

## Systemic Disease and Neuro-Ophthalmology: Annual Update 2000 (Part II)

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In this issue, we will update the general, neurologic, and ocular manifestations of four interrelated rheumatologic disorders: Sjogren syndrome; scleroderma; calcinosis, Raynaud phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasias (CREST) syndrome; and Raynaud disease/phenomenon. Although these disorders are rarely reported to be associated with neuro-ophthalmic disease, recent expansion of these clinical syndromes and improved understanding of their etiopathogenesis will likely lead to better recognition and their more frequent implication in visual and neurologic disease processes. This update is not meant to be a comprehensive review article on these entities but rather an update on the newer features of interest to the neurologist, ophthalmologist, and neuro-ophthalmologist.

### SJOGREN SYNDROME

The original description of Sjogren syndrome (SS) was a triad of dry eyes, dry mouth, and rheumatoid arthritis (1). Like many of the rheumatologic syndromes, SS may be an isolated entity (primary SS), or as secondary SS, it may be a feature of a broader autoimmune/rheumatologic illness, including entities such as rheumatoid arthritis, scleroderma, and systemic lupus erythematosus (SLE, e.g., 20% of patients with SLE develop secondary SS). Sjogren syndrome is not rare; it occurs in 2 to 3% of adults and is more common in women. Five percent of cases have onset of symptoms earlier than 12 years of age (2).

Generally, the neuro-ophthalmologist encounters SS when assessing a patient with unexplained ocular pain, and a diagnosis of dry eye (possibly in conjunction with other related symptoms) is made. SS, however, can have

many systemic, neurologic, ocular, or neuro-ophthalmic manifestations beyond a dry eye or mouth.

### General signs and symptoms of Sjogren syndrome

The classic symptoms of SS are caused by lymphocytic infiltration of exocrine glands. Oxholm and Asmusen (3) have proposed a new classification system for clinical involvement in primary SS, dividing the picture into three exocrine and four nonexocrine types (Table 1).

Anaya et al. (4) reported on the spectrum of illness in men, raising the question of whether the course is different in men than women (the disease is much more common in women). They pointed out that in their series of 13 men with primary SS, keratoconjunctivitis sicca (KCS) was the presenting sign in 62%, with extraglandular features being the presenting sign in the rest. Throughout the course of their illness, 92% of these men developed some extraglandular manifestation, with polyarthralgia and lymphopenia being the most common. As for serologic assays, they reported that antinuclear antibodies were abnormal in 85%; rheumatoid factor was elevated in 73%; and anti-SSA, anti-Rho, anti-LA, and anti-SSB were positive in 62% and 46% of cases, respectively. Based on this small series, they conclude that the incidence of extraglandular manifestations and serologic abnormalities is not different in men and women.

The disease can also occur in children. Kobayashi et al. (5) reported four cases of a childhood variant of SS that were accompanied by thyroiditis, interstitial nephritis, or sweat gland inflammation. In one of these four cases, there was also central nervous system (CNS) involvement. The authors point out that this spectrum of illness is not rare in adults with SS.

### Ophthalmic involvement and manifestations of Sjogren syndrome

Plugfelder et al. (6) has studied ways of using ocular tests to identify SS patients from amongst the total pool of dry eye cases. They found that absence of mucosal epithelial membrane mucin expression in the bulbar and tarsal conjunctiva was more typical of SS. Similarly, severe ocular surface rose bengal staining was also a marking of SS.

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Manuscript received December 15, 2000; accepted April 5, 2001.

Supported in part by a grant from Research to Prevent Blindness, Inc. and the Eye Institute of New Jersey

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TABLE 1.

A) Exocrine types
1) Type 1—surface exocrine disease
a) Keratoconjunctivitis sicca
b) Xerostomia
1) Upper airway disease
2) Rhinitis sicca
3) Xerotracheitis
c) Xeroderma
2) Type 2—internal organ exocrine disease
a) Involvement of the excretory parenchyma of the lungs, hepatobiliary system, pancreas, intestinal tract, and kidneys
3) Type 3—monoclonal B-lymphocyte disease (lymphoma)
B) Nonexocrine manifestations
1) Type 4—inflammatory vascular disease
a) Vasculitis and perivasculitis
2) Type 5—noninflammatory vascular disease
a) Raynaud
3) Type 6—mediator-induced disease
a) Hematologic cytopenia, fever, and fatigue
4) Type 7—autoimmune endocrine disease

### Neurologic manifestations of Sjogren syndrome

The first reported neurologic manifestations were described by Sjogren (7) himself and were facial nerve paralysis and involvement of the sensory branches of the trigeminal nerve. Lafitte (8) has recently reviewed the neurologic manifestations of SS. He states that they occur in 20% of cases of SS. Nonfocal findings that have been reported include mental status changes and seizures. Multiple cranial neuropathies and sensory and motor polyneuropathies have been seen. In reviewing his personal series of patients with SS, Lafitte finds the incidence of peripheral neuropathy to be 8%, and the KCS complex preceded the neurologic symptoms in nine of ten patients (90%) by a mean of 4.5 years.

In looking at the laboratory evaluation that the patients with neurologic SS have undergone, Lafitte (8) points out that the patients with peripheral neuropathy who have undergone electromyography (EMG) typically demonstrate a pattern consistent with denervation. Nerve conduction velocity (NCV) shows velocities that were normal or slightly reduced, sometimes with prolongation of distal latency. Lumbar puncture is typically normal, and slight pleocytosis or elevation of protein has been seen.

As for pathologic findings, Lafitte (8) reports that peripheral nerve biopsies from patients with SS and peripheral neuropathy have typically shown vasculitis (which may be acute or chronic), or perivasculitis. Demyelination is not uncommon. Muscle biopsies have shown vasculitis, perivasculitis, or myositis. One autopsy case of CNS disease was found and reported necrotizing arteritis of small arteries and arterioles; an autopsy case with spinal cord involvement also showed a necrotizing vasculitis.

Amoura et al. (9) pointed out that although peripheral nervous system manifestations are more common, CNS findings do occur. These manifestations include encephalitis, focal or diffuse involvement of the spinal cord, and acute aseptic meningitis. He states that psychi-

atric changes are not uncommon in these patients. Sagawa et al. (10) state that the most common psychiatric findings are depression and anxiety.

Belin et al. (11) found that 100% of his series of 14 female patients with SS had abnormalities on formal neuropsychologic testing. The abnormalities were typically frontal lobe syndrome and memory deficits. These findings did not seem to be correlated with other neurologic abnormalities findings on magnetic resonance imaging (MRI) scans but did correlate with the results of 99m-technetium-hexylmethylpropylene amineoxine (HMPAO) single photon emission computed tomograph of the brain (SPECT) (see "Diagnostic techniques for Sjogren syndrome").

Govoni et al. (12) systematically studied 87 unselected patients with primary SS (4 men, 83 women) for evidence of neurologic involvement. They found that seven patients had CNS disease (8%), largely a nonfocal illness. Twelve patients (14%) had peripheral nervous system (PNS) disease, largely sensory or sensory-motor polyneuropathy; one patient had CNS and PNS disease. They found that CNS disease tended to occur in the younger patients, and neither serologic assessment nor other extraglandular disease activity served as useful markers for the development of neurologic involvement.

Niemela and Hakala (13) recently reported a case and reviewed the literature on neurologic involvement in SS. Their patient had primary SS and had lymphadenopathy and myositis, after which she developed severe CNS disease, vasculitic lesions on her hands, and a neurogenic bladder attributed to spinal cord involvement. Although she did not respond to corticosteroids alone, she did respond to the addition of cyclophosphamide. Niemela pointed out that the incidence of CNS disease in SS is not well characterized in the literature, with statements ranging from its being rare to being present in approximately 25% of cases. This group feels that MRI is the most sensitive test and cerebral angiography the most specific test for detecting neuro-SS. They also point out that no controlled therapeutic trials have been performed, and the typical therapy of neuro-SS is that of vasculitis.

Escudero et al. (14) reviewed the neurologic involvement in 48 patients (7 men, 41 women; mean age: 58.2 years) with primary SS. The most common CNS features were migraine (52%), neuropsychiatric disease (29%), and focal neurologic deficits (23%). MRI scanning detected small hyperintense subcortical lesions in 51.3% of patients (36.6% in age- and sex-matched controls,  $P < 0.001$ ). They point out that the coexistence of late onset migraine-like episodes with prolonged sensorimotor deficits and coexisting neuropsychiatric disease may be a typical symptom complex in SS patients who present with neurologic manifestations. In their series, a multiple sclerosis-like course was rare.

Perhaps the highest incidence of neurologic disease was reported by Tajima et al. (15) in a series of 21 female Japanese patients with primary SS. Sixteen of these 21 patients (76%) showed neurologic symptoms. The most common finding was trigeminal neuropathy, seen in

50%. Multiple mononeuropathy was seen in 31% of cases. CNS involvement was only observed in three cases (14%).

van Dijk et al. (16) have looked from the reverse perspective (i.e., has tried to assess the incidence of occult SS in 65 patients with idiopathic axonal polyneuropathy), using an interview focusing on ocular and oral sicca symptoms, a physical examination, tests for objective assessment of KCS, serologic investigation, and sublabial salivary gland biopsy (done in only 49 of the cases). Three of the 49 (6%) had a biopsy consistent with SS. Although such symptoms were revealed in the study, none of these three patients had spontaneously complained about sicca symptoms. The authors conclude that in patients with chronic idiopathic axonal polyneuropathy, a systematic investigation for Sjogren syndrome should be completed. Parkinson disease has been reported in association with SS. Walker et al. (17) described three cases and cites five more in the literature.

Tumiati et al. (18) have examined the incidence of hearing loss in SS. In comparing 30 patients with SS with 40 age-matched controls, they found that 46% of patients with SS had sensorineural hearing loss compared with 3% of controls. Of note was that of the patients with hearing loss, 64% had positive titers for anticardiolipin antibodies.

As is the case with many autoimmune diseases, patients with SS may display a clinical syndrome and MRI findings similar to multiple sclerosis. Watanabe et al. (19) described a 40-year-old woman with primary SS who had a slowly progressive neurologic course. Neurologic signs and symptoms included spasticity and monoparesis of the left leg, slurred speech, nystagmus, hyperreflexia, and positive bilateral Hoffmann reflexes and Babinski signs. MRI scanning showed multiple nonenhancing plaquelike lesions in the white matter of the cerebrum and brainstem. Notable serologies included an abnormal antinuclear antibody (speckled) and anti-SSA/Ro antibody. Spinal fluid showed 8 cells/mm<sup>3</sup>, a protein of 42 mg/dL, four oligoclonal bands, and an elevated IgG index. Because of her dry eyes, lacrimal and salivary secretion tests were performed and demonstrated hyosecretion of tears and saliva. This finding led to a biopsy of the lip with demonstration of destruction of the minor salivary gland ducts with periductal lymphocytic infiltration, which confirmed the diagnosis of primary SS.

### **Neuro-ophthalmic manifestations of Sjogren syndrome**

Optic neuropathy is occasionally seen as a manifestation of primary SS, with approximately ten cases having been reported, most recently by Rosler et al. (20) and Harada et al. (21). Rapoport et al. (22) has described the case of a 68-year-old woman with well-documented primary SS (keratoconjunctivitis sicca with abnormalities in salivary gland biopsy and serologic abnormalities) who developed ischemic choroidopathy (shown on fluorescein angiography) and optic neuropathy. The optic neuropathy was accompanied by pain, the disc was swollen,

and the visual loss partially responded to prednisone. Several months later, she experienced visual loss in the other eye, associated with hypoesthesia of the left side of the body. Fluorescein angiography indicated that this visual loss was caused by choroidal infarction. Because of symptoms of KCS, a minor salivary gland biopsy was performed, which confirmed the diagnosis of SS. This patient later developed transverse myelopathy.

DeGuzman et al. (2) have described a fascinating case of a 14-year-old boy who presented with a fever and a generalized tonic-clonic seizure. Approximately 1 year later, involuntary spasms of the gastrocnemius and quadriceps muscles and episodes of limb ataxia began; another tonic-clonic seizure occurred. At this point, a poorly documented episode of loss of vision OD that lasted 2 weeks was noted. Six months later, bowel and bladder incontinence and lower extremity numbness were seen. Five months later, he developed what was described as nonerythematous, nontender, right periorbital swelling and reported decreased vision and seeing gray spots.

The ophthalmic exam showed acuities of no light perception OD and 20/20 OS. The right eye showed keratoprecipitates and inflammatory cells in the anterior chamber and vitreous. Blood was reported as being present in the neuroepithelium from the optic disc to the ora serrata, with venous tortuosity and intraretinal blood in all four quadrants. An inflammatory nodule was seen anterior to the optic disc. Perivenous sheathing was recorded, especially around the larger veins in the posterior pole. Fluorescein angiography showed significant slowing of venous return and poor arteriolar perfusion of the fovea, with diffuse leakage from both veins and arteries, especially on the venous side.

The MRI scan showed a linear focus of abnormal signal in the frontal periventricular white matter on T2 sequences. On T1 sequences, there was enhancement at the level of the right trigeminal nucleus. The spinal tap was remarkable for a mild pleocytosis; no oligoclonal bands were seen, and myelin basic protein was normal. Key serologic findings included an erythrocyte sedimentation rate (ESR) of 52 mm/h, a marked elevation of serum IgG, and a slightly elevated CH50. Antinuclear antibody, anti-double-stranded DNA, anti-ribonuclear protein, anti-SM, anti-SSA (Ro), anti-SSB (La), antiphospholipid antibodies, and antineutrophilic cytoplasmic antibody (ANCA) were all normal. Rheumatoid factor and angiotensin-converting enzyme (ACE) results were not mentioned. The serum anti-Ro converted to positive, and 6 months later, a minor salivary gland biopsy was performed, revealing a pathology of focal lymphocytic sialoadenitis, which is consistent with (although not absolutely specific for) SS. The patient was treated with corticosteroids and monthly intravenous cyclophosphamide. On this regimen, his CNS and ocular disease progressed, with bilateral panuveitis, sensorineural hearing loss, and a central facial paresis. He also developed a mild thoracolumbar myelopathy. The CNS disease responded to intravenous corticosteroids, and his mainte-

nance therapy was changed to prednisone and chlorambucil, which controlled his symptoms (2).

Bachmeyer et al. (23) has reported a case of bilateral Adie tonic pupil in primary SS. This patient had antibodies to Ro (anti-SSA). Whereas the patient's necrotizing gingivitis responded to systemic therapy (corticosteroids and antimalarials), the pupillary abnormality did not. The authors postulate that the source of the Adie pupil was an inflammation of the ciliary ganglion.

### Diagnostic techniques for Sjogren syndrome

The use of MRI scans in the detection of neurologic lesions in primary SS has recently been studied by Coates et al. (24). The frequency of deep white matter and subcortical lesions was significantly increased in the SS patients (with and without neurologic illness) compared with age-matched controls. The presence of these lesions did not correlate with serologic markers such as anticardiolipin antibody, serum IgG levels, or titers of rheumatoid factor, nor did they correlate well with neurologic signs and symptoms. In addition, corpus callosal lesions were not seen in the SS patients, thereby being a marker that may be used to help differentiate these patients from those with MS.

Kao et al. (25) used 99m-technetium-HMPAO brain images with fanbeam SPECT to study 48 SS patients, all of whom had undergone a normal MRI or computed tomograph (CT) of the brain. In the group with neuropsychiatric symptoms and signs, 53% showed local hypoactivity in the cortex, whereas only 20% of the group without neuropsychiatric signs had this abnormality. Similarly, hypoactivity was seen in the basal ganglia and thalamus of 14% of those with symptoms and none without neuropsychiatric symptoms. In those with neuropsychiatric symptoms, the parietal lobes were the most common areas of brain involvement. The authors feel that this method of SPECT scanning may prove to be a sensitive tool for detecting regional cerebral anomalies in SS patients.

Kao also compared the usefulness of 18F-2-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomograph (PET) scanning and 99m-technetium-HMPAO SPECT scan in patients with neuropsychiatric manifestations of primary SS. It was found that 99m-technetium-HMPAO SPECT was superior, with abnormalities detected in 81% of patients and with the parietal and temporal lobes the most common sites of brain involvement. 18F-FDG PET scans were abnormal in only 19% of patients, with the temporal lobes being the most frequently affected site (26).

Lass et al. (27), in trying to explain neuropsychologic changes seen in SS patients, studied cerebral blood flow via 99m-technetium-HMPAO brain SPECT. They studied 21 patients with SS and found that focal interhemispheric perfusion deficits were seen in 17 of 21 patients (80.9%). Although their patient sample was small, these changes were independent of whether or not the patient had psychologic or neurologic symptoms. These perfusion changes were mainly in the prefrontal and frontal areas and the occipital lobes and occipitoparietal area.

Diffuse hypoperfusion of the frontal lobes was seen in 29% of patients. They state that although the mechanism of this alteration in cerebral blood flow alterations is unknown, it might be the result of diffuse cerebral vasculitis.

## SCLERODERMA

Scleroderma is also known as systemic sclerosis or progressive systemic sclerosis. It targets numerous organ systems, including the skin, blood vessels, synovium, gastrointestinal tract, kidneys, heart, and lungs. The subtype known as CREST syndrome will be discussed later.

The lesions of scleroderma are typified by inflammation and fibrosis; the etiology of these lesions is not well understood. One theory is that activated inflammatory cells liberate cytokines, which in turn stimulate collagen production. As in Wegener granulomatosis, the disease may be diffuse or localized. Eighty percent of patients are women (28).

The skin changes are typified by overabundant deposition of collagen, presumably leading to skin thickening, tightness, and diminution of mobility with contracture. Telangiectasia and calcinosis are often seen. A second feature of this disorder is vascular insufficiency and vasospasm. Raynaud phenomenon is a typical feature of scleroderma, occurring in perhaps 95% of cases.

### Ophthalmic manifestations of scleroderma

The most recognized feature is KCS, present in as many as 70% of cases. This symptom is complicated by the foreshortening of the conjunctival fornices (28). Choroidal disease is not uncommon in scleroderma; one series reported that 53% of cases had patchy areas of non-perfusion on fluorescein angiography. The authors point out that this nonperfusion is not detectable on funduscopy (29).

### Neurologic manifestations of scleroderma

The CNS is typically spared in scleroderma. A few cases of stroke have been reported, presumably related to fibrosis occurring in artery walls (30). PNS disease is unusual in scleroderma and is typically related to nerve entrapment. When the PNS is involved, a distal mononeuropathy of the median nerve is a typical feature (31). Mouthon et al. (32) have recently reported brachial plexopathy in a case of scleroderma. Pulse cyclophosphamide therapy led to improvement of the cutaneous and neurologic manifestations in this patient.

One series reported a much higher incidence of neurologic disease in scleroderma. This group found that 11 of 31 patients (35%) had neurologic findings, consisting of trigeminal neuropathy or polyneuropathy. They also felt that the subpopulation of scleroderma patients harboring the antibodies anti-U1RNP and possibly those with anti-Scl-70 might be more prone to develop neurologic illness (33).

This same group also studied the potential genetic basis for altered immune function playing a role in scleroderma. They reported that patients with neurologic illness had a higher frequency of human leukocyte antigen

(HLA) types DR5 and B8 than scleroderma patients without neurologic illness. They conclude that genetic substrate may be associated with different clinical subsets of systemic sclerosis (34).

Autonomic nervous system dysfunction is not unusual and appears to be a key factor in the development of microvascular, cardiac, and gastrointestinal symptoms (31,35).

Recent evidence has emerged that nerves may be a target in this disorder, independent of direct compression. Malandrini et al. (36) recently performed rectal biopsies on three patients with limited and early scleroderma of the gastrointestinal system. Axonal degeneration with mast cells in close proximity to nerve fibers was seen.

### Etiology of scleroderma

It is generally accepted that the fibrosis that is the main feature of scleroderma is secondary to persistent overproduction of collagen. The question is why. Jimenez and Saitta (37) pointed out that the overproduction results from altered regulation of expression of the alpha 1(I) collagen gene (*COL1A1*) in patients with sclerosis.

Recent work by Shi-Wen et al. (38), using fibroblasts from the skin of patients with scleroderma, supports that an upregulation in a gene may cause the fibrosis that characterizes this disorder. They found that the gene that codes for human connective tissue growth factor (CTGF) is consistently present and that the protein that it codes for is seen in cultured fibroblasts of scleroderma patients but not in healthy patients.

Another question that has been raised is whether altered arteriolar response to vasoconstrictors might play a role in the pathogenesis of scleroderma. Flavahan et al. (39) has recently demonstrated that dermal arterioles from skin biopsies of scleroderma patients have increased vasoconstriction in response to alpha-2 adrenergic receptor agonists. They postulate that this finding may play a role in the vasospasm that is a prominent feature of this illness.

As for the basic trigger of the altered gene regulation or vascular sensitivity, Kahaleh and LeRoy (40) point out a line of evidence for unsuspected cytomegalovirus infection being the trigger. This evidence includes the detection of increased levels of anticytomegalovirus antibodies in patients with scleroderma and similarity between the vascular disease of cytomegalovirus and scleroderma.

### Diagnostic techniques for making the diagnosis of scleroderma

Salojin et al. (41) has postulated that antiendothelial cell antibody (AECA) may be a marker that allows one to prognosticate disease severity, because it tends not to be positive in those patients with milder forms of scleroderma.

Stucker et al. (42) have used digital subtraction angiography of the digits to study vasooclusive disease in scleroderma. They studied a total of 29 scleroderma cases, 14 with acroscleroderma and 15 with proximal

ascending sclerosis. They found that 27 of 29 (93%) patients demonstrated stenosis. The involvement tended to be more prevalent in the distal upper extremity. The severity of Raynaud phenomenon seen in these patients did not correlate with the angiographic findings.

Heron et al. (43) looked at the usefulness of CT scans of the brain in the detection of intracerebral calcifications in scleroderma. They studied 37 consecutive scleroderma patients with noncontrast brain CT. Of these, 43% had diffuse scleroderma and 57% had the limited form. They found intracerebral calcifications in 32% of their scleroderma patients. Although the age of the patient did not seem to be correlated with the presence of calcifications, the duration of Raynaud phenomenon did, with the duration being twice as long in those with calcifications. In general, the calcifications did not correlate with symptoms—the sole exception being disease of the digestive tract. Calcifications were also seen in the basal ganglia in 30% of patients (the incidence in the population is said to be 0.2–2%). The authors postulate that the calcification is a marker for chronic vascular injury in the disease.

### Therapeutic strategies for scleroderma

Trials of the use of immunomodulatory drugs in this disorder have lagged behind that of other entities such as vasculitis. Morton and Powell have recently used cyclosporine and tacrolimus in patients with scleroderma. In a retrospective review of their experience, they found that half of their patients treated with cyclosporine for skin tightness noted improvement. Of the patients treated for digital vasculitis, 25% noted resolution. They also report that most patients could not tolerate the drug. They have a smaller experience with tacrolimus; it appears to be better tolerated than cyclosporine and seems to yield similar results (44).

Numerous agents are being tested for therapy of specific features of this disorder, including the agent saprorelate hydrochloride, which has shown some promise in a small study (45).

### CREST SYNDROME

The CREST (Calcinosis, Raynaud phenomenon, Esophageal motility disorders, Sclerodactyly, Telangiectasias) syndrome is considered by most professionals to be a subtype of scleroderma. The first case was reported by Thibierge and Weissenbach in 1910, although the use of what was then ACRST syndrome did not appear until 1964. Identifying the CREST subtype is important; the prognosis is better in this form than in diffuse scleroderma. Fifty percent of CREST syndrome patients demonstrate anticentromere antibodies (as opposed to the diffuse scleroderma type, which is associated with anti-Scl-70 [topoisomerase I] antibodies in approximately 25% of patients or with anti-RNA polymerase III in approximately 20% of patients) (46).

### Ophthalmic manifestations of CREST syndrome

Al-Husainy and Deane (47) have reported on a patient with bilateral keratomalacia in CREST syndrome. This woman had CREST syndrome for 18 years and had been using lubricant eyedrops for 7 years for a mild dry eye

that became symptomatic after cataract surgery 7 years before presentation. She developed paracentral corneal melts sequentially (1 month passed before the second eye ulcerated). The ulcers were unresponsive to a regimen that included lubrication, antibiotics, topical corticosteroids, and botulinum-induced ptosis. In evaluating her, it was noted that her vitamin A levels were low (0.07 mg/L, normal: 0.2–1.8 mg/L), and her serum beta-carotene was undetectable. She was given nasogastric and intravenous vitamin A supplements, and the ulcers began to heal, although she died 10 weeks later. The authors postulate that the ulcer was secondary to xerophthalmia from nutritional deficiency in CREST syndrome.

Santos et al. (48) have reported on a patient with CREST syndrome, primary biliary cirrhosis, and bilateral granulomatous uveitis. Proctor et al. (49) have described a case of parafoveal telangiectasia, also known when acquired as idiopathic juxtafoveal retinal telangiectasia, in a patient with CREST syndrome. She presented with visual loss in one eye 11 years after her CREST syndrome manifested. Although the symptoms were monocular, she was noted to have telangiectasia bilaterally in the temporal parafoveal zone, with retinal thickening. The fluorescein angiogram showed enlargement of the foveal avascular zone and leakage from the telangiectatic vessels. The authors suggest that there may be a common pathophysiologic mechanism for the CREST and the retinal findings.

#### Neurologic manifestations of CREST syndrome

Dyck et al. (50), using the patient population of the Mayo Clinic, identified 536 people with CREST syndrome. Of these, seven (1.5%) had peripheral neuropathy not attributable to another cause. The range of time from the onset of CREST syndrome to development of peripheral neuropathy was from 0 to 25 years. This typically was a multiple mononeuropathy. Sural nerve biopsy was performed in four cases, revealing multifocal fiber loss and perivascular inflammation. Three of the cases either were frankly diagnostic of or suggested necrotizing vasculitis. Note that this finding is similar to what Lafitte (8) has reported as the pathology of peripheral neuropathy in Sjogren syndrome.

Blanco et al. (51) reported two cases of CREST syndrome with extensive cerebral calcification noted on CT scan. The first patient presented with typical systemic symptoms, depression, and mental slowing. During the next 6 months, his cognitive changes progressed; the rest of the examination was normal. His CT scan showed bilateral calcifications in the dentate nucleus, basal ganglia, and subcortical white matter. The second patient developed transient ischemic attacks (express aphasia and right hemiparesis) 1 year after diagnosis of CREST syndrome. Her neurologic exam was normal; her CT scan showed bilateral calcification of the basal ganglia and faint calcifications of the dentate nuclei and rubrum nucleus, with moderate cerebral and cerebellar atrophy. Carotid ultrasonography and Holter monitor were normal; an echocardiogram showed calcification of the mitral valve leaflets with thickening and an ejection

fraction of 60%. Aspirin was given, and no further ischemic attacks occurred. The authors postulate, as did Heron et al. (43) in their cases of scleroderma, that chronic vasculopathy led to the calcification.

Heron et al. (52) described two patients with neurologic involvement in CREST syndrome who underwent autopsy. One had dementia, and the other had transient ischemic attacks and a balance disorder. Both cases showed extensive wall calcification of small arteries and arterioles in the brain, especially in the basal ganglia and in the frontal lobes and the cerebellar area in the second case. Because no other known cause of the calcification was found, the authors postulated that calcification might be a marker for CREST-induced vasculopathy. Note that this group later performed the study of CT scans in patients with scleroderma, mentioned in the preceding section, "Diagnostic techniques for making the diagnosis of scleroderma" (43).

Kambara et al. (53) have reported a case of myasthenia gravis in a patient with CREST syndrome. Ortiz et al. (54) have reported on a patient with CREST syndrome who developed multiple intracranial aneurysms.

#### Neuro-ophthalmic manifestations of CREST syndrome

Neuro-ophthalmic disease has not been a feature of CREST syndrome. In the previously mentioned case of Ortiz et al. (54), the patient had bilateral optic neuropathy. The authors postulate that there may have been components of direct aneurysmal compression of the optic nerves and an intrinsic vasculopathy.

#### Diagnostic techniques for CREST syndrome

This syndrome may overlap with several other autoimmune diseases. Furthermore, other conditions such as rheumatoid arthritis or SLE may evolve into CREST syndrome. Of note is that when this event occurs, it may be heralded by the patients seroconverting to positive for autoantibodies such as the anticentromere antibody (55).

Lundberg et al. (56) also reported on the usefulness of an IgG autoantibody against fibrillin as a marker for CREST syndrome in a small group of patients. Although this marker is present for long periods, it is not specific for CREST and is seen in other disorders, such as mixed connective tissue disease.

### RAYNAUD DISEASE AND RAYNAUD PHENOMENON

Raynaud disease (RD) is typically a bilateral symmetric illness seen predominantly in women. Raynaud phenomenon may be a prominent feature in RD. Raynaud phenomenon is the typical blanching of the distal digits, often accompanied by pain. A typical color progression of white to red to blue is seen as cyanosis develops from vasospasm. Raynaud phenomenon may be secondary to RD or to other illnesses—especially collagen vascular diseases such as rheumatoid arthritis, scleroderma, or CREST syndrome—or even mechanical causes, such as use of a pneumatic drill.

Raynaud phenomenon is not uncommon. Brand et al. (57), reviewing data from the Framingham study, found

a slight preponderance in women (9.6% of women, 8.1% of men). Eighty-one percent of this was primary Raynaud disease. They found that the most common causes of secondary Raynaud phenomenon were carpal tunnel syndrome, rheumatoid arthritis, and use of beta-blockers.

#### **General signs, symptoms, and associations of Raynaud disease**

Raynaud phenomenon may be a feature of another disease of interest to neuro-ophthalmologists. Recently a case of Raynaud phenomenon was reported secondary to giant cell arteritis. This biopsy-proven case had angiography, which demonstrated occlusion of the subclavian and axillary arteries with abundant collaterals. Therapy with oral corticosteroids led to resolution of the Raynaud phenomenon, which was attributed to the involvement of the subclavian artery (58).

Another case where Raynaud was a presenting feature of a more widespread systemic disorder was published by Boortz-Marx et al. (59). The patient in this study presented at age 29 with livedo reticularis, hypertension, and Raynaud phenomenon. Antiphospholipid antibodies were absent. This patient underwent leptomeningeal biopsy, which revealed a granulomatous infiltration. Ultimately, a final diagnosis of Sneddon syndrome was established.

It has long been known that Raynaud phenomenon may be related to repetitive vibrational injury, such as occupational use of a pneumatic drill. Cherniack et al. (60) have shown that these abnormal vascular responses were worse in smokers. Furthermore, among those people who ceased their occupational exposures, those who also stopped smoking had much fewer symptoms of Raynaud phenomenon than those who continued smoking.

Raynaud phenomenon may also be iatrogenic. It appears to be a consequence of therapy with both interferon-alpha and -beta. Ene et al. (61) reported on a patient who had preexisting Raynaud in chronic hepatitis C. This patient was treated with interferon-alpha-2b and developed episodes of severe headache, worsening of the Raynaud, and blurred vision that occurred within 1 hour of the interferon injection and resolved within 1 day. Cruz's patient did not have preexisting Raynaud and developed severe manifestations 2 weeks after beginning interferon-beta therapy for multiple sclerosis, including digital necrosis and livedo reticularis. These manifestations improved after discontinuation of the therapy (62). Raynaud (with livedo reticularis) has also been described as a result of methimazole therapy for Grave disease (63).

#### **Ophthalmic manifestations of Raynaud disease**

Terwindt et al. (64) has described a Dutch family with a pedigree that features Raynaud phenomenon in conjunction with migraine and a vascular retinopathy. Although the age of diagnosis of the retinopathy ranged from 26 to 62 years, the authors point out that these patients typically did not consult their ophthalmologist until retinopathy was advanced, so the age of onset is not

clear. The younger patients typically had capillary occlusions, whereas the older patients also had large vessels involved. A typical feature was parafoveal telangiectasia and microaneurysm. When the disease affected larger vessels, it tended to involve the arteries more than the veins. Neovascularization and shunt vessels were seen, and 30% of those with retinopathy developed optic atrophy. The authors comment that there seemed to be a disparity between fundus appearance and visual acuity, with the acuity sometimes remarkably spared.

#### **Neurologic manifestations of Raynaud disease**

Ferraccioli et al. (65) have recently investigated regional cerebral blood flow in patients with Raynaud phenomenon by employing SPECT scanning. The scans were done and then repeated within a week, with tracer injected within 1 minute of completion of a cold test (whereby the patient's hand is immersed in 4°C water for 15 minutes or until the pain became intolerable).

Among the 12 patients with Raynaud secondary to SLE, 75% had cerebral perfusion defects, as opposed to 57% in SLE cases without Raynaud. Of note was that the cold test elicited new perfusion defects in two cases, and seven of nine (78%) of those who had shown perfusion defects at normal temperatures had worsening in response to cold. No patient without Raynaud showed such a response to cold. Also of note was that there was a significant association between such a response to cold and the presence of anticardiolipin antibody and/or lupus anticoagulant. The authors feel that these findings may be related to the common occurrence of headaches in patients with Raynaud phenomenon, although no patient developed a headache during the cold test.

#### **Neuro-ophthalmic manifestations of Raynaud disease**

A case of light-induced visual loss has been described in a patient with migraine and Raynaud phenomenon by Safran and Boschi (66). It was felt that this patient, who did not have carotid artery disease, had vasospasm in response to light exposures lasting 5 to 10 minutes. Kuhl et al. (67) have reported a case of trochlear nerve palsy in a patient with recurrent Raynaud of the tongue.

#### **Etiology of Raynaud disease**

Harel et al. (68) postulate that some cases of Raynaud phenomenon may be an occult manifestation of infection with parvovirus B19. This virus is already known to be associated with erythema infectiosum, transient aplastic crisis, and hydrops fetalis, and it has various rheumatologic symptoms. Harel et al. describe two patients who had onset of Raynaud with generalized polyarthralgia, and the entire work-up was negative except for the parvovirus titers. They postulate that immune-mediated endothelial damage leads to platelet activation and vasoconstriction and recommend that in cases of Raynaud of unknown etiology, serology for parvovirus 19 should be included in the evaluation of the patient. Gasbarrini et al. (69) postulate that Raynaud may be another symptom that is attributable to *Helicobacter pylori* infection and claim that eradication of the bacteria leads to improvement in Raynaud.

### Therapeutic strategies for Raynaud disease

The traditional therapy for Raynaud has been the use of calcium channel blockers, especially nifedipine. Approximately 67% of patients respond to calcium channel blockers; newer such agents with fewer side effects (amlodipine, isradipine, nicardipine, and felodipine) also appear promising (70).

Other classes of agents are being tested for Raynaud. Dziadzio et al. (71) have studied losartan, an antagonist of angiotensin II-receptor type 1, for the management of primary and secondary Raynaud phenomenon. Outcomes such as the severity and frequency of episodes of Raynaud phenomenon and findings on thermography and laser Doppler flowmetry were used. In this series, the drug was tolerated and had significant beneficial effect. Other agents that have shown promise for Raynaud in scleroderma include prazosin and iloprost (72–74), although another group did not find the latter agent, a prostacyclin analog, to be effective (75). Varela-Aguilar et al. (76) report that misoprostol, a prostaglandin E1 analog, is approximately as effective as nifedipine.

A novel approach to therapy of the vasospastic component of Raynaud phenomenon is being investigated by Tucker et al. (77). This group, using the theory that some of the vasospasm is related to impaired generation of or lack of sensitivity to nitric oxide, has developed a gel that locally generates nitric oxide. They found that this gel can increase local circulation in Raynaud patients and healthy people.

Raynaud is 60% more prevalent in patients with carpal tunnel syndrome than in the general population. Chung et al. (78) report that there are selected cases where surgical decompression of carpal tunnel syndrome may alleviate Raynaud phenomenon in patients with both syndromes. The authors caution that to use this approach, professionals must carefully select patients who do not have Raynaud as part of an underlying systemic illness.

Much exciting work is being done in the diagnosis, therapy, and understanding of the pathogenesis of these related disorders. It is hoped that increased awareness of the potential for neurologic and ocular findings will lead to increased recognition of the underlying conditions, allowing for specific therapies to be used.

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