Gliomas and exposure to wood preservatives

S CORDIER,¹ M POISSON,² M GERIN,³ J VARIN,⁴ F CONSO,⁴ D HEMON¹

From INSERM U170 Villejuif,¹ France, Service de Neurologie,² Hôpital Pitié-Salpêtrière, Paris, France, Département de Médecine du Travail et d'Hygiène du Milieu,³ Université de Montréal, Montréal, Québec, Canada, and Institut de Médecine du Travail,⁴ Paris, France

ABSTRACT A case-referent study was undertaken to look for occupational risk factors among patients with glioma treated in a neurological hospital in Paris between 1975 and 1984. In the study group were 125 men with gliomas (aged ≤ 65) and 238 patients (also ≤ 65) admitted for non-neoplastic, non-malformative vascular diseases in the same department during the same period constituting the reference group. All diagnoses were confirmed by tomodensitometry. Information on occupational history was obtained from a postal questionnaire and from medical records. Comparison of cases and referents showed a significant excess risk among teachers (OR = 4.1) and a raised risk among wood workers (OR = 1.6). Four of nine cases of glioma who had been employed as wood workers reported that a colleague had suffered from glioma (those reports were confirmed by hospital records). None were reported among 11 referent wood workers. Using a complementary questionnaire on wood work, exposure assessment to wood preservatives and solvents showed that frequent exposure to organochlorine wood preservatives and to organic solvents occurred more often among cases than referent wood workers ($p < 0.10$).

After observations of clusters of brain tumours in some occupational groups in the Paris area,¹ a survey was carried out to assess occupational risk factors among patients treated for glioma in one neurology department of La Pitié-Salpêtrière hospital in Paris. This hospital has a long tradition in the treatment of neurological disorders and both surgical and clinical departments treat up to half the tumours of the central nervous system registered in the public hospitals in Paris

Methods

All male patients aged 65 or under at diagnosis who had been treated in that department for glioma (glioblastoma, astrocytoma, oligodendroglioma, or ependymoma) between 1975 and 1984 were identified. All cases were histologically confirmed.

Similarly, medical records of all male patients aged 65 or under admitted during the same period for non-neoplastic, non-malformative vascular diseases were abstracted as a reference group. All diagnoses were confirmed by tomodensitometry. The age limit of 65 was chosen to avoid misclassification of diagnosis between glioma and cerebrovascular disease or

differential access to hospital according to social class which is suspected to occur among older patients.² Moreover, 89% of patients with glioma identified in the department were under 65 at diagnosis.

A short questionnaire was sent to all patients (or their next of kin) asking for a brief occupational history: type of industry, type of job, year of beginning, year of ending for all their working life. If no answer was received after three approaches information on the occupation recorded in the medical files was used, if available. All occupational histories were coded using International Labour Office (ILO) codes for classification of occupation.³

Odds ratios in each occupational group were computed and adjusted on age and area of residence (city of Paris, Paris area, other) using the Mantel-Haenszel procedure.

Results

A total of 141 questionnaires were sent to cases or their families and 267 to referent patients or their families. After three approaches a 65% response rate was obtained among cases and 71% among referents (table 1). For 33 additional cases and 49 referents some occupational information was collected from medical records. Altogether some occupational information was obtained for 125 cases and 238 referents.

Table 1 Sources of information of occupational history

	Cases	Referents
No of questionnaires sent	141	267
No of answers	92 (65.2%)	189 (70.8%)
Information obtained from medical file	33 (23.4%)	49 (18.4%)
No of questionnaires with some occupational information	125 (88.7%)	238 (89.1%)

Odds ratios in occupational groups where at least 10 cases and referents have worked are presented in table 2. The only occupational group for which the risk of glioma is significantly raised is teachers (OR = 4.1, 95% confidence interval = 1.4–12.3).

A second group of wood workers drew our attention because the odds ratio was raised, although not significantly (OR = 1.6), and the medical staff reported that three of the nine wood workers with glioma spontaneously reported that one of their work colleagues had suffered from "brain tumour." A complementary survey was then started among the 20 wood workers or their families (nine cases, 11 referents) asking whether they had been informed of any type of "cerebral disease" having occurred among their work colleagues and asking more specifically about type of wood work (carpentry, joinery, cabinet making), type of wood, and type of products (glues, varnishes, dyes, wood preservatives) they used. One brain tumour was reported by the wife of a dead case but none among the referents. Medical records for all additional cases (three previously mentioned plus one reported by his wife) were obtained and diagnosis of malignant glioma was confirmed (two had histological confirmation, two were dead without surgery or biopsy but with a strong suspicion of glioma).

All work descriptions were blindly reviewed by one

of us (MG) who assessed potential exposure to three classes of compounds: solvents, creosote wood preservatives, and wood preservatives based on organochlorine pesticides. The latter type was introduced in France in the 1950s and was typically composed of a solution of pentachlorophenol (ca 5%) acting as a fungicide and of lindane (ca 1%) acting as an insecticide in a petroleum derived solvent. Other constituents of this type of preparation are potential impurities such as other chlorophenols and low quantities of polychlorinated dibenzopara-dioxins and polychlorinated dibenzofurans.⁴ The methodology used to assess exposure was derived from Gerin *et al*⁵ and included an estimation of the reliability or degree of certainty of exposure (0 certainly not exposed or unlikely, 1 possibly exposed, 2 probably exposed, and 3 certainly exposed) and of the frequency of exposure (1 exposed less than 5% of the time, 2 exposed between 5% and 30%, and 3 exposed more than 30%).

An assessment was also made of two other important potential exposures—namely, wood dust and formaldehyde. Wood dust was evaluated as having certainly been present in all the subjects' work environment. Exposure to formaldehyde was assessed to be possible, but at low average levels, in all but one subject from the use of formaldehyde containing glues or work with freshly manufactured plywood or pressed wood. Owing to the ubiquitous nature of exposure to wood dust and the degree of uncertainty surrounding exposure to formaldehyde in this particular subset of workers no epidemiological analysis was deemed to be valid on these two agents.

Description of the wood workers and results of their exposure assessment are given in table 3 for cases and table 4 for the reference group. Comparison of

Table 2 Odds ratios for gliomas by occupational group (occupations held by at least 10 subjects)

ILO code	Occupation	No of cases	No of referents	OR crude	Age	OR adjusted residence
02-03	Architects, engineers	19	30	1.1	1.0	1.4
06-07	Physicians, dentists	3	10	0.6	0.6	0.6
13	Teachers	10	5	4.1*	4.8*	4.2*
20-21	Executive, managerial workers	14	25	1.1	1.2	1.0
30-39	Clerical workers	23	43	1.0	0.9	1.0
40-49	Sales workers	13	39	0.6	0.7	0.7
50-59	Service workers	12	22	1.0	1.6	1.5
60-64	Farmers	8	28	0.5	0.5	0.5
70	Foremen	5	13	0.7	0.8	0.8
77	Food industry workers	3	13	0.4	0.4	0.3
7-2, 8-3, 8-4, and 8-7	Metal workers	11	33	0.6	0.7	0.6
95	Masons, construction workers	16	29	1.1	1.0	1.0
98	Transportation workers	3	22	0.8	0.7	1.0
7-31, 9-54, and 8-1	Wood workers	9	11	1.6	1.8	1.6
	Total	125	238			

*p < 0.05.

Table 3 Description of wood workers with a diagnosis of glioma

Case No	Diagnosis	Year of diagnosis	Age at diagnosis	Type of work	Period of work	Exposure assessment					
						Organochlor		Creosote		Solvents	
						Rel	Frq	Rel	Frq	Rel	Frq
1	Astrocytoma	1981	44	Wood treatment	1960-83	3	3	0	0	3	3
2	Astrocytoma	1981	32	Cabinet making	1975-84	3	1	0	0	3	3
3	Astrocytoma	1982	51	Carpentry	1945-84	3	1	3	1	3	2
4	Glioblastoma	1982	63	Cabinet making	1934-50	0	0	1	1	1	1
5	Astrocytoma	1983	33	Joinery	1968-82	1	1	0	0	2	1
6	Glioblastoma	1983	22	Carpentry, joinery	1978-82	3	1	3	1	3	1
7	Glioblastoma	1984	49	Carpentry	1965-73	3	2	3	1	3	2
8	Glioblastoma	1984	51	Carpentry, joinery	1951-84	3	2	3	1	3	2
9	Glioblastoma	1984	64	Carpentry	1945-62	3	2	3	3	3	3
<i>Cases of brain tumours reported among work colleagues</i>											
Astrocytoma (HC)	1976	25	Work colleague of case No 2								
Glioma	1980	55	Work colleague of case No 3								
Glioma	1983	65	Work colleague of case No 4								
Glioblastoma (HC)	1984	50	Work colleague of case No 8								

Rel, reliability of exposure assessment: 0, certainly not exposed; 1, possibly exposed; 2, probably exposed; 3, certainly exposed.

Frq, frequency of exposure: 1, exposed less than 5% of the time; 2, exposed between 5% and 30%; 3, exposed more than 30%.

Organochlor, organochlorine based wood preservatives.

Creosote, creosote based wood preservatives.

HC, histologically confirmed.

exposure to three classes of compounds among cases and referents according to different levels of specificity is presented in table 5. Exposure to organochlorine compounds and solvents was assessed more often among cases than referents ($p < 0.10$).

Discussion

The results presented above are reported here as observations which might be worth discussing. Indeed, this survey was exploratory, using medical records as its main data source. The use of confirmed diagnoses in both case and referent groups is an improvement over case-referent studies using death

certificates, where misclassification of diagnosis may occur.⁶ Nevertheless, the choice of one highly specialised hospital department as the study centre and of non-tumoural vascular diseases as a reference group may have introduced other types of bias. Referrals to this particular centre may vary according to age and social class and may differ between cases and referents. We tried to minimise the effect of this selection by including only younger patients (65 and under) and by stratifying on area of residence. In our sample the distribution of socioprofessional groups do not differ significantly between cases and referents; in particular, white collar jobs are not overrepresented among cases.

The choice of non-tumoural vascular diseases as a

Table 4 Description of wood workers in the referent group

Case No	Year of diagnosis	Age at diagnosis	Type of work	Period of work	Exposure assessment					
					Organochlor		Creosote		Solvents	
					Rel	Frq	Rel	Frq	Rel	Frq
1	1977	56	Carpentry	1934-40	0	0	0	0	2	1
2	1978	43	Cartwright	1952-60	1	1	1	1	1	1
3	1979	61	Joinery	1932-59	0	0	3	1	3	2
4	1981	53	Carpentry	1959-80	3	1	1	1	3	2
			Cartwright	1942-56	0	0	3	1	3	1
			Joinery	1962-81	3	1	0	0	3	2
5	1982	44	Shipbuilding	1957-58	0	0	0	0	3	1
6	1982	58	Carpentry	1945-50	0	0	1	1	0	0
				1950-68	1	1	0	0	1	1
7	1982	61	Joinery	1936-39	0	0	0	0	1	1
8	1983	54	Joinery	1943-85	3	1	0	0	3	1
9	1983	59	Cartwright	1940-48	0	0	3	1	1	1
			Carpentry	1959-83	3	2	0	0	3	3
10	1983	60	Joinery	1933-73	1	1	1	1	2	1
11	1984	60	Carpentry	1939-46	0	0	1	1	1	1
				1952-84	1	1	1	1	1	1

For abbreviations see table 3.

Table 5 Comparison of exposure to three classes of compounds among wood workers in the two groups

	Case Nos	Referents	Significance*
Organochlorine wood preservatives:			
Possibly exposed	8/9	8/11	NS
Certainly exposed	7/9	4/11	p < 0.10
Certainly exposed > 5% of time	4/9	1/11	p < 0.10
Creosote:			
Possibly exposed	6/9	7/11	NS
Certainly exposed	5/9	3/11	NS
Certainly exposed > 5% of time	1/9	0/11	NS
Solvents:			
Possibly exposed	9/9	11/11	NS
Certainly exposed	7/9	5/11	NS
Certainly exposed > 5% of time	6/9	3/11	p < 0.10

*Using Fisher's exact test.

reference group should not carry with it a problem of misdiagnosis since all diagnoses have been carefully ascertained and updated. This choice puts cases and referents in similar situations for answering complementary questionnaires on occupational history: in both groups the next of kin had to answer on some occasions because the patient's memory had failed. The main problem related to this choice is the possible existence of aetiological factors common to both groups of diseases, which would lead to an underestimation of the relative risk.

The information on occupational history is slightly better than information used in record linkage on death certificate studies since in more than 70% of the sample occupational history was obtained from a questionnaire. The average number of jobs reported in the answers to the questionnaire was 2.2 among cases and 2.6 among referents.

The two salient observations made in this survey are an excess risk for gliomas among teachers and a cluster of gliomas among some categories of wood workers. Several categories of white collar occupations have been repeatedly associated with an excess of brain tumours. Recently, Thomas⁷ reviewed the published studies showing such an excess⁸⁻¹⁰ and in her own case-referent study⁶ pointed specifically at teachers, health diagnosticians, and artists as showing an increased risk of brain tumour among white collar professionals. The usual explanation for these findings, which have no immediate aetiological explanation, is the probable better diagnosis and reporting of a brain tumour among professional and white collar occupations compared with blue collar categories. This might be true in routine recording but is certainly less true in hospital records. Furthermore, in our study, as in Thomas's study,⁶ the excess risk seen among teachers remained when the analysis was restricted to white

Cordier, Poisson, Gerin, Varin, Conso, Hemon collar occupations. We verified that there was no obvious agreement between the "Complementary Health Insurance for Teachers" and this particular health department which could have been a reference centre for teachers. All types of teaching specialties were reported but only two might have necessitated exposures to chemicals: one case taught mechanics and one referent taught chemistry.

As we explained before, our attention focused on the group of wood workers, although the level of significance for increase in risk was not reached, since we had anecdotal evidence for four more gliomas among the work colleagues of the cases. In two instances reports from occupational health physicians confirmed that those people had the same tasks and working conditions as their colleague.

Types of exposure occurring in wood work are numerous and several are proved or strongly suspected human carcinogens^{4,11} but not specifically linked to cancers of the central nervous system—wood dust and formaldehyde, for instance. Some others are neurotoxic after acute high level exposure¹² or chronic exposure.¹³ A few studies have reported excess of gliomas among wood workers. Preston-Martin in the Los Angeles Cancer Registry found a proportional incidence ratio (PIR) of 252 for neoplasms of the central nervous system among wood workers aged 25 to 64 compared with other categories.¹⁴ Dubrow in Massachusetts observed an excess of mortality from brain tumours among carpenters in the 20–54 age group⁸ and living in the vicinity of a saw mill was associated with an excess risk of astrocytoma in a Swedish study.^{14a} Englund and colleagues studied the proportion of glioblastomas among brain tumours in the Swedish cancer registry between 1974 and 1976 and found 59% among wood workers compared with 44% for all categories of occupations.¹⁵ In her recent study Thomas did not separate out wood workers.⁶ McLaughlin found no excess risk of gliomas in this category (SIR = 0.9).¹⁶ In the evaluation made in 1981 by IARC on the risk of cancer in the wood industry no mention is made of a possible existence of an excess risk of brain tumours.⁴ In a prospective mortality study of wood workers the standardised mortality ratio for eye and brain tumours is 132 in the subcategory of carpenters and joiners, and 83 in lumber and sawmill workers.¹¹ Because of the low incidence of brain tumours, however, cohort studies probably lack sufficient power to detect an increase in risk of the order of two.

In our survey we have seen that frequent exposure to organochlorine wood preservatives and to organic solvents occurred more often among cases than referent wood workers. These two exposures were, however, strongly correlated, organochlorine pesticides being present as solutions in organic solvents.

These exposures were not assessed in the whole sample and these results are only indicative. Organochlorine compounds have been suspected on some occasions to play a part in the aetiology of gliomas: Musicco reported an excess risk of glioma among farmers in Italy which he related to the extensive use of organochlorine pesticides in agricultural work in Italy after 1960.¹⁷ This excess risk among farmers was not seen in our survey. In a necropsy study Unger found a high level of two organochlorine compounds (PCBs and DDE) in the adipose tissue of glioblastoma cases compared with controls.¹⁸ Gold, studying the aetiology of childhood brain tumours, suggested that exposure to herbicides or pesticides might increase the risk of brain tumours among children.¹⁹ Such a finding was reported by Ahlbom in a study of astrocytomas among adults in Sweden.²⁰

Because of the ubiquitous nature of exposure to wood dust in this subset of wood workers the potential aetiological role of this agent is difficult to evaluate. Low potential levels of exposure to formaldehyde render this gas unlikely to have played a significant part in causing cancer.

If the carcinogenic role of wood preservatives based on organochlorine pesticides is assumed then constituents other than the chlorophenol pesticides or organochlorine insecticides may also be implicated. These include petroleum derived solvents and their impurities or other impurities such as dioxins that have been associated in non-negligible amounts with chlorophenols in some formulations.⁴

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