therapy with succimer (intramuscular injection of 0.25 g/day for 3 consecutive days) was prescribed, and the level of mercury in the urine was normal several days later.

Because of the evidence indicating mercury as the cause of the condition, we established a diagnosis of secondary MN and prescribed prednisone (30 mg/day) and FK506 (2 mg/day). Exposure to mercury-containing preparations was stopped. Two months later, the patient's protein excretion had decreased to 3600 mg, and her albumin level had increased to 3.46 g/dL. The patient eventually voluntarily discontinued medication after 3 months. At the last follow-up evaluation in 2020, the patient's 24-hour urine protein excretion had decreased to 1200 mg, and her albumin level had increased to 3.94 g/dL with remaining normal renal function.

Discussion

Organic or inorganic mercury has long been known to affect all organ systems, depending on the type and route of exposure. Historically, Minamata disease, which was found in Minamata Bay, Japan in the 1950s, has been associated with mercury poisoning. The World Health Organization warned of the dangers of mercury-containing compounds.[3] However, skin lightening cream and hair dyes, which contain inorganic mercury, are still widely available to customers in Asian countries, especially in China. Inorganic mercury can be absorbed via the sweat glands, sebaceous glands, and hair follicles, and after absorption, it is distributed to all tissues. Repeated topical applications can result in systemic toxicity, including nervous system and kidney damage.

Long-term exposure to mercury-containing preparations can cause nephrotic syndrome, and the most common renal pathological patterns reported in the literature are MN and minimal change disease.[4] Over the last decade, other similar cases have occurred in our hospital, which has been cause for alarm. In 2010, Li and colleagues retrospectively evaluated 11 cases of mercury-induced MN and analyzed the clinical and pathologic features.[1] All of the patients had a clear history of contact with mercury-containing preparations; four cases involved skin-lightening cream and one involved hair dyes. The clinical symptoms of all of the patients included proteinuria and normal renal function without microscopic or macroscopic hematuria. Four patients were antinuclear antibody-positive and were negative for anti-dsDNA, anti-Sjogren's syndrome A, anti-Sjogren's Syndrome B, and other antinuclear antibodies. They also had normal C3 and C4 levels. According to the pathological findings, all patients exhibited MN, but none had any other secondary cause of nephropathy, such as systemic lupus erythematosus, malignancies, or viral hepatitis, and no culprit medication was ever used. Our patient had the same clinical and pathologic features, with an increased urinary concentration of mercury; therefore, mercury-associated MN was confirmed.

Mercury is also known as a neurotoxicant, but sufficient attention has not been paid to peripheral neuropathy. After absorption, lipid-soluble mercury can enter the central nervous system through the endothelial cells of the blood–brain barrier.[5] It can damage the peripheral nerve myelin or axons,[6] which is seldom reported. Binding of mercury to glutathione induces an increase in reactive oxygen species in a variety of cell types including neurons, glia, T cells, B cells, and monocytes.[7] Additional neurotoxic effects include upregulation of vascular endothelial growth factor expression within astrocytes, toxic accumulation of intracellular calcium, mitochondrial dysfunction, direct DNA damage, and voltage-

Table 1. Summary of previously reported the clinical and pathologic features of mercury toxicity associated with peripheral neuropathy.

Case	Author	Age /sex	Etiology of mercury poisoning	Neuropathic symptoms	Diagnosis	Nerve examination	Nephropathy	Therapy
1	Gaioli et al.[2]	14 y	fluorescent lamp	muscle weakness	GBS	albuminocytologic dissociation	microhematuria	
2	Miller et al.[3]	60 y/M	contaminated fish	paresthesias of both hands and fatigue	peripheral neuropathy	a distributed slowing of conduction in distal sensory and motor fibers	FSGS	–
3	Evans et al.[8]	13 y/M	mercury vapor	bilateral ptosis, areflexia, disordered gait	GBS	elevated CFP, EMG, NCS disorder	–	chelation therapy and supplementation with selenoenzymes
4	Swaiman et al.[9]	14 y/M	mercury vapor	fasciculation, no tendon reflex, depression	GBS	elevated CFP, EMG disorder	–	penicillamine
5	Ross et al.[10]	4 y/M	ammoniated mercury ointment	rapidly progressing difficulty in walking	polyneuropathy	albuminocytologic dissociation	–	dimercaprol
6	Pérez et al.[11]	19 y/F, 17 y/M	elemental mercury	proximal muscle weakness, limb rigidity, muscle spasms	polyneuropathy	EMG disorder	–	chelation therapy and rituximab

EMG: electromyography; NCS: nerve conduction study; CFP: cerebrospinal fluid protein; GBS: Guillain–Barre syndrome ; FSGS: focal segmental glomerulosclerosis

gated channel dysfunction. Only a few researchers have evaluated mercury toxicity in peripheral neuropathy; therefore, we summarized the clinical and pathologic features in Table 1. Evans et al described a 13-year-old boy with a history of long-term exposure to mercury vapors from a broken thermometer who developed acute-onset GBS.[8] Miller et al discussed a presentation of subacute-onset focal segmental glomerulosclerosis caused by mercury toxicity from contaminated fish in a 60-year-old man.[3] His presentation with nephrotic-range proteinuria coincided with the identification of peripheral neuropathy. Electromyography showed a consistent distributed slowing of conduction in distal sensory and motor fibers. Gaioli et al presented a 14-year-old patient with acute, symmetric, ascending, and progressive muscle weakness who was diagnosed with GBS and did not respond to conventional treatment.[2] Considering the etiology, heavy metal neuropathy was suspected, and then mercury poisoning from a fluorescent lamp was confirmed. Swaiman et al described a 14-year-old boy who developed acrodynia and then GBS from mercury vapor poisoning.[9] Ross et al described a 4-year-old boy who, after prolonged use of ammoniated mercury ointment for skin lesions, developed a benign motor polyneuropathy syndrome.[10] Pérez et al described two siblings with proximal muscle weakness, limb rigidity, muscle spasms, and stiffness following accidental exposure to elemental mercury.[11] Singer and Valciukas studied the toxicity of inorganic mercury via occupational exposure in 16 workers.[12] Slowing of median motor nerve conduction was found. Sensory deficits seemed to occur with short-term exposure to mercury vapor, whereas motor nerve impairment occurred with longer periods of exposure. In our case, the patient's sensory deficit was not noticeable after long-term exposure, and motor nerve impairment had obviously occurred; therefore, mercury can cause injury to sensory and motor nerves. Considering that multiple systems are involved in mercury poisoning, it seems worth considering whether mercury may have played a contributory role to the development of MN and GBS in this case.

The mechanism by which mercury induces MN or GBS is still uncertain, but it is well known that the immune mechanism plays an important role. The mechanism of mercury-induced glomerulonephritis has been well discussed. The immunofluorescence findings of renal biopsies have shown codeposits of C3 and/or C1q associated with the IgG subclass in the glomerular capillary loop, indicating activation of the classical complement pathway. Deposits of IgG1, IgG2, and IgG4 were observed in this case and other reports,[1] which differs from the finding of only IgG4 deposits in idiopathic MN. This finding indicates that both Th1 and Th2 participate in mercury-induced autoimmunity. Mercury-induced autoimmune diseases may have characteristics of a Th2-type reaction, but they are critically dependent on Th1 cells, and this was confirmed by Th1 deviation accelerating mercury-induced autoimmune disease in a mouse model.[13] Autoimmune disease is characterized by T cell-dependent polyclonal B cell activation, resulting in the production of autoimmune antibodies,[14] which explained why only anti-nuclear antibody positivity without any other evidence of autoimmune disease was found in our patient. The additional direct immune effect of mercury can trigger production of anticardiolipin-antibodies, antineutrophilic cytoplasmatic antibodies, C3 complement, immune complexes, and antinucleolar antibodies, which may result in autoimmune disease.[6] In a case of peripheral neuropathy caused by exposure to elemental mercury,[11] treatment of neuropathy with chelation therapy, glucocorticoids, and immunoglobulin was unsuccessful, but

complete resolution of symptoms was achieved with rituximab. The improved response to immunotherapy indicated the role of mercury in the etiopathogenesis of neuropathy. Our case provided valuable information about the association of mercury-induced immune-mediated peripheral neuropathy and MN. Although we cannot prove coexistence of the two pathologies as independent entities, the common immune characteristics favor the presence of MN and GBS as one pathological entity rather than two separate entities.

In conclusion, although it is currently rare to encounter severe mercury intoxication, efforts remain necessary to reduce the risk to human health caused by long-term and low-level exposure from mercury-containing cosmetics. The public should be warned of the danger of using such products. Mercury poisoning caused by cosmetic products should be considered in the diagnosis of women and when taking a patient's medical history in cases of multisystemic involvement without a clear explanation. This case emphasizes the importance of thorough diagnostic evaluation and an open-minded approach to unusual cases.

Ethics statement

Because this case report does not contain identifying or protected health information, ethical approval was not required. The patient provided verbal informed consent for the publication of this case report.

Declaration of Conflicting Interest

The authors declare that there is no conflict of interest.

Funding

This work was funded by the Natural Science Foundation of TianJin (Youth Program, 18JCQNJC79900) and the Natural Science Foundation of TianJin (18JCYBJC25000).

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