

could occur in North America. Physicians should therefore be aware of the possibility of dengue fever in cases of undiagnosed fever, especially when associated with hemorrhagic manifestations.

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Urine Mercury Levels in Kawasaki Disease

The temporal and geographic relationship between the description of the mucocutaneous lymph node syndrome (MLNS) or Kawasaki disease, and the Minamata Bay contamination with mercury in Japan is impressive. Also, the appearance of MLNS in the United States has paralleled the increasing concern with environmental pollution of natural bodies of water with mercury.<sup>1,2</sup> Because of the many similarities between acrodynia (pink disease or mercury poisoning) and MLNS, we became concerned that MLNS might represent a disease related to environmental poisoning with mercury. This report describes in detail the urinary excretion of mercury in six patients seen at the Cleveland Clinic Foundation with Kawasaki disease or MLNS. Three of the six patients had urinary mercury levels higher than the established normal level for mercury in the urine, and considerably higher than levels in control subjects matched by age, sex, and geographic location.

We believe that the MLNS may represent a hypersensitivity reaction to environmental pollution with mercury.

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MATERIALS AND METHODS

Six of seven patients seen at the Cleveland Clinic between 1974 and 1978 with a diagnosis of Kawasaki disease or MLNS had mercury levels determined on 24-hour urine collections. Urinary excretion of mercury in 24 hours is believed to be the best index of exposure to mercury.<sup>3</sup>

Mercury levels were determined by flameless atomic absorption specific for mercury on a Coleman MAS-50 and were expressed as mercury excretion in micrograms per 24 hours and as micromoles of mercury per 24 hours.<sup>4</sup>

Control subjects were hospitalized patients matched by age, sex, and geographic location.

Established international<sup>3,4</sup> and Cleveland Clinic laboratory normal levels were used to determine whether the mercury levels were excessive.

Each of the patients fulfilled the established major diagnostic criteria for Kawasaki disease or MLNS and had many of the minor criteria as shown in Tables 1 and 2.<sup>1</sup>

RESULTS

Statistical analysis by paired *t*-test showed a significant difference between patients and matched control subjects for the urinary excretion of mercury in micrograms per 24 hours and micromoles per 24 hours (Table 3).

Patient 1 was considered critically ill and an attempt was made to chelate mercury from her system. An elaboration of her case history follows.

**TABLE 1.** Major Criteria for MLNS in Six Patients

Patient No.	Duration of Fever (days)	Conjunctivitis	Pharyngitis with Strawberry Tongue	Peripheral Erythema with Subsequent Desquamation	Truncal Exanthem	Cervical Adenopathy
1	26	+	+	+	+	+
2	12	+	+	+	+	+
3	10	+	+	+	+	+
4	17	+	+	+	+	+
5	14	+	+	+	+	+
6	11	+	+	+	+	+

## CASE REPORT

Patient 1, a 13-year-old girl had fever, rash, and a sore throat 26 days before admission to the Cleveland Clinic. Two days later she noted joint pains and a stiff neck, and a temperature spiking as high as 106 F. She complained of malaise and lethargy and remained confined to bed at home until 14 days prior to admission to another hospital as a possible case of meningitis. She was treated with gentamicin, chloramphenicol, tetracycline, and hydrocortisone sodium succinate intravenously. Cultures of blood, urine, and cerebrospinal fluid were sterile and on September 25, 1974, she was transferred to the Cleveland Clinic. On admission she was acutely and critically ill with a temperature of 104F, heart rate 140, erythema of her face and trunk, with early desquamation of the skin over her fingertips and marked injection of conjunctivae and throat. She had diffuse adenopathy especially of the cervical chains. Some clinical and laboratory data are listed in Tables 1 and 2. Antibiotics and steroids were withdrawn. Prior to admission electrocardiograms had shown ST segment elevations in V<sub>2</sub>-V<sub>4</sub> precordial leads and T-wave inversion in V<sub>3</sub> on September 16, progressing to first-degree A-V block on September 23, and then sinus arrest with frequent premature ventricular contractions on September 24. On admission she had T-wave inversion in V<sub>1</sub>-V<sub>3</sub> and on September 26 the T-waves were inverted in V<sub>1</sub> and V<sub>2</sub> but upright in V<sub>3</sub>. Myocarditis was considered possibly secondary to a collagen-vascular disease. On September 27 she underwent a left deltoid muscle biopsy that was interpreted as showing interstitial and perivascular inflammation with thickened capillary and arteriolar walls. Electron microscopy revealed myofibers containing numerous lipid droplets and redundancy of the basement membrane and mononuclear cells in the vicinity of capillaries.

The patient remained critically ill and prednisone, 20 mg three times a day, was commenced on September 29, with only transient improvement in her clinical status. Urinary excretion of mercury was reported as 16.34  $\mu\text{g}/24$  hr (0.082  $\mu\text{mole}/24$  hr), and when repeated five days later was still abnormal at 14.82  $\mu\text{g}/24$  hr (0.074  $\mu\text{mole}/24$  hr). Because she was not improving clinically, penicillamine, 250 mg orally every six hours for seven days, was prescribed on October 8.<sup>5,6</sup> Mercury levels in the urine excreted increased to 15.6  $\mu\text{g}/24$  hr on October 10 and 18.4  $\mu\text{g}/24$  hr on October 12. She was discharged home much improved on October 16 on a regimen of prednisone, 30 mg/day. The steroid dosage was gradually tapered over

six weeks and urine mercury excretion repeated at that time was 5.05  $\mu\text{g}/24$  hr.

## DISCUSSION

About 120 cases of methyl mercury poisoning between 1953 and 1960, caused by eating contaminated fish in Minamata, Japan, have been reported, and approximately 48 cases in Niigata between 1964 and 1965 have also been reported.<sup>7</sup> The original 50 cases of the MLNS came to the attention of Dr Tomisaku Kawasaki, a Japanese pediatrician, during a seven-year period from 1961 to 1967.<sup>1,8</sup> Shortly after the publication of Kawasaki's original report, it became apparent that many other Japanese physicians were encountering the same syndrome, and in 1970 the Japan Ministry of Health and Welfare established a special MLNS study group. Between 1960 and 1976 nearly 10,000 cases were identified in Japan.<sup>1</sup>

In 1970 concern over methyl mercury poisoning of the Great Lakes in North America greatly increased with the discovery of dangerously high mercury concentrations in fish caught in Lake Saint Clair and Lake Erie.<sup>2,9</sup> With the report of MLNS in an American publication by Kawasaki et al in 1974,<sup>8</sup> physicians became aware that this syndrome had existed in the United States as early as 1971. Since then, the Center for Disease Control has received information about more than 400 cases of MLNS occurring in the United States.<sup>1</sup>

The criteria for the diagnosis and symptoms of MLNS are listed in Table 4 and compared with the established symptoms of acrodynia or mercury poisoning.<sup>1,10-13</sup>

The possibility that Kawasaki disease (MLNS) might represent heavy metal poisoning was originally questioned by Dr Donald Cheek of Australia in 1975.<sup>10</sup> Dr Kawasaki replied that he believed MLNS could be differentiated from acrodynia clinically, and that the mercury concentration measured in the hair of seven patients with MLNS was not significantly different from the concentrations measured in healthy adult Japanese citizens.<sup>11</sup> The concentrations in patients and in normal adult con-

TABLE 2. Minor Criteria for MLNS in Six Patients\*

Patient No	Sedimentation Rate—Erythrocyte or Zeta	Acute Phase Reactants (mg/100 ml)	ASO Titer (Todd units)	WBC/PMN (/cu mm)	Platelets (/cu mm)	SGOT/SGPT (IU/liter)	IgE ( $\mu$ /ml) 25–570	Pyuria/Diarrhea	ECG Changes	Arthritis Arthralgia	Pneumonia	Meningismus
1	58 ZSR 10 ESR	FIB 490 GLY 150	250	6,200/4,460	175,000	75/ND		+/+	ST-T wave	+	0	+
2	31 ESR	FIB 1,050 GLY 229	0	22,500/18,675	414,000	30/ND		+/0	ST-T wave	+	+	0
3	40 ESR	FIB 500	100	12,100/10,480	nl	170/140	4,500	0/0	ST-T wave	0	0	0
4	53 ESR	FIB 600	60	15,600/12,320	438,000	28/24		0/0	0	0	0	0
5	39 ESR	FIB 390	500	17,100/13,170	550,000	80/20		+/+	0	0	0	0
6	54 ZSR 13 ESR	GLY 225 CRP 4+	166	15,600/12,950	nl	25/25		+/0	0	+	0	+

\* Abbreviations used are: ESR, erythrocyte sedimentation rate; ZSR, zeta sedimentation rate; FIB, fibrinogen; GLY, glycoproteins; CRP, C-reactive protein; ASO, antistreptolysin-O; PMN, polymorphonuclear leukocyte count; ND, not determined; nl, normal by smear. Normal range of values is as follows. Sedimentation rate: ZSR, 40% to 58%; ESR < 20 mm. Acute phase reactants (mg/100 ml): FIB, 200 to 400; GLY, 100 to 145; CRP, negative. ASO titer (Todd units): < 166. Platelets 150,000 to 400,000/cu mm. SGOT/SGPT 8 to 33/3 to 36 IU/liter.

TABLE 3. Urinary Excretion of Mercury in Patients with MLNS and Control Subjects

Patient	Age (yr)/Sex	Mercury Excretion	
		$\mu$ g/24 hr (normal <10)	$\mu$ moles/24 hr (normal <0.07)
1	13/F	16.34	0.082
2	5/F	6.02	0.030
3	18/M	25.00	0.125
4	7/M	6.31	0.030
5	11/M	5.80	0.030
6	17/F	22.40	0.112
Control subject			
1	13/F	<1.0	<0.005
2	5/F	<1.0	<0.005
3	18/M	<1.0	<0.005
4	7/M	<1.0	<0.005
5	11/M	0.6	0.003
6	17/F	2.38	0.012
Paired <i>t</i> -test significance:		<i>P</i> < .01	<i>P</i> < .01

TABLE 4. Comparison of Symptoms of MLNS and Acrodynia (Mercury Poisoning)

Symptoms	MLNS	Acrodynia
Fever of 5 or more days	+	0
Bilateral conjunctival injection	+	+
Injected pharynx, lips, and strawberry tongue	+	+
Peripheral extremity edema and erythema with pink to red palms and soles	+	+
Membranous desquamation of finger tips, palms, and soles	+	+
Polymorphous exanthem	+	+
Cervical lymphadenopathy	+	+
Photophobia	+	+
Arthralgias/arthritis	+	+
Thromboses	+	+
Anorexia, irritability	+	+
Loss of teeth	0	+
Coronary artery aneurysms	+	0

trol subjects, however, exceed what might be considered normal levels.<sup>7,13–16</sup>

Historically, we know that there is a marked individual susceptibility to mercury which leads to a considerable variation in clinical presentation and course. Whether acrodynia represents an allergic reaction to mercury as originally suggested by Helmick,<sup>17</sup> or is merely an expression of individual idiosyncrasy to the toxic effects of the metal as elaborated by Warkany and Hubbard,<sup>12</sup> remains to be determined. It is interesting that recently levels of serum IgE in patients with MLNS have been reported to be highest from one to two weeks after the onset and then decline over one to two months.<sup>18</sup> The elevated IgE levels implicate an allergic aspect to Kawasaki disease and this IgE response might be precipitated by exposure to a toxin such as mercury.

Myocardial infarction due to coronary artery thromboarteritis has been reported to occur in 1% to 2% of patients with MLNS,<sup>8</sup> and 20% to 30% of patients in the convalescent stage of MLNS have been found to have coronary artery aneurysms<sup>19</sup> by angiographic studies. Three of the patients in this study demonstrated ST-T wave changes on ECG during the acute phase of their illness, but the ECG abnormalities resolved during the convalescent stage. With a normal cardiovascular physical examination, normal ECG, and normal chest roentgenogram, it was decided that coronary arteriography was not justified.

Coronary arteritis and aneurysms have never been reported in mercury poisoning, although an immunologic or hypersensitivity reaction to the heavy metal could theoretically produce a collagen vascular disease or vasculitis. Further research in this area would seem justified.

## SUMMARY

Six patients with diagnostic criteria for Kawasaki disease had abnormally high urinary excretions of mercury. They were compared by age, sex, and geographic location with matched controls. Improvement of one patient was temporally related to chelation of mercury with penicillamine. There are numerous clinical similarities between acrodynia and Kawasaki disease and the appearance of the mucocutaneous lymph node syndrome (Kawasaki disease) has been related temporally and geographically to environmental pollution with mercury. The mucocutaneous lymph node syndrome (Kawasaki disease) may represent a disease caused by environmental pollution with mercury, or clinical symptoms compatible with Kawasaki disease may indicate environmental exposure to mercury.

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