Intracerebral Calcification in Systemic Sclerosis

Emmanuel Heron, MD; Anne Hernigou, MD; Gilles Chatellier, MD, PhD; Paul Fornes, MD, PhD; Joseph Emmerich, MD, PhD; Jean-Noël Fiessinger, MD

Background and Purpose—Advanced cerebrovascular wall calcification was recently observed at autopsy in 2 patients with systemic sclerosis. To further investigate this issue, we conducted a prospective CT study of scleroderma patients to detect intracerebral calcification.

Methods—Thirty-seven consecutive patients with systemic sclerosis underwent unenhanced brain CT. Images were blindly interpreted, together with those of 2 age-matched (±1 year) and sex-matched control subjects per patient.

Results—Intracerebral calcification was found in 12 patients (32.4%) and 7 controls (9.5%) (P=0.006). Among the patients, intracerebral calcification was associated with the duration of Raynaud’s phenomenon (P=0.005) and not with age (P=0.086).

Conclusions—Intracerebral calcification is closely associated with scleroderma, which suggests that scleroderma causes primary cerebrovascular changes. (Stroke. 1999;30:2183-2185.)

Key Words: basal ganglia • calcification • scleroderma, systemic • tomography, x-ray computed

Small-artery changes have been observed in nearly every organ in scleroderma.1 One exception is the brain, where the distinction between primary lesions and lesions secondary to arterial hypertension and renal disease could not be established in the few available pathological reports.2 We recently described 2 patients with scleroderma, central nervous system (CNS) manifestations, and autopsy evidence of small cerebral artery wall calcification, mainly in the basal ganglia.3 Both patients also had mild basal ganglia calcification on brain CT, which is the most frequently observed CT abnormality in the brain of patients with cerebral lupus.4 Because of the young age of the 2 patients and the absence of other known causes of cerebrovascular calcification, we postulated that the latter were primarily related to scleroderma.3 To confirm this we conducted a prospective CT study to detect intracerebral calcification in patients with systemic sclerosis.

Subjects and Methods

Subjects

Between October 1997 and June 1998, 37 consecutive scleroderma patients hospitalized in our department, mainly for elective investigations, underwent unenhanced brain CT. There were 31 women and 6 men, aged 21 to 78 years (mean±SD 54±14 years). The main characteristics of the study population are shown in the Table.

Sixteen patients (43%) had diffuse scleroderma according to the American Rheumatism Association (ARA) criteria,5 and 21 (57%) had the limited form of systemic sclerosis. Among the ARA diagnostic criteria: all the patients had Raynaud’s phenomenon, 68% had sclerodactyly, 49% had a history of digital ulceration, 35% had pulmonary fibrosis, and 16% had cutaneous sclerosis proximal to the knees and/or elbows. Screening for antinuclear antibodies was positive in all 37 patients, at a dilution of 1/500 or more in 32 (86%).

Methods

Brain CT studies were performed with an electron beam CT (Evolution, Siemens Inc) with 6-mm unenhanced contiguous slices through the whole brain. Between January 1997 and June 1998, 1240 patients underwent brain CT studies at Broussais Hospital with the same imaging system and acquisition protocol. Because no association has been reported between intracerebral calcification and any of the main cardiovascular risk factors (except aging), each patient with scleroderma was matched for age (±1 year) and sex with 2 otherwise unselected patients from this list of 1240, who were used as controls. Images obtained with standard brain settings were interpreted by a senior radiologist (A.H.), who was blinded to clinical status.

Data are presented as means (1 SD), or as medians (range) for data with a non-Gaussian distribution. Means were compared using the Student unpaired t test. The Mann-Whitney nonparametric test was used in case of non-Gaussian distribution. We used the Fisher exact test to analyze 2×2 tables. Probability values of <0.05 were considered to denote significant differences.

Results

Intracerebral calcification was found in 12 (6 with diffuse and 6 with limited scleroderma) of the 37 patients (32.4%) and in 7 of the 74 controls (9.5%; P=0.006). The mean age of the patients with intracerebral calcification (59±13 years) was not significantly different from that of patients without intracerebral calcification (51±14 years; P=0.086). The median duration of Raynaud’s phenomenon among the pa-

Received April 8, 1999; accepted July 9, 1999.

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tients with intracerebral calcification (26 years; range 2 to 55 years) was significantly longer than that of patients without intracerebral calcification (13 years; range 2 to 35 years; $P < 0.005$). As shown in the Table, there was no relationship between the presence of intracerebral calcification and any of the patients’ main clinical and immunological features, except for digestive symptoms ($P < 0.01$). Calcifications were located in the basal ganglia (globus pallidus; Figure) in 11 patients (unilateral in 2) who had an otherwise normal brain CT and in the right temporal lobe in 1 patient who also had sequelae of a clinically asymptomatic parietal infarct and elevated levels of antiphospholipid antibodies. Two patients with pallidal calcification had a history of unexplained CNS manifestations, comprising 2 episodes of transient brachiofacial hemiparesis at age 31 in one and an episode of transient global amnesia at age 62 in the other (the episode began shortly after leaving home on a cold winter day and lasted several hours). Among the patients without CT evidence of brain calcification, a 45-year-old woman had regular headaches for several years, often preceded by visual or sometimes language disorders (diagnosed as “accompanied” migraine by neurologists). The other 34 patients had no clear history of CNS manifestation. The patients were not assessed for psychological disorders.

**Main Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients (%)</th>
<th>Relationship With Intracerebral Calcification, $P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raynaud’s phenomenon</td>
<td>37 (100)</td>
<td>...</td>
</tr>
<tr>
<td>Dysphagia and/or pyrosis</td>
<td>27 (73)</td>
<td>0.015</td>
</tr>
<tr>
<td>Sclerodactyly</td>
<td>25 (68)</td>
<td>0.711</td>
</tr>
<tr>
<td>Telangiectasias</td>
<td>21 (57)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>History of digital ulcerations</td>
<td>18 (49)</td>
<td>0.170</td>
</tr>
<tr>
<td>Calcinosis cutis</td>
<td>17 (45)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Pulmonary fibrosis†</td>
<td>13 (35)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension‡</td>
<td>7 (19)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Proximal cutaneous sclerosis</td>
<td>6 (16)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Renal involvement§</td>
<td>4 (11)</td>
<td>0.582</td>
</tr>
<tr>
<td>Anti-centromere antibody</td>
<td>18 (49)</td>
<td>0.728</td>
</tr>
<tr>
<td>Anti-Scl-70 antibody</td>
<td>6 (16)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

*By Fisher exact test.
†Bibasilar fibrosis on pulmonary CT and/or ≥20% reduction in the diffusing capacity on pulmonary function testing.
‡Systolic pressure measured by cardiac echo-Doppler ≥35 mm Hg.
§Creatininemia >120 μmol/L and/or proteinuria >0.05 g/d.

**Discussion**

Histologically, mild to moderate cerebrovascular mineralization, predominantly in the basal ganglia, hippocampus, and dentate nucleus, is a common incidental finding in elderly brains and is considered a nonspecific aging phenomenon. There is also a great variety of rare causes of advanced and/or more severe cerebrovascular calcification, mostly in the basal ganglia, such as hypoparathyroidism or pseudohypoparathyroidism (exceptionally hyperparathyroidism), idio-

pathic cerebrovascular ferrocalcinosi (Fahr disease), hereditary diseases such as Albright’s osteodystrophy, Cockayne’s syndrome, Down’s syndrome, mitochondrial cytopathies (oculocoxisomatous disease, mitochondrial myopathy), birth anoxia, carbon monoxide poisoning, lead intoxication, CES infection (such as cytomegalic inclusion disease, toxoplasmosis, cysticeriosis, herpes or measles encephalitis, and tuberculous meningitis) or hemorrhage, acute leukemia, therapeutic cranial irradiation, and methotrexate therapy. Basal ganglia calcification has also been described in patients with AIDS and was the most frequent CT abnormality of the brain of patients with cerebral lupus, in whom it may correspond to scars of vasculitis. Basal ganglia calcification is thus a sensitive, nonspecific marker of cerebrovascular changes. The prevalence of incidentally detected basal ganglia calcification in brain CT studies ranges from 0.24% to 2%. The higher prevalence of calcification observed in our control subjects (9.5%) is probably explained by the fact that our general population at Broussais Hospital is mainly composed of patients with overt, often complicated, polyvascular atherosclerotic disease who are exposed to early cerebrovascular aging phenomena. Indeed, of our 7 controls with basal ganglia calcification, 1 had a history of malignant hypertension, 1 had autoimmune uveoretinitis diagnosed 15 years previously, and 3 had polyvascular atherosclerotic disease and a history of ischemic stroke (the clinical history of the remaining 2 controls was not obtained). Yet a significantly

CT-detected bilateral (top) and unilateral (bottom) basal ganglia calcification in 2 patients with scleroderma.
higher prevalence (32.4%) of intracerebral calcification was observed in the patients than in the controls. In addition, a statistically significant positive relationship was found in the patient group between intracerebral calcification and the duration of Raynaud’s phenomenon, contrasting with a borderline association with age and a lack of any association with the other main clinical complications of the disease. Raynaud’s phenomenon is the most frequent (100% in our patients) and usually the earliest clinical manifestation of scleroderma, and it is therefore a sensitive marker of the onset of the disease. Thus, it is reasonable to consider that the positive relationship between intracerebral calcification and Raynaud’s phenomenon indicates a strong link between intracerebral calcification and the duration of scleroderma. This suggests that intracerebral calcification may develop slowly during the disease process in response to chronic cerebrovascular injury. Indeed, we assume, on the basis of our autopsy findings and of published (radio)neuropathological data, that the CT-detected cerebral calcifications in our study patients were of vascular origin. The primary site of vascular involvement in scleroderma is at the level of small arteries and capillaries. Early endothelial dysfunction has been demonstrated from the onset of the disease, progressively followed by more severe endothelial damage, necrobiosis, and devascularization. The cause of vascular injury in scleroderma remains unknown but might involve a circulating factor, which may be a protease or an autoimmune factor. Interestingly, cerebral hypoperfusion, suggestive of impaired quantitative microcirculation, was recently observed in scleroderma patients. Intracerebral calcification might result from necrosis of smooth muscle cells of the small cerebral arteries, which contain large amounts of calcium that could therefore be trapped and accumulate in the arterial wall. Cerebrovascular involvement often seems quiescent in scleroderma but might contribute to the onset of CNS disorders during low-flow states, as described in 1 patient, or via vasospastic phenomena, revealed by serial angiography in a case report. Increased vaso spasms has been demonstrated in the main internal organs (heart, kidney, and lung) in scleroderma and might explain why some middle-aged scleroderma patients have otherwise unexplained transient ischemic attacks with focal neurological defects or transient global amnesia, both of which were observed in our patients. In addition, various psychological disorders have been reported in scleroderma patients and may be partly due to organic brain involvement; indeed, it has recently been shown that patients with basal ganglia calcification frequently have neuropsychological alterations. We believe that the use of sensitive tools for assessing CNS involvement should be included in a comprehensive assessment of the neuropsychological disorders observed in systemic sclerosis. Further studies, based on neuropsychological testing and sensitive measurements of cerebral perfusion, are needed to determine the clinical impact of cerebrovascular changes in scleroderma.

Acknowledgments
The authors thank E. Perrier, L. Perrier, and M.F. Reznar for their technical assistance.

References
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Stroke. 1999;30:2183-2185
doi: 10.1161/01.STR.30.10.2183

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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