Neurologic Complications of Progressive Systemic Sclerosis

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Abstract

Neurologic manifestations/complictions of systemic scleroderma have received less attention in the literature than cardiac, pulmonary or gastrointestinal manifestations. We describe briefly three autopsied and proven cases of progressive systemic sclerosis in which there had developed prominent neurologic symptoms and signs, and discuss the relationship of those symptoms and signs with progressive systemic sclerosis. A review of neurologic complications is presented specifically to direct the attention of physicians to such symptoms which may later result in increased reporting of neurologic symptoms and signs. Already there is increased awareness due to reports of conditions such as trigeminal neuropathy and myopathy in more recent years. Cerebral, and specifically cerebrovascular, manifestations may be recognized more frequently in the future. A brief note of etiopathology and treatment is also mentioned.

Key words: *Progressive systemic sclerosis, neurologic complications, trigeminal neuropathy, peripheral neuropathy, myopathy, transient ischemic attacks*

Introduction

Progressive systemic sclerosis (PSS) sclerosis or diffuse scleroderma is a disorder of uncertain etiology affecting the connective tissue.[1] In addition to localized or generalized sclerosis of the skin, there are various systemic manifestations known to occur in this disorder and were described as far back as 1895.[2] Most reports describe cardiac, pulmonary, renal and gastrointestinal manifestations along with skin and musculoskeletal abnormalities. Neurologic manifestations, however, have been recorded on few occasions in the past.[3] These reports note a variety of nervous system disturbances such as peripheral neuropathy[4] or neuropathy and myopathy,[5] some related or non-related vascular and non-vascular changes in the brain,[6-8] some electroencephalographic[9,10] and even cerebrospinal fluid abnormalities.[10] In perhaps the largest study (727), cases, Tuffanelli and Winkleman[1] reported only one patient with seizure; otherwise no neurologic abnormalities were noted. During the last two decades, more and more neurologic abnormalities have been reported.[3,11-15]

This report concerns three autopsied cases of PSS to highlight the neurologic complications in this disease.

Case Report I

A white male, 55 years of age at death, first developed Raynaud's phenomena of the toes in 1938 and two years later started experiencing joint pains. Symptoms gradually progressed until 1942 when bilateral lumbar sympathectomies afforded some relief and the bluish discoloration of his toes disappeared. By 1950, the skin of his fingers on both hands showed tightness and superficial ulceration and contractures developed. Bilateral cervical sympathectomies performed in 1950 afforded further relief. He was hospitalized in 1954 and both laboratory and radiological tests showed evidence of

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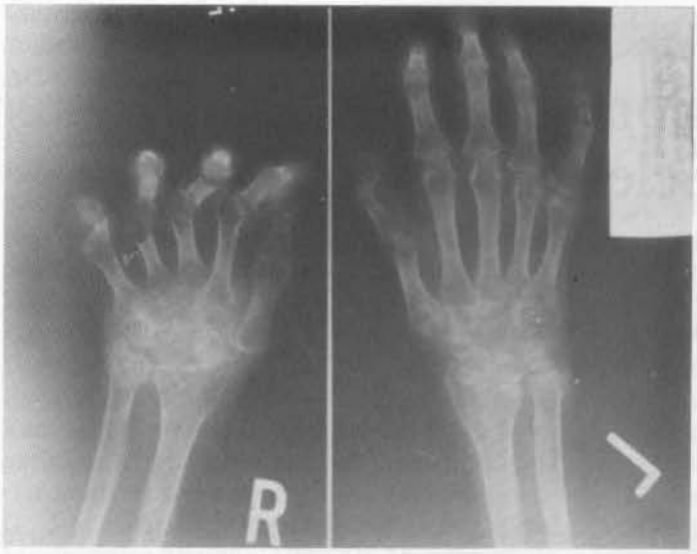
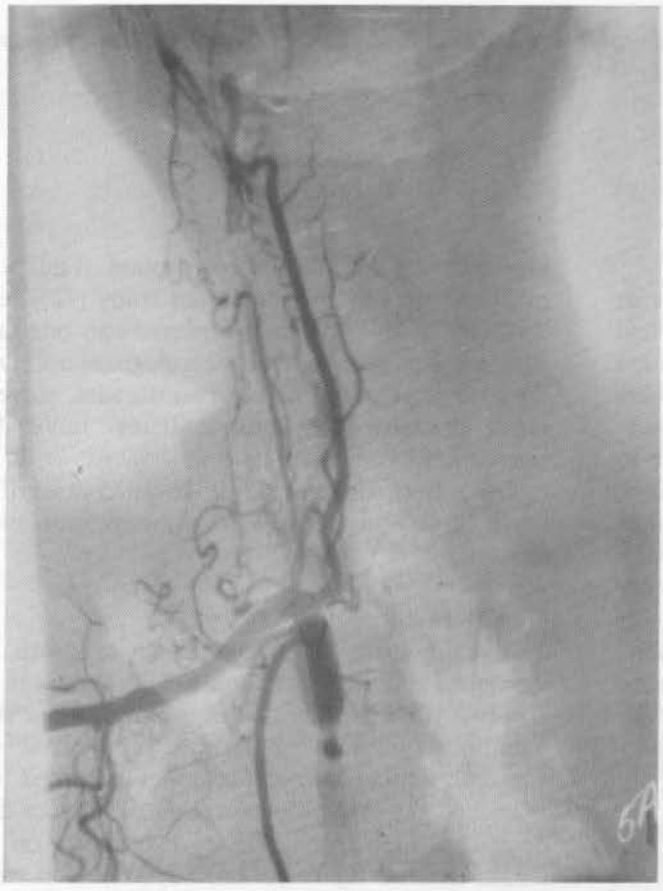


Case I
Neurotropic changes of both hands in PSS.



Case I
Arteriosclerotic disease of Innominate and non-filling of right common carotid artery. Note cervical collaterials that higher up reconstitute the external carotid.

esophageal and pulmonary involvement, and neurotropic changes in the bones of the hands and periarticular calcification of the right foot. During 1960-61 he suffered many episodes of numbness of his left face and limbs. For several days there were left-sided hemiballistic movements. All these complaints disappeared when he was treated with warfarin sodium. It later had to be discontinued because of epistaxis and hematuria. A right carotid bruit was first noted in 1968, but no neurologic symptoms were experienced by him. Cerebral angiography at this point revealed severe atherosclerotic disease of major extracranial arteries. In 1970, examination revealed thin atrophic skin of fingers, upper limbs, face, upper chest and neck and bilateral carotid bruits. There was generalized wasting of muscles, but reflexes and plantar responses were normal without any sensory deficit. He suffered exacerbations and then remissions of arthritis that would respond to increased dosage of prednisone and aspirin. He also received potassium para-aminobenzoate during his final seven years of life. He did not suffer any significant gastrointestinal or pulmonary symptoms until September, 1970, when he developed a respiratory illness that rapidly worsened until he died.

At autopsy the cause of death of was found to be a rapidly growing undifferentiated lymphoma infiltrating the lungs and myocardium which did not show interstitial sclerosis, but lungs and esophagus did show lymphocytic infiltration and sclerosis. Unfortunately the neck vessels and brain were not examined.

Case Report II

A German-born, mentally retarded woman was 57 years of age at the time of her death. She had had little education, immigrated to the U.S. during infancy and spent her childhood in an institution. In 1952, at the age of 39, she developed pain and swelling of the small joints of both hands. A diagnosis of rheumatoid arthritis was made and she received aspirin and corticosteroids at various times during the subsequent seven or eight years. She had no fever or rash and no history of Raynaud's syndrome. In 1961 she developed lassitude, weakness, loss of weight and macrocytic anemia with hyperplastic marrow. She developed tightness of the skin of the fingers and hands, and pain in the chest. Roentgenograms of the chest revealed bilateral bronchopneumonia with small pleural effusions. The hands showed demineralization of bones with loss of terminal phalanges characteristic of scleroderma. Radiologically, the esophagus was seen to be widened and rigid with only a few contractions in its lower half. Skin and muscle biopsy demonstrated atrophy of epithelium and increased density of connective tissue of the corium. The striated muscle appeared normal. She had symptomatic treatment and recovered from pneumonia. During her final ten years of life, she continued to lose weight with progressive decrease in the mobility of the joints of her hands, elbows and shoulders. She also developed wasting of muscles in the lower extremities.

In addition to thin, atrophic skin with thin lips, pinched nose, numerous spots of vitiligo and areas of subcutaneous calcinosis, she showed several neurologic signs. There was horizontal nystagmus on looking to the right. Muscles showed generalized wasting, especially in the lower limbs, with absent tendon reflexes. There was neither nerve nor muscle tenderness. She was unable to walk during the last few years of her life. EEG, brain scan, EMG and nerve conduction studies were not performed.

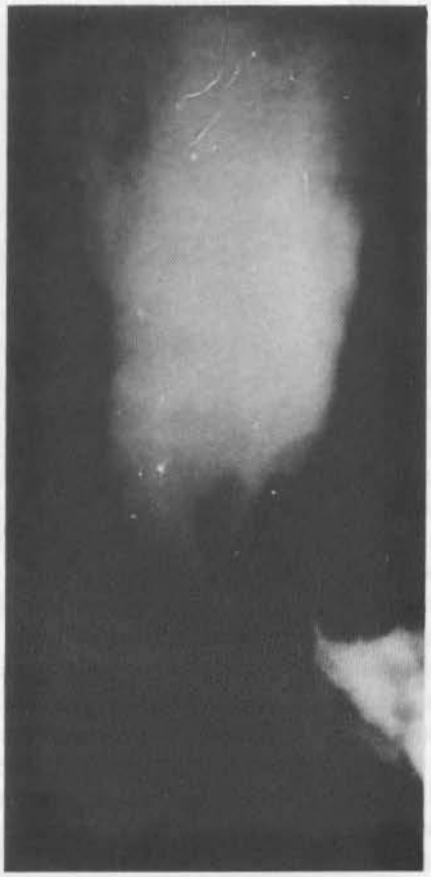
She had episodes of pneumonia in 1964 and 1965. A skin biopsy in 1967 was reported to be consistent with scleroderma. In 1970, she suddenly collapsed with abdominal pain. A roentgen film of the abdomen showed gas under her diaphragm. She died two days later.

At autopsy, sclerodermatous changes were observed in several organs and a large ulcer was noted in the stomach that had ruptured. The brain was small (850 gm); meninges were normal. Symmetrical atrophy was observed in the temporoparietal regions with the cystic degeneration of the cortex and microgyria in the "watershed areas" of the territories of the main cerebral arteries. There was a small, old organized infarct in the left thalamus; cerebellum, brainstem and their arteries were normal. Microscopically, there was a generally malformed cortex with blurring of laminar structure and bizarre distribution of neurones (areas of microgyria). Scattered larger pyramidal cells were noted throughout the thickness of the cortex. In the normally developed gyri, focal blurring of architecture with slight generalized increase in astroglia was seen. Basal ganglia showed perivascular spongy degeneration and hemosidrin infiltration of the walls of many vessels. Most of the larger neurones showed increase in lipofuscin contents. In the striatum, small interstitial calcific concretions were noted. In the insula, increased satellitosis and scanty lymphocytic perivascular infiltration were seen. The peripheral nervous system was not examined.

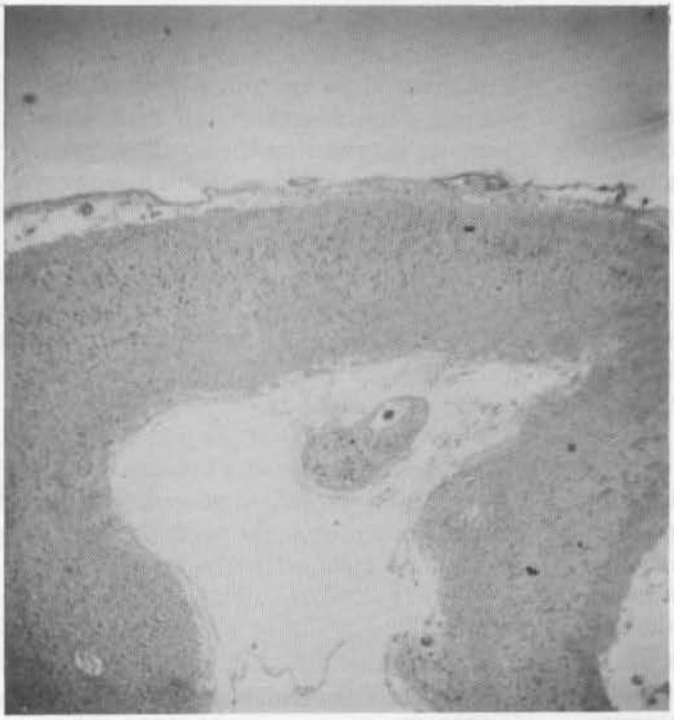
It was the opinion of the pathologist that the findings were consistent with hypoxia in early life (birth injury?) with ischemic degeneration and malformation of the cortex at the border zones of watershed areas of the main cerebral arteries.

Case Report III

This Caucasian female was 78 at the time of death in 1984. She first presented in 1976 with two episodes of unconsciousness preceeded by vertigo, heaviness of the lower extremities and numbness on the right



Case II
Dilated esophagus in PSS



Case II
Temporal lobe cortex
note the poor organization of cortex with obvious cystic change.

side. She also complained of occasional sharp pains in the right temple. She was found to have a very sensitive carotid sinus. Electronystagmography was interpreted as being compatible with brainstem disorder and she was treated conservatively for vertebral basilar insufficiency and improved. Four years later, mental symptoms began as "change of personality" described by her daughter (an R.N.) and she also started having Raynaud's phenomenon of her fingers. At this point she was hospitalized for investigations. She was oriented normally and had expressed some delusional ideation with resultant arrogance in behavior towards some of her friends and neighbors. This, according to her daughter, was completely unlike her. The only neurologic abnormality was diminished light touch and pinprick sensations on the left half of her face, but corneal reflexes were equal.

Skin of the fingers appeared normal and Raynaud's phenomenon was intermittent. Some telengiectasia were noted on the face. Cardiopulmonary examination was unremarkable.

Cerebral angiography showed left vertebral artery stenosis, Other extracranial and intracranial arteries were normal. An electroencephalogram was normal. The patient was referred to rheumatology service and was hospitalized in the medical unit of a university hospital where further investigations confirmed the diagnosis of systemic sclerosis. In December, 1984, she developed an acute respiratory illness and had a seizure episode. She later developed cardiorespiratory arrest and could not be resuscitated.

At autopsy skin changes typical of scleroderma were confirmed. Some interstitial fibrosis in the lungs, some areas of microabscesses and consolidation of the right lung were found. Renal vasculature showed sclerodermatous changes.

The brain showed generalized atrophy. Microscopic examination was unremarkable. The number of senile plaques appeared to be consistent with her age. There were no inflammatory cells and no lacunar or other infarcts. Calcific atherosclerotic changes were found in the proximal left carotid and innominate arteries. Ulcerated plaques were noted in the arch as well as lower abdominal aorta, indicating atherosclerotic disease.

Discussion

Neurologic signs and symptoms occur in any systemic illness either due to direct involvement of the nervous system by the specific disease process, or indirectly when the specific disease affects other organs or organ systems in the body that secondarily affect nervous system function. There also are coincidental neurologic signs and symptoms unrelated to the primary disease, and lastly, neurologic dysfunction of iatrogenic origin. The following neurologic signs and symptoms can be extracted from these case reports:

1. Episodic unilateral sensory and/or motor symptoms (hemiballismus)
2. Episodic vertigo and ataxia
3. Episodic psychiatric symptoms
4. Mental retardation
5. Nystagmus
6. Trigeminal neuraliga/neuropathy
7. Diminution or loss of deep tendon jerks
8. Generalized weakness and wasting of muscles
9. Seizures

In addition, many other neurologic manifestations in PSS have been described, including intra-cerebral hemorrhage or infarction, EEG abnormalities and CSF abnormalities, but these are not specific for PSS.

The first three (cases I and III) of the symptoms may be grouped under the term transient ischemic attacks (TIAs). That the TIAs occur in the territory of intracranial arteries due to their involvement in atherosclerotic or other diseases is now well established.[16] These attacks generally are not associated with areas of infarction in the central nervous system. Atherosclerotic disease of the arteries (carotid or vertebral basilar) seems to be responsible for the TIAs reported here and not the arterities of PSS, which has only very rarely been reported in the literature, affecting carotid arteries.[17] Microangiopathy due to PSS affecting intracerebral arteries producing a rupture and resultant intracerebral hemorrhage has also been reported.[18] Undoubtedly confusion and disorientation occurring in episodic form can be considered TIA, but in our report here, the personality change and delusional behavior seem unlike the TIA syndrome. It is true that such mental symptoms do occur in PSS, and these symptoms of delusion or hallucinations, etc., respond to steroid administration. A vaguely defined term, "scleroderma cerebritis",[13] has been applied to such cases in which CSF or EEG abnormalities may or may not be found. It is important to make sure that hepatic or renal function is not impaired in such patients. Due to lack of appropriate investigations in our third case, the psythiatric symptoms cannot be said to represent scleroderma cerebritis, but it remains an intriguing possibility. Considering that Alzherimer's disease is a popular diagnosis these days, a few words about the diagnosis of dementia, as for example, the mental symptoms of Case III mentioned above would be in order. When the neurofibrilary tangles and senile plaques are seen in various parts of the cortex in large numbers, the diagnosis of Alzheimer's is obvious, but as we see in Case III, the number of senile plaques seen is no higher than one would expect at the age of 77. As for mental retardation seen in Case II, with cortical and other abnormalities of cystic changes described above, the association with PSS is coincidental. Mayers[6] described a number of abnor-

malities such as focal areas of softening, adherent dura, gyrus induration and other cortical defects in his autopsied cases, but lack of clinical correlation makes these abnormalities coincidental to systemic scleroderma.

It is clear from the recent reports that unilateral or bilateral trigeminal neuropathy with neuralgia or without significant pain occurs more commonly in PSS than would be expected by chance.[3] Indeed, Farrel and Medsger,[3] describing 25 patients with trigeminal neuropathy, mention five patients in whom this neuropathy antedated the onset of PSS. This is almost the case in Case III, who had pain in the temple and diminished sensation prior to the onset of Raynaud's phenomenon. This neuropathy is more common in young females. Diminution of sensations in one or all branches of the trigeminal nerve is consistently found, and it tends to be progressive and does not remit. Other cranial nerves have also been reported to be involved but less frequently.[19]

Peripheral neuropathy in the limbs is not common. It is to be noted here that collagen tissue is present in peripheral nerves and not in the central nervous system. Peripheral neuropathy is of glove and stocking type or ascending type as described by Richter,[5] but it cannot be said with certainty that what he described was coincidental with Guillain-Barré syndrome in PSS. Other reports of neuropathies in PSS given in more recent literature[20] suggest that more cases will be reported as newer electrodiagnostic studies are more commonly available now.

Generalized muscle wasting is frequently observed in patients with PSS,[21] and chronic myopathy seems to be clinically apparent. However, electrodiagnostic studies and biopsies were performed less frequently and on many occasions negative reports were observed. It is hoped that the true incidence of chronic polymyopathy will be found when more attention is paid for electromyographic and biopsy studies. Our Case II shows some chronic polymyositis features. Other complicating factors, however, in evaluating the true incidence, is the "overlap" syndrome. There are some patients with scleroderma who will show more obtrusive polymyositis, and the clinical picture may show the mixture of scleroderma or systemic sclerosis and dermatomyositis, or as some would call it, "sclerodermatomyositis". In addition to other reviews of muscle involvement, one interesting report of ocular inflammatory myopathy in association with PSS appeared in 1973 in which myopathy associated with PSS was discussed well.[22]

The etiology of PSS is not clear. Auto-immune mechanisms are definitely involved, but the exact pathogenetic mechanism is not known. Chronic infections, chemical intoxication and such have been discussed in the past and theories of pathogenesis revolve around vascular and/or neurogenic abnormalities. Recent thinking may be more in favor of angiopathy[23] but earlier, Rodnan[24] discussed the following theories at length.

1. Auto-immune abnormal responses of the connective tissue
2. Infection (e.g. tuberculosis)
3. Chemical intoxication
4. Endocrine disturbance
5. Neurogenic theory

In cases of localized or linear scleroderma, a neurogenic basis in etiopathological mechanism is more convincing;[25,26] in the generalized scleroderma this claim is probably doubtful. Older literature[27,28] perhaps attached too much significance to the neurogenic basis. Nevertheless, the following observations are still worthy of considerations in support of the neurogenic theory:

1. Symmetry of skin lesions
2. Evidence of vasomotor instability (Raynaud's phenomenon)
3. Beneficial results from sympathectomy and from use of acetyl b-methylcholine chloride
4. Reports of scleroderma associated with:
   Facial hemiatrophy
   Complete hemiatrophy and cerebral lesions[29]
5. Changes in the spinal fluid
6. EEG abnormalities[9]

The exact significance of these observations and the relationship between localized and generalized scleroderma is not fully understood.

The views expressed in the article do not reflect official policy of the Department of Veteran Affairs.

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