

Vascular pathology in three cases of progressive cognitive deterioration

Leonardo Pantoni^a, Julio H. Garcia^{a,b,*}, Gregory G. Brown^a

^a Departments of Pathology (Neuropathology) and Psychiatry (Neuropsychology), Henry Ford Hospital, K-6, 2799 West Grand Boulevard, Detroit, MI 48202, USA

^b Case Western Reserve University School of Medicine, Cleveland, OH, USA

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Abstract

The clinical condition known as vascular dementia remains poorly defined. Few studies have attempted a correlative link between the clinical syndrome and the structural abnormalities of the brain. Classically the clinical progression of the vascular dementing process is thought to be a multi-step process punctuated by repeated episodes of ischemia, that are clinically expressed as strokes. In most instances it has been assumed that the substrate of vascular dementias consists of atherothrombotic infarcts. The objective of this report is to illustrate 3 cases of progressive (rather than stepwise) cognitive deterioration without clinical evidence of stroke, evolving over a period of several years, in which there were prominent vascular lesions. A complete autopsy and detailed neuropathologic examination demonstrated cerebral vascular lesions involving small arterial vessels (< 200 μm in diameter). The lesions consisted of moderate-to-severe arteriosclerosis in two cases, and mild-to-moderate arteriosclerosis in a case of Alzheimer's disease with severe cerebral amyloid angiopathy. Parenchymal lesions consisted of small cortical and subcortical infarcts, most of them smaller than 0.1 cm in average diameter, and subcortical leukoencephalopathy severe in two cases and mild-to-moderate in the third case. Severe atherosclerosis not accompanied by large infarcts was also present in one case. Arterial changes affecting small, distal branches causing sometimes small parenchymal lesions in association with diffuse cerebral white matter disease, appear to be the anatomical substrate that accompanies progressive cognitive impairment in some patients who are frequently diagnosed with Alzheimer's disease because in their clinical records there is neither history of strokes nor stepwise progression of symptoms.

Keywords: Dementia; Vascular dementia; Alzheimer's disease; Small vessels disease; Ischemic leukoencephalopathy; Brain ischemia

1. Introduction

The contribution of vascular pathology to the syndrome of cognitive impairment is incompletely defined. Vascular dementia (VaD) encompasses a wide spectrum of disease processes (Scheinberg, 1988; Muñoz, 1991). Several pathogenetic mechanisms have been proposed to explain VaD (Garcia and Brown, 1992; Wallin and Blennow, 1993), but the pathological substrates of these diseases remain incompletely defined. In particular, many studies of patients with cognitive impairment of possible vascular origin have failed to illustrate the pathological changes in the cervical or cerebral vessels and in the brain parenchyma. It is commonly believed that a minimum volume of cerebral tissue loss at specific locations determines cognitive impairment in patients with vascular diseases (Tomlinson

et al., 1970; Erkinjuntti et al., 1988; del Ser et al., 1990). Accordingly, VaD is often seen as a disease associated with brain infarcts of presumed arterial etiology. However, ischemic injury to the brain has more than one morphological expression, and lesions other than arterial territorial infarcts, may be associated with deteriorating cognitive functions (Garcia and Brown, 1992). In a series of 175 consecutive autopsy cases of dementia, pathology of small vessels disease was the most important alteration described among the cases with cerebrovascular diseases (Brun, 1994).

We report a detailed neuropathological study of three cases presenting with progressive, non-stepwise, cognitive deterioration over a period of several years. In two cases the pathological abnormalities were exclusively vascular; both Alzheimer's disease (AD) and vascular pathology were present in the third case. Alterations in small cerebral vessels accompanied by brain parenchymal changes, other than large territorial infarcts, were present in all three

* Corresponding author. Tel.: (313) 876-2269; Fax: (313) 876-7120.

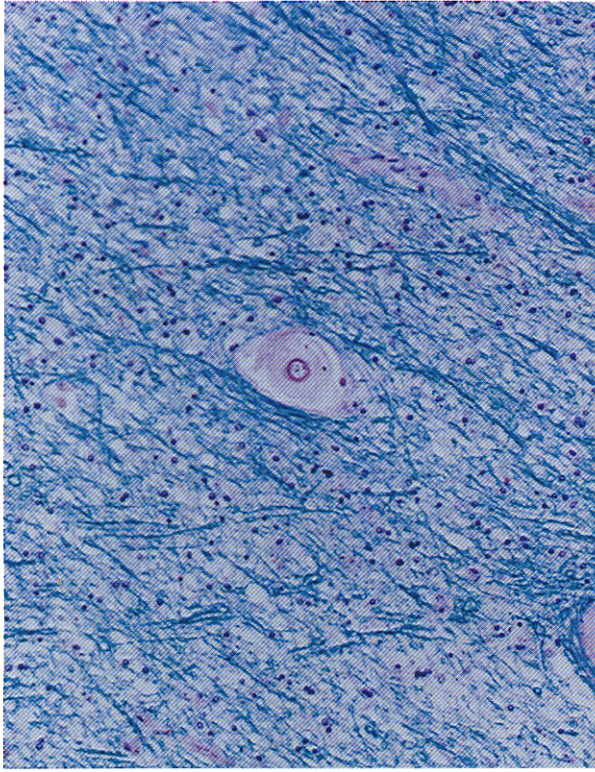


Fig. 2

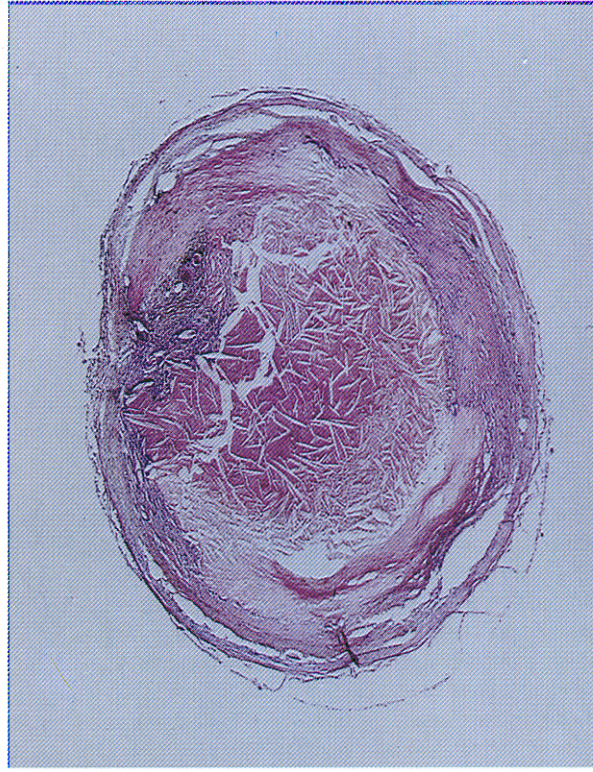


Fig. 4

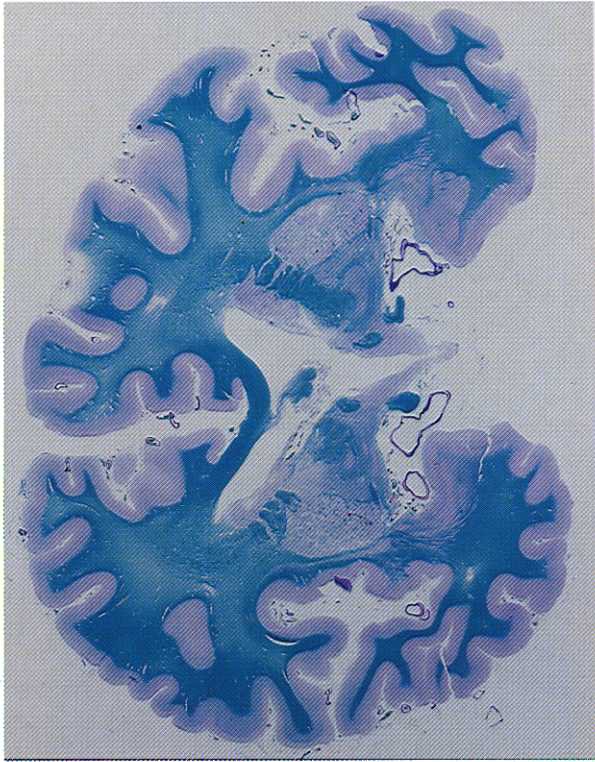


Fig. 1

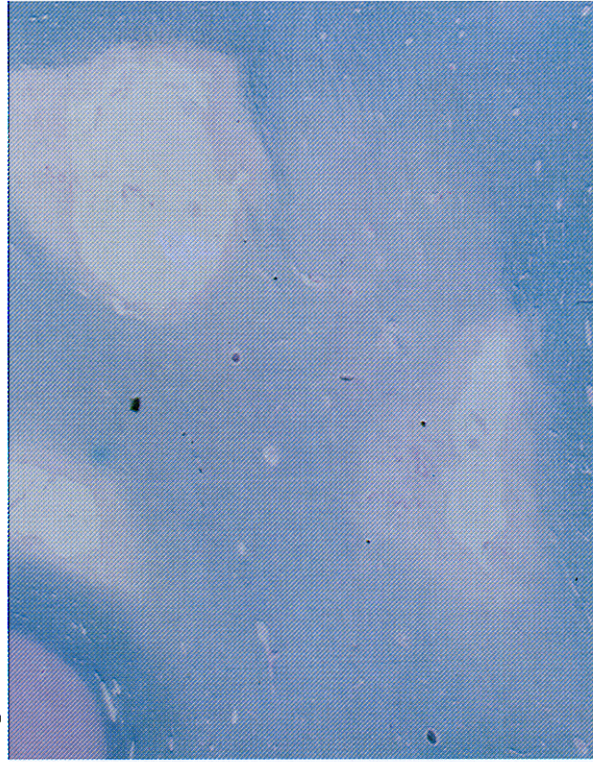


Fig. 3

cases; the parenchymal lesions were small or diffuse and involved the cerebral cortex and white matter.

2. Methods

The brain and the spinal cord were removed in all three cases about 8–10 h after death and fixed in 10% buffered formalin. Coronal sections of the whole cerebrum and about 20 samples from several areas of the brain were processed for histologic evaluation. In addition to hematoxylin-eosin, the following stains were utilized: Luxol fast blue/periodic acid Schiff, Masson's trichrome, Prussian blue, Verhoeff-van Gieson, Congo red, and Bielschowski's silver impregnation. Immunohistochemical demonstration of glial fibrillary acidic protein, β -A4 amyloid, and ubiquitin was done by the avidin-biotin peroxidase complex method (Hsu et al., 1981).

3. Case reports and neuropathological findings

Case 1 was a Caucasian normotensive man in his mid-fifties when he began to exhibit changes in personality. Previously polite and well mannered, he became verbally abusive and unusually belligerent, hypersomnolent and presented with diminished energy and libido. Subsequently he showed topographical memory loss even in familiar places, and memory loss for new events as well as his own actions. Because of this, the patient was forced to retire from his job. He became less concerned with his personal care, started to eat meals at irregular intervals and gradually became unable to perform daily skills. There was no history of stroke or transient ischemic attacks, arterial hypertension, diabetes mellitus, cardiac dysrhythmias, myocardial infarction, thyroid disease, or head trauma. A neurologist who examined him on several occasions diagnosed possible AD. The patient was not known to take any medication on a regular basis, according to his wife. At the age of 59, he was taken to an emergency room because according to his wife he suddenly fell down and when he stood up he had "forgotten how to walk". The patient had been ambulatory until a few days before, when he complained of nausea and vomiting. On this occasion, the neurologist described him as being awake and alert, ori-

ented to person, but disoriented to time; judgement and abstract thought were impaired, gait was apraxic, and frontal releasing signs were present. Motor, sensory, and cranial nerves examinations were normal. A computed tomography (CT) scan of the brain showed an ill-defined single site of low attenuation in the right basal ganglia (suggestive of a lacunar infarct), and ill-defined irregular areas of decreased attenuation in the periventricular white matter of both cerebral hemispheres. A diagnosis of acute myocardial infarct was followed by continuous deterioration of his general condition; death supervened four days later.

The autopsy disclosed recent atherothrombotic occlusion of the right coronary artery and a recent, large myocardial infarct. The brain weighed, after fixation, 1210 g (normal = 1307 g \pm 319) (Ho et al., 1980). There was slight atrophy of the cerebral mantle with ventricular dilatation. Three lesions could be identified by direct examination: a 2.5 cm in diameter cavitory infarct in the left middle frontal gyrus; a 2.0 cm in diameter, ill defined subacute infarct in the head of the right caudate nucleus extending into the adjacent fibers of the anterior limb of the internal capsule (Fig. 1); and a 1.0 cm in diameter cavity surrounded by brown pigmentation in the dorsal nucleus of the right thalamus. The hippocampus did not appear atrophic. Microscopically, the large extracerebral arteries contained large, partly calcified atheromatous plaques that narrowed the lumen by an average of 30%. The small intraparenchymal arterial vessels (15–20 μ m in diameter) in the basal ganglia, thalamic nuclei, subcortical white matter, and base of pons appeared markedly thickened and hyalinized (Fig. 2). In the white matter, the subcortical U fibers were normal. The periventricular white matter, however, had extensive patchy areas of prominent rarefaction with myelin pallor and marked reactive astrogliosis. There was multifocal parenchymal destruction with cavitation and lipid-laden macrophages (Fig. 3). The gliosis and rarefaction were more prominent around vessels, which displayed enlarged perivascular spaces. The corpus callosum was of normal thickness; hippocampus, thalamus, nucleus basalis, and mammillary bodies were unremarkable. In the cerebral cortical, basal ganglia, cerebellar, and brain stem grey matter there were no neurodegenerative changes (neuritic plaques, fibrillary tangles, granulo-vacuoles, Lewy bodies).

Fig. 1. Case 1. Pallor of the white matter and several small infarcts are visible in the left middle frontal gyrus, in the right and left caudate nuclei. Multiple enlarged perivascular spaces and subacute infarct in the anterior limb of the right internal capsule are also visible (Luxol fast blue/periodic acid Schiff).

Fig. 2. Case 1. Thickening and hyalinization of the wall of a small penetrating vessel in the white matter which appears rarefied. Existing glial cells appear intact (Luxol fast blue/periodic acid Schiff, 50 \times).

Fig. 3. Case 1. Hemispheric white matter: multiple areas of tissue destruction (cavitation) and myelin rarefaction, as existed in the frontal lobes. The subcortical U fibers are spared (Luxol fast blue/periodic acid Schiff, 2.5 \times).

Fig. 4. Case 2. Basilar artery: severe atherosclerosis with occlusion of lumen in the proximal segment of the artery (hematoxylin-eosin, 5 \times).

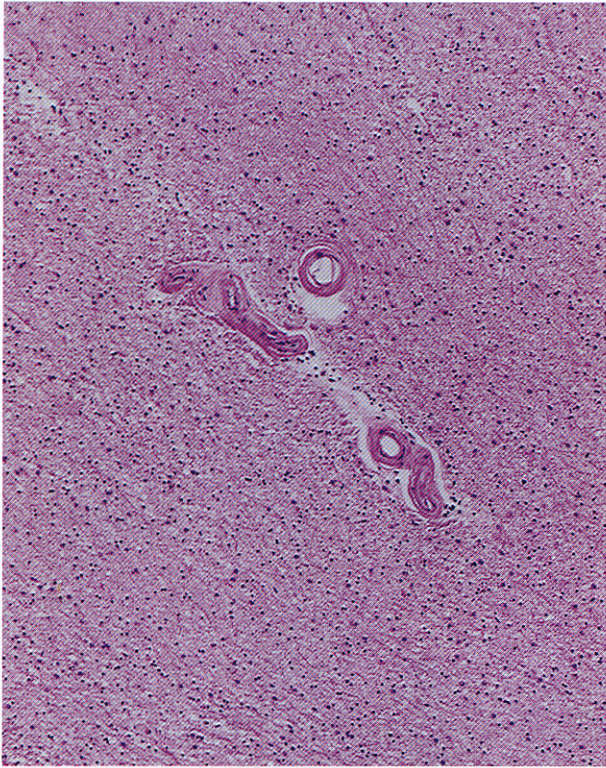


Fig. 6

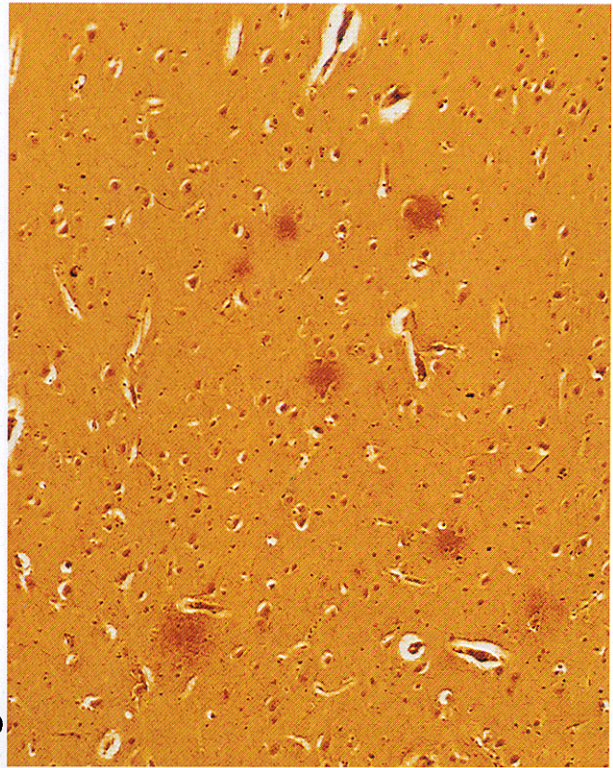


Fig. 8

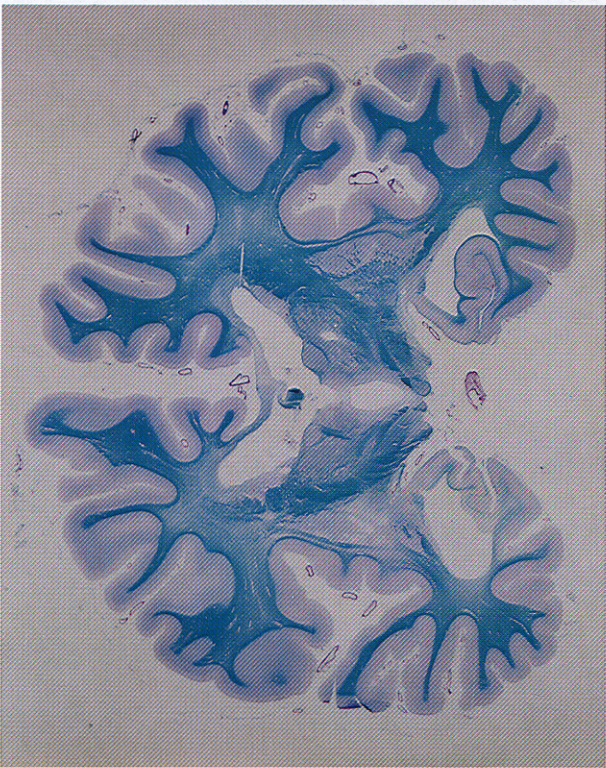


Fig. 5



Fig. 7

Case 2 was an obese (124 kg) 68 year-old black man who was first diagnosed with arterial hypertension at the age of 42. Marked and repeated postural hypotensive episodes were described following anti-hypertensive treatment with a thiazide diuretic and a beta blocker. At the age of 52, his clinical record revealed uncontrolled hypertension, non-insulin dependent diabetes, and congestive heart failure. At the age of 60 he became belligerent and aggressive towards his wife; over the next few years the patient developed apraxic gait and urinary incontinence. Several episodes of slurred speech resolving within a few minutes were described by family members, but other focal neurological deficits were never observed. He also developed memory difficulties, confusion and tended to wander. The onset of memory problems followed the onset of irritability. The family described a generally progressive downhill course for the memory problems, with some daily fluctuations. A psychiatrist diagnosed probable AD. Because of his behavioral difficulties he was confined to a chronic care facility for the last five years of his life where he was described as being oriented only to person. At the age of 65, his wife noted a left facial droop; over the next days his condition declined and he was no longer able to get up from his chair because of apparent gait apraxia. Emesis prompted the final hospital admission. On his final admission he was alert and awake, oriented to person, but not to time or place, able to follow commands and answer simple questions. Motor deficits were not detected; he withdrew appropriately from noxious stimuli and there was central palsy of the left facial nerve. Frontal releasing signs were present. Two days later he was febrile and stuporous, responding to verbal and physical stimuli but unable to verbalize or follow commands. The quality of a CT of the brain obtained at this time was somewhat impaired by the patient's motion; but, it showed moderate and diffuse cerebral atrophy and low attenuation in the periventricular white matter. Acute ischemic or hemorrhagic lesions were not demonstrable. The patient's condition deteriorated over the next few hours and death supervened on the same day.

The autopsy disclosed bacterial pneumonitis and pulmonary congestion. There was cardiomegaly with left ventricular hypertrophy (weight: 400 g), and coronary atherosclerosis with 20–40% narrowing of the lumen in the large arteries. Arteriolar nephrosclerosis was present in both kidneys. The brain weighed 1260 g after fixation (normal = 1262 g \pm 293) (Ho et al., 1980). All brain arter-

ies had extensive, calcific atherosclerosis. The distal third of the basilar artery had 90–95% luminal narrowing, and its proximal segment was completely occluded over a segment about 1.0 cm long (Fig. 4). The right posterior communicating artery was also occluded, and both middle cerebral arteries had 50–60% narrowing of their lumen. Coronal sections of the brain disclosed slight dilatation of the lateral ventricles. Small, irregularly shaped patches of grayish discoloration and increased granularity were visible in the corona radiata, and the corpus callosum was markedly thinned (Fig. 5). Several lacunae (average diameter: 0.8 cm) were seen in the right putamen. The right hippocampus was markedly atrophic while the left one was grossly normal. A small area of softening (0.2 \times 0.2 cm) involved the left side of the base of the pons. A large (4 \times 1.5 cm) healed hemorrhagic infarct was visible on the ventral surface of the right cerebellar hemisphere. The microscopic evaluation demonstrated, in addition to the complicated obstructing atherosclerotic lesions in the extracerebral arteries, marked medial thickening and hyalinization of arterioles (15–20 μ m in diameter) in basal ganglia and hemispheric white matter (Fig. 6). The white matter had extensive patchy areas of rarefaction with decreased number of myelinated fibers, diffuse astrocytic gliosis, and small areas of tissue destruction with cavity formation. The perivascular spaces were widened, especially around the hyalinized vessels. In the cerebral cortex neurodegenerative findings of the AD type were not detected, except for occasional senile plaques of the diffuse type as defined by Alafuzoff (1992) (Fig. 8). The right Ammon's horn showed almost complete absence of neurons and extensive reactive astroglia (Fig. 7). Multiple cavitory lesions (lacunes) measuring 0.1 cm in average diameter were present in the right thalamus and basal ganglia. In the brain stem there were several lacunar infarcts (< 0.3 cm in diameter), one at the left crus cerebri and three at the basis pontis, and a recent (0.6 \times 0.3 cm) infarct involved the left lateral medulla.

Case 3 was a Caucasian man, University professor, who was first noted as being mentally impaired at the age of 70 when he retired from the University. Significant past medical history included chronic atrial fibrillation (sick sinus syndrome), not associated with either arterial hypertension or diabetes mellitus. Over the next several years, the patient had developed a slowly progressive decline in cognitive functions accompanied by rigidity and tremor at

Fig. 5. Case 2. Pallor of the white matter, marked atrophy of the corpus callosum, atrophy of the right hippocampus, and mild dilatation of the lateral ventricles (Luxol fast blue/periodic acid Schiff).

Fig. 6. Case 2. Thickening and hyalinization of the tunica media of small arterioles (15–20 μ m) of the white matter (hematoxylin-eosin, 21.25 \times).

Fig. 7. Case 2. Right hippocampus: loss of pyramidal cells with marked reactive astroglia (hematoxylin-eosin, 4.25 \times).

Fig. 8. Case 2. Cerebral cortex (superior temporal gyrus): senile plaques of the diffuse type (Bielschowski's silver impregnation, 21.25 \times).

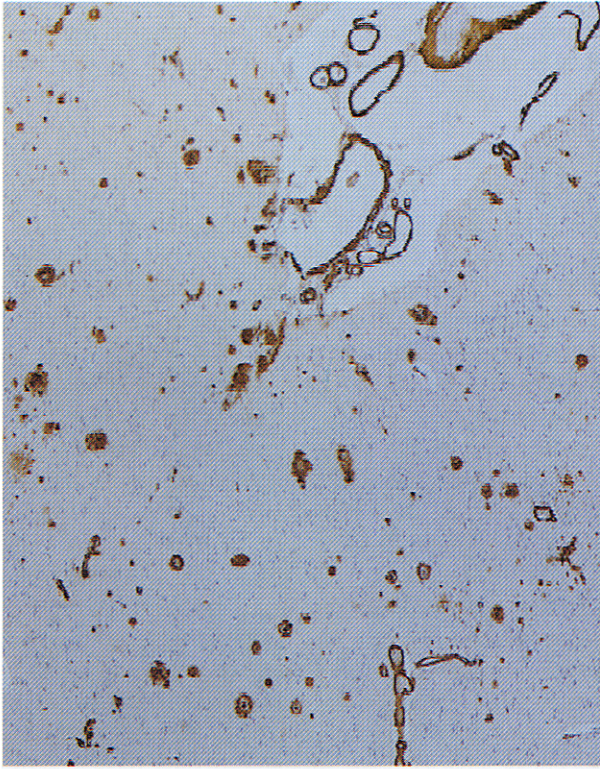


Fig. 10

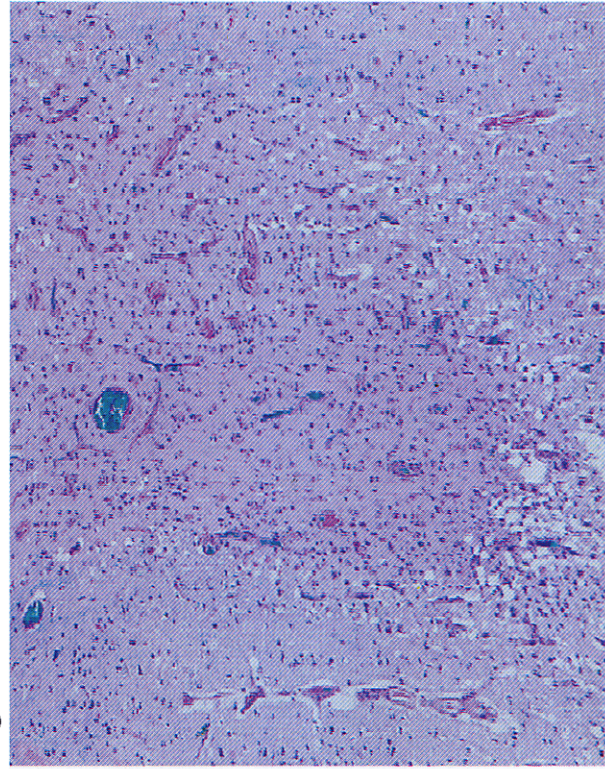


Fig. 12

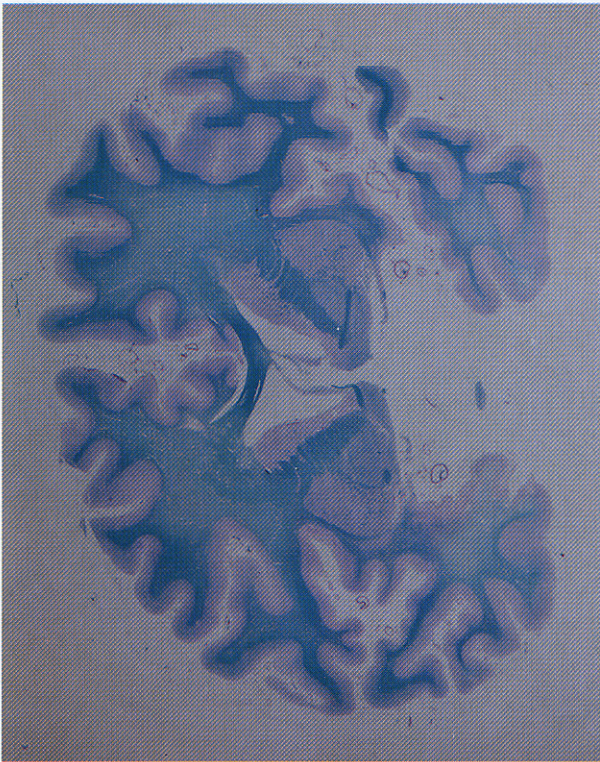


Fig. 9

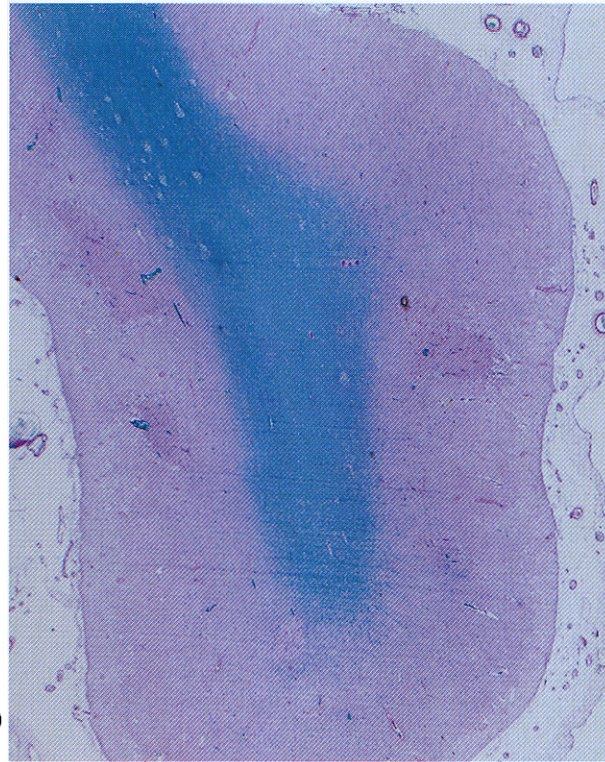


Fig. 11

rest, which severely impaired his locomotion; therapy with L-Dopa was administered for several years without clear evidence of beneficial effects. A history of stroke or focal neurologic events was not recorded in any of the numerous medical examinations the patient underwent over a period of 12 years; a diagnosis of AD with complicating parkinsonism was advanced. A CT scan of the head obtained 14 months before death when he was completely incapacitated to care for himself showed “ill-defined hypodensity within the right temporal lobe and brain, which may represent areas of subacute infarct”, or may be ‘artificial’. Cortical atrophy and bilateral periventricular white matter lucencies were also visible. Despite these findings, examinations on two separate occasions did not uncover any focal neurological deficits. The patient died at the age of 82 with bacterial pneumonitis.

At autopsy there was cardiomegaly (400 g) with ventricular hypertrophy and mild coronary atherosclerosis, bilateral extensive bacterial pneumonitis, and slight arteriolar nephrosclerosis. The brain was edematous and weighed 1500 g (normal = 1250 g \pm 280) (Ho et al., 1980). The large arteries at the base of the brain had scattered small atheromatous plaques. A large, recent hemorrhagic infarct (4.5 cm in largest diameter) was visible in the right occipital lobe in the territory supplied by a branch of the posterior cerebral artery. No brain atrophy or remote infarcts could be detected grossly (Fig. 9), and the substantia nigra was well pigmented. Microscopically, there were more than 15 neuritic plaques per microscopic magnification \times 200 field in the neocortex, and numerous neurofibrillary tangles, granulo-vacuoles and Hirano bodies more abundant in the hippocampus, amygdala and nucleus basalis. There were also frequent plaques in the striatum. Most pial and cortical arteries had extensive amyloid deposits in the tunica media (Fig. 10), a few of them displaying a classical ‘double barrel’ appearance. A few intracortical arterioles showed hyalinization without amyloid deposits; similar hyalinizing change could be observed in the white matter vessels. In the cerebral cortex there were haphazardly distributed glial scars and multiple (as many as 6 per block of neocortex) recent or subacute (< 0.1 cm in average diameter) infarcts (Figs. 11 and 12). The periventricular white matter was diffusely paler than the subcortical zones, and had focal areas of cavitation (< 0.5 cm in diameter) with gliovascular luminal bridging. The substantia nigra was well pigmented. There were

no changes of Parkinson’s disease (Gibb, 1992) in the brain stem or cerebrum.

4. Comment

We describe 3 patients with progressive cognitive decline, two of these with few lacunar infarcts and a third with AD and cerebral cortical micro-infarcts, and all of them with prominent leukoencephalopathy and arteriolar sclerosis. We suggest that ischemic lesions involving cerebral cortex and periventricular white matter, alone or in association with AD, may be responsible for progressive mental deterioration in the absence of stepwise progression.

The progressive decline in cognitive function was associated in all three cases with pathological changes in the small vessels and in the brain parenchyma. We suggest that in all three cases the parenchymal lesions are of ischemic origin and may be etiologically related to the structural abnormalities of the pial and intraparenchymal vessels. The nature of the vascular abnormalities has not been entirely defined in previous publications dealing with VaD and many authors imply that atherosclerosis and the consequent large brain infarcts are the main cause of VaD (Garcia and Brown, 1992). Severe intracranial atherosclerosis was present in case 2 but this condition was accompanied by small infarcts in the cerebellum and the brainstem; unilateral hippocampal sclerosis, also found in this case, may have been the result of the atheromatous occlusion of the ipsilateral posterior communicating artery and the effects of the repeated hypotensive crises (Schmidt-Kastner and Freund, 1991). Hyalinization of the small intracerebral arterial vessels was prominent in Cases 1 and 2; this abnormality is usually accelerated by aging and hypertension (Furuta et al., 1991; Ostrow and Miller, 1993). Remarkably, neither of these risk factors applied to case 1. Amyloid deposits were abundant in the brain vessels in case 3. The structural changes affecting the small brain vessels can be the cause of structural changes in gray matter (case 3) and white matter (all our cases).

The leukoencephalopathy in these three cases was characterized by loss of myelin fibers and gliosis; comparable changes in AD brains have been interpreted as being the result of ‘incomplete ischemic infarction’ (Brun and Englund, 1986). Interstitial edema (Feigin and Popoff, 1963)

Fig. 9. Case 3. Pallor of the hemispheric white matter and absence of infarcts detectable to the naked eye (Luxol fast blue/periodic acid Schiff).

Fig. 10. Case 3. Immunohistochemical demonstration of amyloid deposits in the vessels of subarachnoid space and superficial cortical layers; most of the senile plaques also contain amyloid deposits (β /A4 amyloid antiserum, 8.5 \times).

Fig. 11. Case 3. Cerebral cortex (inferior temporal gyrus): multiple microinfarcts of various age (Luxol fast blue/periodic acid Schiff, 3.4 \times).

Fig. 12. Case 3. Cerebral cortex (inferior temporal gyrus): detail of a microinfarct in which abundant lipid-laden macrophages are present (Luxol fast blue/periodic acid Schiff, 13.6 \times).

and Wallerian degeneration (Leys et al., 1991) are alternative potential explanations for the white matter changes. Hemispheric white matter abnormalities associated with cerebral amyloid angiopathy has been reported in several instances (Gray et al., 1985; Bogucki et al., 1988) and microinfarcts in the cerebral cortex, of the type found in Case 3, have been mentioned in at least one postmortem analysis of cerebral amyloid angiopathy (Okazaki et al., 1979). Repeated hypotensive crises, resulting from cardiac arrhythmia, could be an additional contributing cause to multiple cortical infarcts of microscopic size.

Only one (case 1) of the three patients had formal repeated neuropsychological examinations, yet, the clinical history of mental decline is well documented in all of them. The correlation between the mental deterioration and the pathological changes in case 3 appears obvious; but the clinical significance of the white matter lesions in cases 1 and 2 is less clear. The clinical significance of white matter abnormalities is still a matter of debate and controversy (Hachinski et al., 1987; Pantoni and Garcia, 1995). The absence of neurodegenerative changes in case 1 suggests that the vascular changes (arteriolosclerosis) and the associated leukoencephalopathy were in some way responsible for the dementing process. The small number and the type of senile plaques in case 2 appear insufficient to explain the cognitive changes (Crystal et al., 1993; Mirra et al., 1993). In this case, three small infarcts, two in the basal ganglia, and one in the left frontal lobe were also present. These lesions, as well as the unilateral hippocampal sclerosis, seem to be an unlikely cause for the progressive cognitive impairment that developed in this patient. In contrast, in patients with leukoaraiosis (Yamaguchi et al., 1994) or multiple sclerosis (Huber et al., 1987) a significant correlation has been shown between atrophy of corpus callosum (present in case 2) and cognitive impairment. In case 3 the number and distribution of senile plaques was adequate for a diagnosis of AD; yet, in this case the contribution of multiple microinfarcts and periventricular focal lesions and white matter degeneration to the cognitive deterioration cannot be ignored.

Cases 1 and 2 had in common personality change and gait disturbances; both findings are suggestive, but not diagnostic, of VaD (Ishii et al., 1986; Kotsoris et al., 1987). New criteria for the diagnosis of VaD have been formulated recently (Chui et al., 1992; Román et al., 1993; Wetterling et al., 1994). According to these consensus papers multiple types of vascular lesions may be responsible for cognitive deterioration. Nevertheless the suggested criteria for the clinical identification of patients with VaD emphasize significant cerebrovascular accidents, that are identifiable either clinically or radiologically; these criteria focus mainly on the clinical correlates of large territorial infarcts. A definite chronological association between development of cognitive impairment and a major cerebrovascular accident is lacking in all three cases. A stroke occurred, in case 2, as a terminal event and the retro-

spective diagnosis of transient ischemic attacks (episodes of 'slurred speech') in the same patient may be questionable. The abrupt onset of 'inability to walk' in case 1 was not accompanied by detectable focal neurological deficits; therefore this episode can hardly be diagnosed as a stroke. Case 3 could have been diagnosed as a case of AD with cerebrovascular disease (Román et al., 1993), but the vascular changes were not accompanied by clinical signs of stroke or neuroimaging changes, except for the unspecific white matter lucencies.

In addition to the type of ischemia leading to a territorial arterial infarct, other patterns of brain injury may develop as a result of variations in either the severity or the duration of the injury (Lassen, 1982; De Girolami et al., 1984; Garcia et al., 1995). If one accepts the concept that ischemic injury to the brain can impair cognitive functions, then it seems logical that types of ischemic injury (other than those secondary to arterial occlusions) ought to be considered among those potentially responsible for causing an encephalopathy, as we have previously outlined (Garcia and Brown, 1992). It is probable that ischemic brain lesions not falling in the category of global ischemia or arterial territorial infarction could have subtle clinical correlates and these would be difficult to detect until the cumulative effect of many of these lesions develop. In these cases, the clinical evolution probably would lack those features thought to be pathognomonic of cognitive impairment of vascular origin, namely: a history of stroke and a stepwise progression.

At present, we are unable to outline well defined clinical criteria for cases of progressive cognitive impairment secondary to ischemic injury. However, overlooking a possible vascular cause of cognitive impairment in patients who have a progressive course can lead to the exclusion of these patients from therapeutic treatment. We suggest that clinico-pathological studies are required before we achieve a more precise understanding of the vascular causes of mental impairment.

A recently published review of subcortical leukoencephalopathy, based on the analysis of over 150 publications, concluded that the brief description of one case provided by Binswanger in 1894 is inadequate to merit attaching his name to a yet-to-be-defined nosological entity (Pantoni and Garcia, 1995).

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