

Multiple sclerosis, dental caries and fillings: a case-control study

C. W. McGrother,¹ C. Dugmore,² M. J. Phillips,³ N. T. Raymond,⁴ P. Garrick,⁵ and W. O. Baird,⁶

Objectives To investigate the association between multiple sclerosis, dental caries, amalgam fillings, body mercury and lead.

Design Matched case-control study.

Setting Leicestershire in the years 1989–1990.

Subjects Thirty-nine females with multiple sclerosis (of recent onset) were matched with 62 controls for age, sex and general practitioner.

Methods Home interview of cases and controls within which there was an assessment of the DMFT index and blood and urine mercury and lead levels.

Results The odds of being a MS case increased multiplicatively by 1.09 (95% CI 1.00, 1.18) for every additional unit of DMFT index of dental caries. This represents an odds ratio of 1.213 or a 21% increase in risk of MS in relation to dental caries in this population. There was no difference between cases and controls in the number of amalgam fillings or in body mercury or lead levels. There was a significant correlation between body mercury levels and the number of teeth filled with amalgam (controls:

$r = +0.430, P = 0.006$, cases: $r = +0.596, P = 0.001$).

Conclusion There was evidence of excess dental caries among MS cases compared with the controls. This finding supports the strong geographical correlation between the two diseases. A further study of this association is recommended.

A remarkable association between the geographical distribution of MS and dental caries has been shown by Craelius who reviewed all available published studies of MS and dental caries including those reported to the World Health Organisation.¹ The correlation coefficient observed was lowest within 48 states of America in the 1950s ($r = +0.55, P < 0.001$), intermediate for 45 countries around the world in the 1970s ($r = +0.78, P < 0.001$) and highest where the information on MS and dental caries was most consistent, as in Australia in the 1940s ($r = +0.97, P < 0.002$). In the UK, USA and Iceland in the 1970s, where information was available on the edentulous proportion of the population, the correlation coefficient was found to be the virtual maximum ($r = +0.99, P < 0.001$).

One German case-control study of the relationship between dental disorders and MS reported an excess of caries, periodontal disease and infective granulomas in MS patients compared to age-matched controls.² A larger case-control study also showed significant associations (odds ratios between 3 and 4), in the 3 months

prior to onset, for trauma including dental extractions, sepsis including dental sepsis and allergic diseases.³ Another study however, showed no relationship.⁴ All three studies used hospital or diseased control groups which may have introduced biases.

The possibility of a dental connection was raised again in 1985 when 'miracle cures' were reported in a couple of MS cases, following wholesale replacement of amalgam fillings.⁵ The debate was fuelled by previous reports relating dental amalgam to mercury levels in the body⁶ and there was also concern about possible low-level toxicity of mercury, particularly in relation to foetal health.⁷ Against this background, demands for replacement with less toxic materials, free of charge, led to a relaxation of the normal policy for patients with MS. There have also been claims for a link with other heavy metals, principally lead, although more recent studies do not support any connection.⁸ The present study aims to measure the association between MS and dental caries, amalgam fillings, body mercury and lead.

Methods

Cases were identified from computerised routine hospital discharge information (Hospital Activity Analysis) for the years 1976–85, for Leicestershire, which has a population approaching one million, having established that admission of all new cases for investigation was the standard practice of local neurologists. All female admissions with the diagnosis of MS (ICD code 340) were selected because of an interest in reproductive outcomes in relation to MS and dental factors. Following the elimination of duplicate admissions and those aged less than 25 years or more than 65 years on admission, all cases who met the following criteria were identified: (i) first episode reported in the medical notes between 1977 and 1985, (ii) had neurological abnormalities on examination, (iii) were thought by a neurologist to have probable or definite MS, (iv) had a minimum of a further two out of the remaining four diagnostic criteria recommended by Schumacher,⁹ (v) were white, (vi) were currently living in Leicestershire, and (vii) had approval from the general practitioner (GP) to be approached.

The GP for each case was traced by the Leicestershire Family Health Services Authority register. A bank of four female controls, who were within 2.5 years either side of the age of each case, were randomly selected from the same GP list. GPs were contacted to obtain their approval to approach the patient and for information about the patient's condition and knowledge of the diagnosis. Controls were excluded if they were reported by their GP as having neurological disorders or if they were not white.

Cases and controls received a full dental examination performed by an experienced dentist at home. Information on the presence, integrity and type of filling of every tooth surface was collected and recorded on a standard dental grid. The decayed, missing and filled index of dental caries for teeth (DMFT) was calculated for each person.¹⁰ The number of teeth restored with amalgam, non-amalgam, either form of filling and crowns was also identified. The number of crowns were not included in the calculation of the DMFT

¹Senior Lecturer in Epidemiology, ⁴Research Associate, ⁶Research Associate, Department of Epidemiology and Public Health, University of Leicester, 22-28 Princess Road West, Leicester LE1 6TP; ²Senior Community Dentist, Pasley Road Dental Clinic, Eynes Monsell, Leicester; ³Lecturer in Mathematical Statistics, Department of Mathematics, University of Leicester, University Rd, Leicester LE1 7RH; ⁵Top Grade Biochemist, Department of Chemical Pathology, Leicester Royal Infirmary, Infirmary Close, Leicester LE1 5WW

REFEREED PAPER

Received 03.09.98; accepted 04.06.99

© British Dental Journal 1999; 187: 261–264

because no information was available for the reason the crown was placed. Recent dental hygiene was estimated on the basis of current dental cleanliness assessed on a defined 3-point scale as 'good', 'fair' or 'poor'. Longer term dental hygiene was estimated on the basis of gingival health on a similar 3-point scale.¹¹ Enquiry was also made of any difficulty experienced with cleaning teeth and the frequency of attending a dentist.

Cases and controls were visited by a physician to obtain a blood sample and provide instruction on collecting a urine sample. The urinary mercury: creatinine ratio ($\mu\text{mol per mol}$) was measured using the method of cold vapour atomic absorption spectrophotometry.¹² Early morning mid-stream urine samples were collected in acid-washed glass beakers to minimise problems of contamination. Blood lead was determined using electrothermal atomisation atomic absorption spectrometry following venepuncture using sterile and wipe.¹³ Subsequently, blood mercury was determined, using stored blood, to eliminate any possibility of conversion or other means of elevation of organic mercury levels.¹⁴

Background information on cases and controls was obtained for a range of social and economic indicators. The levels of educational qualification achieved was used to adjust for social differences prior to the onset of the disease. Educational qualification level correlates well with socio-economic group (Spearman's coefficient = 0.393, P -value < 0.001 on 7,790 subjects, as calculated using data from the General Household Survey).¹⁵

Statistical analysis was performed using conditional logistic regression¹⁶ with SAS statistical software. This enabled an estimate of the relative risk (odds ratio) for a risk variable to be obtained. This relative risk is the multiplicative factor by which the odds of being a case is multiplied when the risk variable is increased by one unit. (If the risk factor is a 2-level dichotomous categorical variable and the first category is being compared with the second then it is assumed that the value of the first category is one unit larger than the second category). A 95% confidence interval (CI) for the relative risk and the p -value for the test of the null hypothesis that the odds ratio is unity were calculated.

Results

A total of 978 female admissions were identified from computer records. Following elimination of duplicates, women with dates of admission for MS before 1977 and women younger than 25 years or older than 65 years on admission, a total of 329 potential cases were identified, for whom medical notes were sought. Of these, 280 cases proved to be ineligible for the following reasons: onset before 1977

Table 1 Background socio-economic indicators for MS cases (n = 39) and controls (n = 62)

Socio-economic indicator	Case:control odds ratio	95% CI	P-value
Home owner ¹	0.34	(0.10, 1.14)	0.081
Social class I and II (women) ¹	0.37	(0.13, 1.05)	0.062
Motor vehicle owner ¹	0.54	(0.14, 1.82)	0.37
Married ¹	0.82	(0.24, 2.78)	0.75
Level of qualification ²	0.99	(0.78, 1.25)	0.90
Left school aged 16 years or more ¹	1.70	(0.74, 3.90)	0.21
	Cases	Controls	
Mean reported height (ins)	64.36	64.02	0.52

¹Compared with leavers less than 16 years old

²High in relation to low

(110); not seen by a neurologist (87); medical notes not found (45); ethnic minority (9); died, moved away or no trace (24); GP described them as 'too ill' (3); a further two cases were excluded after interview because of a subsequent revised diagnosis. Among the 49 cases who were eligible and approached, nine cases refused to participate and no controls agreed to be interviewed for one case. The 39 cases who participated in the study constituted a response rate of 81%.

By the end of the study, 105 controls had been located and approached, in relation to the 39 cases, of whom 62 agreed to participate in the study, (59% response rate). 23 cases were matched with two controls and 16 cases were matched with one control. A comparison of background social and economic indicators between cases and controls is shown in Table 1. There was a tendency for cases to be relatively disadvantaged particularly with regard to their current employment and related major financial commitments to home and car ownership. Cases commonly reported adjusting their employment following the onset of the disease. However, there was no evidence of disadvantage in the indicators of educational attainment or reported height, achieved prior to the onset of MS.

The odds of being a case increased multiplicatively by 1.09 for every additional decayed, missing or filled tooth, (95% CI 1.00, 1.18) (Table 2). Adjustment for indicators of social status prior

Table 2 Association between dental indicators and multiple sclerosis

Dental indicator	Case (n = 39)		Control (n = 62)		Odds ratio DMF Tooth (95% CI)	P-value
	Mean	SD (range)	Mean	SD (range)		
DMFT index	19.46	6.22 (9-32)	17.22	5.69(6-32)	1.09 (1.00, 1.18)	0.049
Number of teeth filled ¹ with amalgam	8.87	5.20 (0-16)	9.69	4.86(0-20)	0.96 (0.87, 1.06)	0.40
Number of teeth filled ¹ with non-amalgam	2.82	4.05 (0-17)	1.29	1.86 (0-7)	1.27 (1.04, 1.54)	0.017
Number of filled teeth ²	11.56	5.74 (0-20)	10.90	5.67 (0-22)	1.04 (0.96, 1.13)	0.36
Number of filled or crowned teeth ³	12.18	6.17 (0-21)	11.53	5.69(0-23)	1.04 (0.96, 1.13)	0.36
Number of missing teeth ²	7.51	9.24 (0-32)	5.66	6.80(0-32)	1.03 (0.97, 1.10)	0.27
Number of decayed teeth ²	0.39	0.63 (0-2)	0.66	1.10(0-6)	0.70 (0.40, 1.23)	0.21

¹Includes teeth displaying both fillings and decay, based on surfaces

²Data used to calculate the DMFT index

³No information was available on the reason the crown was placed, therefore they were not included in the DMFT index

Table 3 Dental hygiene and dental care among MS cases and controls

	Cases (n = 39) N (%)	Controls (n = 62) N (%)	P-value ¹
<i>Dental cleanliness</i>			
Good	19 (53)	36 (60)	0.44
Fair	15 (42)	18 (30)	
Poor	2 (6)	6 (10)	
<i>Gingival health</i>			
Good	15 (42)	28 (47)	0.83
Fair	11 (31)	15 (25)	
Poor	10 (28)	17 (28)	
<i>Difficulty cleaning teeth</i>			
No	32 (87)	59 (98)	0.019
Yes	5 (14)	1 (2)	
<i>Manage to clean satisfactorily</i>			
Yes	31 (84)	53 (88)	0.53
No	6 (16)	7 (12)	
<i>Attend a dentist</i>			
Every 6 months	26 (67)	46 (74)	0.40
Once a year	6 (15)	8 (13)	
Less than once a year	7 (18)	8 (13)	

¹The P value is for the goodness-of-fit test of the null hypothesis that there is no difference in proportions between cases and controls.

to the onset of MS was made using the level of educational qualification achieved, with no change in the odds ratio. There was no significant difference in the number of teeth filled with amalgam. However, cases were significantly more likely than controls to have teeth filled with non-amalgam substances. This was explained by evidence of wholesale replacement of fillings in four MS cases. Overall, there was a tendency for cases to have more fillings than controls but the difference was not significant. There were no significant differences in dental hygiene or attendance at a dentist. Cases expressed more difficulty cleaning their teeth than controls, but nevertheless claimed to clean their teeth satisfactorily by taking compensatory action. (Table 3). However, all the markers of dental care were a little lower in cases than controls.

Blood mercury analyses were undertaken on 23 cases and 31 controls and excluded four cases (and their controls) with clear evidence of deliberate amalgam replacement. The mean (\bar{x}) mercury: creatinine ratio was 1.90 (standard deviation (s) = 1.84) in cases and 2.74 (s = 4.59) in controls. Excluding outliers, (cases 10.0, controls 13.8, 28.2) probably because of contamination, the values changed to \bar{x} = 1.65, (s = 1.14) for cases and \bar{x} = 1.83, (s = 1.22) for controls. The difference was not statistically significant (P = 0.51). There was also no difference in the mean blood mercury (cases \bar{x} = 8.91 nmol⁻¹ s = 5.17 and controls \bar{x} = 8.58, nmol⁻¹, s = 4.92; P = 0.81). There was however, a significant linear relationship between mean mercury levels and the number of teeth filled with amalgam in controls (correlation coefficient (r) = +0.430, P = 0.006) and in cases (r = +0.596, P = 0.001), excluding outliers. Previous exposure to mercury in the workplace was reported by three cases and three controls, odds ratio = 2.06, 95% CI (0.31, 13.51). There were no significant differences in mean blood lead levels (cases: \bar{x} = 0.33 μ mol⁻¹, s = 0.15; controls: \bar{x} = 0.36 μ mol⁻¹, s = 0.15; P = 0.42).

Discussion

The results show a significant association between MS and dental caries and a relationship between the severity of dental caries and MS incidence. We found an odds ratio of 1.09 for each carious tooth increment and a mean difference of 2.24 carious teeth between MS cases and controls. Such a difference translates into an odds ratio of

1.213 or a 21% increased risk of MS in relation to dental caries in this population. Methodological considerations which could affect these results include:

Selection bias

There was a clear difference in the response rate for cases and controls (81% cases, 59% controls). The difference in dental caries rates found could be explained if a bias had operated to select a control group with artificially low levels of dental caries. The relationship of dental caries with social class shows inconsistencies worldwide, but in the UK dental caries is less frequent in social classes I and II, although this tendency is less marked in older subjects.^{17,18} Comparison of socio-economic indicators suggests a potential small selection bias of this type but there are no significant differences between cases and controls and no change in the odds ratio when these are controlled for in the analysis.

Confounding

The association between dental caries and MS could reflect an independent association of each with a third genuine risk factor which is not recognised. There are very few accepted risk factors for MS and all of them are controlled for in the design of the study with the possible exception of social class. The influence of social status is likely to have been reduced by having selected each set of cases and controls from the same GP. There is conflicting information about the relationship of MS with social status but, in the UK, the weight of evidence suggests that incidence may be higher in social classes I and II.¹⁹ Adjustment for negative confounding by social status would be expected to increase the strength of the association between MS and dental caries, but it had no effect in practice.

Reverse causality

It is possible that the difference in dental caries arose after the onset of MS as a result of its debilitating nature. There are problems, both with determining the onset of MS and with obtaining a sufficient number of incident cases for study, which make it difficult to eliminate this complication in a preliminary study of this kind. Our assessment of dental hygiene and reported problems with dental care suggests that within 10 years of onset MS cases compensated for their disability but perhaps not entirely.

Other bias

DMFT may not be an entirely valid measure of dental caries because of the practice of prophylactic restorations in the past. However, it is unlikely that incident MS cases of recent onset would have been singled out or otherwise treated differently from controls in this respect, to account for these results.

Other studies have found similar results.³ In a German case-control study, dental examination revealed 272 carious teeth among 50 MS cases compared with 148 in 48 epileptic controls. A radiograph confirmed 29 cases of infective granuloma among 51 MS patients but only 8 cases among 51 epileptics, representing an odds ratio of 7.1 (95% CI, 2.8–18.1).² However, one other study showed no such relationship.⁴ Our finding of marginally fewer amalgam fillings in MS cases is also consistent with other results.² We found no differences in mercury levels between MS cases and controls. However, mercury levels were correlated significantly with the number of amalgam fillings in both cases and controls, confirming previous findings.^{6,20} Mercury levels in blood were well below accepted toxicity levels making it unlikely that mercury poisoning is the basis of MS, but excessive sensitivity, as described for lead,²¹ has yet to be excluded. Our results support other studies of lead and MS showing no difference between blood levels in cases and controls.⁸

Dental caries is commonly attributed to the influence of fluoride

and refined carbohydrate, especially sucrose, in the diet, however, a range of other factors have also been implicated including minerals, excess fat and deficiency of vitamins C and D.^{22,23} In recent years the important role of *streptococcus mutans*, a member of the viridans group, have also been shown.²⁴ Streptococci have a reputation for cross-reactivity in a small minority of individuals and a cross-reaction mechanism has been proposed for MS, in the form of a predicted model, in relation to a commensal organism.²⁵ Several studies have suggested a more general activation of the immune mechanism involved in demyelination by some common bacterial pathogens.^{26,27} Elsewhere recent studies have described links between periodontal disease and heart disease which raise the plausibility of dental caries as a possible aetiological factor for disease.²⁸

Conclusion

This study shows a statistically significant excess of dental caries among MS cases compared with controls. The risk of MS appears to increase with the extent (or dose) of dental caries. These findings are unlikely to be caused by selection bias, confounding or problems maintaining dental hygiene among MS cases, and support the strong ecological correlation between MS and dental caries. There was no association between MS and the number of mercury fillings nor with body mercury. In the light of these results, it is possible that reports of miracle cures following wholesale replacement of amalgam fillings could relate to the incidental resolution of incipient dental infection. It is also possible that this was caused by a placebo effect. Further research should concentrate on the possible aetiological connection between dental caries and MS.

The authors wish to thank Dr Andrew Taylor, Analytical and Pharmacokinetics Unit, Robens Institute, University of Surrey for analyses and advice on specimen collection and the WHO Global Oral Data Bank. The authors also wish to thank Consultant Neurologists Dr P Millac, Dr I Pye for their advice and cooperation, and Emma Beresford and the Leicestershire Health Authority for assistance with the fieldwork and analysis. Mercury analyses were supported by a grant from the Multiple Sclerosis Society.

- 1 Craelius W. Comparative epidemiology of multiple sclerosis and dental caries. *J Epidemiol Community Health* 1978; 32: 155-165.
- 2 Firnhaber W, Orth H. Über die pathogenetische Bedeutung von Zahnerkrankungen und Zahnbehandlungen bei der Multiplen Sklerose. *J Neurol* 1977; 215: 141-149.
- 3 McAlpine D, Compston N. Some aspects of the natural history of disseminated sclerosis. *Q J Med* 1952; 21: 135-167.
- 4 Alter M, Speer J. Clinical evaluation of possible etiological factors in multiple sclerosis. *Neurology* 1968; 18: 109-116.
- 5 Miller A. *Observer* 1985; 21 July.

- 6 Abraham J E, Svare C W, Frank C W. The effect of dental amalgam restorations on blood mercury levels. *J Dent Res* 1984; 63: 71-73.
- 7 Kuntz W D, Pitkin R M, Bostrom A W, Hughes M S. Maternal and cord blood background mercury levels: A longitudinal surveillance. *Am J Obstet Gynaecol* 1982; 143: 440-443.
- 8 Birmingham Research Unit of the RCGPs. Lead and multiple sclerosis. *J R Coll Gen Pract* 1976; 26: 622-626.
- 9 Schumacher G A, Beebe G, Kibler R F, et al. Problems of experimental trials of therapy in multiple sclerosis. *Ann N Y Acad Sci* 1965; 122: 552-568.
- 10 *Oral health surveys: basic methods*. 3rd edition. Geneva: WHO, 1987.
- 11 Todd J E, Dodd T. *Childrens dental health in the United Kingdom*. London: OPCS/HMSO 1985; SS1189.
- 12 Lindstedt G. A rapid method for the determination of mercury in urine. *Analyst* 1970; 95: 264-270.
- 13 Miller D J, Paschal D C, Gunter E W, Stroud P E, D'Angelo J. Determination of lead in blood using electrothermal atomisation atomic absorption spectrometry with a L'vov platform and matrix modifier. *Analyst* 1987; 112: 1701-1704.
- 14 Sharma D C, Davis P S. Direct determination of mercury in blood by use of sodium borohydride reduction and atomic absorption spectrophotometry. *Clin Chem* 1979; 25: 769-772.
- 15 *General Household Survey 1989. OPCS Series GHS20*. London: HMSO, 1991.
- 16 Breslow N E, Day N E. *Statistical methods in cancer research*. Ch 6. Lyon: International Agency for Research on Cancer, 1980.
- 17 James P M C. Epidemiology of dental caries: the British scene. *Br Med Bull* 1975; 31: 146-148.
- 18 Todd J E, Lader D. *Adult dental health 1988 United Kingdom*. OPCS Social Survey Division. London: HMSO 1992.
- 19 Russell W R. Multiple sclerosis; occupation and social group at onset. *Lancet* 1971; 2: 832-834.
- 20 Eley B M. The release, absorption and possible health effects of mercury from dental amalgam: a review of recent findings. *Br Dent J* 1993; 175: 355-362.
- 21 Doss M, Laubenthal F, Stoeppel M. Lead poisoning in inherited delta-amino bevalulinic acid dehydratase deficiency. *Int Arch Occup Environ Health* 1984; 54: 55-63.
- 22 Helle A. Comparison of minerals of drinking water, serum, stimulated saliva and deciduous teeth of healthy children and caries status. *Proc Finn Dent Soc* 1997; 73: 1-34.
- 23 Rugg-Gunn A. *Nutrition and dental health*. Oxford: Oxford University Press, 1993.
- 24 *Diet and health: implications for reducing chronic disease risk*. National Research Council (US) Committee on Diet and Health. Ch 26. Washington DC: National Academic Press, 1989.
- 25 Morris J A. The age incidence of multiple sclerosis: a decision theory model. *Med Hypotheses* 1990; 32: 129-135.
- 26 Burns J, Littlefield K, Gill J, Trotter J L. Bacterial toxin superantigens activate human T lymphocytes reactive with myelin autoantigens. *Ann Neurol* 1992; 32: 352-357.
- 27 Sun D. *Streptococcal enterotoxin* enhances the activation of rat encephalitogenic T cells by myelin basic protein. *J Neuroimmunol* 1993; 46: 5-10.
- 28 Seymour R A, Steele J G. Is there a link between periodontal disease and coronary heart disease? *Br Dent J* 1998; 184: 33-38.

Submitting illustrations to the BDJ

Authors submitting manuscripts for publication in the BDJ are reminded that two copies of all illustrations must be supplied. This will assist in speeding up the refereeing process — manuscripts and illustrations are always sent to referees and a set of illustrations is required at the editorial office for reference. If you choose to submit 35-mm transparencies then one set of these and one set of prints (colour or black & white) will be acceptable.

We strongly advise authors to keep copies of all illustrations submitted in case letters are lost or damaged in transit. Please do not send glass-mounted transparencies — even when securely wrapped the glass will often arrive cracked or shattered, resulting in damage to the surface of the slide which usually renders it unsuitable for reproduction.