ORIGINAL ARTICLE

The risk for multiple sclerosis in female nurse anaesthetists: a register based study

A-M Landtblom, M Tondel, P Hjalmarsson, U Flodin, O Axelson

Occup Environ Med 2006;**63**:387–389. doi: 10.1136/oem.2005.024604

See end of article for authors' affiliations

Correspondence to: Dr A-M Landtblom, Department of Neuroscience and Locomotion, Division of Neurology, Faculty of Health Sciences, Linköping University, SE-581 85 Linköping, Sweden; anne-marie.landtblom@lio.se

Accepted 9 November 2005

Background: Previous studies have suggested that exposure to organic solvents, including volatile anaesthetic agents, may be a risk factor for multiple sclerosis (MS), possibly in combination with genetic and other environmental factors.
Aims: To further investigate the role of volatile anaesthetic agents having similar acute toxic effects to other organic solvents.
Methods: Female nurse anaesthetists, other female nurses, and female teachers from middle and upper compulsory school levels were identified and retrieved from the 1985 census, Statistics Sweden. By means of the unique personal identity number in Sweden, these individuals were linked with the disability pension registers at The National Social Insurance Board and also with data on hospital care 1985–2000 at The National Board of Health and Welfare.
Results: The cumulative incidence rate ratio of MS was found to be increased in female nurse anaesthetists in relation to other nurses (statistically not significant) and teachers (statistically significant), respectively.
Conclusions: These findings give some support to previous findings of an increased risk for MS in nurse anaesthetists. This is interesting in the context of previous observations of organic solvents in general as a potential risk factor in MS.

The aetiology of multiple sclerosis (MS) is generally thought to be a complex interplay between genetic[1] and environmental[2 3] factors. The findings regarding environmental factors have been inconsistent,[4] however, and many single observations on the possible role of factors such as infection[5] or diet[6] have later often not been confirmed when systematically analysed in larger populations. Only a few environmental factors have repeatedly been shown to be associated with an excess risk for MS—that is, exposure to organic solvents as first suggested by Amaducci and co-workers[7] and later confirmed by others,[8–10] and Epstein Barr virus (EBV) infection.[11 12] Ionising radiation,[13] late childhood infections,[5] and tobacco smoking[14] are examples of recently identified environmental risk factors. Our group has a particular interest in the topic of organic solvent exposure,[15–17] including exposure to volatile anaesthetic agents,[18] as a particular kind of occupational solvent exposure. Opinions about the impact of solvent exposure, however, have differed.[19] We have proposed that the magnitude of the risk from solvent exposure is twofold,[8] with a population attributable fraction of about 9–17%.[20 21] As the incidence of MS in Scandinavia is low at around 4–9/100 000 inhabitants a year,[22 23] even a twofold increase in risk must be considered as being too low to be detectable by ''clinical practice impression''. Nor is it likely that general health surveys and mortality statistics of nurse anaesthetists would reveal an increase in risk when this is normally so very low.[24 25]

The anaesthetic gases of interest in the operating theatre are various types of halogenated ethers, especially halothane. There has been a change over time in the way these agents are used, and exposure levels for anaesthetic personnel in Sweden are lower nowadays than in 1985 when the study population was collected.

In this study, we compare the MS incidence among female nurse anaesthetists with nurses in general—that is, nurses lacking exposure to solvents in laboratory work or to *x* rays,[13] and also with women from another unexposed profession, namely teachers.

METHODS

We have identified nurse anaesthetists with exposure to volatile anaesthetic agents in 1985 in order to compare their MS morbidity with two unexposed professional groups.

In the census of 1985 in Sweden, each person had to fill in a form and declare which occupation they held during the period 4–10 November. Based on the information from the census, the occupations of interest were identified (female nurse anaesthetists as the exposed group; other female nurses and female teachers as non-exposed groups) and coded according to a system used in the census. We were thus able to identify female nurses with specific tasks: firstly, nurse anaesthetists, the primary interest group; and secondly, nurses potentially exposed to agents mentioned in the context of MS risk (organic solvents, ionising radiation[8 13])—that is, midwives, *x* ray nurses, theatre nurses, laboratory nurses, and nurse anaesthetists in veterinary medicine, in order to exclude them from the study. Furthermore, we identified other female nurses not having any of the work tasks mentioned above, and female teachers from middle and upper compulsory school levels; these constituted our reference group. We thus identified three female occupational cohorts: nurse anaesthetists, other nurses, and teachers.

The criteria for being included in our study as an MS case were either hospital care as an inpatient with MS diagnosis, or disability pension due to MS.

All persons in Sweden have a personal number, and we used this unique identity number which identifies every individual in Sweden, to link the three cohorts to two registers, namely The National Social Insurance Board and The National Board of Health and Welfare.

From the first register we retrieved persons who had a disability pension because of MS in 1985. From the second register we identified persons who had been treated as inpatients under the diagnosis of MS during 1985–2000. The ICDX (International Classification of Disease, X-edition) code ''multiple sclerosis G35'' was used. To increase sensitivity, the

diagnoses G36 (other acute disseminated demyelination) and G37 (other demyelinating diseases of central nervous system) were also included.[26] In the older ICD version 9 these codes correspond to 340, 340.99, and 341 respectively. The data were checked for death and emigration; no person had died or emigrated by the end of the follow up period (31 December 2000).

Age restriction to the interval 30–50 years was applied in all analyses because of a skewed age distribution in the teacher group towards higher age. We also performed an age standardisation with the nurse anaesthetists; those aged 30–50 years in 1990 were taken as the reference population. The population was stratified into four strata: 30–35, 36–40, 41–45, and 46–50 years of age.

The study was approved by the ethics committee and the use of registers for collection of data was taken care of by the authorities responsible for the various registers used in the study—that is, the Swedish National Statistics Office (SNSO), The National Social Insurance Board (NSIB), and The National Board of Health and Welfare (NBHW). The data extracted from these registers were delivered unidentified, but with information on age, occupation, and MS diagnosis. Cumulative incidence rate ratios (CIR) were calculated from incidence data retrieved from NSIB and NBHW divided by number of person-years acquired from SNSO.

The computer program used for statistics was Strata version 6.0, Epiinfo 2000.

RESULTS

The cumulative incidence of MS was higher in the nurse anaesthetist group when compared with both the other nurse and the teacher groups respectively. However, the numbers were small and only some of the cumulative incidence rate ratios (CIR) were statistically significant (see table 1). In the time period 1990–2000, the CIRs between the nurse anaesthetist and teacher groups were statistically significant, whereas when comparing the anaesthetic nurses with other nurses, an almost doubled but statistically insignificant risk was seen.

The cumulative incidence in the nurse anaesthetist group during 1985–2000—that is, over 15 years, was 5/907 for ages restricted to 30–50 years in 1990, or (5×100 000)/(907×15) = approximately 37/100 000 person-years, all anaesthetist nurses surviving this time period. This is twice as high as in the reference groups: the female teachers had an incidence density of 17/100 000 person-years and the other nurses, 19/100 000 person-years.[8]

DISCUSSION

The data presented here suggest an increased risk for MS among female nurse anaesthetists compared with other female nurses and teachers. The risk deduced from our data concern exposure prior to 1985; the exposure to volatile anaesthetic agents may thus reflect an earlier situation with less stringent restrictions which should be kept in mind when discussing safety in anaesthetic departments. From our clinical experience we have the impression that the exposure levels may have been high. The nurse anaesthetists that we encountered as MS patients have to a large extent had potentially very high exposure to ether when working with paediatric anaesthesia, often with the child on their lap. Several of them describe toxic symptoms afterwards, such as headache, nausea, and fatigue.

The specificity based on our number of cases may be considered adequate, based on existing register information and therefore of totally objective character. The sensitivity, however, is low as several cases have not been admitted to hospital or do not have a disability pension due to the disease. There is hardly any reason, however, why MS nurse anaesthetists should have been registered in any other way than the other nurses or teachers, which could have systematically biased the results obtained. With regard to the number of exposed subjects, it is noteworthy that we, in a separate analysis without age restrictions, only found 997 anaesthetist nurses, whereas there were about 2000 in 1985 according to information from statistics in the National Board for Health and Welfare database. This difference in number can partly be explained by the exclusion of males, but there are other reasons. The questionnaire used in the census does not require information regarding specificity of working tasks. Furthermore, the information asked for in the census, where only work in one specified week was asked for, resulted in a certain loss because of vacation, and maternity and sick leave for some individuals. Thus all specialties are under-reported, which in our case leads to the nurse anaesthetists being too few, both in nominator and denominator. The number of other female nurses can be assumed too high, both for cases and healthy subjects (that is, in nominator and denominator), since an under-reporting of anaesthetic nurses was made in the census of 1985, before

Table 1 Number of incident cases of MS in female nurse anaesthetists, other female nurses, and female teachers, with cumulative incidence rate ratios (CIR) and 95% confidence intervals (95% CI)

Observation period		Teachers	Other nurses	Nurse anaesthetists (crude)	Nurse anaesthetists (adjusted)
1985–2000	No	50	113	5	
	CIR	1.0*		2.2	2.3
	95% CI			(0.8–5.5)	(0.9–5.8)
	CIR		1.0*	1.9	1.7
	95% CI			(0.8–4.7)	(0.6–4.1)
1990–2000	No	34	80	4	
	CIR	1.0*		2.6	2.8
	95% CI			(0.9–7.3)	(1.0–8.1)
	CIR		1.0*	2.2	1.8
	95% CI			(0.8–5.9)	(0.6–5.0)
1995–2000	No	17	38	3	
	CIR	1.0*		3.9	4.1
	95% CI			(1.1–13.3)	(1.2–14.3)
	CIR		1.0*	3.5	2.9
	95% CI			(1.1–11.2)	(0.9–9.5)

*Reference.
Age of subjects restricted to 30–50 years in 1990.
Nurse anaesthetists (n = 907), other nurses (n = 39 703), teachers (n = 20 053) according to the census of 1985.
CIR presented as crude and adjusted by age standardisation.

Main messages

- Nurse anaesthetists can be exposed to volatile anaesthetic agents which, due to their toxicological effects, can be classified as organic solvents.
- Exposure to organic solvents has been associated with an increased risk for MS. An increased incidence was also found in this study of nurse anaesthetists.

the onset of MS. Hence, no distortion of the CIR is to be anticipated.

However, there are distinct problems in making a good age standardisation when cases are so few. Even single cases will change the prevalence in the actual stratum because the total number of cases is small.

The MS incidence densities of the reference groups (17/100 000 person-years for female teachers and 19/100 000 person-years for other female nurses) are not in complete agreement with existing MS incidence densities of two groups of women from Denmark and Gothenburg, respectively, being approximately 10–12/100 000 person-years in this age group.[22 27] According to the Danish researchers, the MS incidence among Danish women in a cohort of nurses[28] was 13.5/100 000 person-years in the age range 30–34 years (personal communication, Koch-Henriksen).

The higher incidence in our reference groups compared with the Danish and Gothenburg incidence data might be due to selection bias, consisting of a higher incidence of MS in middle and upper socioeconomic classes compared with the average population.[30–32]

Exposure to microbial agents in public places, especially viruses, is a potential risk in all the groups investigated, nurses as well as teachers. By using teachers and other nurses as reference groups, the possible effect of a potential infectious agent was taken care of in the analysis of the effect of anaesthetic agents.

After the publication of our first paper on the risk for MS in nurse anaesthetists,[18] another paper on that topic has been published.[29] In that Danish study, no excess risk for MS was observed among Danish nurse anaesthetists. However, the material was rather small, and a power analysis reveals that the possibility of finding a tentative risk from anaesthetic agents is limited (about 30% chance).

In conclusion, despite weaknesses in our data extraction procedure, this somewhat crude study has the benefit of utilising only objectively registered data, and seems to further support previous results suggesting an increased risk for MS in solvent exposed populations, including nurse anaesthetists.

ACKNOWLEDGEMENTS

This study was financed by research funds at the University Hospital in Linköping. Drs Stenager, Brönnum-Hansen, and Koch-Henriksen, connected with the Danish MS register, are acknowledged for sharing their basic data with us for comparison of incidence figures between Denmark and Sweden.

Authors' affiliations

A-M Landtblom, Department of Neuroscience and Locomotion, Division of Neurology, Linköping University, Sweden
M Tondel, P Hjalmarsson, U Flodin, O Axelson, Division of Occupational and Environmental Medicine, Department of Molecular and Clinical Medicine, Faculty of Health Sciences, Linköping University, Sweden

Competing interests: none declared

Policy implication

- Exposure to organic solvents/volatile anaesthetic agents should be minimised globally.

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