Mixed Dementia in Clinical Trials of Alzheimer's Disease

The term "mixed dementia" refers to the coexistence of more than one possible cause of dementia in a given patient and has been subjected to much controversy in the past literature[1-3]. Practically, "mixed dementia" usually refers to the coexistence of Alzheimer's disease (AD) with a vascular contribution. It is a commonly used clinical diagnosis although published guidelines lack consensus on a clear definition. The National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) diagnostic criteria for vascular dementia did not include a definition for "mixed dementia", and proposed the use of the term AD with cerebrovascular disease[4]. In the Alzheimer's Disease Diagnostic Treatment Center (ADDTC) criteria, "mixed dementia" is defined as a condition in which there is evidence of vascular disease with the coexistence of one or more disorders that may be causally related to the dementia[5]. In the most recent statement on Vascular Contributions to Cognitive Impairment and Dementia, the term Vascular Cognitive Impairment (VCI) represents the whole spectrum of cognitive impairment associated with vascular brain injury including coexistent AD[6]. The term "mixed dementia" is not used or defined even though authors mention that the neuropsychological diagnosis of VCI is "complicated by the difficulty of clinically differentiating Alzheimer disease or VCI from mixed (Alzheimer disease plus cerebrovascular disease) disease, which may be more common than either "pure" Alzheimer disease or "pure" VCI."

The Canadian Cohort Study of Cognitive Impairment and Related Dementias (ACCORD) study, evaluated the distribution of clinical diagnoses of patients referred to Canadian memory disorders clinics between 1997 and 1999. This study including 1136 subjects showed that 59% had dementia 47.2% of which were due to Alzheimer's Disease, and 27.5% were mixed (AD with another diagnosis)[7]. In the Cardiovascular Health Study, a community-based study, 33% of dementia cases were due to AD with a vascular contribution[8]. Clinico-pathological studies of individuals with dementia show that "mixed dementia" is even more prevalent. For example, the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) , a community-based study of elderly individuals showed that 61% of dementia cases displayed AD pathology and 54% displayed vascular pathology and most cases had mixed pathology at autopsy[9]. In the Rush Memorial and Aging Project, 50% of dementia cases had mixed disease on neuropathological examination[10]. Few studies have made clinico-pathological correlations in the setting of specialized memory disorders clinics or in clinical trials of AD.

In this issue of the Canadian Journal of Neurological Sciences, Wang et al describe the neuropathological findings of 16 individuals with a clinical diagnosis of AD who were also enrolled in clinical trials[11]. Five of these patients (31%) had pure AD pathology, ten had mixed pathology (AD with contribution from another condition, most commonly vascular in nature) and only one patient had non-AD pathology. Individuals with mixed AD had poorer performance on the baseline Functional Rating Scale (FRS) in problem-solving and community affairs. The good news from this study is that 94% (15 out of 16 cases) were correctly diagnosed with AD, validating the expertise of this specialized memory disorders clinic. The bad news is that most cases of AD were mixed, and this was not recognized clinically despite a thorough clinical evaluation including the use of neuroimaging. In fact, neuroimaging showed white matter abnormalities in only four out of the ten patients with comorbid vascular neuropathology (and two out of the five patients with pure AD). One can argue that clinically silent vascular events may have occurred during the three years on average separating the last clinical assessment from death and may explain, at least in part, this discordance. The small sample size and possible referral bias to autopsy may limit the interpretation of these results but, inasmuch as these 16 patients are representative of individuals recruited in clinical trials of AD, discussion is warranted about the design and conduct of such trials in the future. First, clinical trials of AD with disease-modifying agents targeting the underlying pathophysiological process may have distinct effects in individuals with pure versus mixed AD pathology. Second, it is well recognized that concomitant vascular lesions commonly unmask (or worsen) clinical symptoms in individuals with AD neuropathology. Hence, for the same level of cognitive impairment, individuals with mixed disease may have less underlying AD pathology[12], and this may in turn influence their response to an agent being tested in clinical trials. Third, the fact that performance on sections of the FRS distinguished individuals with pure AD from those with mixed pathology is of interest. It suggests that those with significant dysexecutive symptoms and functional impairment at initial evaluation are more likely to have mixed pathology. If this finding is replicated in larger clinico-pathological studies, the FRS or similar scales may be used as inclusion or exclusion criteria for selection of individuals with pure AD. Fourth, brain magnetic resonance imaging is more sensitive to vascular pathology than CT scan and may help select individuals with pure AD in future clinical trials. Finally, imaging and cerebrospinal fluid biomarkers of AD are promising and are increasingly being used in clinical trials of AD[13]. Unfortunately, these markers correlate closely with AD neuropathology but do not exclude a concomitant, and possibly clinically significant, process. Cerebrospinal fluid biomarkers, such as the CSF-albumin index and concentrations of different metallo-proteinases, are being developed for the specific diagnosis of VCI[14].

For clinicians, this study reiterates that a significant proportion of AD cases are "mixed" in nature and this is even truer in older cohorts and in community samples. The most

common concomitant condition being vascular, this opens the door to possible preventive interventions. There are no clinical trials targeting vascular risk factors in individuals with overt dementia. Nevertheless, a retrospective study in a memory disorders clinic showed that individuals with a diagnosis of AD progressed significantly more slowly when most of their vascular risk factors were treated[15]. These findings underscore the importance of optimal control of vascular risk factors in individuals with dementia.

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REFERENCES

1. Langa KM, Foster NL, Larson EB. Mixed dementia – emerging concepts and therapeutic implications. JAMA. 2004;292:2901-8.
2. Zekry D, Hauw JJ, Gold G. Mixed dementia: epidemiology, diagnosis, and treatment. J Am Geriatr Soc. 2002;50:1431-8.
3. Korczyn A. Mixed dementia – the most common cause of dementia. Ann NY Acad Sci. 2002;977:129-34.
4. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology. 1993;43:250–60.
5. Chui H, Victoroff J, Margolin D, et al. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology. 1992;42:473–80.
6. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia – a statement for healthcare professionals from the American Heart Association / American Stroke Association. Stroke. 2011; 42:2672-713.
7. Feldman H, Levy AR, Hsiung G-Y, et al. A Canadian cohort study of cognitive impairment and related dementias (ACCORD): study methods and baseline results. Neuroepidemiology. 2003; 22:265-74.
8. Lopez OL, Kuller LH, Becker JT, et al. Classification of vascular dementia in the Cardiovascular Health Study Cognition Study. Neurology. 2005:64:1539-47.
9. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet. 2001:357: 169-75.
10. Schneider JA, Arvanitakis Z, Bang W, Bennet DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology. 2007;69:2197-204.
11. Wang BW, Lu E, Mackenzie IRA, et al. Multiple pathologies are common in Alzheimer patients in clinical trials. Can J Neurol Sci. 2012;39(5):592-9.
12. Zekry D, Duyckaerts C, Moulias R, et al. Degenerative and vascular lesions of the brain have synergistic effects in dementia of the elderly. Acta Neuropath. 2002;103:481–7.
13. Hampel H, Wilcock G, Andrieu S, et al. Biomarkers for Alzheimer's disease therapeutic trials. Prog Neurobiol. 2011;95:579-93.
14. Moorhouse P, Rockwood K. Vascular cognitive impairment: current concepts and clinical developments. Lancet Neurol. 2008;7:246-55.
15. Deschaintre Y, Richard F, Leys D, Pasquier F. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. Neurology. 2009;73:674-80.