

Mercury Intoxication: It Still Exists

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Abstract: A 3-year-old boy presented to the Hospital for Sick Children with systemic symptoms and oropharyngeal and peripheral extremity changes suggestive of Kawasaki disease. He was found to have severe hypertension. Investigation for a catecholamine-secreting tumor was negative. Toxins were considered when the patient's 20-month-old brother presented with similar symptoms, and the boys were subsequently diagnosed with elemental mercury poisoning. We review the literature on mercury intoxication and discuss the historical context, clinical syndrome (acro-dynia), treatment, and radiologic findings of this unusual diagnosis.

CASE REPORT

A 3-year-old boy was transferred to the Hospital for Sick Children with a 4-week history of systemic symptoms manifesting as irritability and fatigue, loss of appetite, a 5 kg weight loss, and diaphoresis. There was no history of fever. He had severe pain in his wrists and legs not relieved by acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), resulting in difficulty in weight bearing. His palms and soles were pruritic, erythematous, and edematous (Figs. 1 and 2), with some desquamation proximally on his hands. His lips were erythematous (Fig. 3). There was no history of conjunctivitis, and no lymphadenopathy was noted. His blood pressure was found to be elevated at his local hospital and was recorded at 162/100 mmHg in our emergency department. The remainder of his physical examination was negative, including no abdominal masses, joint effusions, cardiorespiratory, or neurologic findings.

The patient was admitted to the general pediatric ward for investigations to rule out malignancy (neuroblastoma, Wilms tumor, or pheochromocytoma). Atypical Kawasaki



Figure 1. Erythematous soles in our index patient.

disease was considered the major differential diagnosis, in view of his palmoplantar and lip changes.

Baseline blood work, including a complete blood count, electrolytes, glucose, renal function, and coagulation profile were all normal. The erythrocyte sedimentation rate was 4 mm/hr. Urinalysis was negative. Ophthalmologic

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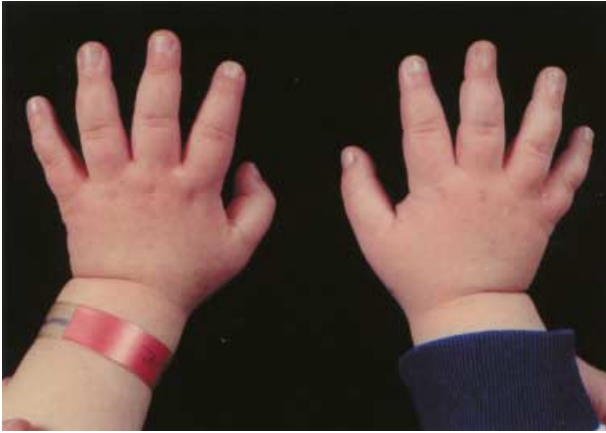


Figure 2. Edematous hands.



Figure 3. Lips show striking erythema.

examination was normal, as was a cardiac evaluation including a two-dimensional echocardiogram. Abdominal ultrasound with a Doppler evaluation of the renal vessels and a Tc 99m dimercaptosuccinic acid (DMSA) scan were normal, as were computed tomography (CT) scans with contrast of the abdomen, chest, head, and neck. An *m*-iodobenzylguanidine scan, specific for neuroblastoma, as well as magnetic resonance imaging (MRI) of the adrenal glands were negative.

A nuclear medicine bone scan revealed increased activity in the proximal and distal femoral and tibial metaphyses. These multiple bony abnormalities were interpreted by the radiologist as strongly suggestive of marrow disease, although subsequent bone marrow aspirate and biopsy specimen findings were both normal. Positive laboratory results included both spot and 24-hour urine samples for vanillylmandelic acid and homovanillic acid (Table 1). His serum renin level was slightly increased at 2.86 ng/L/sec (normal 0–2.8 ng/L/sec) and serum catecholamine levels were also above normal (Table 2).

TABLE 1. Urine Catecholamine Levels in the Index Patient and His Younger Brother

Test (units)	Index patient (normal) ^a	Younger brother (normal)
24-hour VMA (μmol/day)	21.7 (0–15)	12.8 (0–12)
Spot VMA (mmol/mol Cr)	11.5 (0–6.5)	
24-hour HVA (mmol/mol Cr)	16.5 (0–14)	13.8 (0–20)
Spot HVA (mmol/mol Cr)	12.9 (0–14)	

^aNormal values are age dependent.

Cr, Creatinine; HVA, homovanillic acid; VMA, vanillylmandelic acid.

The patient's blood pressure was significantly elevated, requiring amlodipine 5 mg once a day (0.3 mg/kg/day) and oral labetalol 25 mg twice a day (3 mg/kg/day) to optimize blood pressure control. His blood pressure ranged from 100/60 mmHg to 140/80 mmHg during this time, necessitating that short-acting nifedipine be used up to three times a day.

Approximately 10 days after the patient's admission, his younger brother, age 20 months, presented to the emergency department with similar, though less severe, symptomatology. He was also irritable, had edematous, erythematous, and pruritic extremities, and was noted to be hypertensive, with a systolic blood pressure of 140 mmHg. Baseline blood work, renal function, and abdominal ultrasound including Doppler studies were also all normal. Urine catecholamines were mildly increased (Table 1) and the serum renin was normal, at 1.01 ng/L/sec (range 0–2.8 ng/L/sec).

Given the presentation of brothers with the same symptoms, infectious and toxic causes were considered as etiologies. The oropharyngeal changes and edema, erythema, and desquamation of the peripheral extremities resembled Kawasaki disease, though the lack of other criteria (fever, nonpurulent conjunctivitis, rash, and lymphadenopathy) precluded this diagnosis. The presentation did not fit with toxic shock or erythema multiforme major (1). Noninfectious mimickers of these features include drug reactions and mercury poisoning (2).

The infectious disease service was consulted, but this presentation was thought to be noninfectious. Mercury poisoning was considered the most likely toxicologic diagnosis. Initial urine toxicology screens were negative with the exception of hydroxyzine, used to treat the

TABLE 2. Serum Catecholamine Levels in the Index Patient

Test	Index patient (μmol/mol)	Normal range (μmol/mol)
Norepinephrine	598	0–80
Epinephrine	61	0–35
Dopamine	1041	0–1130



Figure 4. A radiograph of the left knee shows diffuse osteopenia. The distal femur shows a dense metaphyseal band (arrow).

pruritus. Abdominal radiographs showed no radiopacities, but in both boys, knee radiographs revealed osteopenia (more marked in the older brother) and a possible sclerotic band at the femoral metaphysis, a finding associated with lead poisoning (Fig. 4). The fibular metaphyses were normal. Blood and 24-hour urine samples for heavy metals were sent to a regional laboratory and analyzed using high-resolution inductively coupled plasma mass spectrometer. Blood lead and zinc levels were normal,

but mercury levels in both boys were found to be markedly elevated (Table 3).

Chelation therapy was initiated with DMSA 200 mg (350 mg/m²) orally three times a day for 5 days, followed by twice daily therapy for 14 days. By the second day of therapy, both boys were less irritable and began to demonstrate an increase in appetite and mobility. Antihypertensive therapy was continued for an additional 3 months, after which the blood pressure remained normal and all clinical symptoms resolved. The mercury levels, however, took almost 2 years to completely normalize. Long-term developmental effects are as yet unknown.

A full history of parental occupations, living conditions, and potential exposures was completed, but no obvious source was identified. The Public Health unit in the boys' community was contacted, and a thorough investigation was initiated. Family members' blood samples were also sent for mercury testing. The Public Health investigation found high mercury levels in the carpet of our index patient's bedroom. The family had moved into the house only 2 months prior to the boys' presentation, and did not return there following the hospitalization. The source of mercury remains unestablished. Of interest is that the varying mercury levels in the family directly correlate with the degree of exposure to the affected bedroom: most severe was the patient who slept in the room; the younger brother and the boys' mother also had significantly high levels; and the father, whose work took him out of town a great deal, had mercury levels that were only mildly elevated (Table 3).

DISCUSSION

Historically, exposure to mercury in children was widespread. In the 19th century, teething powders containing calomel (mercurous chloride), other mercury-containing medicinal agents such as cathartics and anthelmintics, and mercury compounds as a part of fungicides and disinfectants were in wide use (3). It is now understood that mercury poisoning may present as different clinical

TABLE 3. *Mercury Levels of the Index Patient and His Family*

	Index patient	Younger brother	Mother	Father	Normal range (units)
Tests prior to chelation					
24-hour urine	185.8	97.6			0–20 (nmol/day)
Spot urine			50.97	10.78	0–1.97 (μmol/mol Cr)
Blood	112.2	54.8	42.9	26.4	0–11.3 (nmol/L)
Tests during chelation					
Spot urine (5 days)	735.78	75.03			0–1.97 (μmol/mol Cr)
Spot urine (12 days)	351.93	114.8			0–1.97 (μmol/mol Cr)
Blood (12 days)	121.6	21.9			0–11.3 (nmol/L)

syndromes, depending on the form of mercury and route of exposure (4). Acute inhalation of elemental mercury most commonly occurs in an occupational setting and leads to respiratory symptoms; acute ingestion of inorganic mercury salts, secondary to accidental battery ingestion in a child for example, produces gastrointestinal and renal symptoms; subacute or chronic exposure to mercurials results in neuropsychiatric, renal, and dermal manifestations; and methyl mercury poisoning from ingestion of contaminated marine life leads to permanent neurologic sequelae (4). Finally, acrodynia is an idiosyncratic hypersensitivity reaction to mercury, and is further discussed below.

By the early 1950s, the connection between mercury exposure in children and the clinical syndrome of acrodynia was established and published in the literature (5). Characteristic symptoms of acrodynia (pink disease) are pink palms and soles, at times with desquamation (Fig.1); red cheeks and nose; loss of hair, teeth, and nails; salivation and marked diaphoresis; transient rashes; hypotonia; itching, burning, and painful extremities; tachycardia and hypertension; photophobia; insomnia; and irritability (5,6). There is clinical variability among patients, and not all children exposed to mercury will develop the symptom complex (3). The reasons behind such characteristics of the syndrome have not been properly studied.

Though mercury toxicity is now relatively rare and consequently acrodynia is less recognized upon presentation, case reports in the literature continue to portray

remarkably classic symptoms. Results of our MEDLINE search for mercury intoxication revealed 16 cases of symptomatic mercury poisoning in 13 households in the pediatric population, dating from 1984 (6–17). All but one of the cases demonstrated features of acrodynia. This patient presented with motor and vocal tics thought to be a result of mercury toxicity secondary to a Chinese herbal mouth spray (14).

One of the most intriguing signs of acrodynia is the marked hypertension, which is consistently reported to mimic pheochromocytoma. As with our index patient, the majority of the patients described in the literature have high catecholamine levels and are investigated extensively for a secretory tumor prior to making the diagnosis of mercury intoxication (6,8,9,11,12,16,17). The proposed mechanism for this finding is related to mercury's ability to bind and inactivate *S*-adenosylmethionine (SAM), an enzyme required to convert norepinephrine to epinephrine (16). The cytosolic enzyme catecholamine-O-methyltransferase, dependent on the intact function of SAM, is also inactivated. This enzyme normally is responsible for the catabolic metabolism of catecholamines (18). Consequently norepinephrine, epinephrine, and dopamine accumulate and serve to clinically mimic a pheochromocytoma.

Modern sources of mercury resulting in toxicity vary, but differ from the older reports. Sources are now usually related to accidental exposures. Of the 13 households in the literature (Table 4), 4 were exposed to accidental spills of elemental mercury (10,11,15,16) and 3 to broken

TABLE 4. *Summary of Mercury Intoxication by Source of Exposure*

Reference	Author	Source of exposure
Elemental mercury spills		
15	McNeil et al	Flask containing elemental mercury brought home with accidental spill onto furniture and carpets
10	Florentine and Sanfilippo	Elemental mercury found among garage tools, spilled on bedroom carpet
11	Henningsson et al	Patient "playing" with elemental mercury with extensive skin contact and spillage into electric coil heater
16	Torres et al	Leaking pressure gauge brought home from work
Broken thermometers		
6	Velzeboer et al	Broken thermometer
8	Baudouin et al	Broken thermometer
9	Cloarec et al	Broken thermometer
Miscellaneous sources		
12	Joaquim de Oliveira and Silva	Mercury vapor, source unreported
7	Agocs et al	Latex paint containing high phenylmercuric acetate content
14	Li et al	Chinese herbal spray for mouth ulcers
Unknown or not reported		
13	Karagol et al	Patient 1: Long-term mercury exposure while playing; specific source not reported Patient 2: Not reported
17	Wobmann et al	No history of exposure identified

thermometers (6,8,9). The remaining patients were exposed to mercury vapor (12), latex paint with a higher than recommended phenylmercuric acetate content (7), and in one instance to a mercury-containing herbal remedy (14). Three did not report or reported not knowing the heavy metal source (13,17). Our patient most likely represents a subacute or chronic exposure to an accidental elemental mercury spill.

While elemental mercury is poorly absorbed from the gastrointestinal tract, it readily enters the bloodstream via inhalation or through the skin, where it is distributed to the brain, liver, and kidney (10). Chelation therapy is recommended to patients who are symptomatic or have toxic mercury levels in their blood or urine. Of the group of available heavy metal chelators, including penicillamine and ethylenediaminetetraacetic acid (EDTA), dimercaprol was, until recently, the mercury chelator of choice (19). Because of its intramuscular route of administration, low therapeutic index, and toxic effects, including hypertension, tachycardia, and seizures, this is not an ideal agent. We treated our patients with DMSA, a water-soluble analogue of dimercaprol, which in animal studies and human use has been shown to be effective. DMSA can be given orally and has less toxicity than dimercaprol. Its common adverse effects include nausea, vomiting, and abdominal bloating. Although its toxicity is minimal, it may cause a transient and mild transaminase elevation (10,19). We used 350 mg/m², given three times a day for 5 days, followed by twice a day dosing for an additional 2 weeks (20). Table 3 shows mercury levels at days 5 and 12 of therapy. It is expected that mercury levels initially rise during the treatment course, as the mercury is chelated and released from the tissues (19). In our patients, DMSA was well tolerated.

Of particular interest in our patients are the radiologic findings, not previously discussed in reported cases of mercury intoxication. The nuclear bone scan in our index patient was suggestive of marrow disease, heightening our suspicion for a metastatic catecholamine-secreting tumor, most likely neuroblastoma. Knee and ankle radiographs showed poor mineralization, interpreted as secondary to a chronic systemic illness. Finally, after the diagnosis of mercury intoxication was made, possible sclerotic metaphyseal bands of the femur were noted on further radiographs of the younger brother (Fig. 4), although the findings may have simply reflected relative sclerosis in the setting of demineralized bones.

The presence of thick radiopaque bands in areas of active bone formation is well described in association with lead poisoning (21–23). The pathophysiology is related to lead's inhibition of osteoclastic remodeling, with a predilection for the zones of provisional calcification. The result is an increase in metaphyseal sclerosis.

This phenomenon is known as a "lead line." Interestingly, the increase in density is due to calcium rather than lead, which is present in amounts far less than calcium. Despite the fact that other heavy metal poisoning, including mercury, is included in the differential diagnosis of the dense metaphyseal band sign (23), a MEDLINE search for the radiographic correlates of either heavy metal or mercury poisoning revealed no literature regarding long bone signs nor bone scan interpretations.

The finding of osteopenia, noted in the radiographs of both brothers, is an interesting radiologic finding and, while nonspecific, has not, to our knowledge, been described in the literature. The finding of metaphyseal sclerosis in these patients, however, should be interpreted with caution. First, the metaphyses of normally growing bones can have an apparent sclerotic metaphyseal line in normal children. The sclerotic metaphyseal line seen here may have simply been the normal metaphysis rendered more conspicuous by definite osteopenia. Second, the adjacent fibular metaphyses demonstrated no evidence of a sclerotic line. The presence of a sclerotic line in the metaphyses of all the long bones around the knee, including the fibula, has been described as specific for heavy metal poisoning (21–23). Nonetheless, the presence of possible femoral "lead lines" is an important consideration in that it may be significant in the context of mercury poisoning and has not been previously reported.

In conclusion, our two young children with mercury poisoning demonstrate features typical of acrodynia, a well-described constellation of symptoms and signs. Our search for more common pathology to explain the clinical picture is also typical of most case reports of mercury poisoning. While mercury poisoning is now rare and not often initially considered, it still occurs through accidental exposure and should be considered as part of the differential diagnosis of hypertension, particularly when screening investigations for the usual etiologies are negative. Further instances of mercury poisoning need to be explored for radiologic correlates before we can draw significant conclusions about the findings in our patients.

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