Case Reports

Brain Involvement in Scleroderma
Two Autopsy Cases

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Background—Neuropathological data are very scarce in systemic sclerosis and fail to demonstrate primary changes in the brains of such patients.

Case Descriptions—A 41-year-old woman with CREST syndrome developed signs of dementia after an episode of severe dehydration and died two months later of septic shock. A 63-year-old woman with CREST syndrome and a history of two unexplained transient ischemic attacks had had balance disorders since age 62. She died of severe pulmonary hypertension. In both cases, the autopsy showed extensive wall calcification of small arteries and arterioles in the brain, primarily in the basal ganglia, and also in the frontal lobes and the cerebellar area in the second case. No known cause of cerebrovascular calcification was found in either patient.

Conclusion—The neuropathological findings in these two patients suggest that systemic sclerosis may induce primary vascular changes in the brain, of which calcification may be a marker. (Stroke. 1998;29:719-721.)

Key Words: basal ganglia ¦ brain ¦ calcification, vascular ¦ scleroderma, systemic

No noteworthy findings have been reported in the few available pathological studies of the brain of patients with systemic sclerosis. Central nervous system (CNS) manifestations seem relatively frequent in such patients but have almost always been considered secondary to the disease process. We describe findings in two consecutive autopsies of women with systemic sclerosis and CNS symptoms, showing advanced cerebrovascular calcifications.

Case 1
A 41-year-old white woman developed Raynaud’s phenomenon during adolescence. She never smoked and did not have diabetes, hypertension, or dyslipidemia. Systemic sclerosis (CREST variant) was diagnosed in her early twenties. She had sclerodactyly, telangiectasias on the face and hands, and tightness of the face skin. Anticentromere antibodies were present at 1:1000 dilution. Antiphospholipid antibodies and cryoglobulinemia were negative. She had a long history of gastrointestinal tract disorders, with dysphagia and esophagitis, constipation, intermittent bloating, abdominal cramping, and anal incontinence. She had been severely depressed since age 24. She was treated with calcium blockers, omeprazole, intestinal antispasmodic agents, and various antidepressant drugs. She never received steroids or immunosuppressive drugs. At age 35 a cutaneous ileostomy was performed after she underwent surgery for a perforated intestinal necrosis; this was complicated by chronic liquid diarrhea.

At age 41 the subject was hospitalized for severe dehydration due to abundant intestinal losses that she failed to compensate for through negligence. The blood pressure was 100/70 mm Hg, the heart rate 120 beats per minute, and the temperature 37°C. She was confused. Physical examination was otherwise normal. She had a generalized seizure on the day of admission. Laboratory assays showed functional renal insufficiency with a serum creatinine of 530 μmol/L, proteinuria of 88 g/L, and moderate metabolic acidosis with a plasma pH of 7.36 and a bicarbonate level of 13 mmol/L. Metabolic disorders normalized after 5 days of intravenous rehydration. The baseline creatinine was 75 μmol/L, and routine laboratory assays were normal. Marked cerebral disorders persisted despite adequate rehydration and included agitation, aggressiveness, loss of appetite, insomnia, periods of groaning, compulsive rubbing of the back of her neck on the bed, urinary incontinence, and total indifference to her surroundings; it was impossible to communicate with her. Neurological examination showed only a hyperactive palm-chin reflex. Cerebral CT was normal except for mild basal ganglia calcification. Lumbar puncture showed a cerebrospinal fluid protein content of 0.69 g/L but was otherwise normal. Thyroid hormones were normal. Two consecutive electroencephalograms showed diffuse abnormalities with an asynchronized, unorganized, slowed, and poorly reactive print. High-dose intravenous antidepressant therapy with clomipramine (Anafranil) had no effect. A diagnosis of dementia was made by psychiatrists and neurologists.

Two months after the onset of neurological signs, the subject died of septic shock of gastrointestinal origin. At autopsy the brain was macroscopically normal except for mild
swelling. Histologically, the extraparenchymal arteries were moderately thickened by intimal hyperplasia. Mineral deposits in the walls of small arteries and arterioles (Fig 1) were abundant in the basal ganglia, hippocampus, and dentate nucleus. They consisted of calcium deposits evidenced by hematoxylin and eosin and von Kossa’s stain but were free of iron (negative Perls’ staining). These areas contained small foci of ischemic neuronal necrosis. There was no glial or inflammatory reaction. Marked parietal fibrosis was found in the whole gastrointestinal tract, as well as wall thickening of small arteries and arterioles. Moderate intimal fibrosis also involved some interlobular and arcuate renal arteries. Other organs were normal.

Case 2
A 63-year-old white woman developed Raynaud’s phenomenon at age 30. She had no cardiovascular risk factors. A CREST syndrome was diagnosed at age 35. She had sclerodactyly; tightness of the face skin with thin and shortened lips; telangiectasias on the hands, face, back, and palate; pyrosis; intermittent dysphagia; and ocular and buccal dryness. She had been on a regimen of trimethylcolchicinic acid and metoclopramide and occasionally H2 blockers since that time. No steroids or immunosuppressive drugs were given. At age 43 she gradually developed exertional dyspnea and pulmonary hypertension.

At age 44 the subject was hospitalized for a transient ischemic attack. On the day of admission she had two consecutive episodes of expressive aphasia, each lasting approximately half an hour. The neurological examination was normal. Cerebral CT, ultrasound examination of the heart and carotid arteries, 24-hour ECG recording, and cerebrospinal fluid examination were normal. Low-dose aspirin was added to her treatment at hospital discharge. No further transient ischemic attacks occurred. At age 62 she complained of balance disorders, but no clear focal neurological deficit was found. Cerebral CT showed moderate cerebral atrophy and mild calcification in the basal ganglia (Fig 2).

At age 63 the subject underwent surgery for unperforated intestinal necrosis that required the ablation of 1.50 m of ileum. The etiology of the intestinal necrosis remained unclear. Her respiratory status worsened postoperatively, and she died 4 months later of refractory right heart failure. At autopsy the brain was macroscopically normal except for mild swelling. Histologically, the extraparenchymal arteries were moderately thickened by intimal hyperplasia. Vascular calcium deposits were observed in the same areas as in case 1 (basal ganglia, hippocampus, and dentate nucleus) and also in small-artery walls of cortical areas, especially the frontal lobes, cerebellar cortex, and mammillary bodies. Small foci of neuronal ischemic necrosis were also observed, but there was no glial or inflammatory reaction. Severe interstitial fibrosis and artery wall thickening were observed in the lungs. The right heart cavities were moderately dilated. The digestive tract showed moderate artery and arteriolar wall thickening and no significant parietal fibrosis. Other organs were unremarkable.

Discussion
Structural changes of the small arteries and arterioles (typically concentric fibrous intimal thickening) have been described in nearly every organ of patients with systemic sclerosis and play a key role in some of its main manifestations, such as Raynaud’s phenomenon, scleroderma renal crisis, pulmonary hypertension, and myocardial ischemia. Blood vessels would also be expected to be involved in the CNS. Cerebral hypoperfusion, suggestive of impaired microcirculation, was recently observed in sclerodermic patients. However, pathological studies have failed to demonstrate primary cerebrovascular changes in systemic sclerosis. Nonspecific cortical ne-
crotic foci were reported in 3 of 17 brains. A cerebral infarct has been linked to arteritis localized in a single internal carotid artery. Other studies showed vascular changes that could be explained by concomitant hypertension or atherosclerosis. Unfortunately, pathological data are lacking in 4 additional sclerodermic patients with neurological disorders (severe headache, generalized seizures, confusion, dysarthria, expressive aphasia, hemiparesis, and hemianalgia). In these 4 cases cerebral arteriography showed bilateral narrowing of several medium-sized and small cerebral arteries, with a suspicion of cerebral vasculitis in 3 cases and evidence of vasospastic phenomena in the fourth case. Leptomeningeal biopsies, performed in 2 cases, were normal.

The neuropathological findings in our patients were striking considering their age. Histologically, mild small-artery mineralization (consisting mainly of calcium but also often of iron deposits), predominantly in the basal ganglia, hippocampus, and dentate nucleus, is a common incidental finding in elderly brains and is considered a nonspecific aging phenomenon. More severe calcifications are usually seen in patients with hypoparathyroidism, idiopathic cerebrovascular ferrocalcinosis (Fahr disease), or hereditary diseases such as mitochondrial cytopathies, Albright’s hereditary osteodystrophy, and Cockayne’s syndrome, and may be associated with clinical disturbances (chiefly extrapyramidal movements). Other causes of basal ganglia calcification include carbon monoxide and lead intoxication, birth anoxia, CNS infection or hemorrhage, cranial therapeutic irradiation, and methotrexate therapy. Hyperosmolality was suspected to be the cause of intracranial damage followed by calcification in a 2-month-old boy with severe diabetic ketoacidosis. Interestingly, basal ganglia calcification was recently described in patients with cerebral lupus, in whom it may correspond to scars of vasculitis.

Hypoparathyroidism was unlikely in our patients, who both had normal calcemia and phosphoremia. They had negative HIV tests. The metabolic disorders during dehydratation in patient 1 were unlikely to cause CNS damage per se, since she had only moderate acidosis and no hypernatremia. Neither patient had a family history or clinical signs of hereditary disease or a personal history suggestive of one of the other known causes of intracerebral calcification. Vascular mineralization is usually asymptomatic. However, cerebrovascular changes appeared to play a role in the late neurological manifestations in patient 1, who had severe dehydration before the onset of neurological signs. In view of the autopsy findings, the most logical explanation is that she had an encephalopathy of vascular origin, as a consequence of both low flow and an impaired brain vasculature. In patient 2, the possible relation between her postural instability and vascular changes in the cerebellar area is more speculative, since she had no patent focal neurological deficit. However, the latter patient had two unexplained transient ischemic attacks, similar to three middle-aged women in a previous report of 50 sclerodermic patients.

In conclusion, the advanced calcifications of small vessels in the brain of these two women with a long-lasting CREST syndrome suggest that systemic sclerosis may induce primary cerebrovascular changes, of which wall calcification may be a marker. Intracerebral calcification can be detected by CT, which should be useful in further prospective studies of CNS involvement in systemic sclerosis.

References

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