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END-STAGE RENAL FAILURE ASSOCIATED WITH OCCUPATIONAL EXPOSURE TO ORGANIC SOLVENTS

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Summary

Occupational organic solvent exposure was assessed by interview and questionnaire in a study of 50 patients with biopsy proven proliferative glomerulonephritis of unknown aetiology. Solvent exposure was heavy in 26 patients and moderate or low in 24 patients. In each of these subgroups renal function was similar at the time of kidney biopsy but differed significantly after mean follow-up periods of 83 (36–139) months and 92 (36–127) months respectively, end-stage renal failure having developed in nine patients with continued heavy solvent exposure compared to none with moderate or low exposure ($p<0.025$).

Introduction

Several studies have suggested that organic solvent exposure may be of aetiological importance in the development of glomerulonephritis. In a heterogeneous group of patients with glomerulonephritis and chronic renal failure Zimmerman [1] claimed that solvent exposure was greater than in patients with other forms of renal disease. These findings were supported by the results of subsequent studies in which high solvent exposure was found in non-uraemic patients with various forms of glomerulonephritis [2–4] and in patients with membranous nephropathy [5].

The evidence presented in these previous studies has been criticized on one or more of the following grounds: 1) the unsatisfactory nature of the control groups; 2) the possible bias of the unblinded interviewers; 3) failure to consider recall bias, and 4) the diversity of histological patterns of glomerular disease [6]. In a study of solvent exposure in non-systemic proliferative glomerulonephritis designed to overcome these criticisms we found that occupational solvent exposure was significantly greater than a closely matched control group of subjects without renal disease [7]. Although the degree of exposure was higher in those patients with the more severe diffuse endocapillary proliferative glomerulonephritis than in those with mesangial proliferative glomerulonephritis this

fell outwith levels of significance [7]. The object of the present study was to determine whether the degree of continued solvent exposure after biopsy diagnosis affected the progression of the renal disease.

Patients and methods

The case records were screened of all patients in the Edinburgh Renal Clinics who had been in-patients for a renal biopsy and in whom a histological diagnosis of proliferative glomerulonephritis was made in the previous nine years (1973–1982). In order to ensure a homogeneous population, patients were selected who satisfied defined criteria for non-systemic proliferative glomerulonephritis in whom there was no clinical or serologic evidence of systemic disease, i.e. normal serum immunoglobulins, antistreptolysin titre, viral serology, negative antinuclear factor and negative anti-DNA antibody. Fifty-five patients with a non-systemic proliferative glomerulonephritis who were alive and living in the Edinburgh area were asked to attend for interview. Reassessment of the 50 patients who responded to this request revealed that 37 had a mesangial proliferative glomerulonephritis (MPGN) and 13 a more severe diffuse endocapillary proliferative glomerulonephritis (DEPGN). The criteria for a light microscopic diagnosis of DEPGN included diffuse proliferation of mesangial cells to a marked degree, often with an accompanying increase of polymorphs resulting in a solid tuft with reduced capillary lumina. A diagnosis of MPGN was made when a diffuse mesangial cell proliferation of minor to moderate degree was present, often accompanied by a notable increase of mesangial matrix with little or no encroachment on capillary lumina. They were a young (mean age ± SEM, 31±2 years), predominantly male group (male/female ratio 3:1). From the light, immunofluorescence and electron microscopic examinations of the renal biopsies, it was known that no patient with mesangial IgA disease or mesangiocapillary glomerulonephritis was included in the study group. Glomerular immunofluorescence showed no specific or consistent pattern.

All participants answered the questionnaire designed by Ravnskov [3] to assess the duration and intensity of exposure to organic solvents and fuels in occupational activities as previously described [7]. In each patient with glomerulonephritis solvent exposure was assessed in a blind fashion until the time of renal biopsy. The interviewer did not know the nature of the patient group and the patients were unaware beforehand of the nature of the questionnaire. The individual's working conditions were taken into account in estimating the intensity factor of solvent exposure which was graded 0.5 to 2 as previously described [7].

Calculation of solvent exposure score For each occupational activity in which there was contact with solvent(s), the patient's estimate of the number of hours of exposure per month was multiplied by the number of months the activity had been practised. This product (duration of exposure) was multiplied by the appropriate intensity factor to obtain the exposure score. The sum of the exposure scores for each activity yielded the individual's total exposure score.

Wilcoxon's Signed Rank Sum Test for paired observations and the two-tailed χ^2 test were used for statistical analyses as appropriate.

Results

At renal biopsy occupational solvent exposure was heavy in 26 patients and moderate or low in 24 patients (Table I). Both high and low exposure subgroups had similar renal function. There was no significant difference in the numbers of patients with DEPGN or MPGN in both subgroups. The two subgroups closely matched each other in terms of age, sex and length of follow-up from renal biopsy. During this follow-up period nine of the glomerulonephritis patients with continued heavy occupational organic solvent exposure developed end-stage renal failure (7 on dialysis, 1 awaiting dialysis and 1 dead) compared to none of those with moderate or low exposure ($p<0.025$). Of these nine patients whose

TABLE I. Patient details in relation to degree of solvent exposure

	Low solvent exposure	High solvent exposure
Patient number	24	26
Mean age (years, ± SEM)	29±2	33±2
Male/female	17/7	20/6
Score at renal biopsy	<1000	>1000
Plasma creatinine at renal biopsy (μmol/l, mean ± SEM)	93±7	130±16
Type of glomerulonephritis	5 DEPGN 19 MPGN	8 DEPGN 18 MPGN
Mean follow-up period from renal biopsy (months)	92 (36–127)	83 (36–139)

disease subsequently progressed to end-stage renal failure only two had renal impairment at the time of kidney biopsy which showed in six MPGN, and three DEPGN. The solvent exposure score at the time of renal biopsy in relation to those patients who subsequently developed end-stage renal failure is shown in Table II. There was a similar risk of developing end-stage renal failure for those patients with a score greater than 10,000 compared to those patients with a score of between 1,000 and 10,000. On developing advanced renal failure, four of the subjects became hypertensive but this was well controlled (diastolic pressure phase IV <95mmHg) with antihypertensive therapy in all instances. One further patient was hypertensive prior to the renal biopsy. Despite subsequent good blood pressure control, his renal function continued to deteriorate.

TABLE II. Solvent exposure at renal biopsy in relation to those patients subsequently developing end-stage renal failure

Solvent exposure score at renal biopsy (mean, range)	<100 (2,0–20)	100–1000 (247,146–479)	1000–10,000 (4085,1089–9806)	>10,000 (49969,12320–108195)
Number of glomerulonephritis patients	14	10	14	12
Number of those developing end-stage renal failure	0	0	5	4
% developing end stage renal failure	0	0	36	33

There was no common HLA B, C or DR antigen in the nine subjects whose renal function deteriorated to end-stage renal failure.

Discussion

In our previous study occupational exposure to organic solvents in patients with non-systemic proliferative glomerulonephritis was significantly greater than a closely matched control group of subjects without renal disease [7]. The exposure to solvents was greater in DEPGN than MPGN, suggesting that the severity of the renal lesion may relate to the degree of solvent exposure [7]. We have shown in the present study that end-stage renal failure developed frequently in patients who remained in occupations associated with heavy solvent exposure. In contrast there was no deterioration in renal function in those patients remaining in moderate or low solvent exposure employment. In the majority of subjects this progression to end-stage renal failure could not be explained by the initial renal injury either in terms of the renal function or histological appearances at renal biopsy. Hypertension was considered to be an unlikely further factor in this deterioration as it preceded the renal failure only in one subject. Four further subjects became hypertensive with progressive renal impairment but in all instances satisfactory blood pressure control was achieved.

The large number of people who are heavily exposed to organic solvents make it unlikely that they are capable of causing glomerulonephritis in the absence of predisposing factors. However, we were unable to define any HLA antigen association in those patients who remained heavily exposed to solvents and progressed to end-stage renal failure.

It is known that chemical damage to either the glomerular capillary wall or

pulmonary alveolar capillary basement membrane or renal tubule induces an antigen antibody response which produces glomerulonephritis [7]. However, the absence of specific immunofluorescence patterns at renal biopsy in these patients implies that organic solvents may produce a proliferative reaction as a direct response to chemical injury of the mesangial cells in the glomerulus.

The weight of evidence now suggests that occupational solvent exposure is a factor in some patients in the aetiology of proliferative glomerulonephritis. This study has also shown that patients with proliferative glomerulonephritis are more likely to develop end-stage renal failure by continuing to work in environments where they are heavily exposed to solvents. On these grounds we would suggest that patients with this disease may be at risk by remaining in heavy solvent exposure employment.

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