Mixed Alzheimer's Disease and Vascular Dementia

The diagnosis of mixed Alzheimer's disease and vascular dementia is likely more common than has been appreciated to date. The diagnosis is generally made on the basis of clinical findings and a radiograph, but can also be made on the basis of clinical findings alone.

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The diagnosis of mixed Alzheimer's disease (AD) and vascular dementia is likely more common than has been appreciated to date. The diagnosis is generally made on the basis of a radiograph, but can also be made on the basis of clinical findings. Treatment includes the judicious management of vascular risk factors and therapy specifically aimed at AD.

Changing Views on Mixed AD and Vascular Dementia

"Everything old is new again" is an epigram that applies as much to medicine as it does to other human endeavours. One of the recent findings that is potentially the most far-reaching, and one with immediate practical importance, is the rediscovery of the link between vascular risk factors and dementia. This link is not limited to the so-called "multi-infarct dementia," but encompasses all causes of the dementia syndrome, including AD.

This rediscovery tells us much about the recent conceptualization of dementia. Even as late as the 1970s, people held somewhat contradictory beliefs about late-life dementia. On the one hand, dementia, in the guise of senility (a synonym for aging), was seen as an inevitable part of normal aging. On the other hand, dementia was believed to be caused by hardening of the arteries. Even though arteriosclerosis was recognized as a disease, the two were somehow lumped together into a problem that would happen to everyone who lived long enough. In the enthusiasm to make it clear that AD was a real illness, and one deserving a systematic approach to diagnosis, the baby—vascular risk factors—was thrown out with the bathwater—senility.

Several lines of evidence now point to a link between vascular risk factors and AD. As reviewed elsewhere,[1,2] epidemiologic studies have shown that hypertension is a risk factor for all causes of late-life cognitive impairment, including AD. Among people with AD, cognitive impairment is worse when cerebral athero-

sclerosis is present.[3] Other cardiovascular risk factors, including high cholesterol, diabetes mellitus and atrial fibrillation, have also been shown to increase the risk of AD.[1,2]

Interestingly, the association between vascular risk factors and AD largely faded from academic consciousness despite several neuropathologic and neuroradiologic studies that suggested otherwise.[1] In case series of patients with AD, presumptive evidence of cerebral ischemia was usually found in about 20% to 30% of patients, although one study (of white matter changes detected by magnetic resonance imaging) put the estimate closer to two-thirds.

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Against this background, it is perhaps not surprising that many clinical dementia scientists believe that the current estimates of mixed AD and vascular dementia, often given as 5% to 15% of dementia cases,[1] should be revised upward. Indeed, it may even be the most common form of dementia: two recent large American neuropathologic studies found pure vascular dementia (*i.e.*, vascular dementia without any evidence of AD) to be very uncommon—in the range of about 1%.[1] It is important to note that these are early data and that this experience is not universal; one British study[4] found an estimate in accord with the usual estimate of 10% to 20% of all dementia cases. Although more work needs to be done, it is clear that patients with cardiovascular disease remain at risk for cognitive impairment from both vascular and non-vascular causes. Although other types of dementia (*e.g.*, dementia with Lewy bodies, frontotemporal dementia) can be seen in the presence of cerebral ischemia, we will restrict our use of the term "mixed dementia" to AD and vascular dementia.

Contemporary Diagnosis of Mixed Dementia

The study of the diagnosis of mixed dementia is a central part of the research of the Consortium to Investigate Vascular Impairment of Cognition (CIVIC). Preliminary data on mixed dementia from CIVIC, a multicentre, Canadian clinic-based study, will be published.[5] These data show that there are two ways the diagnosis of mixed dementia is generally made. Most commonly, patients with clinically typical mild to moderate AD have white matter changes or other ischemic lesions such as cortical and subcortical strokes, including so-called lacunar infarcts on computed tomography (CT) scanning. Patients will have clinical features of both AD and vascular dementia less frequently (Table 1). For example, a patient with insidious onset and gradual progression of cognitive impairment early in the course of dementia may have a history of interval stroke with a precipitous decline followed by gradual progression. A clinical diagnosis of mixed dementia could be made with reasonable confidence in such an instance. In the CIVIC study, a diagnosis of mixed dementia was not made by the coincidence of typical AD and vascular risk factors without other evidence of ischemia, given that vascular risk factors are now understood to be risks for AD (Table 2).

The CIVIC experience means that, for individual physicians, the proportion of patients diagnosed with mixed dementia will depend on access to neuroimaging. Physicians who strictly follow the recommendations of the Canadian Consensus Conference on Dementia for referral for neuroimaging are likely to diagnose mixed dementia less often than those who have adopted more liberal criteria. The same holds true for those who adopt more liberal criteria for referral; the CIVIC data suggest that dementia specialists order CT scans for the great majority of patients seen in consultation.

Focal findings on a neurological examination can be used to make a clinical diagnosis of mixed AD and vascular dementia. More often, though, the diagnosis is based on a history of focal symptoms (including transient ischemic attacks and strokes), sudden onset and sudden worsening of otherwise typical AD (Table 1).

Contemporary Treatment of Mixed Dementia

The contemporary treatment of mixed dementia has two components: treatment of the vascular risk factors and treatment of the cognitive impairment.

Treatment of the vascular risk factors begins with the treatment of high blood pressure. Although there has been some concern that treatment for

Table 1

HINTS POINTING TO MIXED DEMENTIA IN A PATIENT WITH OTHERWISE TYPICAL AD

From the history

Consider:

- sudden onset
- delirium precipitating or unmasking AD
- prolonged plateau
- subclinical decline / slowly progressive AD variant
- episodes of stepwise progression
- interval medical illnesses
- focal motor or sensory symptoms
- other space-occupying lesions

On examination

Consider:

- unilateral rigidity
- early onset of parkinsonism
- other focal / lateralizing features
- other space-occupying lesions or spinal nerve root entrapment

Table 2

FEATURES IN OTHERWISE TYPICAL AD THAT WOULD NOT ON THEIR OWN BE SUPPORTIVE OF A DIAGNOSIS OF MIXED DEMENTIA

Feature

Consider:

- vascular risk factors
  (known also as risks for AD, not just VD)
- episodes of confusion
  (fluctuation can be part of the AD spectrum; delirium is common in AD)
- isolated focal signs
  (unilateral signs in isolation can arise outside the cranium; suspected brain lesions require confirmation by neuroimaging)

hypertension can cause cognitive impairment, the most recent data do not support this. In the SYST-EUR study of the treatment of systolic hypertension in elderly people,[6] the incidence of dementia in the treatment group was half of the placebo control group. In the treatment group, those with systolic hypertension (defined as a systolic pressure between 160 mm Hg and 219 mm Hg and diastolic pressure below 95 mm Hg) were assigned to first-time treatment with nitredipine, a calcium-channel blocker. If necessary, this could be combined or substituted with enalapril, an angiotensin-converting enzyme inhibitor. The diuretic hydrochlorthiazide was prescribed as a third choice. Of the patients with complete cognitive data, 21 of 1,180 in the placebo group were diagnosed with dementia, compared with 11 of 1,238 in the treatment group, after a median two years follow-up ($p = 0.05$). These treatment data are compelling but have yet to be replicated. Earlier studies of systolic hypertension treatment tended not to measure cognition precisely enough for an effect to be demonstrated.

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Two recent population-based studies have shown conflicting results. Guo et al[7] studied patients in

Sweden aged 75 years and older, and demonstrated the protective effect of diuretics on cognition impairment in hypertensive patients. In contrast, in the Canadian Study of Health and Aging, Maxwell and colleagues[8] showed an increased risk of cognitive impairment in elderly people who were treated with calcium-channel blockers. Taking all the data into account, it appears that elderly patients with systolic hypertension, good cognitive function and otherwise stable health (*i.e.,* those most like the SYST-EUR patients) can tolerate antihypertensive treatment. In such patients, benefit is likely to include a reduced risk of heart attack, stroke and dementia. The benefit for elderly hypertensive patients with multisystem disorders or mild cognitive impairment is uncertain, and cognitive function in such patients should be monitored carefully. Aggressive lowering of systolic blood pressure in such patients is generally unwise. Although other vascular risk factors appear to be important and their control is linked to a decreased incidence of stroke, such control has yet to be shown to decrease the incidence of dementia. This may be because larger studies with better characterization of cognitive endpoints need to be conducted or it may reflect the fact that stroke and vascular dementia are induced by different mechanisms.

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More specific treatment of mixed dementia focuses on treatment of the AD component. Although separate mixed dementia studies have yet to be conducted, most of the AD studies to date have included patients with so-called incidental subcortical or lacunar infarcts or minor degrees of white matter changes. Given these data and the lack of treatment alternatives, I usually opt for a trial of donepezil, the only approved treatment for AD in Canada.

Conclusion

The syndrome of mixed dementia has much to teach us, both about mechanisms of disease and fads of diagnosis. Perhaps our experience over the next few years will be as revealing as those gone by.

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