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Parkinson's disease and occupational exposure to organic solvents, agricultural chemicals and mercury - A case-referent study

by Carl-Göran Ohlson, MD, Christer Hogstedt, MD¹

OHLSON C-G, HOGSTEDT C. Parkinson's disease and occupational exposure to organic solvents, agricultural chemicals and mercury — A case-referent study. *Scand j work environ health* 7 (1981) 252-256. Parkinson's disease has been associated with heavy occupational exposure to carbon disulfide, and this solvent, as well as other organic solvents, may cause neurotoxic effects. Therefore, the hypothesis was raised that organic solvents in general may be associated with Parkinson's disease. A case-referent study design was applied, and some other suspected exposures were studied as well. The diagnosis registers of two Swedish hospitals were used as the source of subjects. Male in-patients with Parkinson's disease (the cases) or subarachnoid hemorrhage (referents), with symptom appearance between 35-69 a of age and residence in the vicinity of the hospitals, were included in the study. Occupational exposure to the chemicals under study were determined from questionnaire answers of 91 cases and 75 referents. No differences in exposure frequency to organic solvents in general were observed, but three cases had been exposed to carbon disulfide compared to none of the referents. Six cases, but only two referents, had been exposed to mercury, and further exploration of a possible association between exposure to mercury and Parkinson's disease is recommended. The outcome of the study does not support the hypothesis that occupational exposure to organic solvents in general increases the risk of Parkinson's disease, but the confidence intervals of the odds ratios do not rule out such possibilities.

Key terms: carbon disulfide, subarachnoid hemorrhage.

Parkinson's disease is a degenerative disease of the central nervous system that mostly affects men 40-70 a of age. The cardinal symptoms are tremor, rigidity, and hypokinesia, leading to disturbances of gait and speech (3). Mental depression is also a part of the clinical picture.

Parkinson's disease seems to be dependent on a depletion of dopaminergic central neurotransmission, operating mainly at the level of the substantia nigra. The disease has been associated with Economo's encephalitis, neurosyphilis, manganese

poisoning, carbon monoxide poisoning, and some neuroleptic drugs (12).

Heavy exposure to carbon disulfide has also been observed among patients with Parkinson's disease (9, 13, 15). Furthermore, it has been observed in rats that this solvent can influence the activity, in general, of neural transmitters in the brain (10). The mental disturbances caused by exposure to organic solvents, including carbon disulfide (2), and the possibility of an influence on the dopamine metabolism in the substantia nigra seemed to justify the hypothesis that occupational exposure to other organic solvents might contribute to an increased risk of contracting Parkinson's disease. Indeed, we had had several painters, lacquerers, etc, with this disease referred to us for evaluation of a

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possible etiologic association, but no information was available in the literature.

Chemical agents used in agriculture have also been reported to cause nerve damage. Recently a case of possible organophosphate-induced Parkinsonism was published (4). Earlier the chlorinated phenoxy acid 2,4-D has been associated with neuropathy following occupational exposure, as well as with acute central nervous disturbances in animal experiments (5, 6).

Mercury is another agent capable of producing central nervous symptoms like tremor and impaired coordination of movement. Measurable effects in tremor and electromyographic tests have been reported in workers exposed heavily to mercury from chloroalkali plants (8), and the possibility that long-time exposure to mercury might cause irreversible extrapyramidal disturbances was considered.

A case-referent (case-control) study design was chosen in an attempt to elucidate the possible association between Parkinson's disease and organic solvents but also any connection between occupational exposure to agricultural chemicals and mercury and the disease.

Material and methods

Source of subjects

The diagnosis registers for 1960–1975 in two middle-sized hospitals in central Sweden were used as the source of subjects for the study. The hospitals were chosen from geographic areas where the exposures were thought to be represented with reasonable frequency.

Subject selection

As cases, male in-patients treated for Parkinson's disease were chosen, and, as referents, male patients with subarachnoid hemorrhage. The case diagnoses had been made by neurologists at one of the hospitals and by an experienced specialist in internal medicine with special interest in Parkinson's disease at the other.

The referent diagnosis entity is highly

specific and not used unless there are typical symptoms in combination with sanguinolent cerebrospinal fluid. Furthermore, the diagnosis is usually confirmed with a radiographic investigation or, in the case of lethal outcome, with a postmortem examination. The pathogenesis of subarachnoid hemorrhage is well known, and there are no reasons to assume a primary relation to the exposures under study. The onset of the hemorrhage is immediate, a situation which allows the victim to work up to the day of appearance, ie, no primary selection due to reduced health should be operating.

The following information was extracted from the medical records: (i) name and address of the patient and his next of kin, (ii) the year of symptom appearance, (iii) occupation and year of retirement from work, and (iv) history of earlier diseases that might have influenced the choice of profession or the risk of contracting the diseases under study.

Restrictions

Only men living within the geographic areas from where emergency patients were admitted to the hospitals have been included to ensure reasonable homogeneity in the industrial background populations. Furthermore, the symptoms should have appeared during the period 1955–1975, as most of the studied chemicals were introduced in the beginning of the 1950s. Since 1975 most patients with Parkinson's disease have been treated as outpatients due to the pharmaceutical progress with levodopa, and admission to a hospital has had social reasons.

The age span of 35–69 a for onset of symptoms was chosen because subarachnoid hemorrhage more often strikes younger people than Parkinson's disease does.

Some cases with schizophrenia and extrapyramidal symptoms caused by neuroleptic drugs were excluded in order to avoid a primary relation to exposure/non-exposure, ie, the chances for those individuals to have been occupationally engaged and exposed were considered less than for the others.

Table 1. Number and reasons for inaccessibility of the study population and the response rate to the questionnaire.

	Cases	Referents	Total
Study population	106	93	199
Inaccessible subjects			
Emigrated	1	—	1
Life events unknown	2	—	2
Living but unknown address	2	1	3
Deceased and no relatives alive	4	9	13
Received questionnaire	97	83	180
Respondents	91	75	166

Table 2. Reasons for exclusion from the study.

	Cases	Referents
Exposure to solvents less than six months	—	1
Exposure to agricultural chemicals less than 15 d	2	1
Incomplete answers ("bad memory")	2	—
Undefined exposures	2	1
Total	6	3

Subject locating

In all, 378 patients had been treated for the case and referent diagnoses at the two hospitals during the period of observation. A total of 93 % of the medical records were found. After application of the criteria for selection and restriction 199 patients remained, 106 cases and 93 referents.

Their vital state and the addresses for live patients or next of kin were traced through the records of the National Health Insurance and the registers of deaths and burials, respectively. In all 13 deceased patients had no live relatives, and six persons could not be located (table 1).

Assessment of exposure

Information about employment and occupational exposure was collected from a questionnaire mailed to living cases and referents and to the next of kin of the deceased. The questionnaire included 27 questions, 14 referring to solvents and 7 to agricultural chemicals. Some questions concerned particular jobs, others par-

ticular agents. A few exposure questions without relevance to the agents under study were added to enable the checking of possible suggestion effects.

The questionnaires were mailed to 180 cases and referents. After the resending of questionnaires to the nonrespondents on two other occasions, 166 answers were obtained, and the final response rate was thus 92.2 %.

Occupational exposure to solvents was defined as more than six months' work with solvents and more than 15 d with agriculture chemicals or mercury, respectively. Thus, the indication of a profession was not regarded as sufficient information for the classification of exposure. Those who had never had any occupational contact with solvents or agricultural chemicals or mercury were classified as nonexposed.

The classification of exposure was performed with blinded diagnoses. Some persons had to be excluded as they could not be properly classified or had too short an employment in exposed work (table 2).

After such exclusions the results could be calculated from the answers of 39 living cases and 30 referents and from the answers of the next of kin of 46 deceased cases and 42 referents (157 answers in all).

Approximate confidence limits of the odds ratio were calculated according to principles based on the Poisson distribution (11).

Results

Occupational exposure to organic solvents was reported for 19 % of the cases and 17 % of the referents, the odds ratio being

1.1. Three cases were exposed to carbon disulfide but no referents were.

Four percent of the cases and 10 % of the referents were exposed to agricultural chemicals. Exposure to mercury, with or without exposure to other agents, had occurred for six cases and two referents (table 3).

The mean age for symptom appearance was similar among the cases and referents, 57 and 54 a, respectively.

Stratifying according to age or the two geographic areas provided no further information.

Discussion

The results do not seem to support the hypothesis that exposure to organic solvents in general or the other chemicals under study was associated with Parkinson's disease. However, the confidence intervals for the odds ratios do not rule out the possibility of an increased risk for solvent-exposed workers to contract Parkinson's disease. The probability ("power") of detecting a threefold increased risk for solvent exposure ($p < 0.05$) was 86 %, and the corresponding figure for agricultural chemicals was 71 % (14). The limitations of the conclusions that can be drawn from "negative results" in epidemiologic studies have recently been reviewed by Hernberg (7) and include small numbers, unknown exposure levels, as well as differences in entity between the case and reference groups, which will be discussed in order

to examine the validity of the present study.

Parkinson's disease and subarachnoid hemorrhage are two fairly well defined diagnostic entities, and similar criteria for diagnosing have been applied at the two hospitals. Subarachnoid hemorrhage is an acute emergency necessitating hospital treatment irrespective of occupation. Among patients with an insidious illness like Parkinson's disease it could be suspected that, eg, salaried employees would be more liable to be admitted to hospital treatment than blue-collar workers, a negative confounding factor therefore being introduced. However, the notations of profession in the medical records revealed that 22 % of the patients with Parkinson's disease and 28 % of the patients with subarachnoid hemorrhage were white-collar workers, a finding indicating that blue-collar workers with Parkinson's disease had not been unfavored in this respect.

Another indication that the referents served as a representative group for the estimation of the exposure frequencies in the area is found in the fact that 14 % of another set of referents from the same geographic area were exposed to solvents (1).

The year of symptom appearance was evenly distributed among the cases and referents within each geographic area, and no bias according to different opportunities of exposure should have operated.

The case and referent diseases are both regarded as grave, and therefore the motivation to answer for both living cases and

Table 3. Exposure to organic solvents, agricultural chemicals, and mercury among the cases and referents. Some individuals belong to more than one exposure category.

	Exposed				Non-exposed	Total
	Solvents	Agricultural chemicals	Mercury	All exposures		
Cases	16	3	6	21	64	85
Referents	12	7	2	20	52	72
Crude odds ratio	1.1	0.4	2.4	0.9	(1.0) ^a	
95 % confidence interval	0.4—2.9	0.1—1.4	0.5—5.0	0.6—1.4		

^a The nonexposed are the standard, their odds ratio being 1.0 by definition.

next of kin should be comparable between the two groups. A more common and less serious referent entity could have impaired the comparability in this respect.

The choice of profession at younger ages cannot be influenced by the risk of contracting Parkinson's disease or subarachnoid hemorrhages later in life, and the referent entity was chosen on account of this characteristic.

Historically, exposure to carbon disulfide has been reported to result in an increased prevalence of extrapyramidal symptoms. Therefore, it is worth emphasizing that three of the Parkinson patients had been exposed to carbon disulfide in modern time but none of the referents, ie, even moderate exposure to carbon disulfide might impose an increased risk of Parkinson's disease. The number of exposed cases was not sufficient to allow for calculations on single solvents. Other exposures than carbon disulfide might impose increased risks even if such a risk was not demonstrated for the whole group of organic solvents.

Six cases had been exposed to mercury, two at a chloroalkali plant and four in farming work, but there were only two referents with such exposure. Organic and inorganic mercury exposures have been grouped together. This procedure could be criticized as the biological effects differ between different mercury compounds, but it seems justified by the small numbers. The increased risk was not statistically significant, but the possibility of chronic extrapyramidal disturbances from mercury exposure in addition to the acute disturbances earlier reported (8) should be further explored.

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