Spatz-Lindenberg Disease
A Rare Cause of Vascular Dementia
A.J. Larner, MD; Desmond Kidd, MD; Paul Elkington, MRCP(UK); Peter Rudge, FRCP; Francesco Scaravilli, FRCPath

Background—Isolated cerebral thromboangiitis obliterans (Spatz-Lindenberg disease) is not well recognized as a cause of vascular dementia.

Case Description—A 58-year-old woman presented with dementia and pyramidal signs. Neuroimaging showed multiple areas of white matter change. Brain biopsy showed intimal thickening of the walls of leptomeningeal and intraparenchymal arteries, almost to complete occlusion, with an intact internal elastic lamina and media and without inflammation or infiltration. The cortex showed only moderate gliosis.

Conclusions—Spatz-Lindenberg disease should be considered in the differential diagnosis of vascular dementia. Additional studies of its pathogenesis are required to determine appropriate treatment. (Stroke. 1999;30:687-689.)

Key Words: dementia • Spatz-Lindenberg disease • thromboangiitis obliterans • vasculopathy

Thromboangiitis obliterans (Winiwarter-Buerger disease, Buerger disease) was originally described as a non-inflammatory occlusive disorder of peripheral blood vessels without involvement of intraparenchymal vessels, occurring almost exclusively in young men who were heavy smokers. Pure cerebral forms of thromboangiitis obliterans were known to Buerger and described by Spatz and Lindenberg in the 1930s, but few cases have been reported since then.

We present an additional case, emphasizing the fact that this disorder may occur in women and in the absence of vascular risk factors and that cognitive impairment may be a prominent clinical feature.

Case Description
A 58-year-old Indian (Gujarati) woman fell and fractured her left hip. Despite corrective surgery, her walking did not improve, and over the following year, she had several more falls due to “stiffness” of the legs. Concurrently, there was a change in her cognition. She became less communicative (for example, speaking less to customers in her husband’s shop) and reverted more to her first language (Gujarati). The family felt she was more forgetful, but there was no report of inappropriate behavior, failure to recognize family and friends, getting lost, or affective disorder. She was admitted to the hospital on an emergency basis when found unconscious and twitching down the left side. There was no personal history of hypertension, diabetes, migraine, or mood disorders. There was no family history of stroke or cognitive problems, but because the rest of the family lived in Gujarat, India, the examination of first-degree relatives was not possible.

On examination, there was marked spasticity of the left arm and both legs, with hyperreflexia, and the plantar responses were extensor. These signs persisted after cessation of her seizure. In addition, she had broken pursuit eye movements, but the fundi were normal, and there was no pseudobulbar palsy. General medical examination was normal: blood pressure was 120/70 mm Hg, and there were no carotid bruits.

Investigations of standard hematological and biochemical parameters, including glucose, were normal. Erythrocyte sedimentation rate was 34 mm in the first hour, and C-reactive protein was 13 mg/L (normal range [NR] <10 mg/L). Coagulation and thrombotic screens (lupus anticoagulant, protein S, protein C, antithrombin III, and activated protein C resistance) were normal. Vitamin B12 (175 ng/L, NR 223 to 1132 ng/L) and red cell folate (167 µg/L, NR 186 to 596 µg/L) were below laboratory quoted NRs, but these values are in fact normal for this ethnic group. Iron studies, including ferritin, yielded normal results. Thyroid function tests were normal, as were serum electrophoresis and quantitative immunoglobulins. Treponemal serology was negative. White cell enzymes were all within normal limits. Autoantibody screen was negative (antinuclear antibody, DNA, gastric parietal, intrinsic factor, endomysial, and reticulin). Cerebrospinal fluid analysis showed a normal cell count and glucose, but the protein was raised (0.71 g/L), as was lactate (2.4 mmol/L).

CT head scan showed marked brain atrophy and multiple areas of low attenuation in the white matter (Figure 1). MR imaging was degraded by movement artifact, making interpretation of T1-weighted scans difficult, but there was a
suggestion of multiple small deep infarcts; marked atrophy was again evident. T2-weighted images showed widespread confluent, hyperintense signal changes in supratentorial white matter, with a few infratentorial signal changes. EEG showed right frontal epileptiform discharges with background slowing (right-left), supporting a diagnosis of partial epilepsy.

Only a limited neuropsychological evaluation was possible (2 weeks after admission) because of the patient’s inability to speak English. There was evidence of severe impairment of memory functions: she was disorientated in time and had difficulty recalling personal details such as age and date of birth. Word-retrieval functions were relatively spared (Oldfield naming test 13/30). She could repeat sentences and was able to generate a grammatically correct sentence. She could perform very simple calculations. A simple dot-counting test could not be performed, suggesting impairment of visual perceptual functions.

Because of uncertainty about the cause of cognitive impairment and the possibility that there may have been an underlying vasculitis amenable to treatment, the patient proceeded to have a brain biopsy (right frontal lobe). The most striking abnormalities were found in the arterial vessels, both leptomeningeal and intraparenchymal. Their walls were considerably thickened, with consequent reduction in caliber, up to almost complete occlusion (Figure 2, top) of their lumina. Although the internal elastic lamina was intact, albeit thickened in both vessels (Figure 2, bottom), the intima of the larger vessels showed extensive proliferation of the elastic tissue, which appeared as concentric layers. There was no thickening of the media nor evidence of amyloid infiltration, eosinophilic granular material, or inflammation. The cortex was devoid of obvious pathological changes. Silver impregnation and immunostaining with antibodies to glial fibrillary acidic protein (GFAP), τ-protein, ubiquitin, β-A4, and prion protein did not reveal, apart from discrete to moderate gliosis, any inclusions or amyloid in the cortex. On the other hand, the white matter showed some rarefaction of the myelin, beading of axons with presence of some axonal spheroids, and glial proliferation.

**Discussion**

The appearances in the biopsy specimen were those of a vasculopathy, with associated white matter abnormalities and absence of any obvious gray matter pathology. The differential diagnosis of adult-onset subcortical leukoencephalopathy is broad and includes inflammatory and granulomatous disorders, congophilic angiopathy, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and Binswanger disease. However, the vascular changes observed in our patient were not those seen in any of the aforementioned conditions. The absence of inflammation and granulomata excluded these diagnoses; likewise, amyloid infiltrates of the media and adventitia were not visualized with the appropriate immunohistochemistry. The thickening of the arterial media in CADASIL contrasts with the intimal thickening in our patient, and the extensive
granular eosinophilic material seen in CADASIL was not seen in this case.\textsuperscript{5} Although the walls of penetrating arteries to the white matter are thickened and hyalinized in Binswanger disease, their lumens are usually wide, and occlusion is an exceptional observation.\textsuperscript{6} Hence, the possibility that the pathology seen in our patient may be a pure cerebral form of Winiwarter-Buerger disease or thromboangiitis obliterans was considered. This disorder includes generalized and pure cerebral forms, the latter described in 1935 and 1939 by Spatz and Lindenberg, respectively. Thromboangiitis obliterans is an idiopathic vasculopathy that has no standardized definition and no pathognomonic histopathological features.\textsuperscript{7} Diagnosis rests on a combination of appropriate clinical manifestations and pathological features, the latter including endothelial proliferation.\textsuperscript{7} Although called a “thromboangiitis,” inflammatory changes are not necessarily seen. Case studies with histopathological confirmation are few.\textsuperscript{1–3}

Unlike Buerger disease, Spatz-Lindenberg disease (SLD) or cerebral thromboangiitis obliterans (CTAO) has been reported to occur in women, nonsmokers, and nonhypertensives.\textsuperscript{1,3} Two types have been described, although there may be some overlap between the categories: type 1 manifests as multiple infarcts involving medium vessels; type 2, apparently the commoner variant, shows symmetrical, sickle-shaped, granular atrophy in a watershed distribution due to involvement of small leptomeningeal arteries.\textsuperscript{1,3} Our patient would seem to fall into the first of these categories. However, in either variety, both gray and white matter are involved, as reported in the scanty literature on this topic, including the original paper by Spatz and Lindenberg\textsuperscript{1} and that by Zhan et al.\textsuperscript{3} However, it is possible that the apparently unusual findings shown in our case represent a sampling error, because other case reports have described autopsy and not biopsy material. Both forms of SLD/CTAO are said to be accompanied by dementia, but accounts of the precise pattern of neuropsychological impairment have not been found.

The pathogenesis of the cognitive impairment is uncertain, as in other dementias that occur after cerebrovascular events.\textsuperscript{8} Although it may be a consequence of brain infarction per se, there are other possibilities. Zhan et al\textsuperscript{3} found loss of immunoreactivity for synaptophysin, a marker for synapses, in areas without necrosis or scar formation (eg, hippocampus and occipital area) of the same order of magnitude as seen in areas without necrosis or scar formation (eg, hippocampus).\textsuperscript{3} Chronic brain hypoxia without infarction might also contribute to brain injury; there is evidence for reduced cerebral blood flow, as assessed with transcranial Doppler velocities, in patients with Buerger disease.\textsuperscript{9} Berlit et al\textsuperscript{2} presented evidence suggesting an immunopathogenesis for SLD/CTAO, viz raised CSF cell count and protein, increased serum IgE, raised titers of anti- elastin antibodies, and immunoglobulin and complement in vasa vorum of temporal artery biopsies. Confirmation of these findings might indicate a place for early immunosuppressive therapy. However, a high index of clinical suspicion and early brain biopsy would be necessary to establish the diagnosis to allow early treatment, there being no confirmed peripheral markers of SLD/CTAO.

Hence, SLD/CTAO should be considered in the differential diagnosis of vascular cognitive impairment.\textsuperscript{10} The cause of dementia and whether it is reversible or irreversible remain to be determined. It may be a commoner condition than the paucity of case reports in the literature suggest, because in the absence of a brain biopsy showing the typical features, the clinical and radiological picture could be mistaken for multiinfarct dementia, vasculitis, or CADASIL.

Acknowledgments

Thanks to Morvarid Karimi for translating Reference 1.

References

Spatz-Lindenberg Disease: A Rare Cause of Vascular Dementia
A. J. Larner, Desmond Kidd, Paul Elkington, Peter Rudge and Francesco Scaravilli

Stroke. 1999;30:687-689
doi: 10.1161/01.STR.30.3.687

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/30/3/687