Vascular Dementia

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Many cases of age-related cognitive dementia are caused by cerebrovascular lesions, and various vascular syndromes can lead to cognitive impairment and dementia. Repeated cortical infarcts due to embolic disease of the heart or major cerebral vessels can cause progressive deterioration towards dementia and incapacitation. In classic multi-infarct dementia, cognitive deterioration is stepwise rather than smoothly progressive. While diagnostic technologies have vastly improved and added to general knowledge of the pathology of cerebrovascular disease, MRI, PET, and transcranial Doppler scans have demonstrated that significant white matter change is possible without clinically recognized TIA or completed stroke. In addition, patients may have initial complaints that are not serious enough to produce changes on mental status examination. Many patients have mixed dementia, exhibiting aspects of both degenerative brain disease and clinical evidence of strokes or significant changes on MRI scan. The overlap between vascular and degenerative disease is significant, yet the exact interaction of the pathophysiology of the vascular lesions and the degenerative changes is not known. The treatment of vascular or mixed dementia involves control of the risk factors for continued vascular events and treatment with the cholinesterase inhibitors.

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In advancing age, many patients begin to develop changes in cognitive and social abilities. Age alone, particularly in the ninth decade, causes us to think more slowly, have trouble remembering names, be slower at processing incoming information (e.g. the staccato sound byte newscasts) and tire more easily. At some point in some elderly individuals, cognitive impairment diverges from the norm (so-called mild cognitive impairment). If the process continues and the patient can no longer function independently, the patient is diagnosed as being demented.

The most common cause of dementia is the degenerative effect of Alzheimer's disease, but many cases of dementia are caused by cerebrovascular disease—vascular dementia caused by cerebrovascular lesions. Factors supporting the diagnosis of vascular cognitive impairment and dementia are:

1. History of hypertension
2. Previous cerebrovascular accidents (CVAs) or transient ischemic attacks (TIAs)
3. A progressive deterioration in mental status
4. The presence of abnormal neurological signs
5. Scattered cognitive defects, e.g. aphasia
6. Extensive ischemic changes on MRI scan

TYPES OF VASCULAR DEMENTIA

Vascular disease of the brain is far from a unitary process, and various vascular syndromes can lead to cognitive impairment and dementia. Since dementia is a process of gradual mental decline, the patient who suffers a single large stroke with resultant devastating cognitive dysfunction is not considered demented.

Strategically Placed Multiple Embolic Infarcts or Hemorrhages

Multiple cortical infarcts can occur in embolic disease of the heart or major cerebral vessels. With each event the patient suffers a neurologic event that often produces a specific cognitive loss (e.g., mild aphasia with left parietal infarct). With repeated events the patient slowly becomes more demented and incapacitated. A similar clinical picture can occur with repeated lobar hemorrhages; these are occasionally seen in hypertension but are more common in cerebral amyloid angiopathy, a condition that is common in Alzheimer's disease. When the hemorrhages are seen with Alzheimer's disease, the dementia is of mixed etiology.

Multi-infarct Dementia

In classic multi-infarct dementia, the cognitive deterioration is stepwise rather than smoothly progressive (1). The cognitive changes vary, but memory loss is usually much less prominent than in Alzheimer's disease. With each event (stroke) the patient suddenly worsens but then improves either completely or partially. As the disease progresses, the patient develops an accretion of abnormal neurologic signs such as asymmetric reflexes, pseudobulbar changes (i.e. swallowing and speech difficulties along with emotional lability), pathologic reflexes (e.g. Babinski signs), and sensory abnormalities. This condition is usually seen in hypertensive individuals and is caused by multiple small infarcts in the white matter of the brain as well as the basal ganglia and cortex. A variant of multi-infarct dementia is Binswanger subcortical arteriosclerotic encephalopathy in which the disease is confined to the white matter of the hemispheres and is usually reported as a fairly rapidly progressing dementia with significant neurologic and cognitive changes.

Dementia With Extensive MRI Abnormalities Without History of Stroke

With the widespread use of MRI it has become apparent that many individuals have a significant amount of white matter change without having had a clinically recognized TIA or completed stroke. Pathologically the white matter lesions are a combination of lacunar infarcts, demyelination and gliosis, all due to small vessel disease and decreased blood flow and tissue perfusion (2). These lesions occur in normal nondemented elderly individuals and in patients with Alzheimer's disease but are most prominently seen in patients with mixed and vascular dementia. Such changes are most commonly seen in patients with hypertension or diabetes but are not restricted to that patient population (3).

In patients with MRI evidence of ischemic brain disease, cognitive impairment will occur as the condition progresses (4,5). Initial complaints may not be serious enough to produce changes on mental status examination but, as the pathology progresses, the cognitive changes begin to show abnormalities on cognitive testing from mild cognitive impairment to eventual dementia. A combination of the extent of the lesions and the strategic location of these lesions seems to be involved in producing the mental changes. As the white matter of the brain is composed of the axons of the cortical brain cells that connect one cell to another, it is not difficult to understand why disruption of these connections will produce cognitive problems.

The mental status changes exhibited by this population of vascular dementia patients is characterized by slowness in mental processes, problems with decision making, poor organizational ability, difficulty adjusting to change (impaired executive functions of the frontal lobe), difficulty sustaining attention, and the appearance of apathy. These clinical features are due to the disconnection of pathways from the basal ganglia and ascending brainstem pathways to the frontal lobes. Clinically this syndrome has been called subcortical dementia. Memory function, while impaired, is not the principal and devastating feature that it is in Alzheimer's disease.

Mixed Dementia

Many patients have aspects of both degenerative brain disease (e.g., Alzheimer's disease) and evidence of either clinical strokes or significant changes on MRI scan. Approximately 35% of Alzheimer patients have autopsy-proven vascular infarcts and 60% have white matter lesions on MRI. A very high percentage (70%-90%) of Alzheimer patients have amyloid changes in their vessels that narrow the vessels and produce hypoperfusion. The overlap, therefore, between vascular and degenerative disease is significant, yet the exact interaction of the pathophysiology of the vascular lesions and the degenerative changes is not known. Can hypoperfusion trigger Alzheimer degeneration? Does the amyloid angiopathy produce white matter vascular changes? These and many other questions remain to be answered.

DIAGNOSTIC TESTS

Imaging

The increased sophistication of cerebral imaging has heightened our awareness of cerebrovascular changes. Initially, CT scanning demonstrated lacunar infarcts as well as patches of white matter disease (leukoaraiosis). MRI scans, particularly with the newer Fluid Attenuation Inversion Recovery (FLAIR) sequences, have dramatically demonstrated not only the extent of the white matter disease (the hallmark of small vessel disease) but also the small cortical lesions that were not identified on the old T1 and T2 sequences. In addition to localizing lesions in the brain, it is now possible to quantitate the extent of the white matter change using an automated magnetic resonance tissue class segmentation technique (6). These data, in concert with localization analysis, may eventually be extremely useful in determining whether the vascular lesions are causal (vascular dementia) or merely contributory (mixed dementia) to the cognitive decline.

In addition to the morphologic imaging techniques, functional scans (PET, SPECT) are able to image perfusion and, in the case of PET, the oxygen or glucose utilization of the cortical grey and subcortical white matter tissue. This is useful in differentiating Alzheimer's disease in which there is a temporal and parietal decrease in uptake from the scattered perfusion defects seen in vascular dementia.

Transcranial Doppler

Transcranial Doppler sonography studies can now provide valuable information on cerebrovascular resistance, cerebrovascular reserve, and cerebral perfusion. Vascular resistance is calculated from the pulsative index (systolic/diastolic ratio); increased pulsative index indicates increased cerebrovascular resistance. Cerebrovascular reserve is calculated from the response of the cerebral vessels to a vasodilatory challenge either with CO_2 elevation, as tested by breath holding, or with acetazolamide injection (7). Cerebral perfusion is assessed as a velocity measure of the individual vessels.

Patients with vascular dementia secondary to small vessel disease have a significant increase in vascular resistance and a decrease in vascular reserve. In Alzheimer's disease, vascular resistance and reserve are normal, and there is a decrease in perfusion through the middle cerebral artery secondary to the atrophic brain tissue that it supplies. Therefore, Doppler studies can be very helpful in sorting out the vascular factors and establishing the diagnosis in dementia patients with abnormal MRIs and a history compatible with cerebrovascular disease.

CASE STUDY

A case illustrative of the difficulty in assigning a definitive diagnosis of vascular dementia was recently evaluated at the Ochsner Neurology Department. A 76-year-old female was in generally good health but had a medical history of hypertension, hyperlipidemia, and a previous carotid endarterectomy for a 99% stenosis of the right carotid artery but no history of clinical stroke. Over the 6 to 12 months prior to her evaluation, the family had begun to notice a problem with her recent memory. On neurological examination, she demonstrated a significant asymmetry of deep tendon reflexes (DTRs) with a right-sided preponderance but no extensor for sign (Babinski). Gait, coordination, sensory, and cranial nerve examinations were all within normal limits. Mental status examination demonstrated problems with learning (recent memory) despite full orientation to time, place, and situation. On a specific test of recent memory where the examiner asks the patient to observe him hide five common objects (i.e., coin, key, pen, comb, and fork) and then name them and recall their hiding place after 5 minutes, the patient could correctly name and place none of the objects. She named one but did not know its location, and knew one hiding place but not the object hidden therein. Her other cognitive functions (language use, attention, calculations, drawing, and simple reasoning) were intact.

In this case we have a history of significant risk factors for vascular dementia yet no history of stroke. The asymmetry of reflexes suggests some type of central nervous system lesion, most likely a subclinical stroke. On the other hand, her history of a slowly progressive memory loss without other cognitive problems such as aphasia is much more typical of Alzheimer's disease than of vascular dementia. In order to establish a diagnosis, three examinations were ordered: MRI, SPECT, and transcranial Doppler.

The MRI FLAIR image (Figure) shows extensive white matter disease with confluent areas of leukoairiosis. The SPECT scan was within normal limits; but the Doppler study showed a significantly elevated vascular resistance in all vessels and some decrease in flow in the middle cerebral artery (seen in Alzheimer's disease). The amount of abnormal tissue is approximately 71 ccs, which is quite high.

The history, examination, and imaging studies are far from diagnostic. The patient could have primarily a vascular dementia or could have a mixed dementia. It would be incorrect, however, to diagnosis her case as a degenerative dementia (e.g., Alzheimer's disease).

TREATMENT

The treatment of cases of pure vascular dementia or mixed dementia involves two basic strategies: 1) control the risk factors for continued vascular events, and 2) treat with the cholinesterase inhibitor drugs initially developed for Alzheimer's disease (donepezil, rivastigmine, galantamine), which have been shown to be effective in vascular as well as degenerative dementia (8).

CONCLUSION

Vascular disease of the brain, particularly hypertensive small vessel disease, is a more important factor in producing cognitive

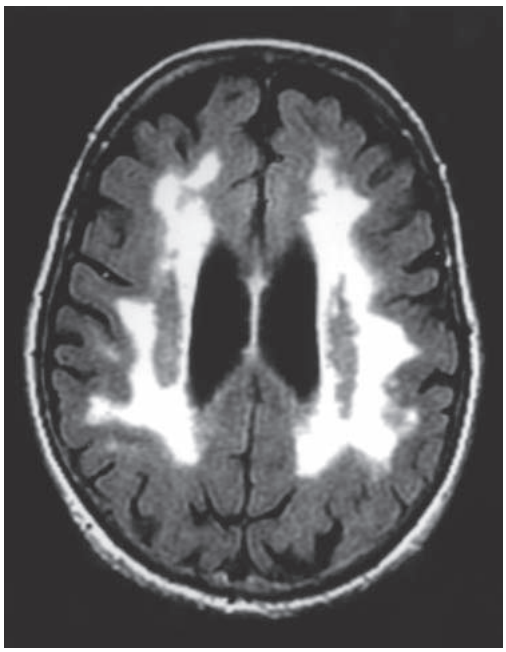

Figure. MRI Fluid Attenuation Inversion Recovery (FLAIR) image showing extensive white matter disease with confluent areas of leukoairiosis.

impairment and dementia than was previously thought. We do not know the true incidence of vascular and mixed dementia nor do we know all the risk factors. We do know that treatment of the dementia with anticholinesterase drugs helps, but we do not know if risk factor control will decrease the incidence and severity of vascular cognitive change. We know a lot about Alzheimer's disease and vascular dementia, but we do not know if there is any common pathogenesis. Our understanding of the interaction between cerebrovascular disease and cognition is just beginning.

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