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Multiple sclerosis and exposure to solvents, ionizing radiation and animals

by Anne-Marie Landtblom, MD,¹ Ulf Flodin, MD,² Magnus Karlsson, BSc,² Sven Pålhagen, MD,³ Olav Axelsson, MD,² Birgitta Söderfeldt, MD,¹

LANDTBLOM A-M, FLODIN U, KARLSSON M, PÅLHAGEN S, AXELSSON O, SÖDERFELDT B. Multiple sclerosis and exposure to solvents, ionizing radiation and animals. *Scand J Work Environ Health* 1993;19:399–404. Earlier studies have indicated an association between multiple sclerosis and environmental factors, especially occupational exposure to solvents. The present study examined such relationships further. From medical files of hospitals in Kalmar and Jönköping, 91 cases of multiple sclerosis, diagnosed in 1983–1988, were identified from population registers corresponding to the catchment areas of the hospitals, and 348 referents were randomly drawn. The cases and referents answered a questionnaire concerning occupational exposure and animal contacts. The men had significantly elevated risks, determined from logistic odds ratios, for solvent exposure, occupational contact with dogs or cats, and leisure-time contact with caged birds. X-ray treatment and previous diseases were risk indicators among the women. For the men and women together, solvent exposure, radiological work, and previous diseases were associated with clearly elevated risks. Although the study concerned rather few subjects, the findings indicate that several exogenous factors might contribute to the development of multiple sclerosis.

Key terms: case-referent study, epidemiologic, exposure classification, occupational, questionnaire, radiological work.

Multiple sclerosis is an inflammatory disease of the central nervous system. It is characterized by primary destruction of myelin. The precise pathogenesis is unclear. Recent studies support the ideas that certain human leucocytocytolysis A (HLA) haplotypes imply increased susceptibility to multiple sclerosis (1–5) and that infections (6–15), for example, retrovirus (16–18), may play a role in the pathogenesis. There are several observations regarding the associated occurrence of multiple sclerosis with other autoimmune disorders (19), like myasthenia gravis (20), thyroid disease (21), and Sjögren's syndrome (22), but also with such clearly HLA-linked conditions as ankylosing spondylitis (23) and narcolepsy (24, 25).

It is also well known that the incidence of multiple sclerosis varies with geographic latitude and that individual risk can be altered by changing residence before adolescence, the result being adoption of the incidence of the new location (26). Many studies have shown that animal contacts could mean a higher risk (27–30), but in a later review of the etiologic importance of such contacts the results have been ambiguous, with some of the nonpositive studies

bearing more weight (31). Hence the pathogenesis is likely to be complex — both genetic and environmental factors may be involved and interact (32).

Regarding exogenous factors, exposure to organic solvents among Italian shoe and leather workers was associated with an increased risk of multiple sclerosis (33). A previous study from our group (34) showed that occupational exposure to solvents, especially in combination with welding, was associated with an increased risk of multiple sclerosis among men. For both genders X-ray examination until five years before diagnosis occurred more frequently than in a reference group. There are also reports of an increased risk among health care workers (35) and persons working in paper manufacturing (36).

General determinants affecting the occurrence of the disease have been discussed with respect to the great variation in risk with regard to geographic and climatologic distribution (37). Examples of such determinants are water chemistry (38) and ultraviolet radiation (39), but also dietary (40, 41) and socioeconomic variables have been suggested as important (31).

Population surveys repeatedly show that multiple sclerosis appears more often among women than among men. According to recent reports the difference can be two- to threefold (42).

The aim of the present study was to determine whether the results of the earlier Swedish study (34) could be reproduced in another adjacent population. Thus potential risk factors like exposure to organic solvents, welding, radiation, and animal contacts were of a priori interest in this study.

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Subjects and methods

Cases

In 1989, cases of multiple sclerosis were collected from the patient files of the neurological departments of the hospitals in Jönköping and Kalmar, representing two administrative provinces with a base population of 540 000 individuals. There are no other neurological departments in the area, and in the Swedish medical system it is not likely that this type of patient would be diagnosed by private practitioners. Therefore there should have been minimal selection bias in the study. All of the cases identified had been diagnosed in 1983 through 1988. Furthermore, the cases were labeled as definite multiple sclerosis, fulfilling the criteria by Schumacher et al (43), or as probable or possible multiple sclerosis according to the criteria of Rose et al (44).

Altogether 97 persons aged 20–61 years at diagnosis were given case status. Of these, 91 responded to the questionnaire (94%). The rest refused to participate. Of the responding subjects the diagnosis had been definite for 48, probable for 21, and possible for 22.

Referents

The referents were randomly drawn from the population registers of the administrative provinces of Jönköping and Kalmar (ie, corresponding to the catchment areas of the hospitals). They were 20 to 65 years of age in 1989 when the selection was performed. Out of 400 selected referents, 348 agreed to be included in the study (ie, the reply frequency was 87%). The deficit was due to refusal to participate.

Assessment of exposure

Information about various types of exposure among the cases and referents was obtained by an identical procedure and without revealing the purpose of the study with respect to multiple sclerosis. A ten-page questionnaire preceded by an introductory letter was sent to the subjects. The questionnaire contained 16 main questions, 10 of which focused on occupational exposures. Some of the questions were further sub-specified with regard to certain details. Five questions were devoted to medical care, particularly to the use of drugs, X-ray treatment, and X-ray examinations.

A minimum criterion of one year was required for exposure time, along with a five-year latency period (ie, the last five years of exposure were disregarded both for the cases and the referents). The mean year of diagnosis was 1986. In the consideration of latency, this year was taken as an anchor point in time for the referents with regard to the various exposures.

Information about solvent exposure in qualitative terms was directly obtained from the questionnaires. To avoid overreporting of the exposure, especially among the cases, all exposure data of a priori inter-

est were critically checked for credibility in telephone interviews with both the cases and the referents. The quantitative classification had five intensity categories formed on the basis of an appraisal applied in some of our other studies, and as originally suggested by Ravnskov et al (45). Hence five categories of increasing intensity were created for solvent exposure, from category 0 = not exposed to category 4 = highest intensity (eg, floor layers). An example of an occupation in category 1 would be staff at day nurseries, one for category 2 would be cleaner, and for category 3 repairman. Categories 0 and 1 (ie, not or only very slightly exposed subjects) were considered practically unexposed. Categories 2, 3, and 4 were merged into an exposed group since the number of subjects was too small for separate analyses of single exposure categories.

Statistical methods

The statistical analyses of the data were based on stratification by age and application of Mantel-Haenszel procedures (46). The approximate confidence intervals of the Mantel-Haenszel rate ratios (odds ratios) were calculated according to Miettinen (47). Multiple logistic regression, based on the Epilog Plus statistical package (48), was used as an additional method in the data analyses for the simultaneous control of several potentially confounding factors. The data for the men and women were analyzed separately since female gender appeared to be a determinant per se (34).

Results

The Mantel-Haenszel rate ratios were elevated among the men for occupational solvent exposure in general, and specifically for exposure to kerosene, with its lower 95% confidence limit exceeding unity. Occupational exposure to domestic animals, like dogs, cats, horses, swine, and poultry, were significant risk indicators similar to caged birds at home (table 1), whereas contact with pet dogs or cats were not (table 2). Among the women occupational solvent and radiological exposures appeared as less clear risk factors (table 3) since the confidence interval included unity and the results were similar for animal contacts. X-ray treatment occurred for five cases and no referents, giving a formally infinite risk. Various previous diseases taken together were more common among the cases than the referents. Similar results were obtained by multiple logistic regression, which resulted in risk estimates with lower 95% confidence limits exceeding unity for solvent exposure, occupational contact with dogs or cats and leisure-time contact with caged birds among the men. Since exposure to farm animals was complex, it was impossible to analyze the separate effects from single species; instead, we had to merge all types of farm animals in the multiple logistic regression (ta-

Table 1. Exposure regarding selected risk indicators among the cases of multiple sclerosis and the referents, along with estimates of the Mantel-Haenszel rate-ratio for the men. The underlying stratification by age has been omitted.^a For an explanation of the solvent exposure category, see the section Assessment of Exposure in the text. (95% CI = 95% confidence interval)

Exposure	Cases (N = 24)	Referents (N = 172)	Mantel- Haenszel rate ratio	95% CI
Solvent exposure (categories 2 + 3 + 4 versus 0 + 1)	14	53	3.4	1.2–9.4
Kerosene	7	7	9.3	2.4–35
Occupational exposure to animals				
Dogs	3	3	9.9	1.4–77
Cats	4	3	15	2.3–115
Poultry	5	3	21	3.5–183
Horses	5	9	6.5	1.4–28
Swine	5	11	4.5	1.1–17.6
Pet caged bird	6	14	3.7	1.1–12.6

^a The subjects were stratified into age groups 20–34, 35–49, and 50–65 years.

ble 4). Similarly, as shown in table 4, X-ray treatment and various previous diseases as a group were risk indicators among the women. For the men and women together solvent exposure, radiological work, and various previous diseases were associated with clearly elevated risk (table 4).

Dividing the material into the subgroups of multiple sclerosis (ie, possible, probable and definite) resulted in small numbers without any distinguishable pattern in the rate ratios when calculable. The three subgroups were therefore merged in all of the analyses.

Discussion

Methodological aspects

This study had a primary study base since the subjects were recruited from the population of two adjacent administrative provinces (49). Hence the cases of multiple sclerosis were searched for in the patient files of the two, and only existing neurologic departments of these provinces and the referents were randomly drawn from the population registers of the same areas. Therefore it seems unlikely that any selection of cases conditionally on exposure should have occurred, nor is any selection bias likely with regard to the referents.

A five-year time criterion was applied in order to avoid the possibility that the disease itself would cause the cases to have particular exposures (eg, exposure to X-rays).

The proportion of men with multiple sclerosis in our material was low, 26%, which is in agreement with recently reported values (42).

Since female gender is associated with multiple sclerosis, most of the analyses were performed separately for the men and women to avoid confound-

Table 2. Status or exposure (examples of nonsignificant risk indicators of some interest were selected for this table) among the cases and the referents, along with estimates of the Mantel-Haenszel rate-ratios for the men. The underlying stratification by age has not been shown in the table.^a (95% CI = 95% confidence interval)

Status or exposure	Cases (N = 24)	Referents (N = 172)	Mantel- Haenszel rate ratio	95% CI
Welding	4	21	1.4	0.4–4.3
Radiological work	2	2	7	0.7–83
Gasoline	5	15	2.9	0.7–10.5
Thinner	6	19	2.6	0.7–7.9
Farming	4	15	2.4	0.5–9.2
Cows	5	16	2.9	0.8–10
Herbicides	1	7	0.9	0.1–7.6
Pets				
Dog	9	62	1.1	0.3–2.7
Cat	7	42	1.3	0.4–3.7
X-ray treatment	—	—	0	—
Previous diseases	2	15	0.9	0.1–4.3
Smoking	6	46	0.8	0.2–2.4

^a The subjects were stratified into age groups 20–34, 35–49, and 50–65 years.

Table 3. Status or exposure among the cases and referents, along with estimates of the Mantel-Haenszel rate ratio, for the women. The underlying stratification by age has not been shown.^a

Status or exposure	Cases (N = 67)	Referents (N = 176)	Mantel- Haenszel rate ratio	95% CI
Solvent exposure (categories 2 + 3 + 4 versus 0 + 1)	10	9	2.8	0.9–8.0
Kerosene	—	1	0	—
Gasoline	1	1	2.2	0.1–175
Thinner	3	5	1.6	0.2–8.5
Welding	—	—	0	—
Radiological work	4	1	8.4	0.8–209
X-ray treatment	5	—	∞	—
Metal work	5	2	6.4	0.9–47
Farming	4	17	0.7	0.1–2.5
Occupational exposure to animals				
Dogs	4	5	2.2	0.4–17
Cats	5	11	1.3	0.3–4.4
Poultry	8	15	1.7	0.5–4.7
Horses	6	14	1.3	0.3–4.0
Swine	7	17	1.3	0.4–3.6
Cows	8	19	1.3	0.4–3.5
Herbicides	—	2	0	—
Pets				
Dog	29	67	1.2	0.7–2.2
Cat	25	65	1.0	0.5–2.0
Caged bird	13	27	1.3	0.6–2.9
Smoking	23	45	1.4	0.7–2.7
Previous diseases	20	20	3.3	1.5–7.5

^a The subjects were stratified into age groups 20–34, 35–49, 50–65 years.

ing from gender when occupational exposures associated with gender were considered. In the correlation analyses of various exposures among the referents it turned out that there was an association between some exposures of interest, most strongly between solvents and farming, and a possibility for confounding existed. Therefore multiple logistic regression was performed as well, but it resulted in rela-

Table 4. Logistic odds ratios for exposure of interest among the cases of multiple sclerosis and the referents with the men and women both separately and combined.

Exposure	Women		Men		Women and men combined ^a	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Solvent exposure	1.9	0.6–5.7	3.3	1.1–9.5	2.8	1.3–5.5
Radiological work	8.2	0.7–90	7.6	0.8–70	7.5	1.5–35
Previous diseases	3.6	1.6–7.7	.	.	2.5	1.2–4.8
Metal work	5.8	0.9–35	1.4	0.4–4.0	1.9	0.8–4.5
Farming	0.5	0.1–2.8	1.5	0.1–18	0.7	0.1–2.9
Plastic work	1.2	0.2–6.3	1.7	0.3–8.1	1.7	0.5–4.9
Occupational exposure to cats or dogs	1.0	0.2–6	18	1.3–265	2.1	0.5–8.3
Occupational exposure to horses, hens, cows or swine	1.5	0.2–9.4	0.6	0.1–10.1	1.2	0.2–5.1
Pets						
Dog	1.3	0.6–2.4	0.8	0.2–2.2	1.2	0.6–1.8
Cat	0.9	0.4–1.7	1.1	0.3–3.5	0.9	0.5–1.5
Caged bird	1.4	0.6–3.1	4.4	1.1–16	1.8	0.9–3.5
X-ray treatment	∞	.	0	.	0	.
Welding	0	.	0.8	0.1–3.4	0.7	0.2–2.7
Female gender	0	.	0	.	4.4	2.2–8.7

^a According to logit $f(y)_{\text{case/referent}} = 10.3609 + 0.6640 (\text{metal work}) - 0.3368 (\text{farming}) + 1.0133 (\text{solvent}) - 0.3061 (\text{welding}) + 0.5053 (\text{plastic work}) + 2.0167 (\text{radiological work}) + 0.7624 (\text{occupational exposure to dogs or cats}) + 0.2179 (\text{horse/hen/swine/cow}) + 0.0951 (\text{pet; dog}) - 0.1027 (\text{pet; cat}) + 0.5976 (\text{caged bird}) + 0.9243 (\text{previous diseases}) + 1.4763 (\text{female gender}) + 0.0039 (\text{age } 34-49 \text{ years}) - 0.3844 (\text{age } \geq 50 \text{ years})$.

tively little new information, except for almost eliminating the effect of animal contacts.

Etiologic aspects

Solvents. Occupational solvent exposure in general, and specifically exposure to kerosene, turned out to be associated with increased risk. In our previous study (34) white spirit gave a significantly high risk for multiple sclerosis. These types of solvents are closely related and are both mixtures of mainly aliphatic hydrocarbons, but they also include a few percent each of many different aromatics. Kerosene has a higher flame point (81°C) than white spirit (57°C). It is not unreasonable to assume that there was no clear distinction between these two solvents in the answers to our questionnaire since these solvents are probably rather intermixed in Swedish colloquial language. They are also used to a great extent for the same purposes among mechanics and repair workers.

Cerebrospinal fluid analyses of men with heavy solvent exposure have in some cases shown blood-brain barrier dysfunction indicated by leakage of protein into the cerebrospinal fluid (50), but the findings are inconsistent (51). Under the hypothesis that multiple sclerosis ultimately has a viral etiology, one could speculate of the possibility of solvents enhancing viral entrance to the nervous system.

X rays. This study indicates that exposure to ionizing radiation might have an increased risk for multiple sclerosis, as observed both for patients treated

with X rays and for radiological personnel. There were five cases of multiple sclerosis being treated with X rays until five years before diagnosis, but no referents had had such an experience. A previous study (34) showed an increased risk in connection with X-ray examinations until five years before diagnosis. This finding was primarily interpreted as simply reflecting the fact that a number of investigations have to be made at an early stage of the disease when the diagnosis is still unclear. However, together with the earlier findings, the new data obtained in this study support the alternative that radiation per se might contribute to the development of multiple sclerosis, since we now have shown an increased risk for multiple sclerosis also in two other situations (ie, X-ray treatment and occupational exposure). Since both ultraviolet and ionizing radiation can induce viral synthesis in lysogenic bacteria (52, 53), one could speculate that radiation might cause primary damage and therefore play an inducing role in a two-step pathogenetic development of multiple sclerosis (ie, if there is a viral or immunologic etiology as well).

Animal contacts. Our results give no clear support to earlier findings (12, 27–30, 34) that animal contact may be a risk factor for developing multiple sclerosis. In the pathogenetic discussion of multiple sclerosis, several infectious agents have been suggested as directly or indirectly inducing or precipitating the development of multiple sclerosis (6–15). By univariate analyses a raised risk of multiple sclerosis also appeared in this study among the men occupa-

tionally exposed to animals. The question arises of why occupational contact with dogs and cats incurs a risk, whereas "pet contact" does not. However, the formal risk for occupational contact with some animals (cow, swine, horse, poultry) as observed in the univariate analyses appears to be confounded by solvent use among farmers (mostly chain-saw petrol) since this risk was almost eliminated by the logistic regression analysis. For occupational contact with dogs and cats there remained a significant risk in the multiple logistic regression analysis which cannot be explained by confounding by solvents.

Previous diseases. In order to detect possible connections between multiple sclerosis and other diseases (eg, inflammatory or infectious in character) the questionnaire contained one question concerning "any long-lasting or serious diseases." In the statistical analysis we focused on the interval five years or more before the diagnosis of multiple sclerosis. Such diseases (eg, diabetes mellitus, allergy, bronchial asthma, epilepsy, thrombocytopenia) turned out to be a significant risk factor for the women. In a study of these diagnoses, however, no distinguishable pattern was observed. The odds ratio was nevertheless rather high when these various disorders were grouped together, and the interpretation could be that various diseases might play a role in precipitating clinically overt multiple sclerosis.

Concluding remarks

Exposure to solvents appears to be associated with an excess risk of developing multiple sclerosis. Both X-ray treatment and radiological work show a risk, indicating that exposure to ionizing radiation might be a factor of interest in the pathogenesis of multiple sclerosis. In our earlier study, X-ray examinations appeared as a risk indicator, and this finding supports the same hypothesis. In analogy with other investigations, we have demonstrated a risk from animal contacts, which was restricted to men with occupational contacts with cats or dogs, or contacts with caged birds. For livestock, however, the risk appears to be confounded by solvent use among farmers. Before firm conclusions about the risks from the exposures analyzed in this study can be made, further studies have to be performed.

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