A Mercury Toxicity Case Complicated by Hyponatremia and Abnormal Endocrinological Test Results

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abstract

Mercury (Hg) poisoning is considered a rare disease by the National Institutes of Health and the diagnosis can present great challenges to clinicians. Children who are exposed to Hg can present with a wide variety of symptoms, including acrodynia, tremor, excessive salivation, and psychiatric symptoms, including insomnia. However, endocrinologic manifestations from Hg exposure are less well known. This is a case report of a 12-year-old boy who presented with body rash, irritability, insomnia, and profuse sweating after returning from a summer camp. The child was initially managed in the outpatient setting, and the investigation was mainly targeted toward infectious etiology, including Rocky Mountain spotted fever and Lyme disease. He was eventually admitted to the hospital with altered mental status and was noted to have hyponatremia with serum sodium of 121 mEq/L. Thyroid studies also revealed elevated free thyroxine levels in the presence of normal triiodothyronine and thyrotropin. The patient developed hypertension and tachycardia, and was found to have elevated 24-hour vanillylmandelic acid and metanephrines. Finally, heavy metal measurements revealed a blood Hg level that was greater than the reference values of 0 to 9 ng/mL. Chelation treatment with 2,3-dimercaptopropane-1-sulfonate was subsequently initiated and over a period of 8 months his symptoms resolved and his thyroid function test returned to normal. This case highlights some of the challenges commonly encountered in identifying Hg exposure. More importantly, it illustrates that exposure to Hg should be considered in children who present with the symptoms and abnormal endocrinologic test results described in this report.

Mercury (Hg) exposure can occur in many ways, including contaminated food, water, dental amalgams, disk batteries, inhalation of vapors from gold-mining activities, environmental accidents, and historically in laxatives and diaper and teething powders.[1,2] Thus, a thorough review of exposure pathways is necessary when Hg exposure is suspected. Metallic Hg is a silver-white liquid at room temperature and is present in various commercially available products.[3] Human exposure to metallic Hg can occur in its vapor form, which, if inhaled, can result in toxic effects on various tissues, as up to 80% of metallic Hg vapor is absorbed from the lungs into the blood.[4] Clinical manifestations of metallic Hg vapor exposure can be diverse, including intention tremors, excessive salivation, insomnia, body rash, and mood and behavioral changes. Several body systems can be affected, including the central nervous system, cardiovascular system, kidneys, lungs, and the gastrointestinal tract.[1,5,6] The

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TABLE 1 Laboratory and Vital Sign Values of a Child Treated for Suspected Hg Poisoning

Laboratory, Reference Range	Na, 135–145 mEq/L	K, 3.5–4.5 mEq/L	Serum Osmolality, 280–295 mOsm/kg	Urine Osmolality, 250–1200 mOsm/kg	Thyrotropin, 0.35–4.01 µIU/mL	Free T4, 0.61–1.37 ng/dL	Total T3, 87–178 ng/dL	Serum Hg, 0–9 ng/mL	Urine Hg, No Established Reference Range	Metanephrines, 69–221 µg/24 h	VMA, <7.0 mg/g Cr	Blood Pressure, <123/<78 mm Hg for Sex/Age/Height	Pulse, 60–120 Beats per Min
1[a]	121	3.4	250	161	1.03	2.24	140	13	—	212	9.9	144/93	125
2[b]	140	3.5	286	774	1.16	1.68	102	17	112	244	10.3	113/73	156
3[c]	141	3.7	—	—	1.29	0.90[d]	—	<1	6	177[e]	11[e]	102/58	100

VMA, vanillylmandelic acid. —, no value.

[a] Initial laboratory samples were collected over a 2-week course, ~1 month after symptom onset.

[b] Before chelation therapy, ~2.5 months after symptom onset. DMPS used for chelation therapy, 5 mg/kg 3 times a day for 2 weeks.

[c] Laboratory samples collected 7 months after chelation therapy, ~9.5 months after symptom onset.

[d] Free T4 level was obtained 3 months after the treatment was started.

[e] Checked 10 days after starting DMPS.

toxicological effects of heavy metals, including Hg, are more devastating in the pediatric population, with respect to the developing central nervous system in particular.[7] Furthermore, the endocrinologic manifestations from Hg exposure are less known, and abnormal laboratory test results may further distract the clinician from making a prompt diagnosis. This case report highlights the effects of Hg exposure on systemic hormonal milieu, including perturbation of thyroid hormone and catecholamine levels, together with sodium imbalance.

PATIENT PRESENTATION

A 12-year-old boy with no significant past medical history presented in the late summer to an urgent care clinic after developing an erythematous macular rash involving the palms and scalp hairline, muscle twitching, irritability, insomnia, and profuse sweating. He had recently returned from a summer camp in the midwestern United States where his symptoms had begun. Over the course of a month, he clinically decompensated with increasing fatigue, headaches, poor sleep, muscle twitching, and more frequent syncopal episodes, in addition to other symptoms. There were no known sick contacts or fever, and history did not reveal any known exposures, ingestions, or intoxications. The patient was initially managed as an outpatient, with the investigation focused on ruling out infectious etiologies, including Rocky Mountain spotted fever and Lyme disease. He was treated with a 10-day course of doxycycline, but continued to worsen clinically. Without improvement, the patient presented to a local emergency department and was found to have serum sodium level of 121 mEq/L, potassium of 3.4 mEq/L, serum osmolality of 250 mOsm/kg, and urine osmolality of 161 mOsm/kg (Table 1). He was transferred to our PICU after receiving 3% hypertonic saline. Initial blood work was suggestive of hyponatremia, secondary to the syndrome of inappropriate antidiuretic hormone. Brain imaging studies, including MRI, were normal with the exception of pars intermedia cyst in the pituitary area. During his 2.5-week hospitalization, his symptoms progressed to include episodes of syncope, tachycardia, hypertension, disinhibited behavior, and muscle fasciculation. Thyroid blood test results showed elevated free thyroxine (T4) and intermittently high total T4, with normal free triiodothyronine (T3) and thyrotropin levels. Thyroid-binding globulin, thyroid-stimulating immunoglobulin, thyroid anti-microsomal antibody, and anti-thyroglobulin antibody studies were normal. Elevated norepinephrine 991 pg/mL (reference range 70–750 pg/mL)[8] and dopamine 39 pg/mL (reference range <30 pg/mL)[8] were noted. These laboratories and the patient's tachycardia, hypertension, profuse sweating, and anxiety prompted investigation for possible pheochromocytoma and paraneoplastic syndrome. Full-body imaging was essentially normal, with the exception of a fine nodular pattern in the left middle lung. These findings resolved on follow-up computed tomography. A fungal serology panel was normal. The patient also had elevated 24-hour vanillylmandelic acid and metanephrines; serum norepinephrine and dopamine levels remained elevated. His hyponatremia resolved with daily fluid restriction of 1500 mL/d. Inductively coupled plasma-optical emission spectroscopy revealed an elevated blood Hg level of 13 ng/mL, greater than the reference values of 0 to 9 ng/mL.[8] This level was inaccurately deemed insignificant by toxicology during his admission due to minimal elevation.

After discharge of the patient, further toxicological consultation resulted in a full investigation. As the local health department and

environmental health protective agencies intervened, it was revealed that the patient was exposed to elemental Hg starting just before summer camp when he accidentally broke an old bottle of Hg that belonged to his grandfather. He had attempted to clean it up by scooping the Hg into a bag, which was then put in his room and also brought to summer camp. High levels of Hg were found in his room, 12 890 ng/m^3; his duffle bag, 26 000 ng/m^3; and on the floor, 11 881 ng/m^3, exceeding a normal reference range of 5 to 10 ng/m^3.[9] A 24-hour urine Hg level was high, 112 ng/mL, just before chelation therapy. Progressions of his laboratory test values are outlined in Table 1. Treatment with 2,3-dimercaptopropane-1-sulfonate (DMPS) was initiated by the toxicologist shortly after the exposure at home was mitigated, 1 month after hospital discharge and 2.5 months after presentation of his symptoms. By 8 months after his initial presentation, his symptomatology, blood pressure, thyroid function tests, and catecholamines returned to normal.

DISCUSSION

As evidenced by this case, the diagnosis of Hg intoxication can be challenging. Unfortunately, the longer the exposure, the greater the intoxication.[1,6] Factors that delayed diagnosis for this patient were a low index of suspicion, initial lack of an exposure history, and nonspecific clinical manifestations, along with multiple irregularities in laboratory data. Our patient had elevated free T4 levels with intermittently high total T4, but normal free T3, thyrotropin, and thyroid antibodies, as stated previously. This was not suggestive of autoimmune disease but can be consistent with Hg exposure. Found normal in this case, brain MRI with pituitary protocol was justified in view of a nonsuppressed thyrotropin with elevated free T4 and to rule out a thyrotropin-producing adenoma. Analyzed blood and urine samples from the US NHANES, 2007–2008 cohort, found an inverse relationship between thyroid levels and blood Hg levels. The survey also showed thyrotropin levels were not altered by Hg exposure.[10] Additionally, in a study of 47 chloralkali workers exposed to Hg vapor, the ratio of T4 to T3 was higher than nonexposed workers. Furthermore, the concentration of reverse triiodothyronine (rT3) was significantly higher in the exposed group.[11,12] Similar to those reports, our patient had an intermittently increased total T4, as well as an increase in the T4 to T3 ratio and an elevated rT3 (44 ng/dL; reference range 8–25 ng/dL). These findings indicate that exposure to Hg may affect the function of type I iodothyronine deiodinase, which is essential in the conversion of T4 to the active hormone T3. A diagnosis of euthyroid sick syndrome with abnormal findings on thyroid function tests was considered, given an elevated rT3 and normal thyrotropin, but the usual pattern would give low T3 and normal T4, which was not seen in our patient.[13] Additionally, medications, such as amiodarone, dexamethasone, propranolol, and anesthetic agents, can cause an increase in rT3 levels.[14] To our knowledge, our patient had not been exposed to any of these medications.

Our patient also presented with euvolemic hyponatremia with decreased serum osmolality and inappropriately increased urine osmolality, suggestive of syndrome of inappropriate antidiuretic hormone. The association between Hg exposure and hyponatremia is not well documented in the medical literature. However, the effect of Hg on serum sodium level is not surprising, considering that inorganic Hg had been used as a diuretic before the advent of modern-day diuretics.[15] A study published in the early 1950s suggests that mercurial diuretics depress the renal tubular reabsorption of sodium.[16] Subsequent to receiving 3% saline, the patient's natriuria appeared to increase, with a urine sodium level of 218 mEq/L, which then decreased to 51 mEq/L within 48 hours. Furthermore, an exaggerated process of pressure natriuresis may have contributed to his hyponatremia. This process is a component of the feedback system for long-term control of arterial pressure, whereby increases in renal perfusion pressure lead to decreases in sodium reabsorption and increases in sodium excretion.[17] This is enhanced because of excess dopamine, which acts on renal receptors leading to excretion of sodium.[18–20] Additionally, because the degree of nephrotoxicity may vary depending on the form of Hg, multiple routes of exposure were considered in our patient, including inhalation and ingestion.

Although rare, there are other cases in the literature that presented similar to our patient, with elevated catecholamines. For example, a 4-year-old boy was exposed to metallic Hg, and developed both hyponatremia and elevated catecholamines, suggestive of pheochromocytoma.[20] Other cases with similar findings were described in the same report and elsewhere.[4,20] The increase in catecholamines relates to interference with the normal catabolic processing of catecholamines via the cytosolic enzyme catechol-amine-O-methyltransferase.[21,22] This enzyme requires the use of the methyl group provided by coenzyme S-adenosylmethionine (SAM). SAM is essential in the conversion of norepinephrine to epinephrine. Hg inactivates SAM; as a consequence, norepinephrine, dopamine, and epinephrine accumulate in increased

amounts in the urine where they can be detected.[20] Additional studies done on bovine chromaffin cells support the hypothesis that high levels of Hg also could affect the calcium channel currents and consequently the release of catecholamines,[23] resulting in an increase in the patient's levels even further.

Hg intoxication is relatively uncommon in the clinical setting. A patient's physical examination and laboratory studies can sway the examining physician to investigate other causes, including catecholamine-secreting tumors, before making the appropriate diagnosis. This renders a timely diagnosis difficult, as seen in the present case and previously referred cases.

CONCLUSIONS

Hg exposure should be considered in children who present with hypertension, acrodynia, insomnia, mood changes, and associated endocrinologic abnormalities, including hyponatremia, elevated catecholamines, and abnormal thyroid hormone studies.

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ABBREVIATIONS

DMPS: 2, 3-dimercaptopropane-1-sulfonate
Hg: mercury
rT3: reverse triiodothyronine
SAM: coenzyme S-adenosylmethionine
T3: triiodothyronine
T4: thyroxine

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