

Section 2 *Clinical reports*

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Symptoms and differential diagnosis of patients fearing mercury toxicity from amalgam fillings

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Clinical signs, somatic symptoms reported by patients, and mercury excretion in urine were studied for 348 patients selected by odontologists or internists as amalgam-free referents, or as subjects with unexplained clinical findings or who were self-selected due to their fear of mercury intoxication from their amalgam fillings. Sixty patients were excluded because other explanations could be given for their complaints. The age distribution was bimodal, with peaks between 30 and 35 years and between 45 and 50 years. Mercury was determined in a morning urine sample and 30 minutes after the injection of 300 mg of 2,3 dimercapto-1-propane sulfonic acid (DMPS), a mercury-chelating agent. The patients were followed for 1—3 years. Among the patients there were 26 who had had their amalgam fillings removed and who, at the time of the follow-up, were subjectively cured. When the patients were classified according to the excretion of mercury after the DMPS challenge, those who belonged to the upper quartile had an odds ratio of 7.2 (95% confidence interval 3.1—15.2) for becoming cured after amalgam removal. The symptoms of the cured patients had been predominantly mental. No consistent clinical picture could, however, be found among the other patients, as various types of mental and physical distress were reported.

Key terms amalgam, clinical findings, DMPS, mercury excretion.

Whether the mercury released from dental amalgam can cause clinical intoxication is under intense debate in Scandinavia, Germany and the United States. It is clear that amalgam is the main source of mercury in persons who are not exposed to elementary mercury from occupational or similar sources (1) although individual variation is very great (2). The amount of mercury in the central nervous system and other organs is proportional to the amount of amalgam surfaces (3, 4). In experiments with sheep and monkeys, mercury from fresh amalgam fillings rapidly appeared in the brain, liver, thyroid and other organs, and also in the fetus (5, 6). There are also reports of mercury intoxication after dental treatment, including the grinding of amalgam surfaces (7).

The term "oral galvanism" has been used, mainly by the lay press, to denote a syndrome of mental and physical symptoms experienced by patients and believed to be caused by mercury released from amalgam (9). Numerous psychiatric and odontological studies have failed to recognize such a syndrome or its relation to mercury (10—13).

The failure to detect a possible disease caused by mercury released from amalgam has usually been due to the fact that most studies have been done on patients who have regarded themselves as victims of intoxication, or have been so regarded by other "believers" in the disease. Furthermore, follow-up studies of patients who have had their amalgam removed have not been reported.

This paper describes the follow-up of patients who had a high mercury excretion in their urine after intravenous administration of the chelating agent 2,3 dimercapto-1-propane sulfonic acid (DMPS).

Material and methods

Patients

Four groups of patients participated in the study. The largest group comprised 248 self-selected patients seeking help from their dentist because of fear of amalgam

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toxicity as a result of symptoms which their physicians had not been able to cure or explain. Fifty-three patients had been referred to the study by dentists or physicians who had observed unexplainable symptoms and signs that suited the description of "oral galvanism". Ten patients were included by one of us (SS) after a thorough clinical examination of somatic symptoms which could not be explained. Thirty-seven patients were volunteers or dental personnel with or without amalgam fillings. Persons without amalgam fillings had either never had any or had had them removed. These persons were, according to their own opinion, in good health.

Altogether 348 persons, 110 of them men, were studied. Fifty-seven of the patients had no amalgam fillings at the time of the first examination. The age distribution was bimodal for both genres, with peaks between 30 and 35 years and 45 and 50 years. Patients older than 65 years were excluded.

Clinical assessment

The patients were requested to provide the investigators with previous dental and medical records and results of previous examinations. Dental and medical examinations were performed. The patients had answered a questionnaire based on the Geissner Symptom Complaints Checklist (14). The list had initially been expanded from 57 to 131 questions by Malt (15) and later by us to 144 questions in order to include also symptoms typical of some endocrinologic and metabolic diseases of differential diagnostic importance. The patient had to choose between five degrees of severity for each symptom (scores 0 = absent, 1 = possibly present, 2 = mild, 3 = considerable, 4 = severe).

The patients had to state their three most serious complaints when interviewed by an internist (SS). A thorough 45-minute interview regarding symptoms relevant for these complaints was done. In addition, dietary habits, medical history, and use of alcohol, tobacco and drugs were recorded. The use of alternative therapy regarded as inappropriate was especially inquired about.

If the patients had signs of mental or physical disorders which needed treatment, they were requested to seek help or were referred to hospital investigations.

Mercury excretion and use of 2,3 dimercapto-1-propane sulfonic acid

Samples of urine were collected in the morning or between 1500 and 1800 in the afternoon. Immediately thereafter 300 mg of DMPS (Unithiol®, October Pharmaceutical Industries, St Petersburg, Russia) was given intravenously in a 5-ml water solution during 5 minutes, and 30 minutes later a second urine sample was collected. Inorganic mercury and creatinine were determined in the urine samples. DMPS is an ionic chelating substance that has its highest affinity for mercury and

copper (16). It is rapidly excreted in the urine after intravenous administration (17).

Statistical analysis

The symptom scores were grouped according to organ, or organ group of origin, as cardiovascular, psychiatric, neurological, musculoskeletal, gastrointestinal, respiratory, general (including fatigue), odontological or oral, infectious, otologic, visual, and skin-related or allergic. The gynecologic and sexual dysfunction symptom scores were not analyzed.

Differences in the total scores for each symptom group were tested by an analysis of variance and post hoc analysis (Tukey's HSD test) if significant results were observed. The covariates were gender, age, mercury excretion without and with DMPS challenge, and the presence or absence of amalgam. Statistica software (StatSoft, Tulsa, OK, United States) was used throughout for the analyses.

Results

Clinical findings

Sixty self-referred patients were excluded either because they had good dental status with only minor amalgam fillings or because their medical examination and history revealed a reasonable dental, medical, or psychiatric explanation for the complaints. Among them were patients with multiple sclerosis, torticollis, amyotrophic lateral sclerosis, and diabetic neuropathy who sought alternative therapy for their diseases. As the result of further medical examinations, one case was excluded due to myasthenia gravis, and one due to infarction of the cerebral trunk as a result of hyperextension of the neck during dental treatment. The latter patient, a 28-year-old woman suspected mercury released during the treatment to be the cause of her acute disability.

The remaining 288 patients were re-examined or interviewed after 1.5–3 years, and, on the basis of these results and the original examination, they were classified according to whether the most predominant complaints or symptoms and signs were still present at the time of the follow-up or not (figure 1). The classifications used for the statistical analysis were psychiatric cases (N = 57 patients), somatic cases (N = 186), oral cases (N = 42), referents (N = 37) and cured patients (N = 26).

The patients classified as cured had initially been regarded as objectively not well, and they did not have any odontologic diseases. After removal of their amalgam fillings they were, according to their own assessment and the clinical examination, completely free of

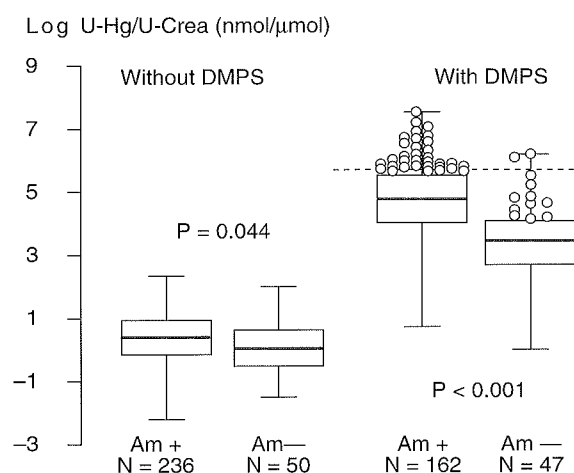


Figure 1. Urinary excretion of mercury in relation to creatinine. [Am+ = patients with amalgam fillings, Am- = patients without amalgam fillings, broken line = upper reference value (mean + 2 SD)]

symptoms and signs at the time of the follow-up, and no other cause for their diseases had been detected. None of the patients who had not removed their amalgam fillings regarded themselves as cured at the time of the follow-up.

Occurrence of symptom analysis in relation to clinical signs

All four groups of patients (psychiatric, somatic, oral, cured) differed significantly from the referents regarding the symptom scores. The differences between the patient groups were minor, and no significant effect was noted for the covariates age, gender, and mercury excretion. The symptom groups reported similarly by all the patient groups were cardiovascular, neurological and respiratory tract symptoms, infections, and allergy.

The four patient groups were characterized as follows. The odontologic cases had the lowest scores, and they had high scores for the taste of metal and changes of the oral mucosa. They complained of increased sound sensibility and foot and hand eczema. Among these patients, no cases of parodontitis or orofacial dysesthesia were found, but craniomandibular dysfunction, oral lichen and metal incompatibilities (various metal fillings in contact with each other) were frequent.

The psychiatric patients had the highest scores of all; they reported fatigue, light sensitivity, nausea and vomiting, and acne more often than the other groups.

The somatic patients did not report any characteristic scores, nor did the patients who, on follow-up, were classified as cured.

Mercury excretion

The mercury content of the urine samples was correlated to the creatinine of the same sample in order to eliminate errors due to physiological variations in water diuresis.

The mercury excretion in the morning urine varied considerably and was higher for patients with amalgam fillings than for those without (the fillings of these persons had been removed). However, overlapping was extensive ($P = 0.009$, figure 1). Of the 50 amalgam-free cases, one dentist and one patient who had had his fillings removed 2 months earlier had values over 21 nmol/l; all the other subjects had lower values. Of the patients with amalgam fillings ($N = 236$), 34 had values higher than 20 nmol/l.

When mercury excretion was correlated to the creatinine contents of the same sample, the log values showed a normal distribution. The following reference values were obtained for mercury:creatinine in the morning urine of patients without amalgam: mean 1.08 nmol/μmol, 95% confidence interval 0.69–1.15 and range for ± 2 SD (reference range) 0.19–4.43 nmol/μmol. For patients with amalgam the values were 1.28 nmol/μmol, 95% CI 1.18–1.47 and 0.21–7.80 nmol/μmol, respectively. Twenty of the 236 patients with amalgam had values higher than the upper reference value of the nonamalgam patients.

An important observation in this study was that four patients had a mercury concentration of over 100 nmol/l in their morning urine; this amount is more than the upper level allowed in industrial exposure. Their excretion in relation to creatinine was also twice as high as the reference value (4.4 nmol/μmol) obtained for amalgam-free patients in this study. The value of these patients ranged from 9.5 to 27.0 nmol/μmol. In two of them the excretion was reduced to normal levels within 1 year after amalgam removal, the two others were not tested again.

All four patients with high mercury excretion levels regarded themselves as free of symptoms after their amalgam fillings were removed. All of them had complained of difficulties in concentrating on demanding mental work and of changes in mood to aggressiveness and restlessness before the follow-up. All these symptoms disappeared after the amalgam was removed. The patient with the highest mercury levels (324 nmol/l, 27 nmol/μmol creatinine) was remitted to psychiatric consultation in a university clinic, where she was regarded as bordering on psychosis. The possible role of mercury in the psychiatric disease was completely neglected by the consulted psychiatrist. The patient also had motor disturbances, namely, difficulties in using her hands as an upholsterer and in writing. All psychiatric and somatic symptoms disappeared after the amalgam removal.

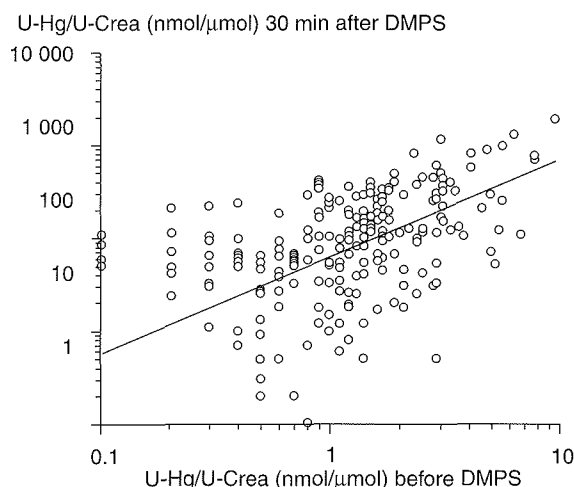


Figure 2. Correlation between the urinary excretion of mercury in relation to creatinine level with and without DMPS challenge.

2,3 dimercapto-1-propane sulfonic acid test

After the injection of DMPS the mercury:creatinine ratio was calculated. The reference values obtained for mercury:creatinine in the morning urine of patients without amalgam were then a mean of 29 nmol/mmol, a 95% confidence interval (CI) of 20–42 nmol/mmol, and a reference range of 2–368 nmol/mmol. For the patients with amalgam the values were a mean of 111 nmol/mmol, a 95% CI of 93–133 nmol/mmol, and a reference range of 10–1180 nmol/mmol. Of the 162 patients with amalgam 13.5% had values higher than the upper reference value for nonamalgam patients. Eighty-five percent of them had values higher than the upper quartile of the nonamalgam patients. The ratios before and after the DMPS challenge correlated with each other ($R = 0.447$, $P < 0.001$) (figure 2).

Effect of amalgam removal

The follow-up mercury:creatinine ratios were tested for 30 patients (figure 3). For the 22 patients who had not removed their amalgam, the excretion had not changed 1–3 years later. On the other hand, for the patients who had had their amalgam removed, the ratio had decreased significantly ($P < 0.001$). This change was especially notable when the DMPS test was used.

Fourteen of the 26 patients who had been clinically classified as cured had mercury:creatinine ratios which were in the upper quartile of the data for all the tested patients after the DMPS test. The odds ratio for being a “curable” patient when no medical or psychiatric explanation was found for the patient’s complaints and the mercury:creatinine ratio after the DMPS test was higher than 260 nmol/μmol was thus 5.5 (95% confidence interval 3.2–9.3).

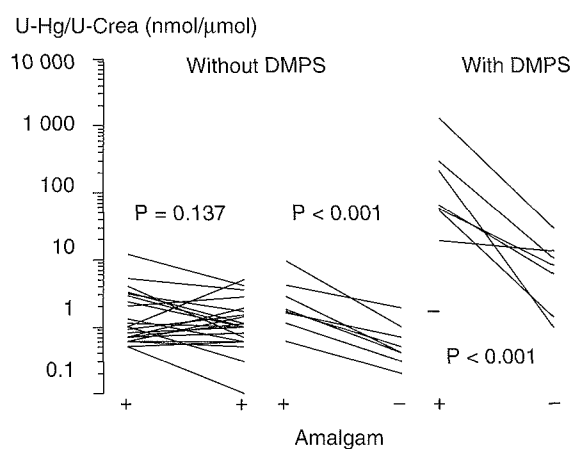


Figure 3. Changes in mercury excretion after removal of amalgam. (Left panel = patients who did not have their amalgam fillings removed, right panels = patients who had their amalgam fillings removed before the second test).

Discussion

Although probable cases of mercury intoxication from amalgam have been described earlier (8, 18), clinicians do not believe in this possibility. In fact numerous clinical studies have suggested that no such disease exists (10, 11, 19, 20). Not even in an extensive and thoroughly controlled recent Norwegian study (15) could any conclusions be drawn on the basis of psychosomatic investigations of 98 patients whose disorder had been confirmed by dentists and physicians believing in the existence of the disease.

There is, however, a severe bias in most of the reports published thus far, namely, that the patients have referred themselves to the studies. The lay press and various patient organizations release information about oral galvanism and mercury intoxication due to amalgam and thus “spread” the disease among persons prone to somatize their mental disturbances (21). Such patients form the major part of the study population of previous studies. This selection of “false positive” cases makes it impossible to identify and characterize a case of real disease.

In the present study we looked for patients with a high level of mercury excretion and symptoms which could not be explained by clinical examination. Among such patients we found cases which fulfill many of the criteria for mercury intoxication. It is probable that such cases are only the top of the iceberg, and further investigations are needed to determine the true level of mercury toxicity in persons with amalgam fillings.

The clinical picture of possible mercury toxicity from amalgam cannot be determined on the basis of our results. However, it is obvious that classical signs of in-

toxication, such as mental changes and motor disturbances, must be regarded as important signs which call at least for the determination of urinary mercury excretion. Such disturbances were detected in at least 4 of our 288 patients, and in their cases mercury intoxication was strongly suspected before the test was done.

Another clinically equally important aspect is to be aware of the fact that patients seeking medical aid for suspected amalgam intoxication have often been induced to do so by the general public concern for such a condition. Many of these patients actually suffer from clinically well-characterized disease, but look for an explanation by suspecting mercury. Especially neurological diseases and their symptoms can mislead a patient. By missing the correct diagnosis, which sometimes happens as a result of consultations with persons claiming expertise in environmental medicine, the patient can be cast into a dangerous situation.

In conclusion, our results indicate that dental amalgam can release mercury in large enough amounts to cause clinical signs of intoxication, which is curable by the removal of amalgam. The clinical picture, however, is not well characterized and many of the numerous symptoms and signs claimed by the lay press to be typical of such a condition need not to be present.

Acknowledgments

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