

Neurologic manifestations of localized scleroderma

A case report and literature review



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ABSTRACT

We describe a young woman with localized scleroderma, seizures, numerous persistently enhancing white matter lesions on brain MRI, and oligoclonal bands in the CSF. The case is remarkable in the widespread bilateral distribution of the lesions and their enhancement during more than a year of follow-up despite immunosuppression. Literature search yielded 54 case descriptions of localized scleroderma associated with neurologic symptoms and neuroimaging findings. All patients had craniofacial scleroderma: linear scleroderma en coup de sabre (LScs), progressive facial hemiatrophy (PFH, or Parry-Romberg syndrome) or both. LScs and PFH should be viewed as variants of craniofacial localized scleroderma as they often manifest in the same patient, share the same neurologic manifestations and imaging features, and evidence pathologic inflammation in skin and CNS. *Neurology*® 2008;71:1538-1545

GLOSSARY

ANA = antinuclear antibody; **LScs** = localized scleroderma en coup de sabre; **MS** = multiple sclerosis; **PFH** = progressive facial hemiatrophy.

A 22-year-old Caucasian woman presented to the emergency room after an episode of confusion followed by a fall and tonic-clonic convulsions for less than 2 minutes. She regained full consciousness within an hour, but tonic-clonic activity of similarly brief duration recurred several hours later in the emergency room. In the days preceding the secondary generalized seizures, she had increasing frequency of migraines, but was otherwise well and attending college full-time. At 2 years of age, she suffered severe herpes stomatitis and esophagitis. At age 4, skin induration appeared in the region of the left knee that slowly increased in size and led to atrophy of subcutaneous tissue over the entire left leg. Concurrently, a hyperpigmented plaque developed on the upper back and a small band-like linear scar with alopecia over the left parietal bone. Diagnosis of localized scleroderma was made on clinical grounds, but no treatment was offered. The lesions evolved over several months and remained static thereafter. She had occasional migraines with and without visual aura since adolescence. Several years prior to presentation she had noticed a mild right eyelid droop, which had persisted. For a number of years she experienced symptoms suggestive of Raynaud phenomenon. There was no family history of scleroderma, neurologic, rheumatologic, or autoimmune disease.

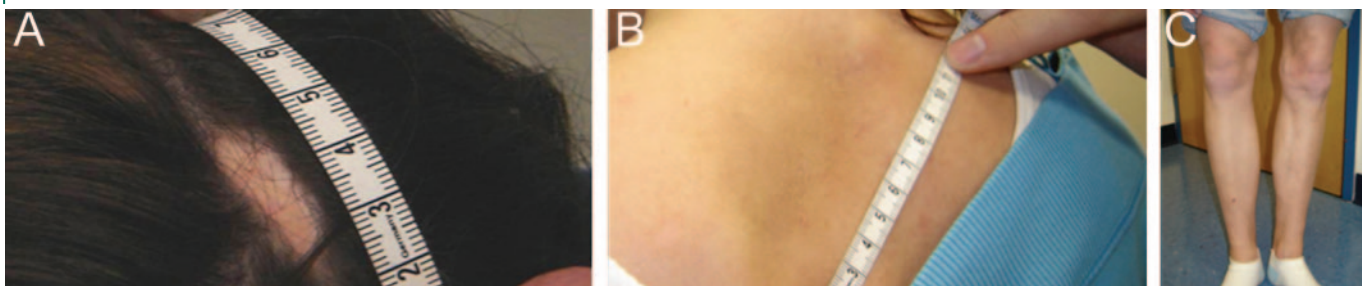
General examination revealed a 2 × 0.5 cm band of sclerotic skin and alopecia over the left parietal scalp, a 10 × 7 cm hyperpigmented plaque over upper back, and marked subcutaneous tissue loss in the left leg and thigh (figure 1). There was no facial atrophy, eyelash or eyebrow loss, or nailfold abnormalities. The neurologic examination was remarkable only for partial right-sided ptosis without miosis and slightly decreased pupillary reactivity in the right eye.

MRI of the brain showed a soft tissue and bone defect in the left parietal bone underlying the skin lesion, and over 25 enhancing lesions in bilateral juxtacortical, subcortical, and periventricular white matter and in the body of the corpus callosum (figures 2 and 3). Perfusion

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Figure 1 Linear scleroderma en coup de sabre over left parietal bone (A), superficial circumscribed morphea on the back (B), pansclerotic morphea affecting the left leg (C)

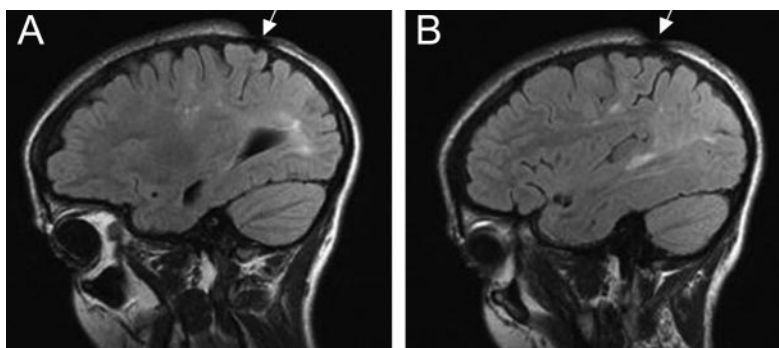


of the lesions was decreased, suggesting focal decrease in blood flow, while diffusion tensor imaging showed increased diffusivity, indicating microstructural abnormalities. MRA of the brain and MRI of the cervical spine were unremarkable. EEG was normal. Antinuclear antibody titers were initially less than 1:40, followed by 1:160 (speckled) 2 months later, and a return to baseline at 8-month follow-up. Rheumatoid factor was initially mildly elevated at 24 IU/mL (range: 0–20), subsequently normalized, and again became mildly elevated eight months later. Anticentromere, anti-Scl70, anti-RNP, anti-dsDNA antibodies were not detected and erythrocyte sedimentation rate was normal. Lyme titers and RPR screen were negative. Spinal fluid contained four well-defined gamma bands not seen in serum; leukocyte count, protein, and glucose were within normal limits.

In the absence of episodes of neurologic dysfunction, focal signs, and the remarkable persistence of contrast-enhancing lesions on

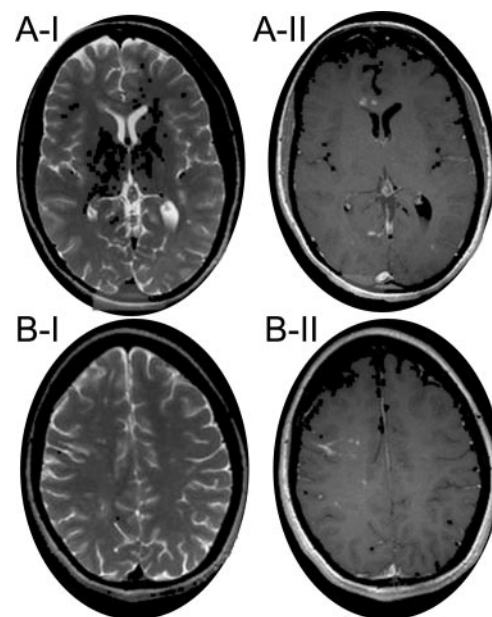
MRI, the possibility of demyelinating, neoplastic, and infectious diagnoses was deemed unlikely. The diagnosis that best accounts for our patient's symptoms, disease course, laboratory and MRI findings is localized scleroderma with CNS involvement. A 5-day course of high-dose IV methylprednisolone (1 g qd) was administered and low-dose azathioprine (50 mg qd) was instituted. Although the patient reported improvement in her headaches, MRI of the brain 13 months after presentation showed slight increase in the number and size of enhancing lesions (figure 4). She was initially treated with topiramate,

Figure 2 Representative sagittal FLAIR images showing multifocal periventricular and cortical-subcortical areas of high signal



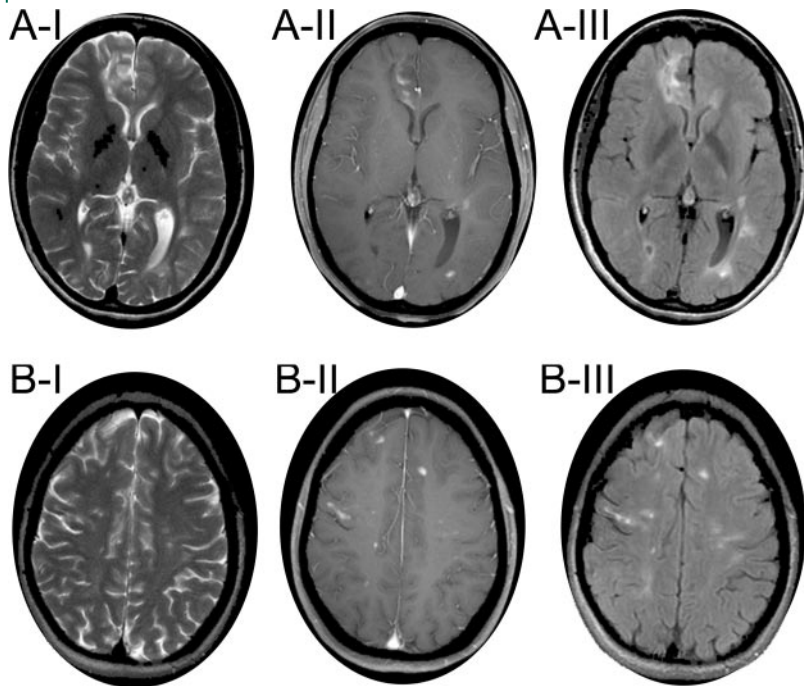
The scleroderma en coup de sabre is seen with focal atrophy of the subcutaneous tissues (white arrow).

Figure 3 Representative baseline axial T2-weighted fast spin echo (A-I, B-II) and corresponding enhanced T1-weighted spin echo (A-II, B-II) images showing multifocal, periventricular, and cortical-subcortical areas of high signal



Most of the T2 hyperintense foci show marked gadolinium enhancement on the enhanced T1-weighted images.

Figure 4 Axial T2-weighted fast spin echo (A-I, B-I, C-I), corresponding enhanced T1-weighted spin echo (A-II, B-II, C-II), and FLAIR (A-III, B-III, C-III) images acquired at 1-year follow-up



Note the increased number and conspicuity of lesions at follow-up.

but experienced large number of olfactory auras and a secondary generalized seizure (tonic-clonic convulsions preceded by very emotional state and disorientation). After a switch to pregabalin she has remained seizure-free for over 10 months.

DISCUSSION Localized scleroderma has an estimated prevalence of less than 3 per 100,000.¹ It is characterized by sclerotic lesions of the skin and underlying tissues and is distinguished from systemic scleroderma by lack of significant internal organ involvement and a generally benign prognosis. However, recent studies have established that localized scleroderma is not an exclusively dermatologic condition: rheumatologic, neurologic, and ophthalmologic symptoms and signs are present in 20% of patients.^{2,3}

Search of the English-language literature through PubMed yielded descriptions of 54 patients⁴⁻⁴⁵ with localized scleroderma who satisfied the following three criteria: 1) had localized scleroderma skin lesions, but not progressive systemic sclerosis; 2) experienced neurologic symptoms/signs not attributable to a comorbid neurologic disorder; 3) underwent a neuroimaging study (MRI or CT of the brain). Patients with craniofacial scleroderma, neuroradiologic abnormalities, but no neurologic manifestations,^{4,53} have been excluded in our review. Although localized

scleroderma can affect almost any part of the body, in patients with CNS involvement localized scleroderma invariably affects the head. The lesion can manifest either as localized scleroderma en coup de sabre (LSCs), a linear induration usually over the frontoparietal bone, or as progressive facial hemiatrophy (PFH, or Parry-Romberg syndrome), in which atrophy extends below skin and subcutaneous tissues and often involves underlying muscle and bone. Although there is some uncertainty as to whether PFH should be included on the spectrum of localized scleroderma disorders, the arguments for its inclusion are compelling. LSCs and PFH coexist in 20–37% of patients with LSCs, a higher rate of overlap than between LSCs and other localized scleroderma variants.^{46,47} Moreover, lesions initially classified as LSCs may progress to full-blown PFH after a delay of several years.⁵⁹ The two conditions have a similar age at onset (mean age of 11 years), disease course (typically, evolution of lesions over a span of a few years followed by stabilization), and predominantly affect women (female-to-male ratio 2–3:1). As will be detailed below, neurologic and ophthalmologic complications and neuroimaging features of both LSCs and PFH are identical. Both conditions may respond to immunosuppression.^{20,43,48,49} Most importantly, dermatopathologic findings in PFH are indistinguishable from those of other types of localized scleroderma.^{46,58} Therefore, for purposes of review of neurologic complications of localized scleroderma, PFH and LSCs will be combined under the rubric of craniofacial linear scleroderma.

The table summarizes clinical and radiographic features of the 54 published patients with craniofacial scleroderma, neurologic symptoms, and neuroimaging studies, alongside relevant data on our patient presented above. The literature cohort is likely skewed toward the more severe and unusual cases and may not reflect relative prevalences of the various neurologic syndromes associated with localized scleroderma. However, it is in close agreement with previously published series with respect to age of skin lesion onset, female-to-male ratio, fraction of patients with both LSCs and PFH, and prevalence of inflammatory eye disease.^{3,46,50,57}

For most patients in the literature cohort, localized scleroderma predated neurologic symptoms by several years (skin lesion appeared at age 9.5 years \pm 7.9, CNS symptom onset 13.8 years \pm 10.0), but in 29%, neurologic and dermatologic symptoms were separated by less than 1 year. In 16% of cases, neurologic involvement preceded dermatologic manifestations, though it is possible that in some cases subtle skin changes initially went undetected. Several patients who presented with neurologic symptoms were

Table	Clinical and radiographic features	
	All patients (n = 54)	Our patient
Female-male ratio	1:3	—
Age at onset of morphea, y, mean (\pm SD)	9.5 (\pm 7.9)	4
Range	1–34	—
Age of onset of CNS symptoms, mean (\pm SD)	13.8 (\pm 10.0)	15
Range	2–43	—
Time between skin lesion and CNS symptoms, y, mean (\pm SD)	4.3 (\pm 7.3)	—
% of patients with CNS symptoms before skin lesions	16	—
% of patients with CNS symptoms within 1 year of morphea	29	—
LSCS present, %	71	Yes
Hemifacial atrophy (PFH) present, %	64	No
Both LSCS and PFH present, %	35	No
Right-sided skin lesions, %	42	No
Bilateral skin lesions present, %	10	No
Craniofacial and non-craniofacial lesions, %	18	Yes
Uveitis, optic neuritis/atrophy, %	22	No
Non-neurologic, non-ophthalmologic symptoms, %	9	Yes
Neurologic symptoms, % at onset/overall or present		
Seizures	58/73	Yes
Intractable seizures	—/33	No
Headaches	27/29	Yes
Focal symptoms*	11/34	No
Neuropsychiatric	2/14	No
Elevated ANA (reported for 29/54 patients), %	26	Yes
Other autoantibodies in serum (reported for <30% patients), %	17	Yes
Leukocytosis in CSF, >5/mm ³	7 of 11 patients	No
Oligoclonal bands/elevated IgG index in CSF	7 of 11 patients	Yes
MRI brain (reported for 49 of 54 patients)		
Normal	11%	No
Single small lesion	31%	—
Multiple or diffuse lesions	63%	Yes
Brain lesion(s) ipsilateral to skin lesion only	88%	No
Calcifications on CT or MRI	37%	No
Enhancement on CT or MRI	8 of 16 patients	Yes
No T2 lesions, but other abnormalities	6%	—
Repeat MRI/CT with new lesions	15 of 29 patients	Yes
Abnormal MRA or cerebral angiogram	6 of 19 patients	No
EEG abnormal (at any point in disease course)	24 of 29 patients	No
Inflammatory lesion on brain biopsy	7 of 10 patients	N/A
Positive effect of anti-inflammatory drugs on CNS symptoms	11 of 15 patients	No

*Focal symptoms refers to any focal neurologic symptom referable to CNS dysfunction, with the exception of facial palsy and extraocular abnormalities, which could be explained by facial hemiatrophy.

LSCS = linear scleroderma en coup de sabre; PFH = progressive facial hemiatrophy; ANA = antinuclear antibody titers; MRA = magnetic resonance angiography.

found to have typical neuroimaging findings of linear scleroderma (focal atrophy, calcifications, T2 hyperintensities), but only years later did they exhibit skin lesions of scleroderma.⁵⁹ The observation that the brain could be affected before the skin raises the possibility that the pathologic process need not start in the integument and then affect CNS secondarily, but may proceed in the opposite direction as well.

Frequency of overlap of LSCs and PFH was 34% in the published cases, consistent with the 20–37% prevalence of co-occurrence in two other series.^{46,47} It should be noted, however, that classifying a particular case as LSCs, PFH, or both involves a degree of uncertainty as the boundary between the two conditions is not always well-defined. For example, some patients start out with a typical sclerotic lesion on the forehead and, after a delay of several months or even years, progress to overt PFH.³⁹ Other patients have more than one sclerotic lesion on the face, e.g., over forehead and maxilla, but do not have overt hemiatrophy. The difficulty in assigning patients to one or the other diagnostic category strengthens the argument that LSCs and PFH represent two ends of a spectrum.

The gamut of neurologic symptoms associated with craniofacial scleroderma is protean: seizures, focal neurologic deficits, and movement disorders secondary to brain lesions,^{28,30,40,41,45} trigeminal neuralgia,³ masticatory spasms,⁴² mimics of hemiplegic migraines,^{12,30,38} behavioral changes,¹⁸ progressive intellectual deterioration due to cerebral hemiatrophy either with focal seizures (Rasmussen encephalitis)^{7,32,39} or without seizures,^{20,54} cerebellar hemiatrophy,^{5,25} and even death due to brainstem involvement.³⁸

Localization-related epilepsy was the most common neurologic manifestation: it was reported in 73% of the 54 patients in the literature cohort, in 33% of whom seizures were described as being refractory to medications. EEG was done in 29 cases and abnormalities were noted in 24 of 29 patients. Brain lesions of localized scleroderma appear to be more epileptogenic than those of other autoimmune disorders of the CNS, such as multiple sclerosis (MS), in which epilepsy is seen in approximately 2% of patients.⁵²

In contradistinction to MS, focal symptoms appear to be relatively uncommon in localized scleroderma—reported for only 11% of patients at presentation and in 35% of patients overall. This estimate excludes facial palsy or extraocular movement abnormalities, which could be due to local atrophy rather than being primarily neurogenic in origin. Neuropsychiatric symptoms were mentioned in 15% of cases and headaches in 35%, but these symptoms

are often underreported and the prevalences are likely underestimates.

MRI of the brain was performed in 49 of the 54 patients, and CT of the head in the remaining 5. Ninety percent of MRIs were abnormal and showed at least one T2 hyperintensity, mostly in subcortical white matter, but also in corpus callosum, deep gray nuclei, and brainstem. Focal tissue atrophy, the dermatologic hallmark of the disease, is often seen in the brain as well. Brain atrophy is sometimes subtle (blurring of the gray–white junction, cortical thickening, sulcal effacement⁴) and highly localized, but at other times widespread, involving entire cerebral hemisphere.^{7,20,32,39,54} Infratentorial lesions and cerebellar hemiatrophy were seen in the more neurologically affected patients.^{5,25,38} The spectrum of brain atrophy parallels that of the skin, ranging from focal to diffuse, but almost always respecting the midline. In general, the more severe the skin and underlying tissue involvement the greater the extent of underlying brain atrophy as well. Calcifications, which are not seen in demyelinating diseases, were noted in 37% of brain MRIs in craniofacial scleroderma. Gadolinium-enhanced sequences were reported for 32% of the patients, half of whom had enhancing lesions. Remarkably, contrast enhancement can persist, and even increase, over a course of more than 3 years despite immunosuppressive treatments^{11,20,40}; our patient demonstrated enhancement of over 25 lesions on four serial MRIs during more than a year of follow-up. Rarely, enhancement is seen in the meninges as well.^{11,19}

Follow-up brain MRIs were carried out for 29 patients, and showed new lesions in 15 of them (52%), though resolution of lesions was also occasionally observed. These results suggest subclinical disease progression in many patients. Neurologically asymptomatic patients with craniofacial scleroderma were not included in this review, but it should be pointed out that these patients, too, may evidence clinically silent brain lesions.^{4,53} Recent brain SPECT series detected abnormalities in each of the seven patients with LScs, who were symptom-free and had normal MRIs.⁵³ Thus, subclinical CNS involvement is likely to be present in most, or possibly even all, patients with craniofacial scleroderma, depending on the sensitivity of the imaging modality. Overt neurologic involvement appears to be not nearly as infrequent as previously believed⁵⁸; clinical symptoms were reported by as many as half of the patients with craniofacial scleroderma.^{3,51}

MRA or cerebral angiograms were performed in 20 patients, demonstrating vascular changes suggestive of vasculitis in 8 (40%).^{7,19,20,22,28,44,48} Biopsy-proven low-grade cerebral vasculitis was documented

in three cases.^{23,31,40} Clinical signs of ocular vasculitis and radiographic evidence of cerebral vasculitis were described in one patient.²² In addition, there are a number reports of cerebral aneurysms and other vascular malformations in patients with craniofacial scleroderma,^{34,54,45} which could represent late sequelae of a vasculitic process.

CSF studies were carried out in 11 cases. Oligoclonal bands were present in seven, and elevated IgG index in one.^{19,27,32,38,40,42} Four of five patients with enhancing brain lesions on MRI who underwent a lumbar puncture had intrathecal antibody production.

Brain biopsy results are available for 13 patients. In three of these, inflammatory changes were seen both in parenchyma (“perivascular lymphocytic cuffing”) and vessel walls^{23,31,40} and in four others in parenchyma alone.^{7,35,39,44} In two patients, abnormal vessel hyalinization, gliosis, with or without calcifications, were present in the meninges.^{10,22} Lesions devoid of an inflammatory component could represent burned out stage of the disease.^{10,13,55} Five patients with craniofacial scleroderma were diagnosed with Rasmussen encephalitis based on clinical presentation and biopsy findings.^{7,13,39}

The etiology of localized scleroderma remains controversial, but a growing body of evidence supports autoimmune origin of the disease.⁵⁶ This hypothesis best accounts for observation that so many of the patients have autoimmune manifestations. Of the 54 patients in our review, 29% had uveitis, optic neuritis, Raynaud phenomenon or arthritis, and nearly 10% had Rasmussen encephalitis. The two largest series of localized scleroderma also reported high prevalences of autoimmune phenomena.^{2,3} Moreover, elevated titers of one or more autoantibodies, most commonly antinuclear antibody (ANA), rheumatoid factor, and anti-ssDNA antibody, were detected in the majority of patients.^{2,3,57} Among 54 patients of the literature cohort, ANA was reported for only 33 of 54 patients and elevated titers were observed in 14 of them (42%).

Frequent finding of contrast-enhancing brain lesions and intrathecal antibody synthesis in our patient, and a number of other similar patients previously described, suggest an active inflammatory process within the CNS. Positive effect of immunosuppressive agents (mainly of corticosteroids and methotrexate) on neurologic symptoms^{19,23} and skin lesions^{48,49} provides indirect support for autoimmune hypothesis, though claims of treatment efficacy must be viewed with caution in a disease that tends to run a self-limited course. Most important evidence in favor of autoimmune hypothesis derives from several brain biopsies, which show inflammatory changes in

the parenchyma and, sometimes, vessel walls and meninges as well. Skin biopsies, too, often reveal an inflammatory process similar to what is seen in the brain.^{12,33,46,59}

Brain involvement has been noted only among those patients in whom localized scleroderma affected face and cranium. Skin and brain lesions of localized scleroderma tend to appear on the same side and in close proximity to one another. Among the 55 neurologically symptomatic patients who are the subject of our review, 78% had brain lesions only on the side as the skin lesion. This is in agreement with the two series of neurologically asymptomatic patients with craniofacial scleroderma, in whom brain lesions were seen exclusively ipsilaterally to skin lesion in 82–100% of cases.^{30,41} Bilateral brain involvement in patients with unilateral skin lesion, as in our case, was distinctly uncommon. Proximity of brain and skin lesions and the fact that skin lesions of craniofacial scleroderma generally do not cross the midline of the face and cranium suggest that an aberrant inflammatory process has a circumscribed field of action. An adequate theory of pathogenesis would need to identify triggers of inflammation, explain self-limited nature of the process in space and time, and account for the often-seen calcifications and vascular malformations in the CNS.

CONCLUSION Survey of the literature demonstrates that CNS involvement in craniofacial scleroderma is much more common than previously suspected.⁵⁸ A thorough neurologic, neuro-ophthalmologic, and neuro-psychological testing of every patient with craniofacial scleroderma, supplemented by electroencephalographic and neuroradiologic studies (MRI, SPECT), would likely disclose abnormal findings in many, if not all, of these patients. It is uncertain whether these investigations are warranted in an asymptomatic individual as the disease course is usually benign and self-limited and no prophylactic treatment has been advocated to date. However, in a patient with neurologic symptoms and characteristic skin findings of localized scleroderma, a gadolinium-enhanced brain MRI is indicated and should be interpreted in the context of known radiographic stigmata of localized scleroderma. Spinal fluid analysis, if undertaken, should include testing for oligoclonal bands and IgG synthesis, especially if the brain MRI reveals enhancing lesions. In a patient with no known history of craniofacial scleroderma, but with MRI findings suggestive of the disease (blurring of gray–white junction, focal atrophy, T2 lesions, calcifications), a search for subtle skin abnormalities, such as skin hardening, areas of alopecia, or mild facial hemiatrophy, should be undertaken.

Our patient with craniofacial scleroderma and neurologic symptoms is similar in some respects to other patients previously described in the literature (table), but is unusual in that she exhibited several variants of localized scleroderma (linear scleroderma en coup de sabre, pansclerotic morphea, superficial circumscribed morphea) and had bilateral diffusely scattered brain lesions that continued to show enhancement and even increased in number during a year of follow-up despite treatment with high-dose steroids and an oral immunosuppressant. Our case illustrates that localized craniofacial scleroderma should be included in the differential diagnosis of MS and among neurologic disorders that cause localization-related epilepsy and headaches.

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