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Exposure to Solvents in Female Patients with Scleroderma

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Abstract: The role of exposure to solvents was investigated in female patients with connective tissue disease and Raynaud's phenomenon using a questionnaire. Sixteen out of the 63 patients with systemic sclerosis had been exposed to solvents. A borderline significance was demonstrated compared to matched female controls ($P < 0.05$). Fourteen out of the 66 patients with undifferentiated connective tissue disease, 18/86 of patients with Raynaud's phenomenon, 6/45 with systemic lupus erythematosus, 1/16 with dermatopolymyositis, 1/15 with rheumatoid arthritis and 0/13 with primary Sjögren's syndrome had been exposed to solvents. None of these groups of patients showed a statistical significance compared to matched controls. Our present findings indicate that, at least in certain areas of the world, exposure to solvents may be a provoking factor in female scleroderma, but it must be emphasised that only a borderline significance was found between the scleroderma patients and controls. A large multicenter study seems to be required to clarify the importance of solvents as provoking factors of scleroderma. Furthermore, exposure to solvents does not seem to be a provoking factor among females for the other connective tissue diseases.

Keywords: Connective tissue disease; Lupus; Raynaud's phenomenon; Scleroderma; Solvents

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Introduction

Several occupational exposures, including vinyl chloride, silica dust, epoxy resin and solvents, have been described as potential provoking factors of systemic sclerosis (SSc) and scleroderma-like disorders [1,2]. An exposure to aliphatic or hydrocarbon solvents, including trichloroethylene, perchloroethylene, toluene, benzene and xylene, and also white spirits, diesel and aromatic mixes, seems to be an important provoking factor for scleroderma-related disorders in different parts of the world [1,3–12], including Hungary [5,6,13–15]. Among the solvents trichloroethylene is a considerable provoking factor [6,9,10,13,16–18]. Other agents, such as perchloroethylene, benzene [6,14], other organic compounds including amines [4], and formaldehyde derivatives [4] are also capable of provoking scleroderma. Anti-Scl-70 positive scleroderma cases seem to be more susceptible to the effects of solvents [19,20]. Previous studies, apart from that by Yamakage and Ishikawa [21] and our previous East-Hungarian publications [22,23], have described predominantly male workers [1,3]

Only a few controlled studies are available about the provoking effect of solvents in scleroderma. In a population-based case reference study, Bovenzi et al. demonstrated a significant association between occupational exposure and SSc with an odds ratio of 9.28 [7]. Based on the investigation of 178 cases, Nietert et al. suggested that male scleroderma patients were more likely to be exposed to solvents than were controls. These cases had a high cumulative intensity score (odds ratio [OR] 2.9, 95% confidence interval [CI] 1.1–7.6) and a high maximum intensity score (OR 2.9, 95% CI 1.2–7.1) for any solvent exposure, including trichloroethylene (OR 3.3, 95% CI 1.0–10.3). Furthermore, among men and women significant solvent–disease associations were observed among SSc patients who tested positive for the anti-Scl-70 autoantibody [19].

Silman et al. also detected an increased risk for developing scleroderma among 56 male cases [24].

Only a few data are available about the potential role of solvents in the other connective tissue disease groups [25–26]. A long-term exposure to trichloroethylene increased the symptoms of SLE [25]. Another previous study indicated that exposure to petroleum distillate solvents may be a provoking factor for undifferentiated connective tissue disease (UCTD) [26].

In the present study, the exposure to solvents was investigated in patients with scleroderma, Raynaud's phenomenon, systemic lupus erythematosus and UCTD. We have demonstrated that exposure to solvents may be a provoking factor for female systemic scleroderma. Conversely, exposure does not seem to play a role in the other connective tissue diseases.

Patients and Methods

This report is based on the analysis of the clinical laboratory findings of patients encountered at the Clinical Immunology Unit of the Second Department of Internal Medicine of the University of Pécs between 1995 and April 2000. In this tertiary reference centre both outpatient and inpatient records were systematically investigated.

For the clinical investigation of the patients with systemic sclerosis, a standard protocol was used [27,28]. Sixty-three female patients with SSc who fulfilled the diagnostic criteria for systemic sclerosis [29] were included in the study. Their mean age was 52±12.6 years. Fifty-three patients had limited cutaneous systemic sclerosis, and 10 had diffuse cutaneous systemic sclerosis [30]. Seventeen additional patients with limited cutaneous systemic sclerosis who did not fulfil the preliminary criteria for scleroderma were also investigated: these patients did not fulfil the ARA criteria for systemic sclerosis [29] but they uniformly had limited cutaneous systemic sclerosis [30].

Sixty-six female patients with UCTD were also investigated. The diagnosis of UCTD was based on criteria used by previous investigators, including Calvo-Alén et al. and Alarcón et al. [31,32] with modifications [33].

Forty-five female patients with systemic lupus erythematosus, 16 females with dermatopolymyositis, 13 patients with primary Sjögren's syndrome and 15 cases with rheumatoid arthritis were also included. All these cases fulfilled the conventional international criteria [34–36].

Eighty-six female cases with Raynaud's phenomenon were also investigated. With regard to the patients with primary Raynaud's phenomenon (pRp), the criteria of Medger and LeRoy were used [37]. Patients with the following characteristics were placed into this category: episodic attacks of acral pallor or cyanosis, and strong symmetric peripheral pulses. Beside the 25 patients with primary Raynaud's phenomenon who did not show any clinical or laboratory signs of the presence of a systemic autoimmune disease, a special group of 61 patients with secondary Raynaud's phenomenon were also included [38]. Clinically, all of these cases exhibited Raynaud's phenomenon as the sole predominant clinical symptom. These cases also had either antinuclear antibody positivity, scleroderma capillary pattern or pitting ulcerations/gangrene, but they definitely did not exhibit any internal organ manifestation (e.g. pulmonary interstitial changes, oesophageal dysmotility, colonic abnormalities, renal symptoms etc.).

We investigated 95 cases as controls. A control group consisted of two patient subgroups. Female patients with a solitary kidney were included. These patients were followed up at the nephrology unit of the university. Patients who needed surgery for malignancy were excluded. The other subgroup of control cases consisted of female patients with type 2 diabetes mellitus attending one of the two diabetic units of the university. Both outpatients and inpatients were included in both subgroups. The inclusion of two different subgroups of controls was necessary in order to achieve age matching. In general, control cases with a solitary kidney belonged to the younger group of cases, whereas type 2 diabetic cases belonged to the elderly population of patients. The geographical distribution of cases, as well as the proportion of rural/urban domiciles, was similar between patients and controls. The controls (95 patients) were age matched for SSc, SLE, UCTD and Sjögren's syndrome. The distribution of domicile and school record of the controls was similar to that of the patients.

For the investigation of Raynaud's syndrome, another control group consisting of 90 patients was randomly selected so as to achieve age matching, because the mean age of these patients was lower.

Data Acquisition

Both outpatients and inpatients were included in the study. The questionnaire about all previous working conditions, and exposure to all solvents. A list of solvents was also included in the questionnaire, which was sent to all groups of patients and controls described above. The proportion of received answers was above 90%. In all cases where there had been an exposure to solvents a second specific questionnaire was also sent, in order to confirm the information or to clarify the answers previously received. Cases where exposure to solvents was questionable were not included in the exposure category. The evaluation was performed without any prior knowledge of the diagnosis of the particular case.

Data Analysis

The χ^2 test was used for group comparisons. Yates' correction was also used when necessary.

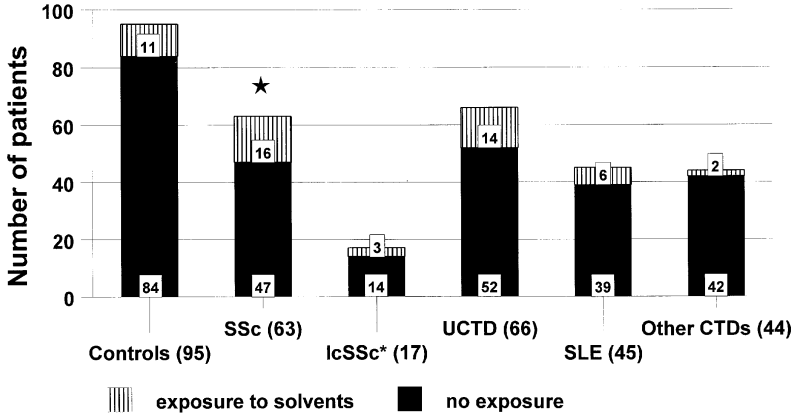
Results

With regard to patients fulfilling the criteria for scleroderma [29], 16 out of the 63 cases with SSc had been exposed to solvents, and 11 of the 95 matched controls had an exposure to solvents in their case history. A borderline significance could be demonstrated between patients and controls ($P<0.05$) (Fig. 1). No difference was detected between cases with lcSSc and those with dcSSc. Two of the dcSSc patients had been exposed to solvents. The presence of antitopoisomerase or anticentromere antibody was similarly demonstrated between the cases with and without exposure (data not shown).

With regard to the 17 cases with lcSSc that did not fulfil the scleroderma criteria [29], three had previous exposure to solvents. If these cases were also added to the cases with lcSSc and dcSSc, the difference between the total group of systemic scleroderma patients and controls did not reach the level of statistical significance (data not shown).

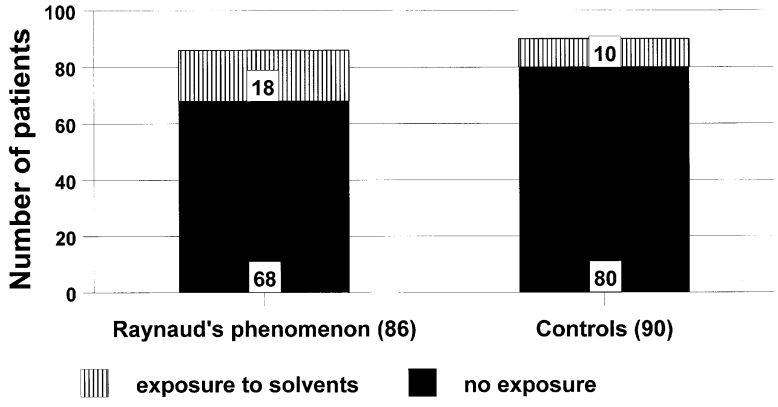
Fourteen out of the 66 patients with UCTD also were previously exposed to solvents. The difference compared to controls was not statistically significant. Eighteen out of the 86 patients with Raynaud's had an exposure to solvents, whereas 10 out of the 90 matched controls were exposed (Fig. 2). No statistical difference was found between the Raynaud's group and controls.

Six out of the 45 patients in the SLE group, one of the 16 patients with dermatopolymyositis, and another one of the 15 patients with rheumatoid arthritis exhibited an exposure to solvents, whereas none of the 13 cases with primary Sjögren's syndrome had an exposure to solvents in their occupational history (Fig. 1). None of these groups showed a statistical significance compared to matched controls.



Abbreviations used: ***SSc***: systemic sclerosis; ***lcSSc* :*** those cases with limited cutaneous systemic sclerosis (30) that did not fulfil the preliminary criteria for scleroderma (29) (see for details "Methods"); ***UCTD:*** undifferentiated connective tissue disease, ***SLE:*** systemic lupus erythematosus; ***CTDs:*** connective tissue diseases: dermato/polymyositis (16); rheumatoid arthritis (15); Sjögren's syndrome (13). The total number of patients are in parentheses. **★: P<0.05,** compared to controls.

Fig. 1. Proportion of the patients with exposure to solvents in different systemic autoimmune diseases.



The total number of patients are in parentheses.

Fig. 2. Proportion of the patients with exposure to solvents in patients with Raynaud's phenomenon.

Discussion

Our study indicates that exposure to solvents may not play a role in the evolution of female SLE, UCTD or Raynaud's phenomenon. Conversely, in systemic sclerosis chemical exposure can be involved in the provocation of disease. In the Hungarian population, a remarkable female predominance was found among the patients previously exposed to solvents [28]. In our previous study in eastern Hungary, 23 of the 171 cases with SSc had an exposure to solvents in their case history, and only three of them were males [27]. Our current southwest Hungarian study also confirms that in Hungary predominantly females were exposed to solvents. During the epoch of 'socialist industrialisation' in the 1950s and 1960s a large number of unskilled female workers from rural areas were employed to do the menial jobs in urban areas, with a concomitant higher risk of exposure to solvents and other chemicals. This may be one of the reasons why a relatively high proportion of females was repeatedly found in Hungary. Furthermore, susceptibility to these agents may differ remarkably, partly because of genetic and environmental differences in distinct parts of Europe [5].

Our present findings indicate that, at least in certain areas of the world, exposure to solvents may be a provoking factor in female scleroderma, but it must be emphasised that our study showed only a borderline significance between the scleroderma patients and controls. This fact makes it impossible to draw a final conclusion in this matter. A large multicentre study is required to clarify the importance of solvents as provoking factors for scleroderma.

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