Mixed Dementia: The most common cause of dementia?

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CLINICAL VIGNETTE

A 75-year-old previously healthy woman comes to her annual appointment to renew her medications: calcium, vitamin D and alendronate. At the appointment, her daughter describes insidious short-term memory difficulties. In the past months, the patient's family has noticed she is no longer able to take care of her finances, prefers to buy frozen meals instead of cooking and sometimes forgets to take her medications.

The patient's blood pressure is 155/90 and her neurological examination is within normal, except for bilateral palmomental reflex and difficulty with tandem gait. She scores 25 on the mini-mental state examination (MMSE; -1 on attention, -3 on recall and -1 on copying the pentagons).

Furthermore, a brain MRI (Figure 1) performed the previous year due to a five minute episode of aphasia shows moderate periventricular white matter disease and hippocampal atrophy.

Do these findings mean she has mixed dementia? What needs to be done?

Alzheimer's disease (AD) is often cited as the most common cause of dementia. However, patients frequently have other concomitant pathologic lesions that may contribute to the cognitive decline. In fact, the frequency of pure AD on autopsy varies from 21% to 56.5%.[1-5] In a U.S. population study, 45% had mixed AD and vascular lesions, indicating that mixed dementia (MD) is actually a commoner substrate of dementia than pure AD.[3]

MD usually refers to AD and cerebrovascular disease (CVD). Vascular cognitive impairment (VCI) is a term that encompasses cognitive impairment of any severity to which CVD is a contributing factor, including MD[6] (Figures 1B, 2, 3, 4, 5). Of note, the NINDS-AIREN group preferred the term "AD with CVD" to MD because, even if AD and CVD is the most common combination, AD can coexist with other pathologic processes. This is explored later in this article in the section "Other Conditions that Occur Together."

DIAGNOSIS

MD represents a spectrum of vascular pathologies combined with AD (Figure 6).[7,8] Currently, there is a lack of consensus regarding the clinical and pathologic definitions of MD.

By common definition, MD is diagnosed when the decline in cognition is sufficient to impair function in daily life and results from the coexistence of AD and cerebrovascular pathology, documented either by clinical criteria or by neuroimaging findings.[9,10] With clinical exam and neuroimaging,

FIGURE 1 Axial T2 FLAIR. Hippocampal atrophy (arrow heads); moderate periventricular and subcortical white-matter hyperintensities (arrows).
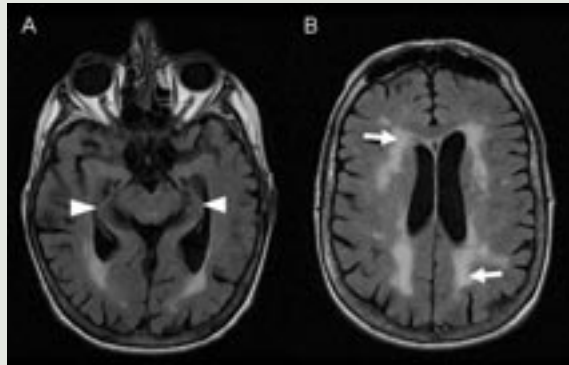
FIGURE 2 Vascular Cognitive Impairment (VCI)[6,44]

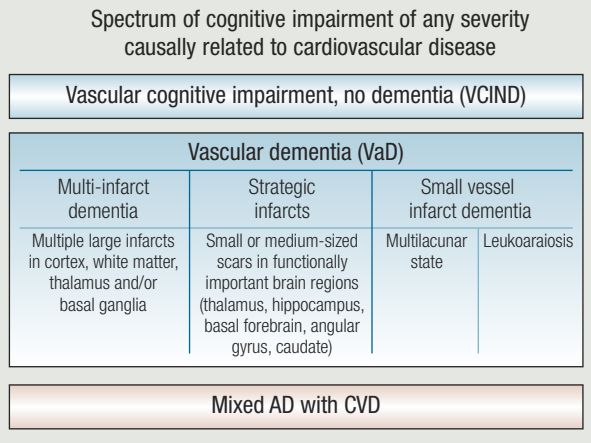| Spectrum of cognitive impairment of any severity causally related to cardiovascular disease			
Vascular cognitive impairment, no dementia (VCIND)			
Vascular dementia (VaD)			
Multi-infarct dementia	Strategic infarcts	Small vessel infarct dementia	
Multiple large infarcts in cortex, white matter, thalamus and/or basal ganglia	Small or medium-sized scars in functionally important brain regions (thalamus, hippocampus, basal forebrain, angular gyrus, caudate)	Multilacunar state	Leukoaraiosis
Mixed AD with CVD			

FIGURE 3
Axial T2 FLAIR. Multiple chronic infarcts in the left parietal lobe, left mesial frontal lobe and splenium of corpus callosum.
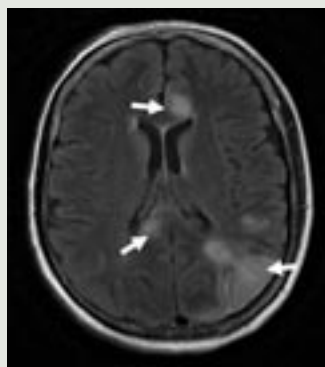

FIGURE 4
Axial T2 FLAIR. Strategic infarct: subacute lacune of the left thalamus and genu of internal capsule.
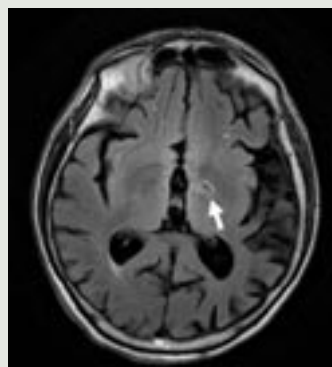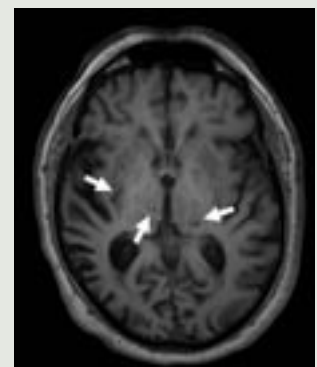

FIGURE 5
Axial T1WI. Lacunes in the basal ganglia and in the thalamus.

it is relatively easy to detect focal lesions due to CVD, but it is difficult to establish a causal role for the vascular injury.

Historically, MD was considered the proper diagnosis in patients with an indeterminate score (5 or 6) on the Hachinski Ischemic Score (HIS; Table 1).[11] However, this scale lacks specificity to distinguish MD from AD or vascular dementia (VaD).[12] MD is included in the categories of possible AD in the NINCDS-ADRDA criteria[13] and of possible VaD using the NINDS-AIREN criteria[14] (Figure 7). Many sets of criteria are available for the diagnosis of VaD, but most lack sensitivity (Tables 2 and 3). It has been argued that any degree of CVD co-existing with AD, including the prodrome of VaD called vascular cog-

FIGURE 6 Clinical Overlap (AD-VaD)[7,8]

AD		VaD	
Probable	Possible	Possible	Probable
MD			
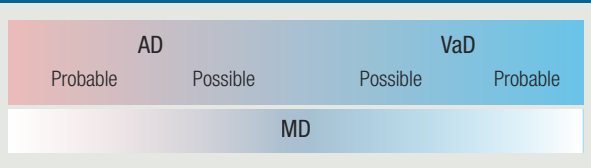
nitive impairment, no dementia (VCIND), should be considered sufficient for the diagnosis of MD.[15] This approach would encourage earlier diagnosis and management of vascular risk factors.

The presence of vascular risk factors alone, in a patient with otherwise clinically typical AD, is not considered enough to support a diagnosis of MD.

TABLE I Hachinski Ischemic Score (HIS)[11]	
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History / presence of hypertension	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2
Total score	

Scores ≥ 7 suggest a vascular etiology for dementia
Scores of ≤ 4 do not support a vascular etiology

The presence of parenchymal damage from vascular disease in AD patients cannot be predicted from presence of vascular risk factors.[9]

On autopsy, MD has been diagnosed when AD pathology co-exists with multiple large infarcts, but it is now known that small vessel disease (lacunes and leukoaraiosis) is also important for the expression of dementia.[5,16,17] No generally accepted and validated neuropathological criteria for the postmortem diagnosis of MD are available.[18]

EPIDEMIOLOGY

The true prevalence of MD is unknown. Epidemiology of MD is limited by the low accuracy of current criteria in distinguishing between AD, VaD and MD.

AD and CVD are frequent in the elderly population and they occur together more frequently than would be expected by chance alone.[19,20] The prevalence of MD has varied in different studies from 0% to 55%, depending on the setting.[3,17,21,22] The lower estimates come from selected groups of patients with a relatively pure phenotype of neurodegenerative disorder, and the higher figures come from population studies. Prevalence of MD also depends on the extent of the investigation. A vascular component is underestimated when no imaging is performed.[20] A review of many epidemiological studies gives an estimated prevalence of MD in the range of 20% to 40%.[20]

ETIOLOGY

Concomitant CVD and AD may have additive or synergistic effects.[16,23] Vascular lesions lower the threshold of Alzheimer pathology required for the development of dementia. In the Nun Study, small infarcts with co-existing AD pathology increased the odds of dementia by 20.[5,24] CVD significantly worsened cognitive impairment in earlier stages of

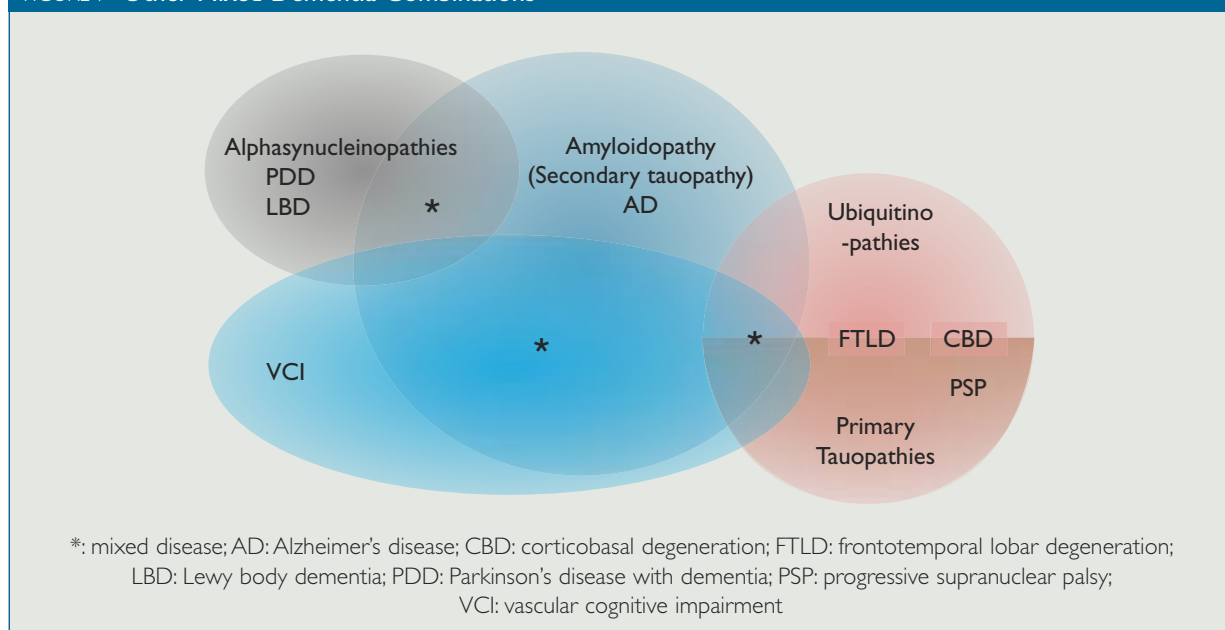FIGURE 7 Other Mixed Dementia Combinations

*: mixed disease; AD: Alzheimer's disease; CBD: corticobasal degeneration; FTLD: frontotemporal lobar degeneration; LBD: Lewy body dementia; PDD: Parkinson's disease with dementia; PSP: progressive supranuclear palsy; VCI: vascular cognitive impairment

TABLE 2 Clinical Criteria for VaD

ADDTC[61]	NINDS-AIREN[14]	DSM IV	ICD-10
Two impaired cognitive domains	Impairment of memory and at least two other cognitive domains Impaired functional abilities as a result of cognitive decline	Multiple cognitive deficits manifested by both impaired memory and at least one of the following: apraxia, agnosia, aphasia, or disturbance in executive functions	Memory impairment and deterioration in judgement and thinking, such as planning and organization
Evidence of CVD	Clinical and radiological evidence of CVD	Focal neurological signs and symptoms *OR* Laboratory evidence of CVD	Significant CVD that may be judged to be etiologically related to the dementia
Probable Clear temporal relationship between the cerebral event and the onset of dementia if only one stroke has occurred *OR* Temporal relationship is not necessary if there is evidence of two or more strokes	Probable Clear temporal relationship between dementia onset and stroke (within 3 months) *OR* Abrupt deterioration *OR* Stepwise course	Decline from a previous level *AND* Substantial impairment in social or occupational functioning *AND* Not exclusively during the course of a delirium	Emotional changes Focal neurological findings (unilateral spastic weakness of the limbs, unilaterally increased tendon reflexes, an extensor plantar response, or pseudobulbar palsy)
Possible Single stroke and no clear temporal relationship between the stroke and the onset of dementia *OR* Clinical and neuroimaging evidence of Binswanger's disease	Possible No neuroimaging, no clear temporal relationship, and an atypical course		

TABLE 3 Sensitivity (SE) and Specificity (SP) of Clinical Criteria for VaD for the Detection of Either VaD or MD[62]

ADDTC[61]		NINDS-AIREN[12]		DSM IV	ICD-10
Possible	SE 52% SP 87%	Possible	SE 41% SP 91%	SE 36%	SE 19%
Probable	SE 21% SP 96%	Probable	SE 19% SP 98%	SP 89%	SP 100%

AD.[16] However, others have found that the effects were independent and additive, rather than interactive.[23]

Interestingly, AD and CVD share common risk factors that independently increase the risk of both disorders independently (Table 4). CVD could be directly related to AD as a cause for neurodegeneration. Failure of elimination and accumulation of Aß could be secondary to age-related changes in small cerebral blood vessels that cause subcortical ischemic vasculopathy.[25]

SYMPTOMS

The symptoms of MD reflect the heterogeneity of its various etiologies and the locations of the lesions. VaD, which is at one end of the spectrum, is often associated with focal symptoms if sensory and motor areas are affected. Patients with MD have a high frequency of focal neurological signs, gait disorder and depressive mood.[26]

It has been suggested that the neuropsychological characteristics of MD are more closely related to those of VCI than AD.[27] By definition, VaD needs to meet

TABLE 4 Common Risk Factors for AD and VCI	
Risk factors	**Comments**
Age	• Effect on small vessels and large vessels • Accumulation of Aß with aging[63]
Hypertension	• During midlife[64]
Diabetes	• Diabetes could be linked to AD via (1) impairments in insulin and insulin growth factor signaling and (2) peripheral insulin resistance with excess cytotoxic ceramide production[65,66]
High serum cholesterol and LDL levels	• During midlife[64] • Enzymatic production of the beta amyloid peptide is affected by membrane cholesterol levels[67]
Homocysteine	• Hyperhomocysteinemia could increase beta-amyloid formation[68,69]
Apolipoprotein E ε4 genotype	• ApoE ε4 is associated with earlier onset of AD[45] • ApoE ε4 is a risk factor for coronary heart disease[67]
Atherosclerosis	• Association of peripheral arterial disease with AD remains even after excluding patients with VaD[70]
Smoking	• Current smoking is associated with incident dementia and AD, but the association is less clear for VaD[52,71] • Could nicotine have a positive cholinergic therapeutic effect?
Obesity	• During midlife[72]
Cerebral amyloid angiopathy (CAA)	• CAA is the most frequent vascular abnormality in AD[6] • CAA is associated with vascular dysfunction and increases the risk of hemorrhagic and ischemic stroke[73]

the criteria for dementia, which requires a decline in memory and in another area of cognition. However, VCI is characterized by patchy cognitive deficits depending on location of injury. The requirement for abnormal memory could lower the sensitivity of the clinical criteria by missing the executive dysfunction typical of VCI.[15,28] Generally, there is greater impairment of executive functions with better performance in memory testing relative to patients with AD.[29] But according to some studies, executive dysfunction might be no more common in VCI than in AD.[30]

BRAIN IMAGING

On MRI, the presence of hippocampal atrophy supports the likelihood of AD when appropriate clinical features are present (Figure 1A).[31,32]

Brain imaging findings in VCI are heterogeneous. They can be associated with multiple infarcts (Figure 3), hemorrhages, strategic infarcts (particularly in the thalamus, hippocampus, basal forebrain, and basal ganglia; Figure 4), leukoaraiosis (abnormal subcortical and/or periventricular white matter changes; Figure 1B) or multiple lacunes (Figure 5). The latter two entities constitute small-vessel disease which is probably the most common cerebrovascular pathological features associated with VCI.[1,17]

Despite progress in imaging techniques, their utility for diagnosis of MD is limited and accuracy is lower than pathologic examination for CVD. The absence of neuroradiographic features of CVD on imaging provides strong evidence against a vascular component to the dementia, but it is not enough to rule it out. Small cystic infarcts, selective neuronal loss and microinfarcts are not visible on brain MRI.[9]

Features of MD on functional imaging (SPECT or PET) have not been well described.[20] Anecdotally, cortical and subcortical infarcts are visible as focal hypoperfusion deficits giving a patchy appearance if there are multiple infarcts. Small lacunes and white-matter hyperintensities usually do not alter blood flow to visual inspection.

PATHOLOGY

MD is characterized by the co-existence of AD and CVD pathology. At autopsy, MD is usually diagnosed when there are sufficient degenerative lesions typical of AD to meet CERAD or Braak and Braak criteria,[33] as well as sufficient vascular damage to contribute to cognitive loss. This paradigm is however far from perfect, for several reasons.
1) MD may not just be the addition of two conditions. Degenerative and vascular lesions may po-

tentiate each other, resulting in dementia, even when the two types of lesions are not severe enough to reach the threshold for dementia by themselves. Concomitant ischemic or hemorrhagic lesions can act synergistically by lowering the threshold of AD changes required for the clinically apparent dementia and by worsening cognitive impairment in earlier stages of AD.[16,20] The Nun Study has shown that expression of dementia in elderly women with AD pathology was markedly influenced by lacunes in the thalamus, in the basal ganglia or in the deep white matter.[5] Patients with CVD show significantly lower densities of plaques and tau pathology than in pure AD for every given level of cognitive deficit.[34,35] The coexistence of large vessel infarcts increased likelihood of dementia in patients with AD pathology from 57% to 75% and the presence of lacunes increased the likelihood to 93%, 20 times the odds.[5]

2) Unlike AD pathology, which correlates fairly well with the severity of cognitive impairment, it is quite difficult to relate structural vascular changes to cognitive decline.[18,36] Cerebrovascular lesions of < 10 mL of volume are considered not to significantly impair cognitive function.[18] In fact, cognitive impairment is proportional to the total volume of infarcts, especially with lesions in limbic and medial association areas, frontal cortex and white matter.[37] There was no accepted neuropathological classification for quantifying cerebrovascular lesions in dementia until the harmonization criteria for VCI published in 2006.[28]

3) Patients may exhibit morphologic changes typical of AD and CVD without clinical evidence of dementia before their death.

Jellinger and Attems suggested that MD could be defined at autopsy by a combination of AD with multiple lacunes or cerebrovascular lesions in cortex, basal ganglia, thalamus, hippocampus, and white matter, with about 30 mL to 50 mL of infarcted or damaged brain volume.[18]

OTHER CONDITIONS THAT OCCUR TOGETHER

AD and Lewy body dementia (LBD) share many features, and they occur together in a substantial proportion of patients. In autopsy series, Lewy bodies, the pathological hallmark of LBD, Parkinson's disease (PD) and Parkinson's disease with dementia

(PDD), have been described in 10% to 22% of AD patients.[1,3,7,8,18] About 55% of cases of LBD are associated with AD pathology.

In a series of patients with pathologically confirmed progressive supranuclear palsy (PSP), a majority of cases had coexisting features of another tauopathy. Sixty-nine percent of patients had Alzheimer-related pathology, but only 18% fulfilled the CERAD criteria for either definite or probable AD. Almost a third of patients had coexisting pathological features of corticobasal degeneration (CBD).[38]

CVD can occur in other neurodegenerative disease and contribute to cognitive decline. However, little information is available about this type of mixed diseases, and how it may influence the clinical picture.

PREVENTION

Results of trials of antihypertensive treatment to prevent dementia in general have been contradictory, but a recent review suggests that some antihypertensives may be more protective than others.[39]

In the Systolic Hypertension in Europe (Syst-Eur) trial, incidence of dementia was decreased by 50% from 7.7 to 3.8 cases per 1,000 patient-years ($p = 0.05$) in patients treated with nitrendipine, a calcium-channel blocker. The study was terminated early because of the benefits of nitrendipine for stroke prevention. The conclusions were based on 32 incident cases of dementia over two years.[40] Over a two-year open-label extension, the results were similar with a 55% reduction in dementia incidence for those receiving long-term therapy ($p < 0.001$).[41]

In the PROGRESS trial, patients in the active treatment group received ACE-inhibitor perindopril, with indapamide added if needed for control. During the four year follow-up, there was a non-statistically significant 12% reduction risk of dementia driven by the group receiving the combination of both drugs. Sub-group analysis suggested the benefits were secondary to stroke prevention rather than a direct effect of cognition.[42]

Other trials (SHEP[43], MRC[44]) did not show protection against dementia with lowering of blood pressure.

The difficulty of demonstrating protective effect of antihypertensive therapy could be due to the fact that hypertension in midlife is associated with dementia and the fact that randomized controlled trials (RCTs) generally have a relatively short follow-up period. In the few years preceding dementia, the blood pressure

TABLE 5	Pharmacological Treatment Studies of Patients with MD or VCI		
Drugs	**Patients**	**Results**	**Comments**
Donepezil	• 565 patients with AD • 16% also had VaD	• Greater cognitive response in AD patients with CVD than without ($p = 0.02$)[54]	• Subgroup analysis
	• 913 patients with AD • 29.6% also had CVD	• Slightly greater proportion of CVD + patients reported improvement compared with CVD patients[74]	• Subgroup analysis • Only 3 months of follow-up
	• 603 patients with possible (29.5%) or probable (70.5%) VaD (NINDS-AIREN)	• Significant improvements in cognition and in global function[75]	• VaD study, designed to exclude patients with AD or MD
	• 616 patients with possible (24%) or probable (76%) VaD (NINDS-AIREN)	• Improvements in cognition and in global function[76]	• VaD study, designed to exclude patients with AD or MD
Galantamine	• 592 patients diagnosed either with probable VaD (43%), AD combined with CVD (48%), or intermediate diagnosis	• Improvement in cognition and global functioning for the overall reated group and the subgroup with AD combined with CVD[77]	• Post-hoc subgroup analysis
	• 459 patients diagnosed either with probable VaD or AD combined with CVD (52%)	• Similar sustained benefits after 12 months[78]	• Open-label extension of the double-blind study[77]
	• 788 patients with probable VaD (NINDS-AIREN) with MRI showing CVD	• Statistically significant improvement in cognition, but not in daily function[79]	• VaD study, no mention of MD
Rivastigmine	• 697 patients with AD • 54% with at least one vascular risk factor by HIS (exclusion if score > 4)	• Improvement in cognition, ADL and disease severity • Treatment effect was generally larger in patients with vascular risk factor(s)[80]	• Post-hoc analysis • Patients were considered to have at least one vascular risk factor if modified HIS was higher than 0
	• 50 patients with VCIND treated with rivastigmine	• Statistically significant improvement on category word generation test[60]	• Pilot study suggesting that rivastigmine might improve executive function
Memantine	• 321 patients with probable VaD (NINDS-AIREN) with modified HIS ≥ 5/10	• Statistically significant improvement in cognition[58]	• VaD study, designed to exclude patients with AD
	• 579 patients with probable VaD (DSM-III-R and NINDS-AIREN, and HIS ≥ 4)	• Statistically significant improvement in cognition[59]	• VaD study, no mention of AD or MD

starts to decline and declines further with progression of the disease.[45]

It is possible that the protection offered by certain antihypertensive drugs is not just related to blood pressure control, but involves additional neuroprotective mechanisms. It has been hypothesized that calcium channel blockers could reduce neuronal damage by decreasing free calcium in neurons,[46] and that ACE-inhibitors may be less protective than AT1-receptor-blockers because they may be amyloidogenic.[39,47]

In the Aspirin for Asymptomatic Atherosclerosis (AAA) trial, 3,350 patients at risk for CVD were randomized to receive either placebo or ASA 100 mg. After five years, there was no difference on a range of cognitive measures.[48]

Despite the results of some observational studies suggesting a reduction in the risk of incident AD with statin therapy,[49,50] RCTs have not confirmed this reduction in the incidence of cognitive decline or dementia.[51-53]

TREATMENT

Although the only approved indication for cholinesterase inhibitors (ChEIs) is the treatment of mild-to-moderate AD, this drug class has been studied in patients with other dementias (Table 5).

Donepezil provides benefits for patients with AD and VaD, but there is no donepezil trial specifically designed for patients with MD. In AD2000, 16% of patients had AD plus CVD. Analysis of this subgroup suggested more benefit than in patients with pure AD, but the goal of the study to delay nursing home placement was not met.[54]

An RCT of galantamine for patients with either probable VaD or AD with coexisting CVD showed treatment benefits for cognitive and functional outcomes. The subgroup with presumed pure VaD did not show statistically significant benefit from the treatment, suggesting positive trial results were driven by the patients with MD.[55]

Overall, the mean treatment effect across ChEI studies for MD has been described as equivalent to a four to six month delay in cognitive decline.[56]

Memantine is indicated for the treatment of moderate-to-severe AD.[57] Although no memantine trial has been designed specifically for patients with MD, it has been shown to have cognitive, but not functional benefits, for patients with mild-to-moderate VaD.[58,59]

PROGNOSIS

Patients with MD tend to have outcomes similar to AD patients.[30]

CLINICAL VIGNETTE: CONCLUSIONS

The patient in question has a cognitive decline interfering with daily function. The screening assessment of her cognition suggests a profile compatible with the deficits typical of AD. However, the MMSE lacks sensitivity to detect a dysexecutive syndrome and underestimates subcortical deficits caused by a small vessels disease. On the Montreal Cognitive Assessment (MoCA), she scores 20/30 (-3 on executive functions, -4 on recall, -2 on attention and -1 on abstraction). A formal neuropsychological assessment, if available, would provide more detailed information on executive subdomains, such as attention, working memory, problem solving and mental flexibility.

The presence of vascular risk factors alone, in a patient with otherwise clinically typical AD, is not enough to support a diagnosis of MD. Considering the severity of white matter changes on imaging, and the amnestic and dysexecutive profile of this patient, the provisional diagnosis is MD. Vascular risk factors should also be investigated and hypertension should be treated. However, at the present time, there are still controversies related to the optimal antihypertensive treatment to cognitively protect the brain.

The patient could be offered a trial with a ChEI. Different ChEIs have been studied in different populations, and there is more evidence for donepezil and galantamine in VCI and in AD with CVD, but benefits with rivastigmine have also been suggested.[60] As in AD, these benefits may be more a class effect of ChEIs than the effect of a particular molecule. In the absence of comparative data, there is no evidence to support the preferential use of one ChEI over another.

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