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Organic solvents and multiple sclerosis: a case-control study

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A case-control study of multiple sclerosis (MS) has been carried out in western Norway. The study included 93% of the patients who had clinical onset of MS in the county of Hordaland during the years 1976–86 (N = 155) and 200 controls, marginally matched for age, sex and residence. There was no statistically significant difference between MS patients and controls with regard to exposure to organic solvents, exposure to the combination organic solvents and welding or to organic solvents and other chemical compounds.

Key words: multiple sclerosis; organic solvents

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Both environmental (1) and genetic factors (2) seem to be involved in the etiology of MS. In the search for possible risk factors, the occupational pattern of MS patients has also been investigated, with inconsistent results (3–10). One study showed an increased frequency of MS in a population of shoeleather workers (3) and another reported increased risk for MS in men with exposure to the combination of organic solvents and welding (4).

This study was designed to investigate the possible role of occupational exposure to organic solvents, alone or in combination with welding or other chemical compounds, as putative risk factors for MS. This was done as part of a case-control study of MS performed during the period 1986–87 in which a larger number of possible risk factors was examined.

Material and methods

Cases selected were 93% of all patients who had a clinical onset of MS when living in Hordaland during the period 1976–86 and who were diagnosed by the end of 1986 (n = 155). Seven percent (12 patients) were not included; four patients did not want to participate, two had moved and could not be traced, one was not able to cooperate due to mental reduction and five were dead. The patients were classified according to the criteria of Bauer (11). The controls comprised patients who had been admitted to the hospital with one of the following diagnosis: traumatic fractures, traumatic rupture of ligaments, sciatica and minor plastic surgical or benign gynecological disorders. Ninety-two percent of these patients voluntered to cooperate in the study (n = 200). The cases and controls were marginally category matched on age (five-year age-groups), sex and residence (inland, coastal and urban area).

All cases and controls were interviewed by use of a questionnaire eliciting detailed information concerning previous medical, professional and social history. A supplementary questionnaire concerning occupational exposure to organic solvents was then presented to all participants who had ever been active workers, 150 cases and 195 controls. The questionnaire elicited detailed information about type of chemical exposure (organic solvents, pesticides, heavy metals, welding fumes), frequency and duration of exposure, symptoms of intoxication due to exposure to organic solvents (headache, tiredness, dizziness, nausea, confusion), and use of protection equipment. The additional questionnaire was answered by 139 (92.6%) of the MS patients and by 161 (83.9%) of the controls.

The question in focus was whether exposure to organic solvents may be associated with later development of MS. Only exposure before the clinical onset of MS was considered. The mean time of onset for the MS patients was 1981. Therefore, only exposure before 1981 was considered for the controls.

A total number of years of exposure to different organic solvents was calculated, taking into account

possible overlapping time periods but not intensity of exposure (unweighted duration of exposure). A weighted number of years of exposure to organic solvents was also calculated. The weights were defined according to the frequency of exposure. Exposure five to seven days a week was given weight 1.0, three to four days a week 0.5, one to two days a week 0.25, one to two days a month 0.05 and less frequent exposure was given weight 0.01. The weighted duration of exposure was calculated as the sum of the products of weight and corresponding number of years of exposure.

An exposure index was also calculated, using the formula of Ravnskov (12) which takes into account the number of years exposed, the frequency of exposure and the expected intensity of exposure in different occupations (i.e. weighted duration times intensity of actual occupation).

To evaluate the load of exposure, an index of intoxication was calculated. This index takes into account the frequency and the number of symptoms of intoxication reported in direct relation to the exposure (headache, tiredness, dizziness, nausea and/or confusion). Symptoms of intoxication three or more times a week was given weight 3.0, one to two times a week 1.5, one to three times a month 0.5 and less frequent symptoms were given the weight zero. Thus, a person reporting 2 symptoms, one 3 times a week and one twice monthly, will be assigned to index value $1 \times 3.0 + 1 \times 0.5 = 3.5$.

Statistical methods

Logistic regression analyses were performed to analyse the association between MS and exposure to organic solvents (alone and in combination with welding or other chemical compounds), duration of exposure and symptoms of intoxication due to exposure. Since the controls were only marginally matched to the cases, the matching variables age, sex and residence were included in the regression model for final adjustments. The maximum likelihood procedure was used in estimating the regression coefficients and odds ratios were calculated as a measure of effect. Differences between exposed cases and controls regarding use of protection equipment were analysed with Fisher's exact test.

Results

Thirty-five of 139 MS patients and 29 of 161 controls reported exposure to organic solvents, before onset of disease and before 1981 respectively. The estimated odds ratio was 1.55 (95% C.I. 0.83–2.90) for subjects reporting exposure to organic solvents versus the non-exposed (Table 1). Exposure to welding was not associated with an additional increase in the odds ratio. Although the odds ratio for those exposed to both organic solvents and other chemical compounds was high in this group, the number

Table 1. Occupational exposure to organic solvents in multiple sclerosis patients and controls. Odds ratio (OR) and 95% confidence intervals (CI) according to type and duration of exposure [1]

Exposure to organic solvents	Cases	Controls	OR	95% CI
Not exposed	104	132	1.00[2]	
Exposed, total	35	29	1.55	0.83–2.90
– without welding	20	16	1.61	0.77–3.38
– with welding	15	13	1.46	0.61–3.51
– other chemical compounds	7	3	3.12	0.74–13.13
Unweighted duration of exposure (years)				
1–5	14	15	1.23	0.55–2.76
>5	21	14	1.97	0.87–4.48
Test for trend		p=0.11		
Weight duration of exposure (years)				
<2.5	16	15	1.39	0.63–3.07
>2.5	19	14	1.74	0.78–3.90
Test for trend		p=0.15		
Exposure index (weighted duration times intensity)				
<2.5	20	18	1.44	0.69–3.00
>2.5	15	11	1.75	0.72–4.25
Test for trend		p=0.16		

[1] Based on logistic regression analysis with adjustment for sex, age and area of residence.
[2] Reference category.

Table 2. Distribution of reported occupations and types of organic solvents among 35 cases and 29 controls

	Cases	Controls	p*
Occupation			
Oil industry	4	1	0.62
Able seaman	5	11	0.35
Worker in textile ind.	2	2	1.00
Worker in mechanical ind.	15	10	0.79
Worker in electro ind.	1	1	1.00
Worker in wood-working ind.	4	5	1.00
Worker in paint industry	2	3	0.65
Worker in printing ind.	1	1	1.00
Worker in plastic and rubber ind.	0	2	0.20
Other occupations	11	7	1.00
Organic solvents			
1. Alkanes, alkenes, white spirit, trichloroethylene	31	23	0.49
2. Aromatic hydrocarbons	21	21	0.43
3. Alcohols	4	8	0.12
4. Ketones	14	14	0.61
Number of solvents			
1	13	11	
2	16	10	
>=3	6	4	0.53'

p* Fisher exact test (two-tail).
' Pearson chisquare.

Table 3. Reported symptoms of intoxication due to exposure to organic solvents in MS patients and controls.Odds ratio (OR) and 95% confidence interval (CI) by number of reported symptoms and an index of intoxication [1]

	Cases	Controls	OR	95% CI
Not exposed	104	132	1.00[2]	
Exposed; unweighted number of symptoms				
- no symptoms	14	6	2.95	1.05–8.26
- 1 symptom	12	15	1.03	0.43–2.46
- ≥2 symptoms	9	8	1.43	0.52–3.94
Index of intoxication				
- 0	16	10	2.08	0.84–4.98
- 0.5–2 symptoms	9	13	0.85	0.33–2.16
- ≥2 symptoms	10	6	2.37	0.79–7.10

[1] Based on logistic regression analysis with adjustment for sex, age and area of residence.
[2] Reference category.

of subjects was too small to draw any definite conclusion regarding the effect of such combined exposure. A non-significant increase in odds ratio with increasing duration of exposure for weighted as well as unweighted duration and exposure index was observed.

Among those exposed to organic solvents, the distribution according to type of work and types of organic solvents reported was similar among cases and controls (Table 2). The distribution of the total number of occupations among the responders in the control group, was similar to that of the total group of cases and controls. The non-responders among the controls had a slightly higher number of occupations in mechanical industry (11.8 *vs* 6.4%) and on ships (4.3 *vs* 2.8%), than the responders. Both cases and controls reported exposure to combinations of several solvents (Table 2). Ten MS patients and nine controls had used protection equipment. The difference is not statistically significant.

Among the exposed, the odds ratio was higher for subjects reporting no symptoms than among those with one or more symptom compared to non-exposed (Table 3). Similar findings were observed for the intoxication symptoms headache and tiredness. There was no definite trend in the estimates by an index of intoxication, and no difference between cases and controls regarding other symptoms of intoxication like dizziness, nausea and confusion. However, the numbers were small in these subgroups.

The clinical characteristics of MS patients with exposure to organic solvents were similar to the cases with no exposure (Table 4).

Table 4. Clinical characteristics of the MS patients according to occupational exposure to organic solvents

	Exposed n=35	Unexposed n=104	p
Definite MS	26	69	
Probable MS	7	28	
Possible MS	2	7	0.68*
Remitting MS	20	58	
Remitting-progressive MS	11	29	
Progressive MS	4	17	0.76*
Mean age at onset of MS (years)	34.7	33.7	0.60'

* Pearsons chiquare.
' Student's t-test.

Discussion

The present study showed no statistically significant difference between MS patients and controls with regard to exposure to organic solvents, use of protection equipment, exposure to the combination of organic solvents and welding or to organic solvents and other chemical compounds. Furthermore, the MS patients who were exposed to organic solvents had the same clinical characteristics as the MS patients who were not exposed.

The use of other hospital patients as controls could introduce selection bias if the reasons for admittance among the controls were related to their occupation. However, the diagnoses of the controls are not known to be associated either with MS or to exposure to organic solvents in their work.

The odds ratio for MS was higher in the group with exposure to organic solvents but with no symptoms of intoxication than in the group with symptoms of intoxication, compared to the non-exposed. This may indicate a recall bias; that MS patients more frequently report minor exposures not causing symptoms of intoxication, compared to the controls. This may indicate that the slightly increased odds ratio for the exposed (OR: 1.55) could partly be explained by such bias. The nonresponders among the controls had a little higher number of occupations in the mechanical industry and on ships, which also would contribute to a falsely increased odds ratio among the exposed cases. Amaducci et al. (3) reported an increased frequency of MS in a population of leather-workers. None of the MS patients in the present study and only one of the controls were engaged in leather industry. A case-control study by Flodin et al. (4) showed that solvents, especially in combination with welding, appeared to be associated with an increased risk for MS in males. However, this was not confirmed in this study or in a co-twin study by Juntunen et al. (5), or in the study by Koch-Henriksen (6). Lauer (7) found in a study from Southern Hesse that more female MS patients than expected were working in commerce and administration whereas male MS patients did not deviate from the pattern of the general population. Other studies have shown an association between

MS and employment in certain occupations (8–10). Furthermore, trichlorethylene poisoning (13) and chronic methanol poisoning (14) have been shown to produce clinical symptoms mimicking MS. The diverging results from the epidemiological studies may be caused by differences in the populations studied, in the types of exposure and in the methods used.

In summary, this study does not provide evidence that exposure to organic solvents is related to increased risk of MS. There are indications in our data that recall bias may in part explain the nonsignificant increased risk observed for exposed workers. However, confidence intervals are wide. Larger studies are needed to more precisely estimate if exposure to organic solvents contribute to the development of MS. However, it seems likely that this contribution is small. In this population only a low proportion of the cases reported exposure to organic solvents. Thus, the increased incidence of MS in the county of Hordaland during the years 1958–87 (15) can not be explained by such exposure.

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