Brief Report

Lead Poisoning Due to *Hai Ge Fen*

The Porphyrin Content of Individual Erythrocytes

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A 45-year-old Korean man developed abdominal colic, muscle pain, and fatigue. Following a 3-week hospitalization, acute intermittent porphyria was diagnosed based on the symptoms and a high level of urinary δ-aminolevulinic acid (378 μmol/L [4.95 mg/dL]). However, discovery of an elevated blood lead level (3.7 μmol/L [76 μg/dL]) subsequently led to the correct diagnosis. No occupational source of lead exposure was identified. The patient reported ingesting a Chinese herbal preparation for 4 weeks prior to becoming ill. A public health investigation revealed that the source of lead exposure was *hai ge fen* (clamshell powder), one of the 36 ingredients of the Chinese herbal medicine. We used fluorescence image–based cytometry to determine the frequency distribution of the zinc protoporphyrin content in circulating red blood cells and found that 70% of the patient's cells contained elevated levels of zinc protoporphyrin, consistent with the duration of lead exposure and effect of lead on heme synthesis. Analysis of zinc protoporphyrin content in circulating red blood cell distributions may be useful in the diagnosis, therapy, and kinetic modeling of lead poisoning. Environmental lead poisoning is best addressed through the close collaboration of clinicians, public health specialists, and laboratory scientists.

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WHILE lead poisoning typically results from well-known occupational exposures and childhood pica, in many instances lead poisoning arises from unexpected sources, including crystal ware, homemade wine, and glazed pottery.[1-6] We report a case of lead poisoning traced to the consumption of tea brewed from lead-adulterated Chinese herbal medicine, which triggered an extensive public health investigation. The investigation included image-based cytometry to determine the zinc protoporphyrin (ZPP) content of individual erythrocytes, a novel analytical technique.

Clinical History

The patient, a 45-year-old Korean man with a 25-year history of smoking, was well until late 1991 when he developed chronic cough, sputum production, and dyspnea. His physician diagnosed chronic obstructive pulmonary disease and prescribed a bronchodilator and prednisone.

Urged by his family, the patient consulted a Chinese herbalist in New York City in April 1992 and obtained multiple bags of dried Chinese herbs. Two cups of tea brewed from these herbs were to be consumed each day. To prepare the tea, a liter of water was boiled with about 5 g of the herbs in a Korean natural medicine electric brewing pot until reduced to 0.24 L (1 cup). The second cup was made in the same manner, using the same herbs.

In late May 1992, the patient visited his physician complaining of severe colicky abdominal pain, weight loss, and anorexia. On June 1, his laboratory tests revealed the following values: hematocrit, 0.32; alanine aminotransferase, 703 U/L; lactate dehydrogenase, 813 U/L; aspartate aminotransferase, 459 U/L; total bilirubin, 44 μmol/L (2.6 mg/dL); and alkaline phosphatase, 233 U/L.

On June 8, the patient was admitted to a community hospital for an evaluation of abdominal pain and elevated liver function tests. The patient reported a decreased libido. A physical examination, including neurological examination, was normal, and a chest radiograph was normal except for an old granuloma. The hematocrit was 0.26 with basophilic stippling present on the peripheral blood smear. The white blood cell count was 7.1×10^9/L, with 0.72 neutrophils and 0.24 lymphocytes. Liver enzyme levels were slightly elevated but lower than previously. Hepatitis A IgM and hepatitis B core IgM and surface antibody test results were negative. Findings on an abdominal computed tomographic scan, abdominal sonogram, hepatoiminodiacetic acid scan, colonoscopy, and barium enema were all normal. Total bilirubin level peaked June 16 at 79 μmol/L (4.6 mg/dL) and was mostly indirect bilirubin (direct bilirubin, 12 μmol/L [0.7 mg/dL]). Urine porphobilinogen level was slightly elevated (12 μmol/L [0.27 mg/dL]) and urine δ-aminolevulinic acid was markedly elevated (378 μmol/L [4.95 mg/dL]). Abdominal pain was treated with intramuscular meperidine. In the hospital the patient did not ingest the herbal tea. He was discharged June 21 with the diagnoses of acute intermittent porphyria, spastic colon, and anemia.

A blood sample drawn during the hospital stay subsequently revealed a blood lead (BPb) level of 3.7 μmol/L (76 μg/dL) and a ZPP level of 2.1 μmol/L. These results were reported to the New York City Department of Health (NYCDOH) by the commercial laboratory performing the tests. When contacted by an NYCDOH investigator, the patient stated that he suspected the herbal medicine to be the source of his lead exposure.

In early July, the patient was referred to the Occupational Health Clinical Center at the Mount Sinai Medical Center, New York, NY, for evaluation and treatment. The occupational history revealed no obvious occupational exposure to lead. The patient taught in a business school before emigrating to the United States in 1981. He then worked as a bookkeeper for 10 years and subsequently operated a shoe repair shop for a year prior to his illness. He denied having any hobbies involving exposure to lead or other metals, and his cooking utensils, made of plastic, glass, and porcelain, were manufactured in the United States.

At Mount Sinai, the patient complained of crampy abdominal pain, anorexia, constipation, fatigue, and diffuse muscular discomfort during the preceding 2 months. Physical examination revealed a thin man in obvious abdominal discomfort. Blood pressure was 105/70 mm Hg. His abdomen showed some tenderness in the right upper quadrant, but exami-

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nation of skin, sclerae, gums, lungs, heart, liver, and nervous system were normal. His BPb and ZPP levels were 3.4 μmol/L (71 μg/dL) and 3.3 μmol/L, respectively. The patient was given a 5-day course of 2,3-dimercaptosuccinic acid (succimer), 1500 mg per day.

Ten days later, the patient reported decreased abdominal pain. Examination showed less abdominal tenderness. His BPb and ZPP levels were 2.4 μmol/L (49 μg/dL) and 3.7 μmol/L, respectively, and an identical second course of succimer chelation was prescribed.

A week later, the patient was much improved and free of abdominal pain and tenderness. His BPb and ZPP levels were 1.9 μmol/L (39 μg/dL) and 2.6 μmol/L, respectively.

On July 8, 1993, a total of 13 months after his initial visit to Mount Sinai, the patient returned. He denied any lead exposure during that interval, and BPb and ZPP levels were 0.9 μmol/L (18 μg/dL) and 0.6 μmol/L, respectively.

Environmental Assessment

At our request, the patient prepared the herbal tea in the usual manner, using the herbs originally provided by the herbalist. On analysis by the Lead Poisoning Laboratory, New York State Department of Health, the tea was found to contain 301 mg/L of lead. This result, obtained by atomic absorption spectrophotometry, was confirmed by inductively coupled plasma atomic emission spectrophotometry, which also showed that the tea contained 64 μg/L of arsenic. Allowable levels of lead and arsenic for drinking water are 0.015 mg/L and 0.05 mg/L, respectively.[7]

Since the patient ingested 470 mL of tea daily for about 5 weeks, his total intake of lead during that period was estimated at 4.7 g, while his arsenic intake was 1.1 mg.

Public Health Investigation

In view of the tea's high lead content, the NYCDOH conducted an investigation to identify and evaluate other potentially exposed persons and to determine if additional public health measures were needed.

Samples of the 36 herbs and other ingredients of the herbal preparation were obtained from the herbalist and were tested for heavy metal content by the NYCDOH Bureau of Laboratories. The ingredient identified as *hai ge fen* (*concha cyclinae sinensis*), or clamshell powder, was found to contain 22.5% (225 000 ppm) of lead and 600 ppm of arsenic. In July 1992, the NYCDOH issued a health alert regarding health hazards associated with clamshell powder imported from China.

Clamshell powder samples were also obtained from two distributors who had supplied the herbalist, and the remaining stock was embargoed. Seven other herbal stores from a total of 23 listed in the *Chinese Business Guide and Directory* were found to stock clamshell powder and provided samples. The lead content of all of these samples was found to be within acceptable limits.

The charts of 1503 customers of the herbalist were reviewed, and two additional persons who had purchased clamshell powder in the previous 6 months were contacted. (A third could not be found.) Their BPb and ZPP levels were found to be within a normal range, and no arsenic was found in their urine.

Image-Based Cytometry of Erythrocytes

When erythropoiesis occurs in the presence of lead, malfunctioning of ferrochelatase causes a small fraction of the hemes of the cell's hemoglobin to be replaced by ZPP. The resulting ZPP-globin is retained by the cell during its circulation time (120 days). The average ZPP level of all circulating cells is easily measured fluorometrically and provides a widely used biological indicator of lead burden.[8-11]

The frequency distribution of the ZPP content of individual red blood cells (ZPP/RBC) in circulation therefore reflects the lead levels that prevailed in bone marrow during the preceding 4 months, when each cell's hemoglobin was synthesized, and is therefore a function of exposure history. It can be determined experimentally by the use of fluorescence image–based cytometry.[12]

When lead is ingested or absorbed in the body, the BPb level initially rises and then falls within days. However, after prolonged exposure, lead is largely stored in the skeleton where its equilibration time with blood and organs is several years.[13] This suggests that acute exposure leads to mild to moderate elevation of average ZPP levels with a minority of red blood cells containing elevated ZPP levels. In long-term exposure, on the other hand, ZPP levels are expected to be high in most cells.

Figure 1 shows transmission and ZPP fluorescence images of the patient's red blood cells drawn 2.5 months after exposure. The images were obtained with a Zeiss Axiovert microscope equipped with a cooled slow-scan charge-coupled device camera (Princeton [NJ] Applied Research) operated at −65°C with details of image acquisition and analysis presented elsewhere.[12] The ZPP fluorescence emitted by a cell was converted to the number of ZPP molecules it contains by relating the average of the cell fluorescence distribution to the patient's ZPP level determined with a calibrated ZPP hematofluorometer (Aviv Biomedical, Lakewood, NJ).

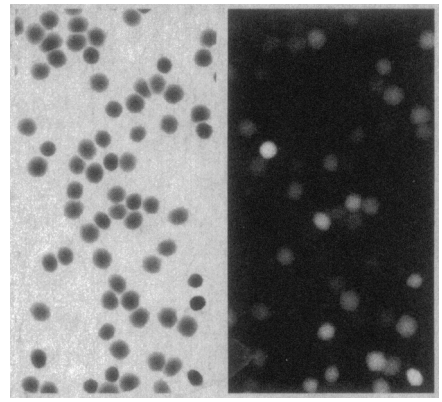

Fig 1.—Transmission and zinc protoporphyrin fluorescence images of a portion of a field of immobilized erythrocytes, acquired at 415 nm (left) and 590 nm (right). The fluorescence intensities of the individual cells, obtained by integrating the photoelectrons recorded by the charge-coupled camera pixels within the cell perimeter, were used to obtain the histograms shown in Fig 2. The fluorescence image was excited at 415 nm with an exposure time of 5 seconds.

The ZPP/RBC distribution for the patient and three other subjects with known exposure histories is shown in Fig 2.

The patient ingested lead during a 5-week period, beginning 3 months before the ZPP distribution was obtained (Fig 2). The fact that 70% of his red blood cells had elevated ZPP levels suggests that the amount of lead retained in his body was sufficient for ZPP-rich erythrocytes to be synthesized well after exposure ceased. This is consistent with his average ZPP levels remaining high while his BPb levels decreased, declining to 0.9 μmol/L (18 μg/dL) 15 months after exposure ceased.

Comment

While nonoccupational lead poisoning is generally rare, the 1992 New York State Registry reported that 150 (13%) of 1128 adults with elevated BPb levels had no occupational exposure (Robert Stone, PhD, Heavy Metal Registry, New York State Department of Health, oral communication, June 1993). Clinicians therefore need to be aware of the potential of occult lead poisoning to avoid delays in identifying the exposure source and initiating therapy.

Lead is one of the few environmental toxins subject to mandatory reporting to public health authorities in at least some states in the United States.[14] This facilitates the only national surveillance program for an environmental cause of morbidity, which showed that 21 241 adults in 18 states had BPb levels of at least 1.2 μmol/L (25 μg/dL) during 1992.[15] The widespread availability of BPb and ZPP assays, in combination with the statutory requirement for reporting elevated levels, have greatly improved

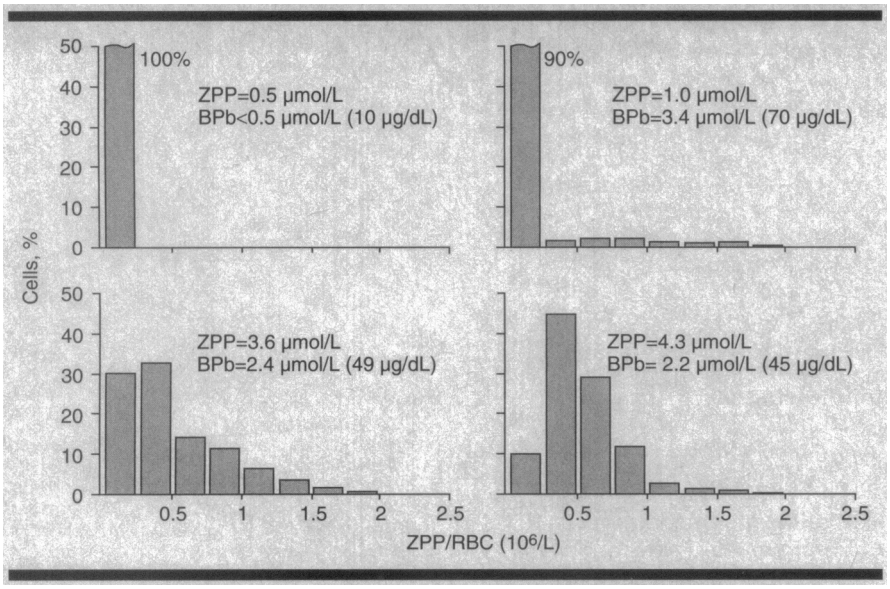

Fig 2.—The fractional distributions of the zinc protoporphyrin content of individual red blood cells (ZPP/RBC) in the blood samples drawn from subjects with known lead exposure histories: an unexposed subject (top left); a painter exposed to lead-bearing paint dust for a 2-week period shortly before blood sample was drawn (top right); the case patient on July 16, 1992 (bottom left); and a lead smelter worker with 12 years of occupational exposure (bottom right). The panels also show the ZPP and blood lead (BPb) levels at the time that the ZPP/RBC distributions were determined. The ZPP/RBC distribution of the case patient 13 months after exposure was identical to the unexposed subject (top left). Each analysis is based on at least 1000 cells.

the public health surveillance of lead disease among adults. Unfortunately, many other cases of environmental toxicity are not reported in part due to the difficulty of assaying toxins, reliance on clinical diagnoses, and physicians' inexperience with these diseases.

The ZPP/RBC distributions have several potential uses. First, they can aid in identifying the source of exposure by providing information about a patient's exposure history when no other reliable information is available (eg, for children and workers with unknown and intermittent exposure). Second, they aid in devising a strategy for chelation therapy by distinguishing between acute and chronic plumbism and may also aid in evaluating the efficacy of chelation: since lead is largely stored in the skeleton in chronically exposed persons, chelation reduces BPb level only slowly, reflecting the slow recruitment of lead from bone.[16]

Finally, ZPP/RBC distributions provide an additional experimental parameter that can be compared with the predictions of computer models for the kinetics of lead transport among body compartments.[13] Such studies have been initiated in our laboratory.

Although excessive arsenic absorption by the patient could not be demonstrated, we believe that he also may have suffered from arsenic toxicity. The rapid changes in liver enzymes during June 1992 suggest that an ingredient of the herbal tea was responsible. Arsenic can produce acute alterations in liver enzyme levels,[17,18] while lead rarely causes significant acute hepatotoxicity.[19,20]

The exact circumstances under which the clamshell powder was adulterated were never fully discovered. Individual cases such as this one serve as sentinel events that can trigger the rapid identification of exposure sources and at-risk populations,[21,22] demonstrating the importance of close collaboration of environmental and occupational clinicians and public health authorities.

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Conversions From Système International (SI) Units to Conventional Units (Modified From *The SI Manual in Health Care*)

System*	Component	SI Reference Interval†	SI Unit	Conversion Factor (Divide by)	Conventional Reference Interval†	Conventional Unit
Ercs	Protoporphyrin	0.28-0.90	µmol/L	0.0177	15-50	µg/dL

*Ercs represents erythrocytes.
†These reference values are not intended to be definitive since each laboratory determines its own values. They are provided for illustration only.