Systemic Manifestations in Localized Scleroderma

Francesco Zulian, MD

Address
Pediatric Rheumatology Unit, Department of Pediatrics, University of Padua, Via Giustiniani 3, 35128 Padova, Italy.
E-mail: zulian@pediatria.unipd.it

Current Rheumatology Reports 2004, **6:**417–424
Current Science Inc. ISSN 1523-3774

In this paper, the various systemic manifestations reported in localized scleroderma, their incidence, their relationship with systemic sclerosis, and their relationship with other autoimmune or connective tissue diseases will be analyzed.

Introduction

The word scleroderma means "hard skin," but the diseases grouped under this term mean a great deal more. However, hardening of the skin is a feature that is most common to all types of the disorder and is the most prominent characteristic of these entities. In clinical practice, two distinct categories are considered: systemic sclerosis (SSc) and localized scleroderma (LS).

Systemic sclerosis is a chronic multisystem connective tissue disease characterized by sclerodermatous skin changes and widespread abnormalities of the viscera. LS is for the most part benign and self-limited with manifestations confined to the skin and subdermal tissues.

Table 1 summarizes the main distinctive features of SSc and LS in children. As shown, the prevalent internal organ involvement and the higher prevalence of autoantibodies are the main features of SSc in children [1–4].

Nevertheless, the relation of LS to SSc is still controversial. For years the clinical and laboratory features of LS have suggested that this condition is not always a purely cutaneous disease. This paper focuses on the systemic manifestations of LS reported in the literature with particular emphasis on the involvement of internal organs in LS, clinical relationship between LS and SSc (association of or transition from LS to SSc), and association of LS with other connective tissue diseases.

Internal Organ Involvement in Localized Scleroderma

General aspects

One of the first reports on internal organ involvement in LS was published in 1984 by Lunderschmidt *et al*. [5]. They found signs of internal organ involvement in 12 of 44 patients (27.3%) with LS. Generalized morphea showed a high rate of organ involvement (two of two patients), in linear and in disseminated subtypes this rate was lower (34% and 14%, respectively). In particular esophageal abnormalities, detected by scintigraphy, manometry, or x-ray, were found in 23% of the patients and mainly in the linear subtype. They consisted essentially in decreased acid clearance associated with manometric alterations in just one patient. Respiratory function abnormalities were reported in six patients (14%): Diffusing lung capacity carbon monoxide (DLCO) was reduced in five patients, two had signs of interstitial lung disease at chest x-ray, and in four there were concomitant esophageal alterations. The degree of systemic involvement was correlated with the type of morphea (generalized > linear > disseminated) and the degree of systemic inflammation. However, the reported findings were generally mild and incomparable, as prevalence and as clinical expression, with those usually present in SSc.

Ten years later, a systematic search for internal organ involvement was conducted by Dehen *et al*. [6••] who studied 76 consecutive patients, adult and children, with LS. They found evidence of visceral involvement in 16 patients (21%). This group included seven of 41 patients tested (17%) who had esophageal abnormalities, and nine of 53 patients (17%) who had pulmonary function abnormalities. Only two of the 16 patients with evidence of internal involvement had symptomatic or severe disease and it was determined one of these patients had SSc later on. The esophageal and pulmonary abnormalities were mild and usually asymptomatic and required no interventions.

Table 2 summarizes the distinctive features of LS patients with internal organ involvement in comparison with patients with exclusive skin disease. As shown, there are not many differences between the two groups. However, in patients with internal organ involvement there seems to be a higher female preponderance, a higher prevalence of patients with serum hypergammaglobulinemia, and a lower number of morphea plaques at the onset of the disease and C4 complement fraction alterations. It was concluded that, unless there are symptoms suggesting abnormalities in pulmonary, gastrointestinal, or other systems, there is no need to screen patients with LS for internal organ involvement.

More recently, a multi-center, multi-national survey involving 66 Pediatric Rheumatology and Dermatology Centers in 26 countries, sponsored by the Pediatric Rheumatology European Society, have been performed. The preliminary

Table 1. Main differences between systemic and localized scleroderma in children

	Juvenile systemic sclerosis*	Juvenile localized scleroderma**
Gender (F:M)	3:1	2,5 : 1
Age at onset, *y*	9,1	7,9
Skin involvement	Diffuse	Circumscribed
Organ involvement, %		
Osteoarticular	70	12.3
Gastrointestinal	73	1.4
Respiratory	67	< 1
Cardiac	27	< 1
Autoantibodies, %		
ANA	80	44.7
Scl70	27	4.5
Anticentromere	6	3.4

**Adapted from* Cassidy and Petty [1] and Martini *et al.* [2]
***Adapted from* Nelson [3] and Zulian *et al.* [4]
ANA—antinuclear antibodies; F—female; M—male.

results, presented at the 2003 American College of Rheumatology annual meeting in Orlando, showed extracutaneous involvement in 25.7% of 688 children with LS with 11% prevalence of internal organ involvement [7•].

Being a retrospective study, only symptomatic patients were reported and this explains the lower prevalence in comparison with the two previous studies. Neurologic involvement was reported in 3.8% of the patients and mainly in en coup de sabre (ECDS) subtype. Ocular involvement was found in 3.3%. Gastrointestinal symptoms, exclusively represented by gastroesophageal reflux (GER), were reported in 1.4% of the patients while respiratory abnormalities were found in 1%. A detailed description of these alterations will be mentioned in the paragraphs below.

More interestingly, 25 children (3.6%) presented multiorgan involvement, intended as the coexistence of two or more extracutaneous abnormalities. Most of the children (22 of 25) were affected by linear subtype and none developed SSc during a mean 4.6 years follow-up. A more extensive study on a larger number of patients with LS is in progress.

Neurologic involvement

Central nervous system (CNS) involvement in LS has been reported by several authors and, particularly, in linear scleroderma ECDS and in progressive facial hemiatrophy (PFH). In Table 3, the various neurologic abnormalities reported in the recent literature are summarized. Most of them are in the form of case reports [8–14,15••,16,17•,18,19•,20–27], and very few are cohort studies [16,17•,24].

In a large multi-center survey including 688 patients with juvenile LS (JLS), neurologic involvement was found in 26 patients (3.8%) [7•]. Nine had epilepsy, four had headache, three had peripheral neuropathy, three had significant white matter abnormalities on magnetic resonance imaging (MRI), two had vascular malformations, and two had CNS vasculitidis. In 11 patients, with ECDS subtype, these findings were unrelated to the site of the skin lesion.

As in other published series, epilepsy was the most frequently reported symptom. It is frequently associated with intraparenchymal calcifications that may also involve basal ganglia, thalami, and dentate nuclei and are usually in the same side of the skin lesion [15••]. MRI provides important information on CNS involvement of and localization of the brain lesions. The most frequent are abnormal white matter signals on MRI [10,19•,25,27], migrational defects [17•], or vascular malformations [16,23,28]. Apparently there is no correlation between the severity of brain abnormalities and the clinical picture [17•]. In fact, some patients with PFH are neurologically asymptomatic in spite of visible brain lesions [22].

The case of scleroderma ECDS reported by Chung *et al.* [17•] is of special interest because the excised cerebral lesion was found to be densely sclerotic with thickened blood vessel walls surrounded by gliotic parenchyma and scattered calcifications. The surgical resection of the involved brain area resulted in epilepsy regression.

The pathogenetic mechanisms underlying brain involvement in scleroderma remain unclear. The "neurovasculitis hypothesis" seems to be widely accepted [16,27,29]. An early cerebral inflammation could be the cause of gliosis with ectatic vessels and intraparenchymal calcification [29]. Conversely, the fact that LS ECDS and PFH concomitantly involve the facial tissues and underlying brain parenchyma that have a common cell progenitor, led to the hypothesis of an early malformation, affecting one side of the rostral neural tube and causing cerebral dysgenesis and facial hemiatrophy [24].

Ocular involvement

Ocular involvement in LS is quite uncommon and has been reported in adult patients. The alterations are polymorphic and the disease can affect adnexa structures, the anterior or posterior segments of the eye, and the CNS. In adults with LS the prevalence of ocular changes is just over

Table 2. Distinctive features of localized scleroderma with internal organ involvement

	Internal organ involvement	No internal organ involvement	Significance, *P*
Age at onset, *y**	33,2 ± 19,7	35,9 ± 21,6	–
F:M	2,6 : 1	0,8 : 1	< 0,05
Initial number of plaques*	7,1 ± 5,8	9,4 ± 6,5	< 0,02
Raynaud's phenomenon, %	7	6	–
Acrosclerosis, %	13	0	–
Sicca syndrome, %	8	9	–
Arthralgia, %	21	3	–
Hypergammaglobulinemia, %	64	19	< 0,005
ANA, %	56	40	–
Low C4 Complement, %	14	47	< 0,05

*mean ± standard deviation
Adapted from Dehen *et al.* [6••]
ANA—antinuclear antibodies; F—female; M—male.

10% [30] and those with hemifacial atrophy is about one-third of the patients [31].

In the large multi-center survey, previously mentioned, ocular involvement was reported in 23 patients (3.3%) and consisted in eyelid lesions, episcleritis, uveitis, xerophthalmia, glaucoma, and papilledema [7•]. The greatest rate of ocular involvement was detected in the linear subtype and, particularly, in patients with ECDS where it was reported in 15% of the cases.

Eyelid abnormalities, consisting in a variable degree of atrophy of the skin and subcutaneous eyelid tissues, are the finding most frequently reported.

They can progressively lead to various degree of xerophthalmia that, complicated by prolonged blink latency and even ectropion, is an important risk factor for exposure keratopathy [32–34]. Involvement of the extrinsic eye muscles and orbit is extremely rare but well documented by computed tomography (CT) and MRI [35,36].

A careful ophthalmologic and systematic assessment and follow-up are recommended for all the patients with LS and particularly for those with early onset ECDS when an appropriate local and systemic treatment have more chance to arrest the inflammatory-fibrotic process.

Gastrointestinal involvement

Gastrointestinal abnormalities, mainly represented by asymptomatic sclerotic changes of the esophagus or abnormal esophageal motility have been described in single case reports [37,38].

Dehen *et al.* [6••] found esophageal abnormalities in seven of 41 patients (17%), with morphea and with or without linear scleroderma. Most of them were asymptomatic patients and some were children. One patient with morphea, who later developed SSc, had total dilatation of the esophagus with hypotonia of the lower esophageal sphincter, in the other six, decreased esophageal peristalsis and/or hypotonia of the lower gastroesophageal sphincter was found. In the large multi-center survey, previously mentioned, the authors reported gastrointestinal symptoms, consisting exclusively in GER, in 10 of the 688 children with LS with a prevalence of 1.4% [7•]. All these patients were symptomatic and this may explain the lower prevalence of gastrointestinal abnormalities of this cohort of patients with respect to the previous series.

In adults with LS, decreased length of the abdominal tract of the lower esophageal sphincter but no GER was reported [39].

More recently, Weber *et al.* [40] documented the presence of GER in four of five children with LS. They stated that in this population, gastrointestinal involvement, evaluated by 24-hour pH intraesophageal monitoring or x-ray, is quite frequent despite the absence of specific symptoms. For this reason they recommend to rule out possible GER in all patients with LS and to carefully follow-up those with GER to detect early dysmotility alterations.

Pulmonary involvement

Pulmonary involvement was detected in nine of 53 patients (17%) explored routinely by functional tests and chest x-ray [6••]. One had restrictive changes with reduced respiratory volume, severe impaired DLCO, and hypoxemia at rest. This patient, a few months after the onset of morphea skin lesions, developed SSc. In the remaining eight patients, mild gas transfer defects were found: they were associated with restrictive ventilatory defects in two cases and with interstitial infiltrate in one.

Similar findings were described by Bourgeois-Droin and Touraine [41] who reported pulmonary involvement with gas transfer defect and reduced respiratory volumes in two patients with LS.

More recently, a case of restrictive pneumopathy as a result of severe cutaneous sclerosis of the thorax has been reported [42].

In the previously reported multi-center study, less than 1% of patients with JLS had respiratory symptoms essentially because of restrictive pneumopathy. Only one

Table 3. Neurologic involvement in localized scleroderma

Clinical Manifestations	Studies
Epilepsy	[8], [15••], [16], [18], [19•], [20–28]
Headache dizziness	[9], [16], [22], [23]
Stroke	[10]
Oculomotor abnormalities	[11], [13], [16], [26]
Transverse myelitis	[12]
Hemiparesis	[14], [19•], [23]
Learning disabilities	[14], [21]
Vertigo	[16]
CNS abnormal imaging	
Calcifications	[14], [15••], [16], [17•], [18], [20]
Vascular abnormalities	[14], [23], [28]
White matter abnormalities (MRI)	[9–11], [16], [17•], [18], [19•], [21], [22], [24], [25], [27]

CNS—central nervous system; MRI—magnetic resonance imaging.

of these patients had basal infiltrate on x-ray, one had DLCO defects, and the others had altered pulmonary function tests [7•].

Cardiovascular involvement

Cardiovascular involvement has been reported very rarely in LS [43]. Electrocardiogram abnormalities, mainly represented by right bundle branch block, have been reported in a group of 43 children with LS systematically evaluated. Abnormal valve function, particularly of mitral valve, was found in 16 patients (37%) while exercise test was normal in all [44]. The meaning of these findings has not been fully explained by the authors.

In a large series of 688 children with JLS, only two were reported to have cardiac abnormalities: one pericarditis and one conduction defect [7•].

A recent case report from India described a 9-year old girl with linear morphea involving the left side of the body associated with preductal aortic coarctation [45]. She had no other internal organ involvement. Laboratory examination showed eosinophilia, mild thrombocytopenia, and presence of antinuclear and anti-dsDNA antibodies.

Unfortunately no epidemiologic studies are available to verify if these cardiac abnormalities have a significant higher prevalence in LS with respect to the general population and if they can be considered early signs of a possible evolution to SSc.

Osteoarticular involvement

Osteoarticular involvement, including arthralgias, arthritis, and joint deformities, is the most frequently reported complication of LS, particularly in the linear subtype. When linear lesions become extensive and spread across articular structures, they cause considerable contractures of the ligamentous and periarticular tissues and wasting of muscle and bone leading even to severe growth failure of the limb.

In the survey of 688 children with LS osteoarticular involvement was reported in 12.3% of the patients [7•]. If we consider the subgroup of patients with linear scleroderma involving trunk and/or limb, the prevalence of this complication ranges from 30% to 52% [7•,46–49].

Of interest is a significant correlation between presence of arthritis and positive rheumatoid factor (RF). This finding, already reported in 17% to 39% of the patients with LS, for some authors appears to be linked to the articular involvement and its aggressive course [7•,47,48,50,51•]. The evidence that RF contributes to the pathogenesis and severe course of synovitis in RF positive rheumatoid arthritis and juvenile rheumatoid arthritis patients and the findings of significant association between RF and severe course arthritis in LS suggests the possibility that a similar mechanism may be operative also in these cases.

Relationship Between Localized Scleroderma and Systemic Sclerosis

Transition from localized scleroderma to systemic sclerosis

Transition from LS to SSc has been reported, even if rarely. The prevalence of such evolution ranges in various series, between 0.9% and 5.7% [6••, 52, 53].

The presence of antinuclear antibodies (ANA) [54] and other immunologic abnormalities in a proportion of patients and coexistence of other autoimmune disorders [55•], is suggestive of the role of autoimmunity. It should, however, be stressed that the importance of ANA with nondistinctive specificity is not clear, and their detection has no diagnostic value.

Of interest is a report by Scarola and Shulman [56] who did a 22-year follow-up of ten patients with linear scleroderma with coexistent ANA and other immune abnormalities. Only in one patient, 5 years after scleroderma regressed, did symptoms of systemic lupus erythematosus appear transitionally.

Blaszczyk *et al.* [57•] evaluated the prevalence of autoantibodies in 466 patients with LS. As shown in Table 4, 120 of 466 patients (25.7%) were found to be ANA positive and 14 (3%) presented positivity for extractable nuclear antigens (ENA) autoantibodies. All except two were children and the

higher prevalence (9 of 14) of such autoantibodies was reported in the linear subtype. Among the 14 patients with positive ENA autoantibodies, only three developed visceral involvement during the long term follow-up. One patient was a 15-year old girl with linear-plaque morphea who, 13 years later, developed Raynaud's phenomenon, respiratory symptoms, and esophageal involvement. ANA and Scl70 were both positive. The course of the disease was mild with no diffuse skin involvement. Another patient had linear scleroderma at the age of 11 years. ANA and Scl70 were both positive. When she was 25, she developed diffuse skin sclerosis without internal organ involvement. A couple of years later, Scl70 became negative. The third patient was a 9-year old child with disseminated morphea, PFH, and Raynaud's phenomenon. ANA was positive (titer 1:640) with U1RNP specificity. During a long term follow-up the patient developed mixed connective tissue disease.

Birdi *et al*. [58••] reported a 15-year old girl with biopsy proven morphea who developed progression to systemic disease 2 years after initial presentation. Of interest, early in the patient's clinical course, she had positive ANA and autoantibodies directed against the 80-Kd and 70-Kd Ku antigens. The authors concluded that the presence of these particular autoantibodies may be a marker for morphea patients whose disease will progress to systemic form.

The difficulty in determining the incidence of systemic progression in LS stems from a number of factors. Sometimes signs like sclerodactyly, Raynaud's phenomenon, or dysphagia are difficult to detect, especially in young patients and systemic involvement may be asymptomatic. On the other hand, localized scleroderma itself may have some mild systemic features such as elevated erytho sedimentation rate, hypergammaglobulinemia, and positive results on immunologic tests that are not considered to denote a more serious systemic disease.

Association of localized scleroderma and systemic sclerosis

Several cases of coexistent LS and SSc have been reported, mainly in adults [59–62], rarely in children [63]. These are in form of single case reports and no cohort studies among patients with LS or SSc have been performed to know the real prevalence of this condition. Coexistence of the two forms of scleroderma and/or the occurrence of systemic disease in children with morphea are rather unusual events. However, especially children with linear or generalized morphea and those with presence of specific autoantibodies should be carefully evaluated for visceral abnormalities.

Association of Localized Scleroderma with Other Autoimmune or Connective Tissue Diseases

Other than SSc, other autoimmune conditions have been reported in association with LS. One of the first reports, published 15 years ago, underlined the presence of autoimmune disorders in 16% of patients with LS [55•]. Indeed, the relatives of these patients have also been found to have an increased incidence of autoimmune disorders such as pernicious anemia, autoimmune thyroid disease, alopecia areata, and diabetes. Systematic search for organ-specific autoantibodies was positive in 52% of the patients that was significantly higher than in healthy controls (8%).

Since this first study, many other autoimmune conditions have been reported in association with LS. The most frequently reported diseases are Hashimoto's thyroiditis [55•,64–67], vitiligo [67–74], and insulin-dependent diabetes mellitus [55•,65]. Case reports of association of LS with primary biliary cirrhosis [71], myasthenia gravis [72], and polyglandular autoimmune disease type 2, characterized by the presence of Addison's disease and thyroid autoimmune disease [73] have also been reported.

As for non–organ-specific autoimmune conditions associated with LS, systemic lupus erythematosus represents the most frequently reported disease [74–79], more rarely rheumatoid arthritis [80–82] and necrotizing vasculitis [83].

Of interest, a recent report has pointed out the role of congenital skin lesions as predisposing factors for the development of LS [84•]. The authors described two individual patients, with family history for autoimmune diseases, who, over congenital hypopigmented areas, developed LS in adulthood. Starting from this observation, the authors proposed that somatic mutations affecting vessels may predispose to increased endothelial cell apoptosis leading to autoimmune response in predisposed individuals [84•].

Conclusions

Systemic manifestations are rarely observed in LS although internal organ involvement is frequently found when they are looked for systematically. These visceral abnormalities, usually mild, may suggest that LS and SSc likely represent two ends of a continuous spectrum of disease. Conversely, the small proportion of patients with LS with symptomatic internal organ involvement and the rarity of transitional forms of LS to SSc may support the existence of a new subtype of LS patients where the disease is not purely cutaneous and not strongly systemic such as in classic SSc.

While the presence of ANA with no distinctive specifity has no diagnostic and prognostic significance, the appearance of scleroderma specific autoantibodies (Scl70, anti-centromere antibodies, and so on) and, detection of nailfold capillaroscopy abnormalities, characteristic for SSc, are predictive features for a possible development of SSc or other autoimmune diseases. Based on the appearance of these findings, patients should be very carefully investigated and followed-up for several years.

Table 4. Extractable nuclear antigen autoantibodies in 120 ANA-positive LS patients

Subtype	Patient, *n*	ENA, *n* = 120	Scl70	U1RNP	Ro/La	Fibrillary, *n*	RNA polymerase 1	Visceral involvement
Linear	Children (51)	9	2	2	4		1	3
	Adult (18)	0						
Disseminate Morphea	Children (5)	2		1		1		
	Adult (8)	2			1		1	
Other*	Children (17)	0						
	Adult (21)	1						
Overall, %		14 (11,7)	2 (1,7)	3 (2,5)	5 (4,1)	1 (0,8)	2 (1,7)	3 (2,5)

*Plaque morphea, generalized morphea, deep morphea, atrophoderma Pasini-Pierini.
Adapted from Blaszczyk *et al.* [57•]
ANA—antinuclear antibodies; ENA—extractable nuclear antigen, LS—localized scleroderma.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Cassidy JT, Petty RE: **The systemic sclerodermas and related disorders.** In *Textbook of Pediatric Rheumatology.* Edited by Cassidy JT, Petty RE. Philadelphia: W.B. Saunders Co.; 2001:505–534.
2. Martini G, Foeldvari I, Russo R, *et al.*: **Systemic scleroderma syndromes (SSS) in children: clinical and immunological characteristics of 181 patients (abstract).** *Arthritis Rheum* 2003, **48:**S512.
3. Nelson A: **Localized sclerodermas.** In *Textbook of Pediatric Rheumatology.* Edited by Cassidy JT, Petty RE. Philadelphia: W.B. Saunders Co.; 2001:535–544.
4. Zulian F, De Oliveira SKF, Lehman TH, *et al.*: **Juvenile localized scleroderma: clinical epidemiological features of 688 patients (abstract).** *Arthritis Rheum* 2003, **48:**S512.
5. Lunderschmidt C, König G, Leisner B *et al.*: **Zirkumskripte sklerodermie: interne manifestationen und signifikante correlation zu HLA-DR1 und –DR5.** *Der Hautarzt* 1985, **36:**516–521.
6. •• Dehen L, Roujeau JC, Cosnes A, *et al.*: **Internal involvement in localized scleroderma.** *Medicine* 1994, **73:**241–245.

The first interesting study that evaluated systematically the prevalence of internal organ involvement in LS.

7. • Zulian F, Russo R, Laxer R, *et al.*: **Is juvenile localized scleroderma really "localized"? (abstract).** *Arthritis Rheum* 2003, **48:**S512.

Despite this being in the form of an abstract, this preliminary study describes the extracutaneous manifestations of children with LS as a result of a multi-center multinational survey.

8. Heron E, Hernigou A, Fornes P, *et al.*: **Central nervous system involvement in scleroderma.** *Ann Med Interne (Paris)* 2002, **153:**179–182.
9. Higashi Y, Kanekura T, Fukumaru K, Kanzaki T: **Scleroderma en coup de sabre with central nervous system involvement.** *J Dermatol* 2000, **27:**486–488.
10. Kanzato N, Matsuzaki T, Komine Y, *et al.*: **Localized scleroderma associated with progressing ischemic stroke.** *J Neurol Sci* 1999, **163:**86–89.
11. Suttorp-Schulten MS, Koornneef L: **Linear scleroderma associated with ptosis and motility disorders.** *Br J Ophthalmol* 1990, **74:**694–695.
12. Littman BH: **Linear scleroderma: a response to neurologic injury? Report and literature review.** *J Rheumatol* 1989, **16:**1135–1140.
13. Fry JA, Alvarellos A, Fink CW, *et al.*: **Intracranial findings in progressive facial hemiatrophy.** *J Rheumatol* 1992, **19:**856–858.
14. David J, Wilson J, Woo P: **Scleroderma "en coup de sabre."** *Ann Rheum Dis* 1991, **50:**260–262.
15. •• Blaszczyk M, Krolicki L, Krasu M, *et al.*: **Progressive facial hemiatrophy: central nervous system involvement and relationship with scleroderma en coup de sabre.** *J Rheumatol* 2003, **30:**1997–2004.

A clear-cut demonstration that CNS involvement is present in all cases of PFH preceeded or not by sclerotic lesions, and in scleroderma ECDS with no signs of PFH, thus confirming a close relationship between these conditions.

16. Liu P, Uziel Y, Chuang S, *et al.*: **Localized scleroderma: imaging features.** *Pediatr Radiol* 1994, **24:**207–209.
17. • Chung MH, Sum J, Morrell MJ, Horoupian DS: **Intracerebral involvement in scleroderma en coup de sabre: report of a case with neuropathologic findings.** *Ann Neurol* 1995, **37:**679–681.

An interesting case report of an epileptic patient with scleroderma ECDS with densely sclerotic cerebral lesion with thickened blood vessel walls surrounded by gliotic parenchyma and calcifications. The surgical resection of the involved brain area resulted in epilepsy regression

18. Luer W, Jockel D, Henze T, Schipper HI: **Progressive inflammatory lesions of the brain parenchyma in localized scleroderma of the head.** *J Neurol* 1990, **237:**379–381.
19. • Flores-Alvarado DE, Esquivel-Valerio JA, Garza-Elizondo M, Espinoza LR: **Linear scleroderma en coup de sabre and brain calcification: is there a pathogenic relationship?** *J Rheumatol* 2003, **30:**193–195.

An interesting case report that raises some questions on the origin and relationship of LS and brain calcification. Whether they are secondary to the cerebrovascular damage of scleroderma or represent a separate mucocutaneous syndrome of vascular dysplasis awaits further elucidation.

20. Grosso S, Fioravanti A, Biasi G, *et al.*: **Linear scleroderma associated with progressive brain atrophy.** *Brain Dev* 2003, **25:**57–61.
21. Goldberg-Stern H, deGrauw T, Passo M, Ball WS Jr.: **Parry-Romberg syndrome: follow-up imaging during suppressive therapy.** *Neuroradiology* 1997, **39:**873–876.
22. Woolfenden AR, Tong DC, Norbash AM, Albers GW: **Progressive facial hemiatrophy: abnormality of intracranial vasculature.** *Neurology* 1998, **50:**1915–1917.
23. Dupont S, Catala M, Hasboun D, *et al.*: **Progressive facial hemiatrophy and epilepsy: a common underlying dysgenetic mechanism.** *Neurology* 1997, **48:**1013–1018.
24. DeFelipe J, Segura T, Arellano JI, *et al.*: **Neuropathological findings in a patient with epilepsy and the Parry-Romberg syndrome.** *Epilepsia* 2001, **42:**1198–1203.
25. Gambichler T, Kreuter A, Hoffmann K, *et al.*: **Bilateral linear scleroderma "en coup de sabre" associated with facial atrophy and neurological complications.** *BMC Dermatol* 2001, **1:**9.
26. Menni S, Marzano AV, Passoni E: **Neurologic abnormalities in two patients with facial hemiatrophy and sclerosis coexisting with morphea.** *Pediatr Dermatol* 1997, **14:**113–116.
27. Schievink WI, Mellinger JF, Atkinson JL: **Progressive intracranial aneurysmal disease in child with progressive hemifacial atrophy: case report.** *Neurosurgery* 1996, **38:**1237–1241.
28. Stone J, Franks AJ, Guthrie JA, Johnson MH: **Scleroderma "en coup de sabre": pathological evidence of intracerebral inflammation.** *J Neurol Neurosurg Psychiatry* 2001, **70:**382–385.
29. Miedziak AI, Stefanyszyn M, Flamagan J, Eagle RC, Jr.: **Parry-Romberg syndrome associated with intracranial vascular malformations.** *Arch Ophthalmol* 1998, **116:**1235–1237.
30. Rees TD: **Facial atrophy.** *Clin Plast Surg* 1976, **3:**637.
31. Muchnick RS, Sherrell JA, Rees DT: **Ocular manifestations and treatment of hemifacial atrophy.** *Am J Ophthalmol* 1979, **88:**889–897.
32. West RH, Barnett AJ: **Ocular involvement in scleroderma.** *Br J Ophtalmol* 1979, **63:**845–847.
33. Lecky BE, Hughes RA, Murray NM: **Trigeminal sensory neuropathy. A study of 22 cases.** *Brain* 1987, **110:**1463–1485.
34. Nancarrow JD, Jawad SM: **A rare case of severe bilateral ectropion from scleroderma.** *Plast Reconstr Surg* 1981, **67:**352–354.
35. Ramboer K, Demaerel P, Baert AL, *et al.*: **Linear scleroderma with orbital involvement: follow-up and magnetic resonance imaging.** *Br J Ophthalmol* 1997, **81:**90–91.
36. Suttorp-Schulten MS, Koorn L: **Linear scleroderma associated with ptosis and motility disorders.** *Br J Ophthalmol* 1990, **74:**694–695.
37. Haim S, Sherf K: **Scleroderma "en plaque" associated with systemic manifestation.** *Harefuah* 1965, **69:**172–174.
38. Tuffanelli DL, Marmelzat WL, Dorsey CS: **Linear scleroderma with hemiatrophy: report of three cases associated with collagen-vascular disease.** *Dermatologica* 1966, **132:**51–58.
39. Zaninotto G, Peserico A, Costantini M, *et al.*: **Oesophageal motilità and lower oesophageal sphincter competence in progressive systemic sclerosis and localized sclerodermia.** *Scand J Gastroenterol* 1989, **24:**95–102.
40. Weber P, Ganser G, Frosh M, *et al.*: **Twenty-four hour intraesophageal pH monitoring in children and adolescents with scleroderma and mixed connective tissue disease.** *J Rheumatol* 2000, **27:**2692–2695.
41. Bourgeois-Droin C, Touraine R: **Sclérodermie en plaque: Perturbations immunologique et viscérales.** *Ann Med Interne (Paris)* 1978, **129:**107–112.

42. Aguayo SM, Richardson CL, Roman J: **Severe extrapulmonary thoracic restriction caused by morphea, a form of localized scleroderma.** *Chest* 1993, **104:**1304–1305.
43. Moore EC, Altri E: **Focal scleroderma and severe cardiomyopathy: patient report and brief review.** *Am J Dis Child* 1991, **145:**229–231.
44. Rokicki W, Dukalska M, Rubisz-Brzezinska J, Gasior Z: **Circulatory system in children with localized scleroderma.** *Pediatr Cardiol* 1997, **18:**213–217.
45. Basu S, Ganguly S: **Homolateral linear morphea and coarctation of aorta.** *Indian Pediatr* 2003, **40:**1108–1109.
46. Peterson LS, Nelson AM, Su WPD: **Classification of morphea (localized scleroderma).** *Mayo Clin Proc* 1995, **70:**1068–1076.
47. Uziel Y, Krafchik BR, Silverman ED, *et al.*: **Localized scleroderma in childhood: a report of 30 cases.** *Semin Arthritis Rheum* 1994, **23:**328–340.
48. Vancheeswaran R, Black CM, David J, *et al.*: **Childhood onset scleroderma: is it different from adult onset disease.** *Arthritis Rheum* 1996, **39:**1041–1049.
49. Marzano AV, Menni S, Parodi A, *et al.*: **Localized scleroderma in adults and children. Clinical and laboratory investigations on 239 cases.** *Eur J Dermatol* 2003, **13:**171–176.
50. Falanga V, Medsger TA, Reichlin M, Rodnan GP: **Linear scleroderma: clinical spectrum, prognosis and laboratory abnormalities.** *Ann Intern Med* 1986, **104:**849–857.
51.• Hanson V, Drexler E, Konreich H: **Rheumatoid factor in children with focal scleroderma.** *Pediatrics* 1974, **53:**945–947.

One of the first reports on the presence of RF in children with LS and its relationship with the course of arthritis observed in some patients.

52. Christianson HB, Dorsey CS, O'Leary PA, Kierland RR: **Localized scleroderma. A clinical study of two hundred thirty-five cases.** *Arch Dermatol* 1956, **74:**629–639.
53. Curtis AC, Jansen TG: **The prognosis of localized scleroderma.** *Arch Dermatol* 1958, **78:**749–757.
54. Jablonska S, Chorzelski TP, Blaszczyk M, *et al.*: **Clinical relevance of immunologic findings in scleroderma.** *Clin Dermatol* 1993, **10:**407–421.
55.• Harrington I, Dunsmore IR: **An investigation into the incidence of autoimmune disorders in patients with localized morphea.** *Br J Dermatol* 1989, **120:**645–648.

An interesting "historical" study on the incidence of autoimmune disorders in a cohort of patients with LS and their relatives.

56. Scarola JA, Shulman LE: **Serologic abnormalities and their significance in localized scleroderma.** *Arthritis Rheum* 1975, **18:**526–527.
57.• Blaszczyk M, Jarzabek-Chorleska M, Jablonska S: **Relationship between cutaneous and systemic scleroderma. Are immunopathological studies helpful in evaluating transition of cutaneous to systemic scleroderma?** *Przeglad Dermatologiczny* 2000, **2:**119–125.

An immunologic study of a large series of patients with LS describing the incidence of scleroderma-specific antibodies and their role in predicting the evolution to SSc during a long term follow-up.

58.•• Birdi N, Laxer RM, Thorner P, *et al.*: **Localized scleroderma progressing to systemic disease. Case report and review of the literature.** *Arthritis Rheum* 1993, **36:**410–415.

A well documented case report of a patient with morphea who developed progression to SSc 2 years after initial presentation. The role of antibodies directed against Ku antigens as predictors of possible transition to SSc is discussed.

59. Temine P, Privat Y, Vallette P: **Sclerodermie en plaques et en gouttes avec hypertension arteriell pulmonaire.** *Bull Soc Fr Dermatol Syphiligr* 1970, **77:**216–217.
60. Ikai K, Tagami H, Imamura S, *et al.*: **Morphea-like cutaneous changes in a patient with systemic scleroderma.** *Dermatologica* 1979, **158:**438–442.
61. Ryckmanns F, Konz B: **Disseminierte zirkumskripte sklerodermie und diffuse sklerodermie vom typ der akrosklerodermie.** *Hautarzt* 1980, **31:**86–90.
62. Mizutani H, Tanaka H, Okada H, *et al.*: **Palindromic morphea: multiple recurrence of morphea lesions in a case of systemic sclerosis.** *J Dermatol* 1992, **19:**298–301.
63. Tufanelli DL, Marmalrat WL, Dorsey CS: **Linear scleroderma with hemiatrophy: report of three cases associated with collagen-vascular disease.** *Dermatologica* 1966, **132:**51–58.
64. Lee HJ, Kim MY, Ha SJ, Kim JW: **Two cases of morphea associated with Hashimoto's thyroiditis.** *Acta Derm Venereol* 2002, **82:**58–59.
65. Tremaine R, Adam JE, Orizaga M: **Morphea coexisting with lichen sclerosus et atrophicus.** *Int J Dermatol* 1990, **29:**486–489.
66. Dervis E, Acbay O, Barut G, *et al.*: **Association of vitiligo, morphea and Hashimoto's thyroiditis.** *Int J Dermatol* 2004, **43:**236–237.
67. Finkelstein E, Amichai B, Metzker A: **Coexistence of vitiligo and morphea: a case report and review of the literature.** *J Dermatol* 1995, **22:**351–353.
68. Lerner AB, Sansung J: **Vitiligo and linear scleroderma.** *Arch Dermatol* 1973, **108:**286–287.
69. Thompson DM, Robinson TWE, Lennard-Jones J: **Alopecia areata vitiligo, scleroderma and ulcerative colitis.** *Proc R Soc Med* 1974, **67:**1010–1012.
70. Brenner W, Diem F, Gschnait F: **Coincidence of vitiligo, alopecia areata, onychodystrophy, localized scleroderma and lichen planus.** *Dermatologica* 1979, **159:**356–360.
71. Reed JR, De Luca N, McIntyre AS, Wilkinson JD: **Localized morphea, xantomatosis and primary biliary cirrhosis.** *Br J Dermatol* 2000, **143:**652–653.
72. Kim HS, Chun YS, Hann SK, Park WH: **A case of linear scleroderma and myasthenia gravis.** *J Dermatol* 2000, **27:**31–34.
73. De P, Lloyd HJ, Rashid AM, Anstey AV: **Morphea presenting shortly after the onset of Schmidt's syndrome.** *Clin Exp Dermatol* 2000, **25:**168–169.
74. Shelkovitz-Shiloh I, Ehrenfeld M, Schewch-Millet M, *et al.*: **Coexistence of family systemic lupus erythematosus and localized scleroderma.** *Int J Dermatol* 1992, **31:**819–820.
75. Mizutani H, Tanaka H, Okada H, *et al.*: **Palindromic morphea: multiple recurrence of morphea lesions in a case of systemic sclerosis.** *J Dermatol* 1992, **19:**298–301.
76. Mackel SE, Kozin F, Ryan LM, *et al.*: **Concurrent linear scleroderma and systemic lupus erythematosus: a report of two cases.** *J Invest Dermatol* 1979, **73:**368–372.
77. Mork NJ: **Clinical and histopathologic morphea with immunological evidence of lupus erythematosus: a case report.** *Acta Derm Venereol* 1981; **61:**367–368.
78. Majeed M, Al-Mayouf SM, Al-Sabban E, Bahabri S: **Coexistent linear scleroderma and juvenile lupus erythematosus.** *Pediatr Dermatol* 2000, **17:**565–569.
79. Wu KH, Dai YS, Tsai MJ, *et al.*: **Lichen sclerosus et atrophicus, bullous morphea and systemic lupus erythematosus: a case report.** *J Microbiol Immunol Infect* 2000, **33:**53–56.
80. Robertson LP, Davies MG, Hickling P: **Generalized morphoea in a patient with Felty's syndrome.** *J Eur Acad Dermatol Venereol* 2000, **14:**191–193.
81. Adebajo AO, Crisp AJ, Nicholls A, Hazleman BL: **Localized Scleroderma and hemiatrophy in association with antibodies to double-stranded DNA.** *Postgrad Med J* 1992, **68:**216–218.
82. Hernandez-Beriain JA, San Roman A, Espinel ML, Segura-Garcia C: **Morphea and rheumatoid arthritis.** *Clin Exp Rheumatol* 1996, **14:**446–447.
83. Morita A, Tsuji T: **Necrotizing vasculitis in a patient with generalized morphea.** *J Am Acad Dermatol* 2001, **45:**S215–S217.
84.• Hardford R, Smith KJ, Skelton H: **Development of histologic features of scleroderma in congenital lesions.** *J Cutan Pathol* 2002, **29:**249–254.

Starting from a case report describing two patients, who, over congenital hypopigmented areas, developed LS in adulthood, the authors proposed that somatic mutations affecting vessels may predispose to increased endothelial cell apoptosis leading to autoimmune response.