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

Dieudonné Bangsi,a,b Parviz Ghadirian,a,b Slobodan Ducic,b,d Richard Morisset,d Sébastien Cicocioppo,a Ed McMullenc and Daniel Krewske

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

Accepted 21 November 1997

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 Craelius14 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.

Ingalls18 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 series21,22 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,
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 incor-
rect diagnosis or because they were prevalent cases. The remain-
ing 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. Controls
were selected from the telephone directory in which the
place of residence, poor health, language problems or refusal to par-
ticipate. Although 202 controls were interviewed, only 128
were interviewed for the following reasons: wrong age group or area
of residence, wrong 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 resid-
ences were then contacted by letter and the aims of the study
explained. Approximately one week later these residences were
contacted and asked to provide a chronological history of dental
我一直

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 author-
ization 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 con-
tacted 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; ana-
lysis 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 regres-
sion.26 The program SAS27 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 amal-
gams 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 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 pri-
mary dentist and other dentists. Data from the primary dentist
were given as the number of amalgams inserted per calendar
These subjects have data from a primary dentist and possibly another dentist. This group does not include subjects with data only from another dentist.

Table 1 Characteristics of the study subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All subjects with dental data</th>
<th>Subjects with data from primary dentist*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Cases</td>
</tr>
<tr>
<td>No. of subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>Females</td>
<td>92</td>
<td>101</td>
</tr>
<tr>
<td>Mean age ± SE (years)</td>
<td>37.9 ± 0.84</td>
<td>36.9 ± 0.76</td>
</tr>
<tr>
<td>Males</td>
<td>41.4 ± 1.66</td>
<td>40.1 ± 1.52</td>
</tr>
<tr>
<td>Females</td>
<td>36.5 ± 0.93</td>
<td>35.5 ± 0.84</td>
</tr>
<tr>
<td>Education (mean years ± SE)</td>
<td>15.0 ± 0.32</td>
<td>13.9 ± 0.23</td>
</tr>
<tr>
<td>Males</td>
<td>16.1 ± 0.69</td>
<td>14.4 ± 0.44</td>
</tr>
<tr>
<td>Females</td>
<td>14.6 ± 0.35</td>
<td>13.7 ± 0.27</td>
</tr>
<tr>
<td>Married (%)</td>
<td>68.8</td>
<td>69.9</td>
</tr>
<tr>
<td>Males</td>
<td>63.9</td>
<td>81.0</td>
</tr>
<tr>
<td>Females</td>
<td>70.7</td>
<td>65.3</td>
</tr>
</tbody>
</table>

Table 2 Family history of multiple sclerosis in cases and controls

<table>
<thead>
<tr>
<th>Relatives</th>
<th>Cases</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Mother</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Brother</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Sister</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>14</td>
<td>17</td>
</tr>
</tbody>
</table>

Results

The characteristics of the study subjects are given in Table 1. Males (mean age 41.4 years) were significantly older than females (mean age 36.5 years) (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 where the lowest one represents income of <$30 000 and the highest $39 000. 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 2.97 (95% CI: 0.73-11.42). 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All subjects with dental data</th>
<th>Subjects with data from primary dentist*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Cases</td>
</tr>
<tr>
<td>No. of amalgams</td>
<td>8.78 ± 0.51</td>
<td>9.36 ± 0.53</td>
</tr>
<tr>
<td>Males</td>
<td>8.67 ± 0.58</td>
<td>7.74 ± 0.82</td>
</tr>
<tr>
<td>Females</td>
<td>8.83 ± 0.62</td>
<td>10.03 ± 0.66</td>
</tr>
<tr>
<td>Time since first insertion (years)</td>
<td>6.50 ± 0.61</td>
<td>6.54 ± 0.52</td>
</tr>
<tr>
<td>Males</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Females</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* 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 ratios (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

<table>
<thead>
<tr>
<th>No. of amalgams</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
<td>13</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>1–5</td>
<td>32</td>
<td>24</td>
<td>2.09</td>
<td>0.70–6.23</td>
</tr>
<tr>
<td>6–10</td>
<td>50</td>
<td>42</td>
<td>1.72</td>
<td>0.62–4.81</td>
</tr>
<tr>
<td>11–15</td>
<td>36</td>
<td>37</td>
<td>2.00</td>
<td>0.69–5.79</td>
</tr>
<tr>
<td>&gt;15</td>
<td>17</td>
<td>12</td>
<td>2.57</td>
<td>0.78–8.34</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Duration of exposure</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No exposure known</td>
<td>8</td>
<td>13</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>≤4 years</td>
<td>57</td>
<td>46</td>
<td>1.97</td>
<td>0.71–5.51</td>
</tr>
<tr>
<td>5–9 years</td>
<td>23</td>
<td>26</td>
<td>1.67</td>
<td>0.54–5.15</td>
</tr>
<tr>
<td>10–14 years</td>
<td>19</td>
<td>9</td>
<td>4.89</td>
<td>1.29–18.56</td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>11</td>
<td>15</td>
<td>1.34</td>
<td>0.38–4.72</td>
</tr>
</tbody>
</table>

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. 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. An association between the risk of contracting MS and higher socioeconomic status or education has been described in some populations. However, not all studies support the view that MS has a predilection for socially favoured subjects. 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. In our study, we found that cases had more family history of MS than controls. This has been reported previously.

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

<table>
<thead>
<tr>
<th>No amalgams</th>
<th>Control (95% CI)</th>
<th>1–5 amalgams (95% CI)</th>
<th>6–10 amalgams (95% CI)</th>
<th>11–15 amalgams (95% CI)</th>
<th>&gt;15 amalgams (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>13</td>
<td>11</td>
<td>17</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>4–9 years</td>
<td>18</td>
<td>(0.66–7.99)</td>
<td>(0.45–5.26)</td>
<td>(0.66–8.28)</td>
<td>(0.12–5.67)</td>
</tr>
<tr>
<td>5–9 years</td>
<td>6</td>
<td>0.78</td>
<td>1.35</td>
<td>1.20</td>
<td>2.81</td>
</tr>
<tr>
<td>10–14 years</td>
<td>4</td>
<td>(0.11–5.66)</td>
<td>(0.31–5.98)</td>
<td>(0.27–5.29)</td>
<td>(0.65–18.83)</td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>0</td>
<td>NA</td>
<td>2.13</td>
<td>6.27</td>
<td>6.12</td>
</tr>
</tbody>
</table>

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. 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.

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.

Acknowledgements
This study was partly supported by the Multiple Sclerosis Association of East Montreal. The first author (Diedonne Bangsø) received a scholarship for his MSc in epidemiology from the Canadian International Development Agency. The authors wish to thank Marie-Claire Goulet who served as the research assistant for the study.

References