

# Dental Amalgam and Multiple Sclerosis: A Case-control Study

<sup>1</sup>Atefeh Tavangar, <sup>2</sup>Masoud Etemadifar, <sup>3</sup>Mona Emamjomeh, <sup>4</sup>Navid Mojtahedi

## ABSTRACT

**Introduction:** Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease, which is associated with demyelination of neurons and which involves various parts of the central nervous system (CNS). Many genetic and environmental factors are taken into consideration in the etiology of this disease. Among the environmental factors affecting MS are heavy metals, such as mercury in dental amalgam. According to studies, blood serum mercury levels are higher in people affected by MS than in normal people. The aim of this study was to compare amalgam fillings and number of involved dental surfaces between MS patients and normal people.

**Materials and methods:** The present study was a cross-sectional case-control study conducted in Al-Zahra MS Clinic and Isfahan MS Association. A total of 174 patients suffering from MS, and 174 normal people were selected for this study. Information, such as the number of amalgam fillings, the number of filling surfaces, tooth type, and duration of filling was recorded.

**Results:** The results showed that 73.1% of patients were women, and the mean number of amalgam fillings ( $p = 0.027$ ), and the mean number of amalgam filling surfaces were greater in people suffering from MS than in normal people ( $p = 0.003$ ), but the difference in dental caries was not statistically significant between the two groups ( $p = 0.292$ ).

**Conclusion:** It seems that dental amalgam and the number of involved surfaces are among the factors associated with MS disease such that the number of dental amalgam fillings and the number of filling surfaces were significantly greater, and levels of exposure to amalgam fillings were significantly higher in people affected by MS than in normal people.

**Keywords:** Dental amalgam, Dental caries, Multiple sclerosis, Risk factor.

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<sup>1,2</sup>Assistant Professor, <sup>3,4</sup>Student

<sup>1</sup>Department of Oral Medicine, School of Dentistry, Dental Research Center, Isfahan University of Medical Science, Isfahan Islamic Republic of Iran

<sup>2</sup>Department of Neurology, Isfahan University of Medical Science, Isfahan, Islamic Republic of Iran

<sup>3,4</sup>School of Dentistry, Dental Students Research Center, Isfahan University of Medical Science, Isfahan, Islamic Republic of Iran

**Corresponding Author:** Navid Mojtahedi, Student, School of Dentistry, Dental Students Research Center, Isfahan University of Medical Science, Isfahan, Islamic Republic of Iran, e-mail: sadeghamiri122@gmail.com

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## INTRODUCTION

Multiple sclerosis is a chronic multifactorial disease with the involvement of various parts of the CNS, which is identified with inflammation, demyelination, and gliosis. After trauma, MS is the most common cause of neurological disability in people from young to middle age. Multiple sclerosis disease involves women, on average, three times more than men, and usually occurs in 20 to 45-year-old adults.<sup>1</sup> According to the latest reports, Isfahan, which is Iran's third largest city, is classified as a city with high frequency of MS in Asia and the Pacific.<sup>2,3</sup> Etiologically, MS is considered the result of genetic and environmental factors and infections. However, the effect of none of these factors has been proved for sure.<sup>4</sup> Multiple environmental factors, such as lack of vitamin D, smoking, stress, reduced exposure to sunlight, exposure to toxins, heavy metals, and certain solvents contribute to the development of MS.<sup>5</sup> One of these heavy metals is the mercury contained in dental amalgam, which has been put forward as one of the MS risk factors that affects health.<sup>6,7</sup> According to a study conducted recently, blood serum mercury levels in people affected by MS have dramatically been different from those in normal people.<sup>3</sup> Larger amounts of mercury were also found in saliva and feces of people with dental amalgam.<sup>8</sup> Amalgam fillings have been in use in dentistry since 1818; although dental materials with more beauty have become available since then, amalgam is still widely used due to its low cost, high strength, and easier technique of use.<sup>9</sup> An amalgam filling contains about 50% mercury in combination with copper, zinc, silver, and tin. It has been proved that this combination gradually releases mercury vapor in small doses; and its dose dramatically increases by chewing, eating, tooth brushing, and drinking hot drinks. Furthermore, the release of mercury depends on the size of fillings, the type of the filled tooth (premolar or molar), the number of involved surfaces, and the patient's history of amalgam fillings.<sup>10</sup> For most people (except those who are exposed to mercury in their jobs), amalgam is considered as the main source of inorganic (solid) mercury.<sup>11</sup> The mercury vapor released from a dental amalgam (Hg) has a greater

tendency to accumulate in the CNS, compared with  $\text{Hg}^{2+}$  cation. The mercury vapor (Hg) in dental amalgam is highly fat-soluble, leading to its convenient entry into the blood through the alveolar membrane of the lungs. Mercury vapor remains in the bloodstream for a long time to be allowed to release from the blood–brain barrier. In the brain, the mercury vapor is oxidized by the intracellular catalase-hydrogen peroxide, and turns into two  $\text{Hg}^{2+}$  cations. Since this form of mercury ( $\text{Hg}^{2+}$ ) is not able to release and exit from neural cells, it eventually accumulates in the brain after this transmission.<sup>12,13</sup> Mercury is also considered a strong antigen in autoimmune diseases.<sup>14</sup> The World Health Organization has estimated that the absorption rate of mercury from amalgam is 1 to 22  $\mu\text{g}$  per day, which is  $<5$   $\mu\text{g}$  in most people; however, there is a significant difference. This range increases up to nearly 100  $\mu\text{g}$  by chewing gum. The Food and Drug Administration considers that it is certain the mercury exposure is about 1–5  $\mu\text{g}$  per day in the present day's amalgams. That is why Norway and Sweden have banned the use of dental amalgams;<sup>15</sup> and Germany and Canada have forbidden its use in pregnant women and children.<sup>16</sup> Since few and contradictory studies have been conducted on the relationship between dental amalgam and MS,<sup>17,18</sup> and on the contrary, considering the high prevalence of MS in Isfahan, we decided to conduct a more thorough study in this regard. The aim of this study is to compare the frequency of amalgam fillings, number of involved dental surfaces, and dental caries between MS patients and normal people.

## MATERIALS AND METHODS

A total of 174 MS patients and 174 normal people, ranging in age from 20 to 60 years, participated in this case–control study. Sampling was done in the MS Clinic of Al-Zahra Hospital as well as in Isfahan MS Association. It took 1 year to collect the samples. The MS patients were neurologically approved in accordance with the McDonald criteria, and were not affected by any other serious and known diseases (such as renal, hepatic, and cardiac failure, different types of cancers, glandular and metabolic disorders, and neuropsychiatric diseases). In order to match the two groups, the members of the control group were selected from the patients' entourage so that the two groups are similar in terms of environmental factors, diet, lifestyle, and physiological characteristics. The basis of this research was a data collection form and dental examination, which were carried out by the researcher after obtaining informed consent from the subjects. This form was common between the sample and the control group. Only the part related to the MS disease was left blank for normal people. This form consisted of several

sections including the patient's demographic information, course of the disease, risk factors associated with the disease, and finally the dental information of those participating in the study. The personal information included gender, age, marital status, place of residence, and phone number. Information regarding the course of the disease included the duration of involvement, the type and severity of MS, and the Expanded Disability Status Scale value. Moreover, since MS disease is a multifactorial disease with unknown and uncertain causes, in order to consider and control other confounders and risk factors, which have been mainly put forward in most studies, we also included information, such as occupation, education level, and risk factors, such as family history of MS, lack of vitamin D, smoking, and stress factors and conditions in part of the questionnaire.

The main part of this form is a dental examination checklist for these people. The form deals with examining the number of amalgam fillings (and other factors related to amalgam fillings, such as the type of the filled tooth, the number of filling surfaces, an approximation of the history of amalgam fillings), and the number of dental caries in the MS and control groups.

All the data obtained using the Statistical Package for the Social Sciences software version 20 were analyzed through descriptive-analytical statistical techniques (such as calculating the mean, standard deviation, and frequency distribution) as well as using the Mann–Whitney test, independent t-test, and chi-square test.

## Results

The results of the present study showed that 73.1% of the MS patients were women, and 26.9% were men. In addition, the average age of the patients was  $36.4 \pm 9.7$ , and the control group  $38.1 \pm 14.1$ .

The results of the present study showed that the number of amalgam fillings and the number of amalgam filling surfaces were greater in MS patients than in normal people. Mann–Whitney test showed that the mean number of amalgam fillings ( $p = 0.03$ ) as well as amalgam surfaces in the mouth of each person ( $p = 0.004$ ) was significantly greater in MS patients than in normal people, but the mean number of dental caries was not significantly different between the two groups ( $p = 0.82$ ; Table 1). Also, both in molar and premolar teeth, the mean number of amalgam fillings separated by the type of the filled teeth was greater in MS patients than in normal people (Table 2).

Table 3 compares amalgam fillings based on their history of filling. As can be seen, fillings with a history of more than 5 years are much more in MS patients than in normal people, and this difference is statistically

**Table 1:** Comparison of amalgam fillings in multiple sclerosis patients & normal patients

Parameters	Case		Control		p-value (Mann-Whitney test)
	Mean	SD	Mean	SD	
Amalgam restorations	4.2	3.54	3.4	3.43	0.027
Amalgam surface	7.6	6.96	5.5	6.24	0.003
Number of caries	1.8	4.51	1.7	2.071	0.292

SD: Standard deviation

**Table 3:** Comparison of amalgam fillings based on time duration of fillings

History of filling	Case		Control		p-value (Mann-Whitney test)
	Mean	SD	Mean	SD	
Less than 1 year	0.3	0.07	0.28	0.65	0.367
1-5	0.83	0.15	1.25	0.18	0.097
More than 5 years	2.9	0.25	1.72	0.22	<0.001
Unknown	0.15	0.07	0.05	0.03	0.309

SD: Standard deviation

significant ( $p < 0.001$ ). According to the chi-square test, marital status was different between the two groups in a way that the number of singles was greater in the patient group than in the control group ( $p = 0.01$ ). Moreover, Mann-Whitney test showed that there was no significant difference between the case and control groups in terms of education level ( $p = 0.112$ ).

In terms of the clinical type of the disease, 77% of the patients were classified as having relapsing-remitting MS, and 13% relapsing-progressive MS. In terms of vitamin D deficiency, 57.8% of the MS patients stated that they had a lack of vitamin D before the disease was diagnosed, which was three times higher than in the control group. This difference was statistically significant ( $p < 0.001$ ).

In addition, 20% of the patients were smokers vs 12% of the control group. Chi-square test showed the significance of these two differences ( $p = 0.03$ ). Finally, to take the simultaneous effects of different variables into consideration, we performed a multiple logistic regression analysis. It was observed that by taking other variables into account, there was still a significant relationship between the MS patients and normal people in terms of the number of amalgam surfaces ( $p = 0.019$ ); however, this relationship was not significant in terms of the number of amalgam fillings ( $p = 0.213$ ).

## DISCUSSION

Multiple sclerosis disease is an inflammatory disorder in the CNS. Although immunological and genetic factors play a key role in the pathogenesis of MS, the definite etiology of this disease is still unclear. Environmental factors also affect the disease process. Exposure to heavy metals, such as mercury is considered one of the reasons causing

**Table 2:** Comparison of amalgam fillings depending on type of teeth

Type of tooth	Case		Control		p-value
	Mean	SD	Mean	SD	
Premolar	1.27	1.51	1.4	0.950	0.023
Molar	2.92	2.443	2.44	2.252	0.04

SD: Standard deviation

the disease. Since 50% of dental amalgam is mercury, the presence of amalgam fillings in the mouth of individuals can be one of the factors causing MS disease.<sup>1-4</sup> Two groups were selected in the present study: The MS group (174 subjects) and the control group (174 subjects). The present study investigated the number of dental amalgam fillings, the number of involved surfaces in the fillings, the patient's history of fillings, and the number of dental caries. It additionally investigated some of the risk factors related to MS, such as marital status, education level, smoking, stress and emotional problems existing in the individuals' lives, and lack of vitamin D.

The results showed that the number of dental amalgam fillings ( $p = 0.027$ ) and the number of involved surfaces in the fillings ( $p = 0.003$ ) were considerably greater in the MS group than in normal people, and these results were statistically significant. However, the mean number of dental caries in the MS group was not significantly different from that in normal people ( $p = 0.292$ ).

In terms of the patients' history of fillings, fillings of more than 5 years were considerably more in MS patients than in normal people ( $p < 0.001$ ), while fillings of less than 5 years were not significantly different between the two groups. In addition to the number of amalgam fillings and involved surfaces, the type of the filled teeth (premolars and molars) was also investigated in this study because the extent of the involved area in amalgam fillings certainly differs depending on the size of teeth. The results of the study showed that based on the size of teeth, the number of amalgam fillings, both in premolars ( $p = 0.023$ ) and in molars ( $p = 0.04$ ), was higher in the MS group than in the normal group. Contradictory studies have been conducted on the impact of dental amalgam on MS disease. A systematic review study by Aminzadeh and Etminan<sup>9</sup> showed that in total, four studies had been conducted in this area.

In a study by Bangsi, dental information of 143 MS patients and 128 normal people was investigated. Although the number of amalgam fillings was greater in MS patients than in normal people, no significant relationship was found between the numbers of amalgam fillings in the two groups ( $p > 0.05$ ).<sup>6</sup> One of the shortcomings of this study was that the size of amalgam fillings and the involved dental surfaces were not taken into consideration. Obviously, the extensive amalgam filling, which



involves occlusal, buccal, and lingual surfaces in a molar tooth, releases a lot more mercury than does a single-surface amalgam filling in a premolar tooth. Moreover, in Bangsi's study, normal people were chosen from among the general public through random dialing. For this reason, the control group members can be different from the case group in terms of environmental factors, diet, lifestyle, genetic status, and social interactions. Therefore, the results of Bangsi's study can be influenced by confounding factors. Perhaps the difference between the results of the present study and those of Bangsi's study is due to these factors. In the present study, not only was a significant difference observed between the two groups in the number of amalgam fillings but also a relationship was observed between the involved surfaces in the filling and long-term exposure to amalgam.<sup>6</sup>

In a study conducted by McGrother et al,<sup>11</sup> they investigated the decayed, missing, and filled teeth index in 39 MS patients and 63 normal people. The results of this study showed that there was no significant difference between the MS group and the normal group in terms of the number of amalgam fillings, the number of missing teeth, and the number of dental caries ( $p > 0.05$ ).<sup>11</sup>

Like in Bangsi's study, none of the size of amalgam fillings, the involved dental surfaces, and the duration of exposure to amalgam fillings have been investigated in this study. Its contradiction to the present study can be due to its failure to take these factors into consideration since the extent of fillings and duration of exposure to amalgam are among the most important factors affecting the level of mercury in the blood. Another reason for the difference between our results and those of McGrother's study is its small number of subjects. The number of MS patients is four times greater in the present study than in McGrother's study, which can lead to more comprehensive results.

A study was conducted by Casetta et al<sup>17</sup> on the dental records of 132 MS patients and 423 normal people. The results of this study showed that although the number of dental amalgam fillings was greater in MS patients than in normal people, this difference was not statistically significant.

No examination was done in Casetta's study to accurately determine the number of dental amalgam fillings, involved surfaces, and their sizes; and only the dental records of patients were used in this regard, which can be considered among the shortcomings of this study. In the meantime, as in the other two studies, only the number of dental amalgam fillings is reported in this study, and the level of amalgam exposure and dental surfaces have not been investigated, which can be the reason for the difference between the results of this study and those of the previous studies.

Bates<sup>18</sup> investigated the long-term effects of amalgam fillings as well. This study was conducted in the form of a retrospective cohort study on the dental records of the study participants from 1977 to 1999, and they investigated the potential risk for these patients to develop systemic diseases, such as MS. This study found a certain significant relationship between the level of amalgam exposure and MS disease. In this regard, these two studies are consistent with each other.

In a study, Attar et al<sup>3</sup> compared blood serum mercury levels between MS patients and normal people. The results of this study showed that blood serum mercury levels were much higher in these patients than in normal people. It can be concluded from this significant increase in blood mercury levels that dental amalgam fillings can be effective in increasing mercury levels because the general public (except for people in certain occupations, who have been excluded from this study) are just chronically in contact with dental amalgam. The mercury present in dental amalgam fillings is released in the body every time persons chew, drink hot drinks, and brush teeth.

Since, in comparison to other studies mentioned, the present study has investigated the number of involved dental surfaces and the level of exposure to amalgam fillings in addition to amalgam fillings and dental caries, this study is more comprehensive than the other studies. Based on the results obtained from the present study, it seems that dental amalgam is one of the influential factors in MS disease. However, since this disease is a multifactorial disease, it is not possible to determine the exact cause and effect relationship between dental amalgam and this disease, which is one of the limitations of the present study. Among other limitations of this study were collection of a sufficient sample size of MS patients and their cooperation for participating in the study because a significant number of these patients were not willing to participate in the study due to their poor physical and mental conditions.

## CONCLUSION

Dental amalgam fillings, the number of involved surfaces in amalgam, and long-term exposure to dental amalgam are among the influential factors in MS disease. The results of this study can open a new vision of the importance of prevention to our society, especially to high-risk people, such as dentists and those who visit dentists. It is recommended that further and more comprehensive studies be conducted in this regard.

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