Childhood Onset Systemic Sclerosis: Classification, Clinical and Serologic Features, and Survival in Comparison with Adult Onset Disease

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ABSTRACT. ***Objective.*** To describe the differences between patients with systemic sclerosis (SSc) having childhood versus adult onset evaluated at a single medical center.

Methods. Patients were divided into those with childhood onset (first SSc symptom or finding before age 16 yrs) and those with early adult and late adult onset. The 3 groups were compared with respect to disease classification, clinical, laboratory and serologic data, and survival.

Results. One hundred eleven childhood onset SSc cases seen between 1960 and 2003 were compared with 2559 adult onset SSc cases (1087 with onset age 16–40 and 1472 with onset after age 40 yrs) first evaluated between 1972 and 2001. Age distribution at onset was unimodal, suggesting that childhood disease is part of the spectrum of adult onset SSc. A significantly greater proportion of childhood onset patients had overlap syndromes, most frequently with polymyositis-dermatomyositis (PM-DM), and skeletal muscle involvement. Children with diffuse cutaneous (dc) SSc had significantly lower maximum mean total skin thickness scores than adult patients with dcSSc. Renal involvement was uncommon in childhood onset cases, and the frequency increased with age of onset. Serum anti-PM-Scl and anti-U1RNP antibodies were detected significantly more frequently in childhood than in adult onset cases. In contrast, anti-RNA polymerase III and anticentromere antibodies were found significantly more frequently in adults. Survival was significantly better among childhood than all adult onset cases combined, but similar to survival in young adult onset SSc cases. Scleroderma heart disease was a frequent cause of death among children with SSc.

Conclusion. Patients with juvenile onset SSc more frequently have an overlap syndrome with PM-DM, higher frequency of skeletal muscle involvement, serum anti-PM-Scl and anti-U1RNP antibody, fatal cardiac disease, and improved survival compared with adult onset SSc cases. (First Release April 1 2006; J Rheumatol 2006;33:1004–13)

Key Indexing Terms:
SYSTEMIC SCLEROSIS CHILDHOOD AUTOANTIBODIES SCLERODERMA

Systemic sclerosis (SSc) is a generalized connective tissue disorder of unknown etiology. Clinically there is a broad spectrum of disease recognized as 2 major categories: widespread severe skin thickening (diffuse cutaneous involvement or dcSSc) and skin thickening limited to the distal extremities and face (limited cutaneous involvement or lcSSc)[1]. These 2 groups of patients typically have different clinical courses, from rapid progression of skin thickening and early vital organ involvement in dcSSc, to much slower evolution with essentially no change in skin thickening over time, but late systemic complications after years or decades, in lcSSc.

Childhood onset SSc is uncommon. Although many individual patient reports and several small series of cases have been published, it is uncertain how childhood onset SSc is similar to, or different from, that beginning in adulthood. The purpose of our study is to describe a large series of patients with childhood onset SSc and to compare them with patients with adult onset SSc evaluated during a similar time period at the same institution.

MATERIALS AND METHODS

The source of patients was the University of Pittsburgh Scleroderma Databank, a registry that includes initial and followup clinical and laboratory data and serum specimens on patients with SSc evaluated from 1959 to the

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present. We obtained information directly from patient interviews and examinations, referring physicians, and medical records on age, race, sex, date of onset of first symptom of disease, date of first physician diagnosis of SSc, organ system involvement, date of death and cause of death, if available. We made a concerted effort to obtain complete clinical and laboratory followup information on all patients in the study. Sixty-four of the 111 childhood onset patients were followed in our Scleroderma Clinic for a mean of 7.0 years after their initial visit. For the remainder, we used telephone calls to patients and physicians and biannual patient questionnaires. Accountability for all SSc patients is 90%.

Diagnosis and disease classification. The diagnosis of SSc was based on clinical and laboratory findings and confirmed by one of the authors (TAM or VDS). Patients were classified as having childhood onset (first symptom attributable to SSc before age 16 yrs) or adult onset disease (first SSc symptom at age 16 or thereafter). Adult onset patients were divided into younger adults (first SSc symptom before age 40 yrs) and older adults (first SSc symptom after age 40 yrs). Age 40 was chosen to separate these 2 groups because it is close to the median age of onset for all scleroderma databank patients (age 42 yrs).

Patients were classified into 3 disease subtypes, i.e., diffuse cutaneous (dc), limited cutaneous (lc), or overlap syndrome. Patients were considered to have dcSSc if they had, at any time, skin thickening involving the upper arms, thighs, anterior chest, or abdomen. For lcSSc classification, skin involvement was restricted to the distal portions of the extremities (distal to the elbows and/or knees) and/or the face, but not affecting the proximal extremities or trunk at any time in the disease course. Patients with Raynaud's phenomenon (RP), a positive antinuclear antibody (ANA) test, and at least one typical visceral involvement of SSc [gastrointestinal (GI) tract, lung, heart, or kidney] without evidence of skin thickening were included in a SSc sine scleroderma (ssSSc) subset of lcSSc. Patients satisfying only the criteria for early SSc proposed by LeRoy and Medsger[2] were excluded.

Cases of SSc in "overlap" with rheumatoid arthritis (RA), polymyositis-dermatomyositis (PM-DM), or systemic lupus erythematosus (SLE) were included. Overlap with PM-DM required satisfying the Bohan and Peter diagnostic criteria for probable or definite PM-DM[3]. For SLE and RA we used the American College of Rheumatology (ACR; previously American Rheumatism Association) classification criteria for probable or definite SLE[4] or RA[5]. Patients referred to us with the diagnosis of mixed connective tissue disease (MCTD) were not excluded. The minimum SSc requirements for overlap were either sclerodactyly or RP plus one or more of the typical visceral involvements of SSc, such as distal esophageal hypomotility, pulmonary fibrosis, pulmonary arterial hypertension, cardiomyopathy, or "scleroderma renal crisis." These involvements are defined in detail below. Thus a patient with PM-DM, SLE, or RA with only RP and a positive anticentromere antibody (ACA) test was not considered to have overlap with SSc. Overlap patients were classified as having either lc or dc involvement as defined above.

Organ system involvement. Organ system involvement was counted as present if it occurred at any time during the course of SSc.

Peripheral vascular disease required a history of RP, digital tip pitting scars, or digital tip ulcers. Skin involvement was determined using the modified Rodnan method[6]. When this examination was completed, the total skin thickness score was recorded and any score > 0 was considered abnormal. Articular involvement was defined as swelling of one or more joints, tenosynovitis (including carpal tunnel syndrome or palpable tendon friction rubs), or finger joint contractures. Skeletal muscle involvement required proximal muscle weakness on physical examination and any one of the following: muscle biopsy showing myositis, electromyogram showing a myopathic pattern, or elevated serum enzymes reflecting muscle disease. GI tract disease was defined as any one of the following: distal esophageal hypomotility or aperistalsis (documented by either cine-radiographic or manometric study), typical small bowel radiographic changes, or colonic sacculations characteristic of scleroderma. Lung involvement was diagnosed by any one of the following: bilateral basilar interstitial fibrosis on chest radiograph or high resolution computed tomography scan; restrictive lung disease (forced vital capacity < 70% predicted and forced expiratory volume in 1 second divided by forced vital capacity > 80% predicted); pleuritis with pleural pain and either a pleural friction rub or pleural effusion; diffusion capacity for carbon monoxide (DLCO) < 70% of predicted normal; or pulmonary arterial hypertension documented by either echocardiogram or right-heart catheterization. Heart disease was characterized by any of the following: symptomatic pericarditis (pericardial pain plus at least one of pericardial friction rub, electrocardiographic or echocardiographic evidence of pericarditis); left-side congestive heart failure; or nodal or ventricular arrhythmia. We defined kidney involvement as rapidly progressive renal failure (renal crisis).

Serologic studies. Serum specimens were obtained at the time of the first Pittsburgh evaluation. Banked sera were stored at –80°C. Antibodies were determined, as described, by protein immunoprecipitation[7] (anti-RNA polymerase III and anti-Ku); RNA immunoprecipitation[8] (anti-Th/To); both protein and RNA immunoprecipitation (anti-aminoacyl tRNA synthetases, anti-U1RNP, -U2RNP and -U3RNP); and indirect immunofluorescence of a 1/40 dilution of patient sera on HEp-2 substrate[8] (ACA). Antitopoisomerase I, anti-PM-Scl, -U1RNP and -Jo-1 were confirmed by immunodiffusion[9]. These tests were performed on all available childhood onset SSc sera. For comparison, we chose an adult SSc group that was a 100% sample of SSc patients first evaluated between 1986 and 1988, and which included 117 younger adult onset and 130 older adult onset patients.

Statistical methods. The chi-square test or Fisher's exact test was used for differences between proportions, Student's t test for comparison of mean values, and life-table methods for cumulative survival rates, with comparisons using log-rank (Mantel-Haenszel) tests.

RESULTS

We excluded 6 childhood onset patients who did not satisfy entry criteria. These patients would have met the expanded criteria for SSc proposed by LeRoy and Medsger[2] since they had both RP and SSc-associated serum autoantibodies. These children had not, at the time of their last followup evaluation, developed either sclerodactyly or any internal organ involvement typical of SSc.

The final study group included 111 childhood onset SSc cases with the first Pittsburgh visit between 1960 and 2003. Twenty-eight cases with onset prior to 1972 were included. Since adult data are incomplete prior to 1972, we used the 2559 adult onset patients evaluated during the 30-year period 1972–2001 for comparison. The latter were divided into 2 groups with onset age 16–40 years (younger onset, n = 1087) and onset after age 40 years (older onset, n = 1472).

Eighty-eight (79%) of the 111 childhood onset patients satisfied ACR preliminary criteria for classification as definite SSc[10]. This proportion is similar to that reported in several other studies of patients with adult SSc[11,12]. The 23 childhood onset SSc patients not satisfying these preliminary criteria had either lcSSc or ssSSc.

Patients were referred to Pittsburgh both from our geographic area and from a distance. The proportion of patients residing within 100 miles of Pittsburgh was 40% for childhood onset and 47% for adult onset SSc (nonsignificant). Some childhood onset cases were referred because we advertised in the National Registry for Childhood Onset Scleroderma during the period 1998–2001.

Demographic and disease classification. Table 1 shows the demographic and disease classification distribution of the

Table 1. Demographic features, clinical subtype distribution, and disease duration in patients with childhood, younger adult, and older adult onset SSc.

Variable	A Childhood Onset, n = 111	B Adult Onset Age 16–40 yrs, n = 1087	C Adult Onset Age 40+ yrs, n = 1472	Significance A vs B + C
Sex and race				
Female, n (%)	92 (83)	905 (83)	1152 (78)	NS
Caucasian, n (%)*	102 (92)	961 (89)	1353 (92)	NS
Clinical subtype**, n (%)				
Diffuse cutaneous	39 (35)	406 (37)	743 (50)	p = 0.0001
Limited cutaneous	40 (36)	555 (51)	634 (43)	
Overlap syndrome	32 (29)	124 (12)	95 (7)	
Overlap diffuse	10 (32)	37 (30)	22 (23)	NS
Overlap limited	22 (68)	87 (70)	73 (77)	
Disease duration				
Onset to diagnosis (median yrs)				
All patients	2.8	2.1	1.1	p = 0.0214
Diffuse (no overlaps)	1.4	0.9	0.7	p = 0.0001
Limited (no overlaps)	12.8	7.9	3.2	p = 0.0244
Overlap	0.9	1.6	1.1	NS
Onset to last followup (median yrs)	17.2	15.9	9.5	NS

* 10 adult onset patients lacked information on ethnicity (7 younger, 3 older). ** 2 younger adult onset patients were unclassified at time of last visit. NS: nonsignificant.

childhood and combined adult SSc patient groups. The proportions of females and of Caucasians in the 2 groups were similar. The female to male ratio was also similar, about 4:1 in both groups. There was no significant difference in sex ratio between prepubertal and postpubertal childhood onset cases using age 11 years as a cutoff (data not shown).

There was a significantly higher proportion of overlap patients in the childhood onset group (29% vs 9%; $p < 0.0001$). The frequency of overlap decreased as the age of onset increased (29% in children vs 12% in younger adults and 7% in older adults). In the overlap group, the proportions of dc and lc were similar in adult and pediatric cohorts. The distribution of CTD found in overlap in childhood onset SSc was 23 PM-DM (17 DM), 3 SLE, one RA, and 5 combinations of these diseases. Among adult onset cases, the frequency of DM declined. Overlap with SLE was most often encountered in the younger adult onset SSc group.

Among all childhood onset SSc patients, there were 5 (5%) that we classified as ssSSc. They had onset of RP at ages 11, 12, 15, 15, and 15 years and the diagnosis of SSc was made at ages 26, 16, 16, 27, and 62, respectively. Three were serum anti-U1RNP antibody-positive and one each had ACA and anti-RNA polymerase III antibody. Four had esophageal dysmotility, 3 had interstitial lung disease, and one subsequently developed renal crisis. Similarly, 84 (3%) adult onset patients had ssSSc. With longer duration of followup, it is possible that some of these childhood and adult ssSSc patients will develop lc skin changes. There were 3 patients with unusual childhood onset dcSSc, who had onset of RP during adolescence and developed diffuse skin changes 26, 35, and 37 years later.

As noted at the bottom of Table 1, the median duration of disease from onset to first physician diagnosis of SSc was 2.8 years for childhood onset and 1.5 years for adult onset patients ($p = 0.0214$). For both lc and dc patients, the first physician diagnosis of SSc was significantly delayed in children. The mean followup duration after the first Pittsburgh visit was 6.8 years for childhood onset and 6.4 years for adult onset patients (nonsignificant).

The number of patients according to age at disease onset increased steadily throughout childhood (4 < age 5; 28 age 5–9; and 79 age 10–16 yrs). Childhood onset patients made up 4.2% of all 2670 SSc cases combined. The frequency continued to increase with age in younger adults, reaching a broad peak at age 35–49 years.

Organ system involvement. Individual organ system involvement was similar among the 3 patient groups, as shown in Figure 1. There were significant differences in the degree and extent of skin thickening between the 2 groups with dc involvement who were examined within the first 3 years after skin thickness began. The mean first-visit total skin thickness score in adult onset dcSSc cases combined (n = 859) was 25.7, while in the 21 childhood onset dcSSc patients who were examined before age 16 years, the mean skin score was significantly lower (19.4; $p = 0.016$). Differences in disease duration at the time of skin evaluation did not explain the lower skin scores in children (data not shown).

Virtually all patients had RP or other evidence of SSc-relat-

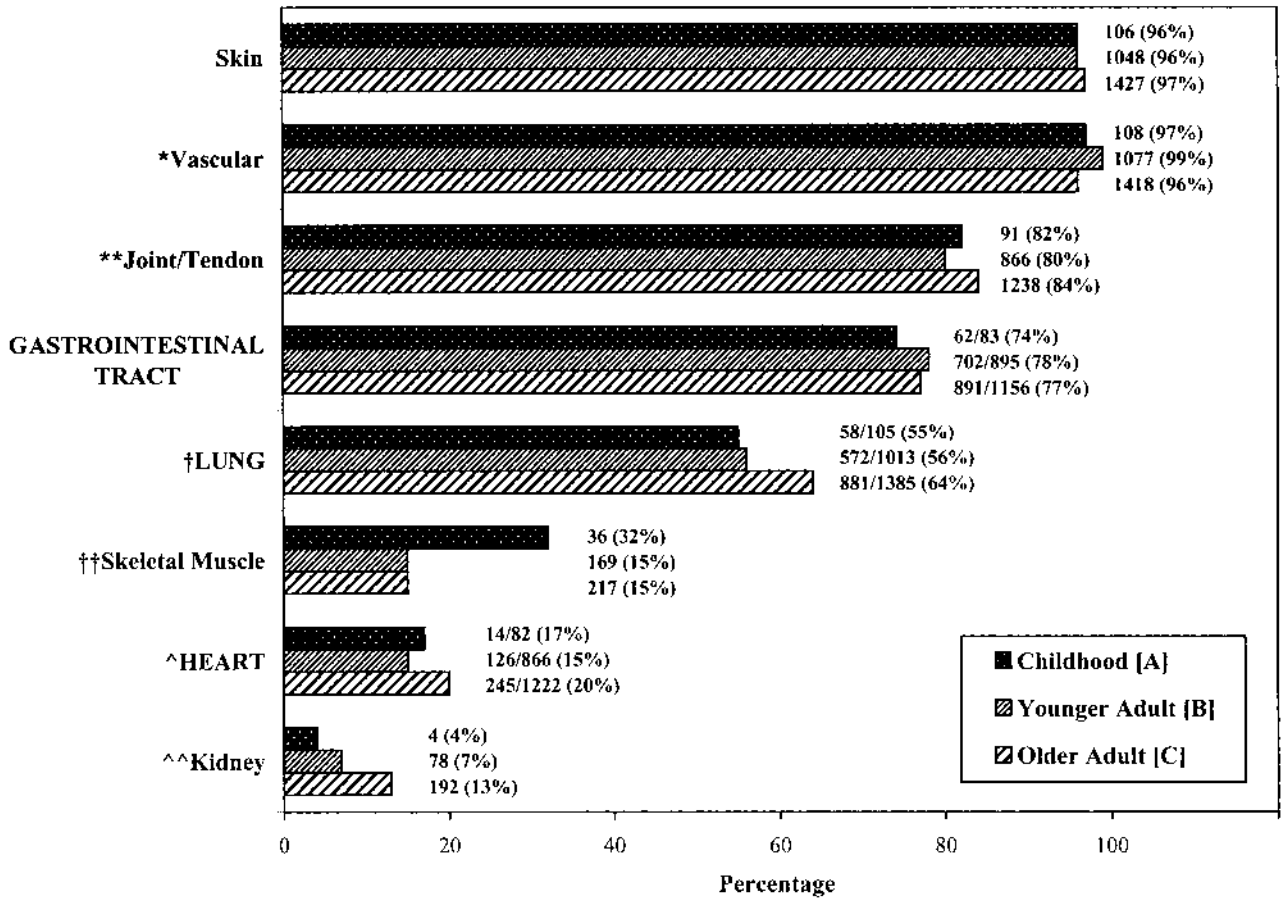

Figure 1. Organ system involvement during the course of SSc by age at onset group. Capital letters: Denominator is the number of patients who had objective testing performed. Significant differences between age at onset groups: *B vs C, $p < 0.0002$; **B vs C, $p < 0.005$; †B vs C, $p < 0005$; ††A vs B, $p < 0.0002$; A vs C, $p < 0.0002$; ^B vs C, $p < 0.002$; ^^A vs C, $p < 0.006$; B vs C, $p < 0.0002$.

ed peripheral vascular disease. Skeletal muscle involvement occurred more than twice as often in the childhood onset group (32%) compared to both adult onset groups (15% and 15%, respectively; $p = 0.0001$). This result is consistent with the increased proportion of childhood onset patients classified as having SSc and PM-DM in overlap. GI tract involvement was frequent and comparable in all 3 patient groups among the patients adequately studied. Severe pulmonary fibrosis (forced vital capacity < 50% predicted) was noted in 10 children. "Intrinsic" (independent of pulmonary fibrosis) pulmonary arterial hypertension was diagnosed in 4 childhood onset patients at ages 10, 19, 28, and 34 years; all with this complication died. Heart involvement was infrequent (15%–20%) and did not differ by age group. Scleroderma renal crisis occurred in 4 childhood onset cases (4%) at ages 8, 10, 34, and 64 years. The proportion with renal crisis was not significantly different in childhood versus young adult onset SSc (4% vs 7%; $p = 0.22$), but was significantly lower in childhood onset than in older adult onset patients (4% vs 13%; $p < 0.0001$).

Autoantibody profiles. Table 2 shows the serum autoantibody results in the 3 SSc age at onset groups. Overall, 102 of the 111 childhood onset patients had serum available for ANA testing and the result was positive in 99 (97%). In the combined 247 adult onset sera tested, 245 (99%) had a positive ANA test, which was comparable to patients with childhood onset SSc.

Antitopoisomerase I antibody was the most frequent autoantibody among childhood onset SSc patients and remained equally frequent in adult onset cases. Childhood onset SSc patients had a significantly higher frequency of anti-U1RNP (16% vs 7% in adults; $p < 0.0001$) and anti-PM-Scl (14% vs 3%; $p < 0.0001$) antibodies compared with all adult onset patients combined (Table 2). In each of these instances, the frequency of the autoantibody declined in older adult patients. In contrast, anti-RNA polymerase III (4% vs 25%; $p < 0.0001$) and ACA (8% vs 21%; $p < 0.0001$) were detected significantly less often in childhood onset SSc than in adult onset SSc patients. The anti-RNA polymerase III antibody frequency increased further in the older adult group. A higher proportion of childhood (20%) than adult (11%; $p = 0.0384$) onset patients were ANA-positive but had none of the 8 specific reactivities.

Survival and causes of death. Figure 2 shows survival curves

Table 2. Comparison of autoantibody frequencies using age at symptom onset versus age at diagnosis to define childhood, younger adult, and older adult SSc.

Autoantibody	A Stratified by Age at	B Childhood, n = 102 (%) n = 57 (%)	C Younger Adult*, n = 117 (%) n = 111 (%)	Older Adult*, n = 130 (%) n = 181 (%)	Significant 2-Group Comparisons, p
One autoantibody					
Anti-RNA polymerase III	Symptom onset	4 (4)	19 (16)	42 (32)	A vs B: 0.003 A vs C: < 0.001 B vs C: 0.019
	Diagnosis	1 (2)	14 (13)	50 (28)	A vs B: 0.002 A vs C: < 0.001 B vs C: 0.003
Anticentromere	Symptom onset	8 (8)	27 (23)	25 (19)	A vs B: 0.002 A vs C: 0.014
	Diagnosis	0 (0)	19 (17)	41 (23)	A vs B: < 0.001 A vs C: < 0.001
Antitopoisomerase I	Symptom onset	20 (20)	27 (23)	27 (21)	NS
	Diagnosis	13 (23)	27 (24)	34 (19)	NS
Anti-U1RNP	Symptom onset	16 (16)	13 (11)	5 (4)	A vs C: 0.005
	Diagnosis	10 (18)	19 (17)	5 (3)	A vs C: < 0.001 B vs C: < 0.001
Anti-Th/To	Symptom onset	3 (3)	5 (4)	4 (3)	NS
	Diagnosis	0 (0)	4 (4)	8 (4)	NS
Anti-U3RNP	Symptom onset	5 (5)	4 (3)	2 (1.5)	NS
	Diagnosis	5 (9)	3 (3)	3 (2)	A vs C: 0.021
Anti-PM-Scl	Symptom onset	14 (14)	1 (1)	6 (5)	A vs B: < 0.001 A vs C: 0.018
	Diagnosis	13 (23)	1 (1)	7 (4)	A vs B: < 0.001 A vs C: < 0.001
Anti-Ku	Symptom onset	0 (0)	1 (1)	1 (1)	NS
	Diagnosis	0 (0)	0 (0)	2 (1)	NS
More than one autoantibody	Symptom onset	8 (8)	7 (5)	2 (1.5)	A vs C: 0.024 B vs C: 0.043
	Diagnosis	4 (7)	8 (4)	5 (2)	NS
None of the SSc-related autoantibodies					
ANA positive	Symptom onset	21 (20)	13 (14)	14 (11)	A vs B: 0.053 A vs C: 0.038
	Diagnosis	9 (14)	16 (13)	23 (12)	NS
ANA negative	Symptom onset	3 (3)	0 (0)	2 (1.5)	NS
	Diagnosis	2 (4)	0 (0)	3 (1)	NS

* All patients evaluated January 1, 1986, through December 31, 1988. NS: nonsignificant.

for the 3 groups of patients from the time of first physician diagnosis of SSc. The cumulative survival rate (CSR) for childhood onset SSc was virtually identical to the CSR for younger adult onset SSc patients at 5 and 10 years after the first physician diagnosis of SSc. However, after 10 years of followup, younger adult onset patients who were age 16–40 at onset of SSc had a somewhat worse prognosis, most likely because many were over age 50 by that time and had acquired other potentially fatal primary or comorbid conditions such as atherosclerotic heart disease and cancer.

Survival in childhood onset SSc was significantly better than in older adult onset SSc ($p < 0.0001$), as expected. The CSR at 5, 10, 15, and 20 years after first physician diagnosis of SSc were as follows: childhood onset 89%, 80%, 74%, and 69%; younger adult onset 85%, 79%, 67%, and 52%; and older adult onset 75%, 55%, 35%, and 20%. When survival was examined separately by SSc classification subset, a similar pattern was noted for both dcSSc and lcSSc patients (no significant difference between childhood onset and younger adult onset).

There were 32 deaths among the University of Pittsburgh childhood onset SSc patients, 17 known to be CTD related. When we compared the causes of death in childhood versus younger and older adult onset groups, childhood onset SSc patients had a higher frequency of deaths due to SSc-associated heart disease than both younger and older adult onset groups (15% vs 9% vs 7%, respectively). The frequency of CTD-related renal death increased with increasing age at SSc onset (4% vs 7% vs 11%). Overall, the proportion of CTD-related deaths among all deaths decreased with increasing age

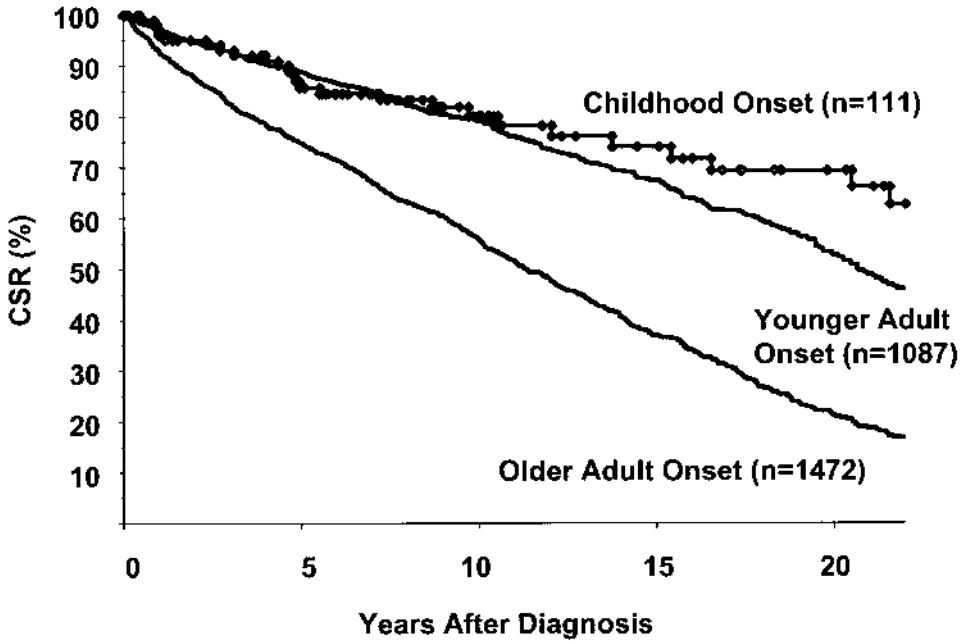

Figure 2. Cumulative survival rate (CSR) from first physician diagnosis in SSc groups by age at onset.

at onset (63% vs 60% vs 55%), as would be expected with the increase in non-CTD competing causes of death in older patients.

Results in patients diagnosed before age 16 years. This series differs from others in the literature because it includes patients with disease onset during childhood whose SSc diagnosis was initially made after age 16. In order to compare our patients more accurately with previously reported patients, we separated the 62 Pittsburgh patients whose SSc was diagnosed before age 16 years and compared them with the 2608 adult-diagnosed SSc patients (2559 plus 49 childhood onset patients diagnosed after age 16). In this analysis, there were no differences in the findings or conclusions compared to those shown in Table 1 and Figure 1. The distribution of patients by disease classification was similar. The age distribution at diagnosis showed a somewhat broader peak, with no SSc diagnosis before age 5 and 60% of all patients diagnosed between ages 35 and 59. The mean maximum skin score conclusions were unchanged. The proportions of patients with internal organ involvement were similar when childhood diagnosis at age < 16 years was substituted for the childhood SSc subset.

There were several differences in serum autoantibody distribution, which are summarized in the shaded areas of Table 2. No SSc patient diagnosed in childhood had either ACA or anti-Th/To antibody, consistent with the typical prolonged duration of symptoms prior to establishment of the diagnosis of SSc in adult patients with these autoantibodies[8]. Only one childhood-diagnosed SSc patient had anti-RNA polymerase III antibody. Anti-U3RNP antibody was significantly more frequent in childhood than in older adult-diagnosed SSc, which was not evident when age at onset was used for analysis.

Conclusions regarding survival for childhood versus adult-diagnosed SSc also were unchanged. The CSR for childhood and younger adult-diagnosed SSc at 5 years were 91% and 91%, respectively; at 10 years 88% and 82%; at 15 years 88% and 73%; and at 20 years 84% and 59%.

DISCUSSION

Occurrence of childhood onset SSc in published case series. Our impression from the literature is that SSc beginning in childhood is rare[13,14]. Only one juvenile patient, age 11 years at diagnosis, was encountered among 86 cases in a US community-wide retrospective hospital survey between 1947 and 1968[15]. Eleven of 727 (1.5%) patients with SSc seen at the Mayo Clinic, Rochester, Minnesota, had onset before age 10 years and an additional 53 (7.2%) became symptomatic during the second decade[16]. A very small proportion of cases with onset before age 20 was reported from Australia (2 of 60; 3.3%)[17]. A similar percentage (2% of children in a large SSc series) was reported from Poland[18]. In contrast, a report of 78 SSc patients from South India included 9 (11.5%) with diagnosis under age 16 years[19]. In our total cohort of 2670 patients with SSc, we encountered 111 (4.2%) whose SSc disease onset occurred prior to the age of 16. The frequency by onset age continued to increase steadily, reaching a peak containing 37.4% of patients between ages 35 and 49 years and declining in the elderly. This distribution suggests that childhood and adult onset SSc form a single spectrum of disease.

Age-specific incidence. The reported annual incidence of SSc under age 15 years in Tennessee was significantly lower than that for all other ages ($p < 0.001$)[15]. In Finland, the annual incidence of childhood onset SSc between 1983 and 1986 was

0.05 cases per 100,000 population, although in that study patients with MCTD were reported separately[20]. MCTD patients often have features of SSc, and some may have qualified as "overlap" patients by our definitions.

Review of literature cases. Although a number of individual patients with childhood onset SSc have been reported, series of cases have been small and infrequent. Several of these publications include patients with localized forms of scleroderma, such as morphea and linear scleroderma, that have no clinical features in common with SSc. To summarize the literature, we chose 6 publications with a minimum of 5 SSc cases containing adequate clinical information to determine organ system involvement and patient outcome (Table 3)[13,21-25]. Fifty-two patients were included in these 6 studies (42 female, 10 male). Age at onset ranged from 3 to 15.5 years (median 5–14 yrs). Inadequate information was provided on ethnicity. The proportion of patients with dc and lc involvement could not be precisely determined, but where an adequate description was given, 11 of 12 patients had dcSSc. For all 52 reported childhood onset SSc cases combined, most organ system involvement proportions were similar to those noted in our patients (Figure 1), the exceptions being lower frequencies of peripheral vascular and joint/tendon findings in the literature cases.

Recently, Foeldvari, *et al* completed a multinational survey on 135 patients with juvenile SSc[26]. The presence of organ system involvement was based on the clinical judgment of the participating physician rather than on standardized definitions. Thus, direct comparison of Foeldvari's patients with our own is not possible. Nevertheless, the proportions of patients in the Foeldvari report with GI tract (65%), pulmonary (50%), and renal (13%) disease were similar to our results summarized in Figure 1. In contrast, heart disease was found to be much more common in children in the multinational survey (44%). This finding is in keeping with other suggestions in the literature about an increased prevalence of cardiac involvement in juvenile onset SSc[14,21].

Serologic studies have been performed with increasing frequency during recent years. Two series of SSc cases with inadequate clinical information on organ system involvement (not included in Table 3) had detailed serologic data[27,28]. Overall, 9 reports, a total of 201 patients with childhood onset SSc, provided serologic results[13,21-25,27-29]. Only 149 (74%) of these patients were ANA-positive, much lower than the 95% typically reported in adult onset SSc[1] and the 97% in our childhood onset series. This lower proportion could, in part, result from the substrates utilized, as some laboratories may have used animal tissues instead of HEp-2 cells. Among the 149 ANA-positive patients, only 4 distinct antibody specificities were identified: 42 (28%) patients had antitopoisomerase I antibody, 8 (5%) had ACA, 3 (2%) had anti-U1RNP antibody alone, and one each had anti-Ro and anti-ssDNA antibody. Incomplete serologic testing could account for this relatively small proportion of patients with SSc-associated ANA specificities detected. In our childhood series, similar proportions of patients were antitopoisomerase I (20%) and ACA (8%) positive, but the overall ANA positivity rate was 99%. In adult onset SSc, the presence of SSc-related serum autoantibodies assists in determining clinical subtypes and predicting prognosis[1,30]. In our study, a higher proportion of childhood onset patients were ANA-positive but did not have any of the

Table 3. Demographic and clinical findings in 52 patients with childhood onset SSc from 6 case series.

Series	No. of Patients	Age at Onset, yrs (range)	Race/Sex	Clinical Findings PV	S	C	J/T	M	GI	L	H	K	No. and Causes of Death
Kass[13]	7	Median 5 (5–15)	3 WF 1 BF 3 WM	5	7 dc	NI	6	NI	5	2	3	2	2 heart, 1 PAH
Cassidy[21]	15	Mode = 10–12 (3–15)	15 F	11	NI	4	0	6	11	11	4	0	2 heart, 1 CNS
Suarez-Almazor[22]	5	Median 10 (8–10)	4 F 1 M	5	4 dc 1 lc	1	5	3	2	2	2	0	1 PAH
Lababidi[23]	5	Median 10 (4–13)	4 F 1 M	5	NI	NI	5	1	2	2	0	0	0
Garty[24]	13	Median 6 (4–14)	7 WF 4 WM 2 BF	9	NI	NI	7	2	10	12	4	0	1 heart, 1 PAH
Martinez-Cordero[25]	7	Median 14 (5.5–16)	6 F 1 M	5	NI	1	5	2	7	7	0	0	0
Total	52 100 %	Median 5–14 (3–16)	42 F 10 M	40 77%	11 dc I lc	6	28 54%	14 31 %	37 71%	36 69%	13 25%	2 4%	9 deaths: 5 heart, 3 PAH, 1 CNS

PV: peripheral vascular; S: skin; C: calcinosis; J/T: joint/tendon; M: muscle; GI: gastrointestinal tract; L: lung; H: heart; K: kidney; NI: no information; PAH: pulmonary arterial hypertension; CNS: central nervous system; W: white; B: Black; F: female; M: male; dc: diffuse cutaneous disease; lc: limited cutaneous disease.

defined ANA specificities (22% vs 11% in both younger and older adults). It is likely that in the future other ANA specificities will be identified in serum from these patients.

At the time of the literature publications cited, 9 (17%) of the 52 childhood onset patients had died (Table 3). Although followup after disease onset is not specifically recorded in all of these reports, we calculated that followup duration ranged from 0.3 to 14 years in 4 studies, and that the mean followup varied from 3.4 to 6.4 years. The rough 5-year survival for these reported childhood onset SSc patients was 94%, as 6 of 9 deaths occurred 5 or more years after disease onset. We added our 17 childhood onset SSc deaths of known cause to those reported in the literature (combined total 26) and compared them with our Pittsburgh adult onset deaths (n = 491). There was a significant increase in the proportion of deaths due to SSc-associated heart disease and a significant reduction in the proportion of deaths due to renal crisis in childhood onset SSc patients (data from Table 3 for childhood onset patients). It is not possible to compare this survival rate more precisely with that of adults, since the proportion of childhood onset patients with dc versus lc involvement could not be ascertained. Cardiac and pulmonary disease were the most frequently listed causes of death (Table 3), and only one of the children died from renal crisis. A similar 4-year survival rate of 95% was reported by Foeldvari, *et al*[26]. In that series, cardiac causes of death were the most common (5 of 8 patients), and 7 of the 8 deaths occurred less than 5 years after disease onset.

Other observations. There was a significant delay in the diagnosis of SSc in all childhood onset compared with all adult onset patients (Table 1). This difference was found in lc and dc SSc patients but not in those with overlap. Possible explanations include the failure of children to notice or communicate, or parents and community pediatricians to appreciate, the significance of RP, subtle skin changes, dyspnea, and esophageal symptoms. Further, pediatricians may not understand the significance of ANA testing and ANA specificities in this group of patients.

Although childhood is routinely defined in the pediatric literature as up to age 16 years, "adolescence" more properly begins at the time of menarche in girls. To determine whether SSc patients with onset during adolescence had characteristics different from children younger than 13 years, we divided our childhood cases into those younger than 13 at onset (n = 67) and age 13–16 at onset (n = 44). There were no significant demographic, clinical, or individual serum autoantibody differences between these 2 groups.

In our group of 111 childhood onset SSc patients, we found a female to male ratio of 4:1, comparable to adult onset patients (Table 1). The frequency of renal crisis paralleled the frequency of anti-RNA polymerase III antibody, significantly increasing with age (Table 2). Similarly, the frequency of SSc in overlap and the frequency of muscle involvement paralleled the frequency of both anti-PM-Scl and anti-U1RNP antibodies. These frequencies both decreased significantly with age (Table 2). ACA also increased significantly with age (Table 2), but the number of patients with childhood onset ACA-positive intrinsic pulmonary arterial hypertension was few (data not shown), and no significant association of ACA with this complication was found.

When adult onset SSc cases were separated into groups of younger and older age at onset, peripheral vascular, joint/tendon, pulmonary, and cardiac involvements were similar in frequency in childhood and the younger adult onset groups, but significantly different (decreased) for joint/tendon, pulmonary, and cardiac disease in childhood versus older adult patients. It is possible that SSc is overestimated as a cause of organ system involvement in older patients where other chronic diseases contribute to morbidity and mortality.

In our experience, 2 other observations tend to distinguish childhood onset from adult onset SSc. First, childhood onset patients who survive to adulthood tend to have shortened middle and distal phalanges and tapered fingers with loss of digital pads (Figure 3). This finding could be the result of growth retardation secondary to chronic digital ischemia. Second, patients with childhood onset dcSSc have significantly lower total skin thickness scores at the time of first evaluation. A limitation concerning this comparison is that the Rodnan skin scoring system has not been validated in children. Late in their course, 10–30 years after onset, children with dcSSc have remarkably thin skin, particularly over the proximal extremities and trunk, such that subcutaneous veins are often visible and prominent. More subtle skin thickness at onset could contribute to the delay in diagnosis of SSc among children.

In our cohort, the causes of death among patients with childhood onset SSc were compared with those in adult onset cases. CTD-related heart disease was a more frequent cause of death in children with SSc than in either younger or older adult onset patients (15%, 9%, and 7%, respectively), in accord with reported series (Table 3) and others' experience[26]. Nine of our 14 patients with childhood onset SSc with heart disease also had skeletal muscle involvement, and 8 of these patients died from their cardiac disease. The association of skeletal and cardiac muscle disease with poor prognosis is recognized in patients with adult SSc[31] and has also been reported in children with SSc[32]. Conversely, fatal renal disease was more common in older adult onset SSc patients.

Separation of adults into younger and older onset groups for comparison with children has not been reported previously in the connective tissue diseases. In our study, there was no significant difference in cumulative survival rate between childhood and young adult onset SSc patients. Rather, the survival difference between childhood and adult onset patients was attributable to reduced survival among older adult onset patients. The effect of age on survival needs to be taken into consideration, as other age-related, non-CTD illnesses, especially malignancy and degenerative vascular and metabolic diseases, may reduce survival in older patients.

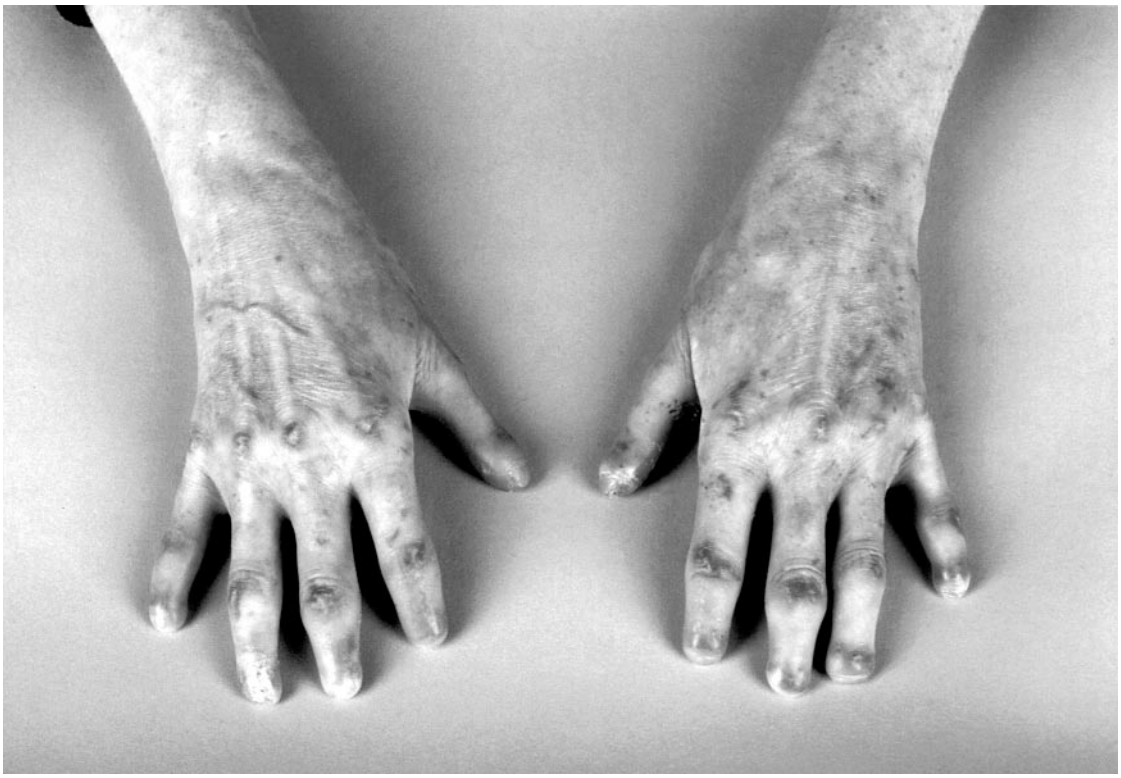

Figure 3. Hands of a 33-year-old woman who developed SSc with diffuse skin changes at age 8 years. The fingers are short and tapered, particularly the middle and distal phalanges, with loss of soft tissue pads.

To address secular trends, i.e., whether changes occurred over the 4 decades of patient accrual that might have influenced the results, we examined both childhood and adult onset SSc patients first evaluated during the earlier (through 1987) compared to later (1988 and after) years of the study. For this purpose, we used patients residing within 100 miles of Pittsburgh to minimize referral bias. There were no significant differences in demographic or clinical features or 10-year survival between the pre-1988 and 1988+ cases. Similarly, we compared the serum autoantibody profile between earlier (1962–91) and later (1992–2003) patients with childhood onset SSc, and found no significant differences.

With regard to late morbidity due to SSc and quality of life in childhood onset SSc, we do not have adequate followup data at this time. In the future it will be important to study the Health Assessment Questionnaire and other measures of quality of life and to determine fertility and pregnancy outcomes in women, as well as occupational and wage earning limitations, in childhood onset SSc.

In summary, children with disease onset under age 16 years contribute less than 5% of all SSc cases. However, SSc appears to be a single spectrum of disease including childhood and adult onset patients. First physician-diagnosis of SSc was delayed in children compared to adults. Children with dcSSc had a lower mean maximum skin thickness score than adult patients with dcSSc, thin skin late in the disease course, and shortened, tapered fingers.

Compared with adult onset SSc, childhood onset patients have increased frequencies of overlap with other connective tissue diseases, particularly myositis. SSc-associated serum autoantibodies were found in nearly 80% of childhood onset patients. Anti-PM-Scl and anti-U1RNP antibodies correlated with classification as myositis overlap and with skeletal muscle involvement. Renal disease is unusual in childhood onset SSc, paralleling the frequency of serum anti-RNA polymerase III antibody. Cardiac involvement as a cause of death is more frequent in childhood onset SSc.

Younger adults with SSc are a more appropriate comparison group for childhood onset disease, particularly for survival. Cumulative survival at 5 and 10 years was found to be similar between childhood and younger adult onset patients with SSc, and was significantly better than in older adult SSc patients. Overall, the prognosis when SSc is diagnosed during childhood is good, with 10 and 20-year cumulative survival rates from first physician-diagnosis of 88% and 84%, respectively.

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