

Original Article

An epidemiological study of mercury sensitization

Kazuhiro Sato,¹ Yukinori Kusaka,¹ Qunwei Zhang,¹ Makoto Yanagihara,^{2*} Keiichi Ueda,² Hironori Morihiro,³ Yasuo Ishii,³ Tomio Mori,⁴ Toshiyuki Hirai,⁴ Takesi Tomiyama⁴ and Kazutada Iida⁴

Departments of ¹Environmental Health, ²Dermatology and ³Dental Surgery, Fukui Medical School and ⁴Fukui Prefectural Institute of Public Health, Fukui, Japan

ABSTRACT

Mercury sensitization has been historically in question and may be related to recent increases of type I allergic diseases. To clarify the epidemiological factors of mercury sensitization, we investigated factors relating to mercury sensitization in 215 medical students. Their allergic symptoms, family histories and lifestyles were studied by questionnaire. Patch tests were performed with HgCl₂ (0.05% aq.) and NiSO₄ (5% aq.). Anti-*Dermatophagoides* and anti-*Cryptomeria* pollen IgE antibodies in sera were also measured. Urinary mercury concentrations were measured in 25 mercury sensitized and 44 non-sensitized subjects (controls). Hair mercury concentrations were also measured in 19 sensitized and 22 non-sensitized subjects. While the positive rate of nickel was 6.0% (13/215), that of mercury was high (13.0%; 28/215). The subjects' individual histories of allergic rhinitis, eczema, urticaria and allergic conjunctivitis were significantly associated with family histories of these conditions ($P < 0.01$, $P < 0.005$ and $P < 0.005$, respectively), as reported in the literature. However, no allergen-specific antibody positivity or past history of allergic disease was associated with mercury sensitization. Mercury sensitized subjects had experienced eczema caused by cosmetics, shampoos, soaps and haircreams significantly more frequently ($P < 0.05$).

The history of mercurochrome usage was not associated with mercury sensitization. The number of teeth treated with metals in mercury sensitized subjects was significantly higher than that in the control group (6.8 ± 4.3 vs 4.8 ± 1 ; $P < 0.05$). There were significant differences in urinary mercury concentrations (specific gravity adjusted levels) between mercury sensitized subjects and non-sensitized subjects (2.0 ± 0.9 and 1.3 ± 0.6 $\mu\text{g/L}$, respectively; $P < 0.001$). There were also significant differences in hair mercury concentrations between mercury sensitized and non-sensitized subjects (2.0 ± 0.9 and 1.2 ± 0.5 $\mu\text{g/g}$, respectively; $P < 0.01$). These results suggest that mercury sensitization is associated with exposure to mercury in the living environment and that skin symptoms are possibly associated as preceding factors.

Key words: amalgam, contact dermatitis, HLA class II, mercurochrome, mercury sensitization, patch test.

INTRODUCTION

Allergic contact dermatitis is an inflammatory reaction mediated by type IV hypersensitivity. In guinea pigs and mice, the genes that control the delayed hypersensitivity reactions have been shown to be in linkage with those of the major histocompatibility antigens.¹ The immune response genes (Ia) of mice have their homologues in the human HLA-DR locus.²

Allergic reactions to dental alloys, especially amalgams that contain mercury (Hg), have been reported by dentists and dermatologists.³ Kidney⁴ and hair⁵ have been known as deposition sites for the excretion of Hg from the body. As Hg is excreted from the body partly by urinary excretion and deposits in the hair,

Correspondence: Dr Kazuhiro Sato, Department of Environmental Health, Fukui Medical School, Matsuoka-cho, Fukui 910-11, Japan. Email: <SATOKAZU@fmsrsa.fukui-med.ac.jp>

*Present address: Department of Dermatology, Kanazawa Medical University, Ishikawa, Japan.

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analyses of urine and hair provide a convenient tool for estimating body burdens of Hg.⁵ HgCl₂ may increase IgE antibodies, as shown by *in vitro*⁶ and *in vivo*⁷ experiments. Moreover, Hg is reported to have various pathophysiological effects on the human immune system.⁸

Currently, the main sources of Hg exposure are dental amalgam restoration and thimerosal preservation in vaccines.^{3,9} We have previously reported¹⁰ that Hg-sensitized subjects had significantly more teeth treated with metals, a higher urinary Hg concentration and had experienced more eczema due to cosmetics, shampoos, soaps and haircreams than did non-sensitized subjects among a study population of 156 medical students.

In the present study we examined more subjects and included another indicator for Hg accumulation. The results further confirm the epidemiological factors relating to Hg sensitization.

METHODS

The subjects in the present study were medical students of the fourth level (total $n = 310$) in 1993, 1994 and 1995. Before any examination, informed consent was obtained from all subjects. Patch tests were performed on 215 subjects (69.4%; mean ($\pm$ SD) age 22.7 ± 2.2 years; male = 158; female = 57). Blood samplings for analysis of allergen-specific antibodies were obtained from 185 (59.7%) subjects. The response rate of the self-administered questionnaire, which consisted of items related to allergic symptoms, lifestyles and family histories, was 92.9% (288/310).

The number of teeth treated with metals was diagnosed by dentists in 26 Hg-sensitized (Hg(+)) and 46 non-sensitized (Hg(-)) subjects. Urinary Hg concentrations were also measured in the same subjects. However, one Hg(+) and two Hg(-) subjects rejected urine samplings. On another day, hair Hg concentrations were measured in 19 Hg(+) and 22 Hg(-) subjects. As a control group for Hg-sensitized subjects, some students were selected, allowing for age and gender, to examine Hg exposure levels.

Questionnaire study

The individual history and family history criteria of bronchial asthma, allergic rhinitis, eczema, urticaria, allergic conjunctivitis and atopic dermatitis were as

follows. If the subject had been diagnosed as having one of these diseases by a doctor, they were considered to have a past history of it. When a subject answered the questionnaire stating that he/she had a family member who had suffered from a disease listed in the questionnaire, the subject was considered to have a family history of the disease. Some questionnaire items regarding respiratory, skin, nasal and eye symptoms are listed below.

(1) Respiratory symptom: when you have not had a cold, have you ever been wheezing?

(2) Skin symptom (#1): have you ever experienced reddish skin, itching or oozing of unknown origin?

(3) Skin symptom (#2): have you ever experienced eczema by metallic accessories, such as body piercing, earrings or watches?

(4) Skin symptom (#3): have you ever experienced eczema by cosmetics, shampoos, soaps or haircreams?

(5) Nasal symptom: when you have not had a cold, have you ever experienced sneezing, nasal discharge or obstruction?

(6) Eye symptom: have you ever experienced eye itching, reddish eyes or tearing?

Blood analysis

Anti-*Dermatophagoides* and anti-*Cryptomeria* pollen antibodies were measured by the radioallergosorbent test (RAST). A RAST score ≥ 2 was judged as antibody positive.

Patch test

Patch tests were performed using textile plaster (Torii Co. Ltd, Tokyo, Japan) with HgCl₂ (0.05% aq.) and NiSO₄ (5%) on the inner part of the subject's upper arm. Forty-eight hours later, a reading was made 20–60 min after removal of the patch, based on the standard of the international contact dermatitis research group (ICDRG),¹¹ by a dermatologist.

Mercurochrome usage history and dental examination

The 26 Hg(+) group and the 46 Hg(-) control group were examined by dentists for the number of teeth filled with metals and subjects reported their mercurochrome usage history ('often', 'sometimes' or 'seldom').

Measurements of Hg concentrations in urine and hair

Mercury concentrations in the urine (from 25 Hg(+) and 44 Hg(-) subjects) and hair (from 19 Hg(+) and 22 Hg(-) subjects) were measured by reductive vaporization-gold amalgam capture-atomic absorption spectrophotometry (Mercury-SP-3D; Nippon Instruments Corp., Japan). The specific gravity of urine was determined by Urigon-PS (Atago Co. Ltd, Japan). The concentration of urinary Hg was adjusted by the specific gravity.

Statistical analysis

Data were analyzed by the Chi-squared test with Yates' correction to compare differences in the prevalences of each descriptive variable. Differences in the means of teeth filled with metals were tested by one-tailed *t*-test between Hg-sensitized and non-sensitized groups to test the hypothesis that the number of teeth treated with metals of the Hg-sensitized group was equal or smaller than that of the non-sensitized group. Significance was accepted at $P < 0.05$.

RESULTS

Patch test with Hg and nickel

While the positive rate for nickel was 6.0% (13/215), that of Hg was high (13.0%; 28/215).

Mercury sensitization and type I allergy

The prevalence of past histories of bronchial asthma, allergic rhinitis, sinusitis, eczema, urticaria, allergic conjunctivitis and atopic dermatitis in the 215 subjects was 23 (10.7%), 64 (29.8%), eight (3.7%), 10 (4.7%), 37 (17.2%), 15 (7.0%) and 19 (8.8%) subjects, respectively.

The positive rates of anti-*Dermatophagoides* antibodies and anti-*Cryptomeria* pollen antibodies in the serum were 51.9 (96/185) and 45.4% (84/185), respectively. Positive anti-*Dermatophagoides* antibody was significantly associated with a past history of bronchial asthma ($P < 0.01$), that of allergic rhinitis ($P < 0.001$) and respiratory symptoms ($P < 0.001$). Positive anti-*Cryptomeria* pollen antibody was significantly associated with a past history of allergic rhinitis ($P < 0.001$), nasal symptoms ($P < 0.001$) and eye symptoms ($P < 0.05$). It -

was confirmed that type I allergic diseases were intensely associated with allergic symptoms of the eye, nose and bronchus.

We then investigated the association between type I allergy and Hg sensitization. Not one of the specific IgE antibody positive reactions (RAST score ≥ 2) was associated with Hg sensitization. A past history of any of the allergic diseases was not associated significantly with Hg sensitization.

Mercury sensitization and skin symptoms

Mercury sensitization was not significantly associated with skin symptoms (#1 and #2). However, the present study found that Hg sensitization was significantly ($P < 0.05$) associated with skin symptom (#3) (Table 1).

Mercurochrome usage history and dental examination

The 26 Hg-sensitized subjects and 46-non-sensitized control subjects reported their mercurochrome usage history since childhood as 'sometimes to often used' or 'seldom used'. 'Sometimes to often used' was reported by 73.1% (19/26) Hg-sensitized subjects, the difference being not significant (by the Chi-squared test).

The number of teeth filled with metals in Hg-sensitized subjects (6.7 ± 4.3 ; $n = 26$) was significantly higher than that in non-sensitized subjects (4.8 ± 4.1 ; $n = 46$; Fig. 1; one-tailed *t*-test $P < 0.05$).

Mercury concentrations in urine and hair

There were significant differences in specific gravity adjusted urinary Hg concentrations between the 25 Hg(+) subjects and 44 Hg(-) subjects ($P < 0.001$; Fig. 2).

Table 1. Association between mercury sensitization and experience of eczema

Eczema*	Mercury sensitization		Total
	(+)	(-)	
(+)	9	24	33
(-)	19	160	179
Total	28	184	212

*Eczema caused by cosmetics, shampoo, soap and haircream.

$P < 0.05$ (by the Chi-squared test); association between mercury sensitization and experience of eczema.

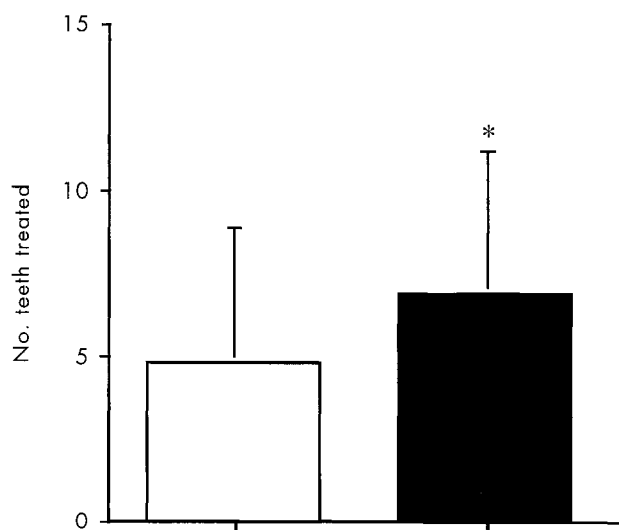


Fig. 1 Number of teeth treated with metals according to mercury (Hg) sensitization. (■), Persons sensitized to Hg, as indicated by the patch test; (□), persons not sensitized to Hg. Values are the mean $\pm$ SD. * $P < 0.05$.

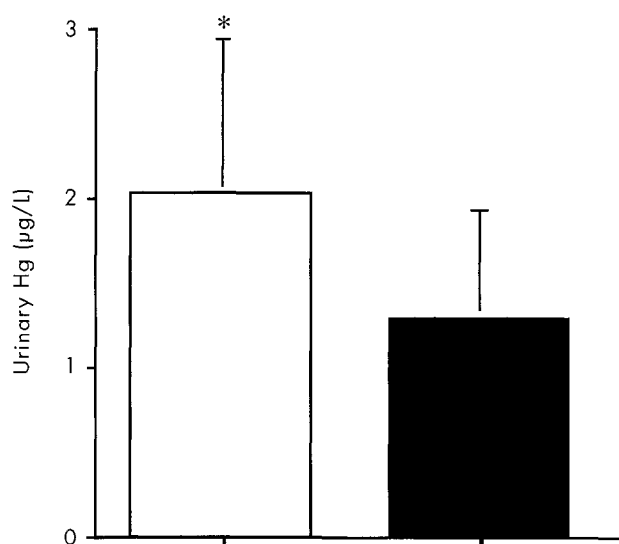


Fig. 2 Urinary mercury (Hg) concentrations (specific gravity adjusted levels) in persons who were positively (□) or negatively (■) sensitized to Hg. Values are the mean $\pm$ SD. * $P < 0.001$.

There were also significant differences in hair Hg concentrations between 19 Hg(+) and 22 Hg(−) subjects ($P < 0.01$; Fig. 3).

DISCUSSION

The patch test is indispensable in determining the cause of allergic contact dermatitis.¹¹ It is also indispensable in

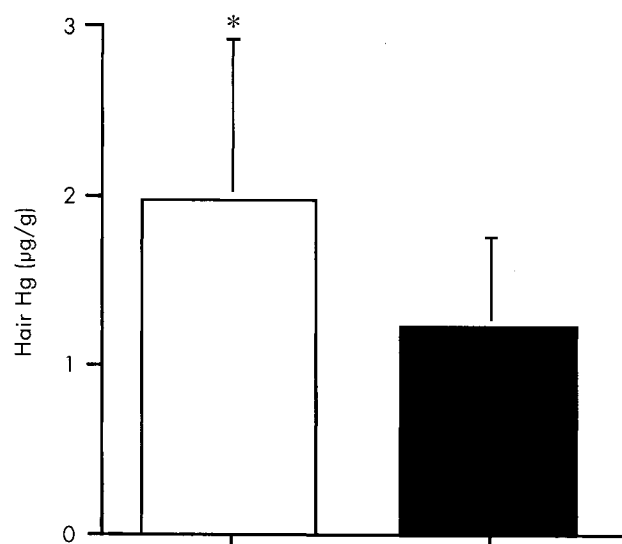


Fig. 3 Hair mercury (Hg) concentration in Hg-sensitized (□) and -non-sensitized (■) students. Each value represents the mean $\pm$ SD. * $P < 0.01$.

diagnosing metallic contact dermatitis, as done in the present study. When Hg salts in aqueous solution react in an aluminum Finn® chamber, false-positive skin test results occur.^{12,13} In 1990, Kubo *et al.*¹⁴ reported a false-positive reaction to a patch test with mercuric chloride aqueous solution in the aluminum Finn® chamber and reported that the chemical irritation by hydrochloric acid formed from the interaction between Hg and aluminum led to the false-positive patch test reaction. We therefore used textile patches (Torii Co. Ltd) in the present study.

Although it has been reported that HgCl₂ increases IgE production in both animal models⁷ and in an *in vitro* system,⁶ the results of the present study showed that Hg sensitization was not associated with any type I allergic diseases or the presence of each allergen-specific IgE antibody, as was found in our previous study.¹⁰ Thus, the hypothesis that Hg had an adjuvant effect on type I allergic diseases among humans was not supported. This is in accordance with the finding that nickel contact dermatitis was not associated with atopic dermatitis.^{15,16}

Various investigators have estimated that the average daily body absorption of amalgam Hg in humans ranges between 1.2 and 27 µg,¹⁷ with levels for some individual subjects being as high as 100 µg/day. At the present time the consensus average estimate is 10 µg amalgam Hg (range 3–17 µg) absorbed per day,¹⁸ an uptake amount corroborated by a more recent daily estimate of 12 µg.¹⁹ By way of contrast, estimates of the daily absorption of all forms of Hg from fish and seafood is

2.3 µg and from other foods, air and water it is 0.3 µg.¹⁸ Thus, it is now proposed that dental amalgam tooth fillings are the major source of Hg exposure for the general population.^{18,20} This position has been clearly validated by a recent demonstration that at least 65% of excretable Hg in human urine is derived solely from dental amalgams and that the amounts of Hg excreted also correlate with total amalgam surface area.²¹

In dental clinics, personnel are occupationally exposed to inorganic mercury from the preparation and insertion of amalgam fillings.^{22,23} Dental students are also often exposed to Hg in amalgams. White *et al.*²⁴ reported a significant increase in the rate of Hg hypersensitivity between prefreshman and the senior class over the 4 years of dental training. In the present study, the number of teeth treated with metals in Hg(+) medical students was significantly higher than that in Hg(−) students. Moreover, there were significant differences in urinary and hair Hg concentrations between the two groups. Taken together, these results suggest that the increase in urinary Hg among Hg-sensitized students is derived from amalgams for filling and that Hg sensitization is associated with exposure to Hg in the living environment, including absorption of Hg through the oral mucosa. If the use of amalgams was to be limited, the prevalence of Hg sensitization would be expected to lessen.

Table 2 shows that Hg-sensitized subjects experienced significantly more eczema caused by cosmetics, shampoos, soaps and haircreams. These findings indicate that Hg sensitization is associated with the preceding factor of skin symptoms.

Our results show that a family history (data not shown) and past histories of allergic diseases, including eczema, were not associated with Hg sensitization. Thus, we could not confirm an association of genetic factors with Hg sensitization. However, our findings regarding the relationship between Hg sensitivity and family history may not exclude the involvement of genetic factors in Hg sensitization, as the 'family history' examined in the present study was of clear manifestations of allergic diseases only.

Several studies have investigated the association between HLA and metal sensitivity. HLA molecules are polymorphic membrane glycoproteins found on the surface of almost all nucleated cells (HLA class I molecules) and cells mainly involved in the immune response (HLA class II molecules). A significant increase in HLA-DRw6 antigen in nickel contact sensitivity patients has been reported.² In our previous study we found an

increase in DR6 among a Hg-sensitized subgroup of subjects in the present study. However, there were no significant differences in the incidence of any of the HLA-DR types between Hg-sensitized and -non-sensitized groups.²⁵ Fisher *et al.*²⁶ reported that there were no differences in HLA-A, B, C and DR between cobalt-sensitized patients and controls. Using genomic typing methods, Olerup and Emtestam²⁷ found a significant association ($P < 0.001$) of contact dermatitis to nickel with a TaqI HLA-DQA allelic restriction fragment. Recently, using a DNA polymerase chain reaction method, Richeldi *et al.*²⁸ found a significant association of DPB1 with chronic beryllium disease ($P < 0.001$). If a definite association between an HLA type and metal sensitivity is found, preventive methods (e.g. antigen exclusion therapy) could be performed on patients who have the HLA type. In addition to environmental epidemiological studies of Hg sensitization, more extensive research by DNA sequence assays is needed to clarify the possible associations between HLA types and metal sensitivity.

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