Clinical Findings in 61 Patients with Progressive Systemic Sclerosis

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In this report the case histories and working conditions of 61 patients with progressive systemic sclerosis (PSS) were evaluated and compared with those of age- and sex-matched controls. An extreme female predominance was found and the sclerodermal involvement of the trunk was also commonly demonstrated. Prior occupational exposure to chemicals (mainly organic solvents) was found in 28 % of the patients. Furthermore a high proportion of menstrual bleeding disturbances was found. ***Key words: Environmental factors; Exposure to chemicals; Gynecological abnormalities.***

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Progressive systemic sclerosis (PSS) is a generalized disorder of unknown origin which affects the skin and certain internal organs. Few clinical studies on PSS have been reported from Central Europe (1, 2). In this investigation, East Hungarian patients were evaluated by commonly used clinical and laboratory methods. The case histories and working conditions of patients were compared with those of sex- and age-matched controls in this present work.

MATERIALS AND METHODS

Pulmonary involvement was investigated by chest X-ray and spirometry. Cardiac involvement was determined by the clinical findings, ECG and occasionally by echocardiography. Myositis was determined by the clinical symptoms and the elevation of creatine phosphokinase (CPK). Renal involvement was shown when azotemia and/or malignant type of hypertension was detected. Schirmer's test and stomatological features of secondary Sjögren's syndrome were investigated in all cases. Esophageal dysmotility was determined by barium esophageal studies. Skin biopsy was performed in 15 cases.

Altogether 61 patients with PSS were investigated. Thirty-seven patients fulfilled one major criterion for PSS (3). Twenty-one cases from the proximal scleroderma group showed an advanced diffuse type of skin involvement. From the 16 patients consistent with acrosclerosis type of PSS, 13 showed a mild truncal skin involvement. Two minor criteria (3) were evident in 24 patients. Sclerodactyly was found in all of these cases. The second minor criterion was bibasilar pulmonary fibrosis in 6, and digital pitting scars on the fingertips in 12 cases. Six patients fulfilled both of these two criteria.

Sixty-one sex- and age-matched normal individuals were randomly selected from the general population of a Hungarian village (Nagyhegyes, 25 km from Debrecen). Anamnestic data, present and previous working conditions, results of the physical examination and ECG were carefully evaluated and compared with those of the controls by the same investigators (L. C., G. C.).

Statistical analysis of data

Differences between patients and controls were evaluated by χ^2-test with Yates' correction.

RESULTS

The mean disease duration was 9.2 ± 8.2 years. The female–male ratio was 60 : 1. Mean age at the onset of disease was 40.7 ± 11.7 years. Our follow-up period was 5.5 ± 4.1 years. No difference in the clinical features and distribution of the cases was evident between patients living in urban and those in rural areas.

Cutaneous symptoms are shown in Fig. 1. The proportion of patients with truncal skin involvement was relatively high. The manifestations of the internal organs are depicted in Fig. 2. The frequency of secondary Sjögren's syndrome was high, because the ophthalmological and stomatological screening tests were performed in all cases. Four patients died from PSS.

A polyclonal increase in the immunoglobulin level(s) was detected in 28 cases (46 %). Antinuclear autoantibodies were demonstrated in 53 cases (87 %) by the indirect immunofluorescence technique, using Hep-2 cell cultures as substrate (4). Antinucleolar specificity was demonstrated in 32 (52.5 %), and anticentromere antibody was found in 5 cases. A mixed-type cryoglobulinemia was found in 13 serum samples.

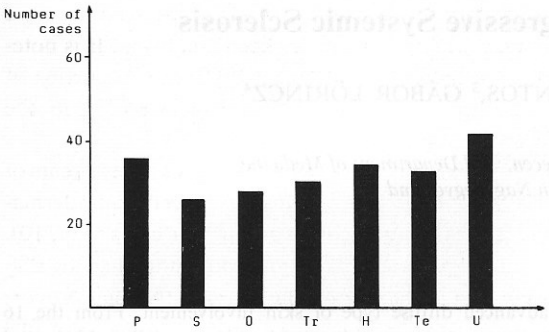

Fig. 1. Skin symptoms in 61 patients with systemic sclerosis. *P*, proximal scleroderma; *S*, sclerodactyly; *O*, edematous phase of disease in the case history; *Tr*, truncal skin involvement; *H*, hypo- and/or hyperpigmented areas of the skin; *Te*, teleangiectasia; *U*, skin ulcers and/or pitting scars on fingers.

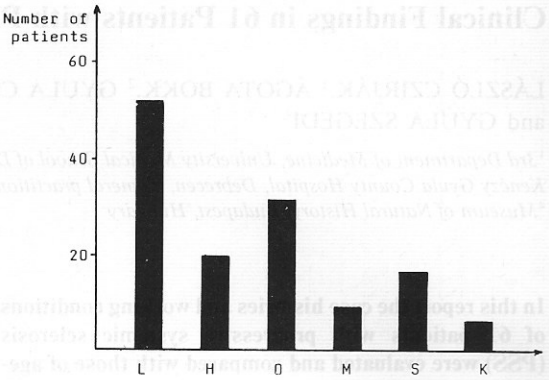

Fig. 2. Manifestations of internal organs in 61 patients with PSS. *L*, lung manifestation; *H*, heart involvement; *O*, esophageal manifestation; *M*, myositis; *S*, secondary Sjögren's syndrome; *K*, kidney involvement.

D-penicillamine was used as basic therapy in 29 cases. An improvement of skin or pulmonary symptoms was documented in 7 cases (24%). The nifedipine therapy showed a dramatic effect for the healing process of skin ulcers in our cases (5).

Social and environmental factors

An occupational exposure to chemicals in the life history was demonstrated in 17 patients (28%). The mean age of these patients was 49 ± 8 years. The exposure preceded the onset of the disease by 9 ± 7 years. The mode of exposure to these chemicals was mainly inhalation. No contact dermatitis or localized scleroderma was detected due to contact exposure to chemicals among our cases. The duration of exposure was 6.3 ± 6.5 years (1–3 years in 8 cases, 4- to 26 years in 9). Since a considerable interval had elapsed between the exposure and our present investigation, the characterization of the exposure was based mainly on the data obtained from the patients. The supposed provoking agents were found to be benzene and petroleum-derived crude solvents in 3 cases. Furthermore, exposure to organic solvents (isopropyl alcohol, terpene derivatives, etc.) was found in 4 cases (hospital laundry worker, paint factory worker, bottle washer in a pharmaceutical factory, stove factory worker). In 3 patients, ethyl acetate and other solvents were identified (production of playing cards and clothing, and synthetic materials processing). The exact chemicals were not well defined but, beside other chemicals, organic solvents were also suspected as provoking agents in 4 patients' case histories (worker in a cosmetic chemical store, dispensing chemist, bottle washer in a pharmaceutical factory, leather industry worker). Exposure to silica dust, paints and solvents was found in one, and ethylene derivatives in another case history. One patient who was exposed to trichlorethylene by inhalation, showed a decreased platelet count. No other symptoms characteristic of chemically induced scleroderma-like diseases were documented among our cases.

The patients with exposure to organic solvents were clinically indistinguishable from the other cases. Neither skin nor internal organ involvement disappeared during our follow-up period of 5.9 ± 6.6 years. In contrast to a previous case report (4), this present systematic clinical study did not confirm the presence of a higher frequency of esophageal involvement among the patients exposed to chemicals.

Occurrence of diseases and symptoms unrelated to PSS

Premature menopause was found in 4, and miscarriage in 5 cases. The frequency of menstrual bleeding disturbances (metropathy and/or menorrhagia) was significantly higher ($p < 0.001$) than in the controls (Fig. 3). No coagulation disturbances and/or decreased platelet counts were detected in these 15 cases.

The proportion of patients with essential hypertension was significantly lower than in the controls, which could be explained by our extensive use of nifedipine (in 72% of the patients) and the better compliance of the patients (Fig. 3).

A high frequency of tonsillectomy and appendectomy was demonstrated in the case histories of the patients with PSS (Fig. 3). These operations preceded

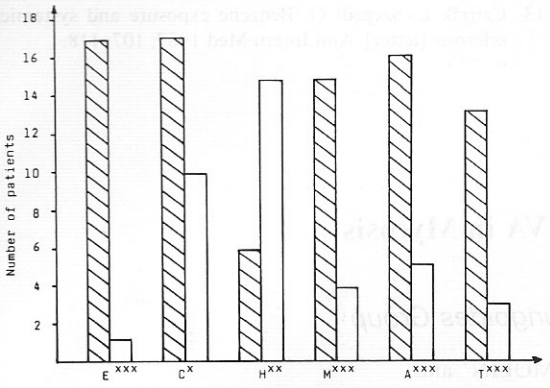

Fig. 3. The case history of 61 patients with systemic sclerosis (▨) compared with age- and sex-matched controls (□). *E*, exposure to chemicals; *C*, cholecystectomy; *H*, hypertension; *M*, menstrual bleeding disturbances; *A*, appendectomy; *T*, tonsillectomy. $*p<0.05$, $**p<0.01$, $***p<0.001$ by χ^2-test.

the onset of disease in each case. Cholecystectomy due to cholelithiasis was performed in 17 cases (Fig. 3).

DISCUSSION

Based on a limited epidemiological study, the prevalence of PSS is 3.89‰ in East Hungary. This report may therefore represent 25–50% of the possible cases in our district (6). The majority of the previous studies showed an F:M ratio of about 3:1. We found an extreme female predominance of the disease. In two other studies from Central Europe the female/male ratio was also high, 9.8:1 (1) and 9.6:1 (2), respectively. The ratio of patients with truncal skin involvement was relatively high, but most of these patients did not have the rapidly progressing type of the disease.

Recently a wide spectrum of agents has been shown to provoke 'classical' scleroderma or scleroderma-like changes. Vinyl chloride disease is a well characterized occupational disorder (7). PSS is more common among patients occupationally exposed to silica dust (8) and trichlorethylene (9, 10). Recently, sclerodermal skin changes were described in patients exposed to organic solvents (11–13). In many of our cases, organic solvents and benzene were the suspected scleroderma provoking agents (13).

In the previous studies, occupational exposure to chemicals was demonstrated mainly among male cases. The surprisingly increased proportion of such females exposed to chemicals would seem even higher if we were to consider that 21 of the patients were housewives and had never been employed. It is noteworthy that in the 1950s and 1960s the proportion of unskilled female workers increased rapidly in the Hungarian industry.

We consider these chemicals as provoking agents of 'classical' PSS. No chemically induced scleroderma-like disease(s) were found among our cases (7, 9, 10).

In the present study, symptoms unrelated to PSS were also investigated. The cause of the high proportion of menstrual bleeding disturbances calls for further clarification. Morphologic changes in the endometrium are suspected. The proportion of the different surgical operations was high, but the low number of patients cautions careful interpretation.

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Retinoids Plus PUVA (RePUVA) and PUVA in Mycosis Fungoides, Plaque Stage

A Report from the Scandinavian Mycosis Fungoides Group

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Sixty-nine patients with mycosis fungoides, plaque stage, were treated in an open study with photochemotherapy (PUVA) or the combination of oral retinoids and PUVA (RePUVA). The response rate of RePUVA was equal to that of PUVA, with complete remission in 73% and 72%, respectively. Remissions were obtained with fewer PUVA sessions, and with a lower UVA dosage, if PUVA was combined with retinoids. A lower UVA dosage was needed if treatment was given four times weekly in stead of twice weekly. The duration of the remissions tended to be prolonged if retinoids were given as maintenance therapy. ***Key words: UVA dosage; Therapeutic response.***

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Photochemotherapy (PUVA) is a well established treatment for mycosis fungoides, effective in plaque stage as well as in limited tumour stage (1–8). In the more advanced tumour stage, PUVA can also be of value as a supplement to systemic chemotherapy (2).

The present study shows that in the treatment of mycosis fungoides, the combination of retinoids and PUVA (RePUVA) is in some respects superior to PUVA given alone.

MATERIAL AND METHODS

At four Scandinavian dermatological centres, 69 patients with erythematous plaque stage of mycosis fungoides were treated in an open study. PUVA alone was given to 47 patients and RePUVA to 22 patients. 38 were males and 31 females, with an age range of 21–82 years, median 68 years.

The diagnosis of mycosis fungoides was verified by histologic examination. No patients with tumours, lymph node involvement or other signs of extracutaneous disease were included.

PUVA

PUVA was given as 8-methoxypsoralen (8-MOP) orally in a dosage of 0.6–0.8 mg per kg body weight, 2 h before the exposure to long-wave ultraviolet light (UVA). PUVA was given twice or four times weekly.

The treatment was discontinued about 2 weeks after complete remission.

RePUVA

In patients treated with retinoids plus PUVA (RePUVA), retinoids were instituted 2 weeks before the start of PUVA treatment. PUVA was given 2 or 4 times per week. The retinoids were given in daily oral dosages. The initial dosage of etretinate (Tigason®) was 0.3–1 mg per kg body weight, and that of isotretinoin (Roaccutan®) 0.5–1.5 mg per kg body weight. The dosages were reduced according to mucosal and skin dryness.

PUVA treatment was discontinued about 2 weeks after complete remission. In 8 cases retinoid treatment was continued as maintenance. The complete remission was always verified by histologic examination.

Statistical analysis

Two-way analysis of variance, unequal groups, log transformation of data (9).

RESULTS

In this series all the patients responded with complete or partial remission (Table I). RePUVA induced com-