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Dental amalgam and multiple sclerosis: a case-control study in Montreal, Canada

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Background The aetiology of multiple sclerosis (MS) remains poorly understood. Dental amalgams containing mercury have recently been suggested as a possible risk factor for MS.

Methods In a case-control study conducted between 1991 and 1994, we interviewed a total of 143 MS patients and 128 controls, to obtain information on socio-demographic characteristics and the number of dental amalgams and the time since installation based on dentists' records.

Results Neither the number nor the duration of exposure to amalgams supported an increased risk of MS. After adjustment for age, sex, smoking, and education those who had more than 15 fillings had an odds ratio (OR) of 2.57 (95% CI : 0.78–8.54) compared to those who had none; for individuals whose first amalgam was inserted more than 15 years prior to the study, we found an OR of 1.34 (95% CI : 0.38–4.72).

Conclusions Although a suggestive elevated risk was found for those individuals with a large number of dental amalgams, and for a long period of time, the difference between cases and controls was not statistically significant.

Keywords Multiple sclerosis, dental amalgams, mercury

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Multiple sclerosis (MS) is a disorder of the central nervous system with an estimated incidence rate of 100 per 100 000 population in Canada.[1] At this time, its aetiology is poorly understood. Dental amalgam is one of the suspected risk factors for MS.[2]

Dental amalgams containing mercury have been in use since 1818.[3] As early as 1830, the question of innocuity of dental fillings was raised and the 'war of dental amalgams' continued for the major part of the 19th century. During the 1920s and 1930s, claims were made that mercury absorbed through different body organs was a health hazard.[4] In the early 1970s, mercury vapours were identified in the buccal cavity of people with dental fillings,[5–9] as well as in different body tissues.[10–13] In some instances, the authors established correlations between the number of fillings and the quantity of liberated mercury in the mouth, as well as in blood and urine contents.[5,14–17] Craelius[14] reported a correlation between high prevalence of MS and dental caries, and a strong linear relationship between mortality rates from MS and the numbers of decayed, missing and obturated teeth in some Australian states.

Ingalls[18] analysed data from areas where clusters of MS were reported, and suggested that this correlation was due to mercury in dental fillings, postulating its possible role in the aetiology of multiple sclerosis. A recent Canadian report stated that certain health problems due to dental fillings may be expected if their number exceeds four.[19,20] The majority of studies attempting to establish an association between dental fillings and MS have either been autopsy series[21,22] or analogies.[23,24] Therefore, we conducted a case-control study of MS taking into account nutrition, lifestyle, family history of MS, environmental factors, and dental amalgams. In this report we concentrate on amalgams and their possible relation to the development of MS.

Material and Method

Case ascertainment

Newly-diagnosed MS cases (incident cases) in greater Montreal from January 1991 to December 1994 were identified with the collaboration of the MS Association of Montreal East,

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neurologists and physicians referrals and by placing regular announcements in city newspapers in order to reach other individuals recently diagnosed with MS. These notices were issued six times during the course of the study, and similar announcements were run on some local radio stations. Eligible incident cases were contacted by phone, and upon informed consent were visited at home and interviewed.

A total of 353 MS cases were identified during the study period. Of these, 87 (24.6%) were not eligible because of incorrect diagnosis or because they were prevalent cases. The remaining 266 (75.4%) eligible subjects were followed-up. Of these, 11 (4.1%) declined to participate and 52 (19.5%) were not interviewed because of poor health, loss of contact, or refusal of the physician to issue permission to contact the patient. Finally, three cases (1.3%) were excluded after the interview because of incorrect diagnosis. We were therefore able to interview 200 subjects (75.1% of the eligible cases). Dental information was available for 143 (71.5%) of these cases.

Control ascertainment

Controls were drawn at random from the general population. For each case, one control (frequency matched) of the same sex and comparable age (± 5 years) was interviewed. The controls were identified through random digit dialling (RDD) method, using the first three digits of the phone number of the case.[25] Controls were selected from the telephone directory in which the corresponding case was listed (all patients studied had a listed telephone number: only 1% of families in the Montreal region do not have a telephone). A page from the telephone directory was randomly selected from the sampling frame and the names and addresses of 10 individuals with the same first three digit telephone numbers as the patient were selected. These residences were then contacted by letter and the aims of the study explained. Approximately one week later these residences were telephoned to see if they contained an individual who matched the original case for age and sex and who agreed to be interviewed. If so, an interview was arranged at the control's home. If not, the procedure was repeated. If more than one eligible control was reached at a given number, this information was kept in a data bank for further use. For cases without a telephone, RDD would have been used to select the control. Non-residential numbers were discarded and a 'no answer' number was redialled up to eight times at various points in time, day and night, weekday and weekend, before being rejected. As with the cases, controls were also contacted by letter and those who assented were interviewed at home. We contacted a total of 236 population-based controls. Of these, 202 (85.6%) eligible controls were interviewed. The remaining 34 (14.4%) were not interviewed for the following reasons: wrong age group or area of residence, poor health, language problems or refusal to participate. Although 202 controls were interviewed, only 128 (63.4%) had dental information available.

Questionnaire

Data were collected by personal interviews conducted by an experienced research assistant. The questionnaire contained about 150 items including socio-demographic characteristics, family history of MS and presence/absence of MS and also several questions regarding known and suspected risk factors. In addition, the study subjects were interviewed for their food habits and nutrient intake by using a food frequency questionnaire. Interviews took place at the homes of the participants or at the Hôtel-Dieu Hospital in Montreal. Cases and controls gave their consent to being interviewed and permission to consult their neurologist and dentist.

Letters to neurologists and dentists

A letter addressed to the neurologist of each case contained an explanation of the nature of the study, a copy of the authorization signed by the patient, and specific questions concerning clinical details of the disease. The requested information was returned in a pre-paid envelope to the Epidemiology Research Unit at the Hôtel-Dieu Hospital. All family dentists were contacted and asked to provide a chronological history of dental treatment including the number and type of dental fillings, crowns, extractions and prostheses.

During the 3 years of data collection, for the main case-control study 402 subjects were recruited for the main study (200 cases and 202 controls), all from the greater Montreal area. Of these 131 (32.6%) had no dental information available: 43 (9.9%) had no dentist, 37 (9.2%) had total prostheses, and the dentists of 51 (12.7%) subjects failed to answer our request for collaboration. The present study includes 271 subjects: 143 cases and 128 controls, with dental information.

Statistical analysis

The first part of the analysis is descriptive, dealing with socio-demographic and family characteristics of the participants; analysis of variance was used to test for differences between groups. The second part is analytical with the presence/absence of MS as the dependent variable and the number of fillings as independent categorical/interval variables.

Analyses were done to compare the cases and controls with no amalgams to those with amalgams considering the number of dental amalgams, duration of exposure to amalgams, and its combination. Cases and controls with at least one amalgam were categorized by the number of amalgams into the following groups: 1–5, 6–10, 11–15, and >15 amalgams. They were also categorized by the duration of exposure (from a baseline date) into the groups: ≤5, 6–10, 11–15, and >15 years. These groups were compared to the cases and controls with no amalgams to obtain odds ratios (OR) and their 95% CI by logistic regression.[26] The program SAS[27] was used for all data analysis; PROC LOGISTIC in SAS was used to fit all logistic models.[28] All models were adjusted for sex, smoking, and education. Also, a linear regression model was fit to the OR from the number of dental amalgams and the duration of exposure to determine if there was a significant linear trend with increasing numbers of amalgams or length of the exposure to amalgams. The date used as the baseline for exposure was the date of diagnosis for the cases and the date of interview for the controls. All 271 study subjects (a) were included in analysis. In analysis (b) and (c), the duration of exposure to dental amalgams was calculated as the year of the baseline date minus the year of installation of the first amalgam. More accurate exposure information could not be obtained because only the year of insertion was available for each known amalgam and only the year of diagnosis was available for some cases. Dental data were available from a primary dentist and other dentists. Data from the primary dentist were given as the number of amalgams inserted per calendar

Table 1 Characteristics of the study subjects

Characteristic	All subjects with dental data		Subjects with data from primary dentist[a]	
	Controls	Cases	Controls	Cases
No. of subjects	128	143	109	118
Males	36	42	33	36
Females	92	101	76	82
Mean age ± SE (years)	37.9 ± 0.84	36.9 ± 0.76	37.7 ± 0.92	37.5 ± 0.84
Males	41.4 ± 1.66	40.1 ± 1.52	41.4 ± 1.72	40.1 ± 1.68
Females	36.5 ± 0.93	35.5 ± 0.84	36.1 ± 1 04	36.3 ± 0.94
Education (mean years ± SE)	15.0 ± 0.32	13.9 ± 0.23	15.3 ± 0.35	13.8 ± 0.25
Males	16.1 ± 0.69	14.4 ± 0.44	16.5 ± 0.72	14.2 ± 0.48
Females	14.6 ± 0.35	13.7 ± 0.27	14.8 ± 0.39	13.6 ± 0.29
Married (%)	68.8	69.9	68.8	70.3
Males	63.9	81.0	66.7	80.6
Females	70.7	65.3	69.7	65.9

Table 2 Family history of multiple sclerosis in cases and controls

Relatives	Cases		Controls		Total
	Male	Female	Male	Female	
Father		3	1		4
Mother	1	1		1	3
Brother		2		2	4
Sister	2	8	1		11
Total	3	14	2	3	22

year back to 1970, and the number of amalgams before 1970. For the other dentists, only the number of amalgams was available. Therefore, if the only data available were from other dentists, the duration of exposure to dental amalgams could not be calculated. Thus, analysis (b) and (c) were carried out for only 227 subjects (118 cases and 109 controls).

Results

The characteristics of the study subjects are given in Table 1. Males (mean age 41.4 years) were significantly older than (mean age 36.5 years) females ($P < 0.0001$). The average number of years of education (13.8) for cases was significantly less than that (15.3) for controls ($P = 0.009$). Men had significantly more education (15.2 years) than women (14.1 years) ($P = 0\ 015$). Comparable proportions of cases (69.9%) and controls (68.8%) were married. Although not shown here, annual income of cases and controls, broken down into five categories, was almost identical. Income, a determinant of the use of dental services, was treated according to Statistics Canada's five income categories[29] where the lowest one represents income of <$10 000 and the highest ≥$40 000. In all but one income category ($30 000–$39 000) cases had an average number of fillings higher than controls, but none was statistically significant. Seventeen cases (11.9%) and five controls (3.9%) reported a positive family history of MS (Table 2).

The average number of amalgams and time since first insertion are shown in Table 3. The time since first insertion was similar for cases and controls (6.50 years based on data from the primary dentist only). Cases had an average of 9.86 dental fillings, compared with 8.91 among controls (data for primary dentist only). However, the difference observed was not significant ($P > 0.05$). The mean number of amalgams for females (9.65) was higher than that of males (8.51) but the difference was not significant ($P > 0.05$).

In Table 4, the risk of MS related to the number of dental fillings was obtained by comparing cases with amalgams to the reference group having no amalgams, adjusted for age, sex, smoking and education. Cases with >15 fillings had an OR of 2.57 (95% CI : 0.78–8.54). A test for increasing trend in the ORs with increasing number of amalgams was not significant. The risk of MS in relation to the duration of exposure to dental fillings was also estimated (Table 5). Although subjects with the

Table 3 Average number of dental amalgams and time since first insertion, ± standard error, for controls and cases

Characteristic	All subjects with dental data		Subjects with data from primary dentist[a]	
	Controls	Cases	Controls	Cases
No. of amalgams	8.78 ± 0.51	9.36 ± 0.53	8.91 ± 0.56	9.86 ± 0.62
Males	8.67 ± 0.88	7.74 ± 0.82	8.91 ± 0.94	7.86 ± 0.94
Females	8.83 ± 0.62	10.03 ± 0.66	8.91 ± 0.70	10.73 ± 0.77
Time since first insertion (years)			6.50 ± 0.61	6.54 ± 0.52
Males	NA	NA	7.41 ± 1.19	5.00 ± 0.82
Females	NA	NA	6.11 ± 0.71	7.21 ± 0.64

[a] These subjects have data from a primary dentist and possibly another dentist This group does not include subjects with data only from another dentist.
NA. Not available from dentists other than primary dentist.

Table 4 Odds ratio (OR) and 95% confidence intervals (CI) comparing cases and controls with no amalgams to those with 1–5, 6–10, 11–15, and >15 amalgams

No. of amalgams	No. of cases	No. of controls	OR	95% CI
0	8	13	1.00	
1–5	32	24	2.09	0.70–6.23
6–10	50	42	1.72	0.62–4.81
11–15	36	37	2.00	0.69–5.79
>15	17	12	2 57	0.78–8.54

All odds ratios adjusted for age, sex, smoking, and education.

Table 5 Odds ratios (OR) and 95% confidence intervals (CI) comparing cases and controls with no amalgam to those with the first amalgam inserted ≤4 years, 4–9 years, 10–14 years and >14 years before the study

Duration of exposure	No. of cases	No. of controls	OR	95% CI
No exposure known	8	13	1.00	–
≤4 years	57	46	1.97	0.71–5 51
5–9 years	23	26	1.67	0.54–5.15
10–14 years	19	9	4.89	1.29–18.56
≥15 years	11	15	1.34	0.38–4.72

All odds ratios adjusted for age, sex, smoking, and education

first amalgam inserted 10–14 years before the baseline date had an OR of 4.89 (95% CI : 1.29–18.56), significantly higher than one, the relationship between duration of exposure and the risk of MS did not increase in a consistent fashion, nor was the test for increasing trend significant. The crude OR exhibited a similar outcome to the adjusted estimates.

Both the duration of exposure and the number of fillings are considered in Table 6. Odds ratios for subjects with exposures of different duration and with different numbers of amalgams were calculated with respect to subjects with no amalgams. The exposure durations and intensity categories are the same as in Tables 5 and 6. This permits comparisons between subjects with no amalgams, and those with protracted exposures to many amalgams, to those with limited exposure to few amalgams. None of the OR were significantly different. The groups with ≥15 years exposure to amalgams did not seem to have larger OR than those with ≤5 and 6–10 years of exposure. The highest OR were observed from cases with 5–9 years and >15 amalgams of exposure; however, because of the small number of subjects in that and other categories, detection of a small increase in risk is difficult.

Discussion

Since a hospital-based study would likely omit the majority of newly diagnosed cases, incident cases were targeted through the media. Information concerning disease onset, the nature of symptoms, as well as the date of diagnosis were collected through interviews. All diagnoses were made by a neurologist leaving little doubt concerning the status of the study cases.

The search for controls via random digit dialling was in keeping with the population-based principle of subject selection.[30] The strategy excluded individuals with unlisted or confidential telephone numbers and households without a telephone, raising the probability that subjects could be drawn from slightly higher socioeconomic classes. However, wealthier individuals are generally less likely to participate, so that controls in this study may represent a subpopulation truncated at both extremes of the social ladder.

The interviewer was aware of the study status of participants. However, since no firm hypothesis was specified, the possibility of observer bias seems remote given the large number of variables covered. It is almost certainly absent as far as dental information is concerned.

The characteristics of cases in this study are comparable to those of other major studies of MS. The majority were 30–49 years old with females younger than males, as previously reported.[23,31–33] An association between the risk of contracting MS and higher socioeconomic status or education has been described in some populations.[34–37] However, not all studies support the view that MS has a predilection for socially favoured subjects.[38,39] In our study, the controls were better educated than cases. The conflicting results regarding education or social status in MS studies may be due, at least in part, to differences in the parameters used to characterize socioeconomic status.[35] In our study, we found that cases had more family history of MS than controls. This has been reported previously.[32]

Table 6 Odds ratios (OR) and 95% confidence intervals (CI) comparing subjects with no amalgams to those with amalgams with various lengths of exposure and numbers of amalgams

		0 amalgams		1–5 amalgams		6–10 amalgams		11–15 amalgams		>15 amalgams	
			OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)
No amalgams	Control	13	–								
	Cases	8									
≤4 years	Control			11	2.30	17	1.55	13	2.34	5	0 83
	Cases			18	(0.66–7.99)	21	(0.45–5.26)	15	(0.66–8.28)	3	(0.12–5.67)
5–9 years	Control			6	0.78	8	1.35	10	1.20	2	8.81
	Cases			4	(0.11–5.66)	7	(0.31–5.98)	8	(0.27–5.29)	4	(0.65–18.83)
10–14 years	Control			0	NA	4	2.13	3	6.27	2	6.12
	Cases			1		5	(0.41–11.07)	7	(0.92–42.89)	6	(118.83–43.77)
>15 years	Control			1	NA	7	0.85	4	1.29	3	2 21
	Cases			0		4	(0.16–4.38)	3	(0.20–8.48)	4	(0.35–13.83)

NA Not applicable because no controls or no cases fell within this category

All odds ratios adjusted for age, sex, smoking, and education.

Subjects whose dental status could not be ascertained, and who were therefore excluded from this study, were significantly older and had less education and income. This is compatible with the findings of cross-sectional studies.[40] Although cases had, on average, more fillings than controls, the difference was not statistically significant, and was not related to either years of schooling or income. In this study, controls had an average of 8.91 amalgams which is comparable with the Canadian average of 8.65.[40]

In conclusion, this study failed to demonstrate an association between either the number of dental amalgams or the duration of exposure to mercury amalgams and MS. To the best of our knowledge, this is the first case-control study focusing on MS and dental amalgams. Confirmation of our negative finding in subsequent investigations is therefore desirable.

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