Myelodysplasia, Chemical Exposure, and Other Environmental Factors

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This paper describes a case-control study of the occupational and environmental exposures of patients with myelodysplasia. The methodology, first described in Canada for solid tumors, estimates lifetime exposures to a number of potential toxic hazards or carcinogens. This pilot study confirms that the methodology, with the use of questionnaires and interviews, can estimate exposures to specific chemicals and shows some significant associations with myelodysplasia, including exposure to petrol or diesel compounds.

INTRODUCTION

MANY STUDIES have linked occupation with hematological malignancies, but no specific chemical other than benzene has been clearly implicated. Simple occupational mortality statistics are frequently misleading because occupations recorded on death certificates are often inaccurate and differ from those on census returns. Even where occupation has been correctly recorded, such a "job title"-based approach may not satisfactorily estimate occupational exposure. This requires knowledge of the work history of each patient and the specific exposures in each job.

Myelodysplasia is a preleukemic clonal disorder of hemopoietic stem cells, commonly associated with peripheral blood cytopenias and an increase in risk of acute myeloid leukaemia (1). Currently no treatment is known to be effective. The incidence of myelodysplasia (MDS) is largely unknown but is believed to be similar to that of acute myeloid leukemia (AML), the majority of cases occurring over the age of 50 years. Between 20 and 50% of MDS patients eventually transform to AML. Follow-up studies have shown that both conditions can arise from benzene exposure (2) and following treatment with cytotoxic drugs (3). Because the etiology of MDS had not been previously investigated, it was decided to carry out a pilot case-control study to record lifetime exposure to chemical agents, environmental factors, and past medical history with the primal?. objective of testing a methodology for investigating previous contact with chemicals. The present paper describes the development of this methodology and the preliminary findings of this pilot case-control study.

METHODS

The methodology was based on the technique described by Siemiatycki (4) for identifying carcinogens in an occupational environment. Consecutive patients with the myelodysplastic syndrome (MDS) in the Department of Haematology at the University Hospital of Wales, diagnosed during the 12 months ending September 30, 1986, were included in this study. Diagnostic criteria were those of the FAB group (5), as modified by May et al. (6). Controls matched for age and sex were chosen from outpatient clinics taking place on the same morning in the same hospital and included surgical and ear, nose and throat (ENT) patients. Patients with blood disorders and those from the dermatological clinics were excluded.

The cases and controls were chosen independently of the interviewer, who was blind as to the diagnosis. All patients were first interviewed in the outpatient department where they were given an introductory letter explaining the study and a short questionnaire asking them to list all jobs they had held for six months or longer. A date and time for the full home interview was arranged and patients took away a checklist of 70 specific chemicals and substances, which they were asked to complete in preparation for the home interview. At the home interview an in depth environment and health questionnaire was completed by the interviewer. Questions were asked on marital status, social class, lifetime residence, medical history including drugs, diagnostic X-ray procedures, radiotherapy, operations, and transfusions, past illnesses, immunizations, smoking and drinking habits, and hobbies.

Patients were requested not to divulge their most recent illness or the name of the consultant they were currently seeing in order to keep the interviewer blind as to whether they were cases or controls. Work history sheets were completed for all jobs held throughout the patient's life. reporting details of chemicals/substances used within the job title. Interviews lasted from 1 to 2½ hr depending on the patient's age and the number and complexity of jobs held.

Data from the environment and health questionnaire and from the individual work history sheets were coded for exposure to solids (dusts), liquids, and gases (fumes and vapors). Each job contributed to a cumulative exposure index for each chemical or substance. Work histories gave the number of years with a particular job title and, for each job title, frequencies and level of exposure to individual chemicals. An exposure index was calculated for each chemical as follows: Exposure index = hr/day × days/year × years × level of exposure (where low level = 1, medium level = 2, and high level = 3).

Only after these data were entered into the computer for analysis was the identification of cases and controls disclosed to the interviewer. Analysis comparing cases and controls was made of past history of exposure to chemicals, radiation, and drugs using a routine statistical package (SPSSX). Two-way tables were analyzed for significance, using the χ^2 test with Yates adjustment for small numbers. The study is described more fully elsewhere (7).

RESULTS

This study confirms that a methodology based on questionnaires together with outpatient and home interviews is capable of estimating lifetime exposure to specific chemicals and radiation as well as other aspects of personal history. There were 39 male and 24 female preleukemia patients diagnosed during the study period. These were compared with controls matched for age and sex. The social class distributions of cases and controls were similar. Significantly more male cases were single (6 cases and 0 control, $p < 0.05$), but this was not so for females (2 cases and 2 control). Among those married, widowed, or divorced there were 15 (27%) cases with no children, compared with 5 (8%) controls ($p < 0.02$). This pattern was observed for both men (11:4) and women (4:1).

Past health was analyzed with respect to 26 common conditions, none of which showed any significant association with

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MDS. Immunization history was compared for seven infectious diseases and a statistically significant association was found for poliomyelitis immunization; only 12 (20%) cases had been immunized compared with 24 (40%) controls; ($p < 0.05$).

There were only small differences in lifetime occupations held by cases and controls and none were statistically significant. However, there were differences in the numbers of cases and controls who reported exposure to ammonia (10 cases, 1 control $p < 0.05$) and petrol/diesel liquids (20 cases, 14 controls, $p < 0.05$) and petrol/diesel liquids (29 cases, 14 controls $p < 0.01$) and fumes (35 cases, 23 controls $p < 0.01$). There were other materials for which twice as many cases as controls reported exposure, including chromium "dusts"/compounds of chromium (6 cases, 3 controls), lead (8 cases, 3 controls), and tin (6 cases, 3 controls), but because of small numbers involved they did not achieve statistical significance (Table 1). More total "fumes" and "dusts" exposures were reported by cases than by controls: for fumes there were 137 cases and 105 control exposures reported and for dusts, 184 and 162, respectively. Furthermore, exposure indices were higher for cases than controls for fumes, liquids, and gases, even for materials for which the numbers reporting exposures were comparable: for example, exposure to copper compounds (dusts) was reported by 8 cases and 5 controls, but the mean exposures were 26,000 hr and 4,000 hr, respectively (Table 1). Similarly, exposures to insecticides, herbicides, and pesticides were higher among cases than among controls. Men with MDS were more likely to have engaged in hobbies involving chemical exposure (12 cases compared with 2 controls, $p < 0.01$).

DISCUSSION

The choice of controls in a case-control study usually lies between hospital or community controls, although in some studies it is possible to use a sibling. Sibling controls were not used in this study because of the familial occurrence of leukemia. Community controls were not chosen for a number of practical considerations, including the difficulty of conducting such a study blind. Controls were selected among outpatients and matched for age and sex. While there was no matching for place of residence, the outpatient specialties chosen had geographical patterns of patient referrals similar to those in the hematology clinic. The study size was considered large enough to test the Siemiatycki (4) approach, which we modified for use in MDS (rather than 13 solid tumors) and for the South Wales industries.

Table 1. Number of Cases and Controls Exposed to Selected Gases, Fumes, Liquids, and Dusts and Mean Exposures

Material (gas, fumes, liquid, or dust)	cases ($n = 63$)		controls ($n = 63$)		Significance of Comparison of Numbers of Cases and Controls
	Number	Mean Exposure[a]	Number	Mean Exposure[a]	
Petrol diesel fumes	35	40	23	17	**
Ammonia	10	8	1	1	
Molten metal fumes	7	112	4	1	
Petrol diesel liquids	29	32	14	8	**
Petrochemicals	6	52	6	1	
Sulfuric acid	13	21	8	4	
Hydrochloric acid	5	21	4	5	
Hydrogen peroxide	4	31	1	0.2	
Analine dyes	3	24	2	1	
Asbestos	7	24	10	5	
Cement dusts	17	17	11	4	
Chromium compounds	6	7	3	2	
Copper compounds	8	26	5	4	
Lead compounds	8	9	3	0.4	
Tin compounds	6	118	3	26	
Silica	11	88	9	44	

[a]Exposure is given in units of 1000 x integer multipler (see text).
*$p < 0.05$; **$p < 0.01$.

The exposure checklist (70 substances) was based on the previous literature and on substances suspected of having causal links with leukemia. The exposure to each chemical was assessed by detailed questioning about the nature of exposure, intensity and frequency, and the number of years under each job title. The main advantage of this exposure-based case-control monitoring method over the more usual occupation title-based method is that it goes some way toward implicating specific chemicals within a multiple exposure environment. Common job titles may refer to widely different exposures to different substances and, conversely, different job titles may reflect similar exposures. This study has shown that the method is feasible and estimates of a number of lifetime exposures have been possible. The extent to which the answers are reliable or valid has yet to be fully explored. In general, people appeared to have good recall of the chemicals or materials that they had worked with and, although possibly not familiar with the chemical names, they knew the properties and were aware of some of the hazards. The significance of finding six single male cases and no single male control should be considered alongside the national prevalence of singleness, about 6%. Explanations for the excess of single male MDS cases in this study, other than chance, may lie in a protective effect of marriage or in selection effect, whereby those in poor health or those exposed to high risks are less likely to marry (8, 9). The finding that there were more childless cases than controls may have several explanations. Living with children might confer some protective effect, perhaps in exposure to viral infections and stimulation of lymphocytes, or by allowing time for pursuing hobbies involving chemical exposure. Furthermore, some chemical toxic hazard or environmental agent may have an adverse effect on reproduction in both males and females as well as an etiological role in MDS (10, 11). Finally, there may be a constitutional abnormality which leads both to infertility and to an increased risk of MDS. The reported deficit of polio inoculation among MDS cases supports a previous study of childhood cancer and the suggestion that immunization might inhibit the development of both solid tumors and leukemia (12).

The principal chemical association found in this pilot study was that MDS patients reported more exposure to petrol and diesel fumes or liquids. Much of this exposure was associated with jobs in the transport industry. Petrol and diesel fumes and exhausts from petrol and diesel engines contain a large number of chemicals in addition to benzene and toluene, and many of the constituents are known carcinogens (13). Elevated relative risks for leukemia have been reported among petrochemical workers (14, 15), benzene workers (16), and rubber workers (17), where the common link with petrochemicals may be benzene. Because of the small numbers involved in this pilot study, the significance of other possible chemical associations is not established.

In conclusion, this study has demonstrated that the exposure-based etiology has potential benefits over job title-based studies in the search for possible etiological exploration of chronic disease. In view of the method of collecting the information,

it is best suited to patients who are well enough to tolerate lengthy interviews. The results justify further study of reliability and validity of the method with respect to patient recall. Although the numbers involved are small and, as a consequence, few statistically significant associations were noted, there was a consistent finding of more exposure and higher exposure among cases. It seems appropriate to study a larger number of MDS patients by these methods to explore past exposure histories more fully.

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