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Is There Pure Vascular Dementia in Old Age?

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Both the prevalence and incidence of dementia increase exponentially with age, doubling every 5 years after age 90, particularly in women [1-3]. Although few recent studies have suggested declining trends of the general incidence of dementia [4], the absolute number of demented people will increase due to the growing of the aging population [5]. Dementia in the oldest-old with a prevalence ranging between 5.7 and 61% [6], is a multifactorial and growing public issue, and established estimates of dementia in general and particularly in oldest-old patients are crucial for public health planning. However, epidemiologic data above 85 years must be interpreted cautiously due to referral biases, diagnostic difficulties, small case numbers and a high frequency of mixed pathologies and co-morbidities [3,7,8]. Neuropathological correlates of dementia in over 80 year-old brains show that multiple pathologies are associated with higher risk of dementia in old age [9,10].

Cerebrovascular disease (CVD) is increasingly recognized as an important cause of cognitive disorder in later life, both by itself or as a catalyst for the conversion of low-grade AD to overt dementia, which in full-blown AD cognitive impairment is mainly related to the severity and extent of tau-NFT pathology [11,12]. Vascular dementia (VaD), vascular cognitive impairment (VCI) or vascular cognitive disorder (VCD) describes a heterogenous group of disorders due to CVD in various stages and subtypes [12,13]. Major types of sporadic VaD/VCI are multi-infarct encephalopathy, small vessel and strategic infarct type dementias, subcortical arteriosclerotic leukoencephalopathy (SAE, Binswanger type), multilacunar state, mixed cortico-subcortical lesions, rare granular cortical atrophy, postischemic encephalopathy, and a mixture of various cerebrovascular lesions. They result from systemic, cardiac, and local large or small vessel disease (SVD); their pathogenesis is multifactorial [12,13]. Cognitive decline is commonly associated with widespread small ischemic lesions involving subcortical brain areas (basal ganglia and hemispheral white matter, less often cerebral cortex). CVLs involve neuronal networks involved in cognition, memory, attention, and behavior (thalamo-cortical, striato/thalamo-subcortical, cortico-subcortical and limbic systems) [13].

Although VAD/VCI is a main cognitive disorder in nonagenerians and centenarians, the validity of clinical criteria for this diagnosis is unknown. Recent evidence indicates that the prevalence and incidence of VAD/VCI increase between age 70 and 90+ from 13 to 44.6%, even less severe than AD (23.6 to 51%) [14,15], with no further increase or even slight decrease after age 95 [16], but these data must be interpreted cautiously due to the high frequency of mixed pathologies in very old subjects [17,18]. A retrospective hospital-based clinico-pathologic study of the prevalence of dementia disorders was performed in 1700 consecutive autopsy cases in two major hospitals in Vienna, Austria (mean age 84.3±5.4 SD, 90% over age 70). Neuropathology diagnosis followed current consensus criteria (see [14]). Four age groups (7th to 10th decade) were evaluated. "Pure" VaD (cognitive impairment/dementia due to CVD without essential other pathologies like Lewy body, tau or TDP-l3 lesions; mean neuritic Braak stage 1.2-1.6) was observed in 12.3% of the total cohort, decreasing between age 60 and 90+ from 15.0 to 8.7%. Morphologic subtypes (multi-infarct encephalopathy /MIE/, subcortical arteriosclerotic encephalopathy /SAE/ - the most frequent subtype -, and strategic infarct dementia /SID/) showed no age-related differences. By contrast, AD (without concomitant pathologies including CVD - 45.6 % of the total), mixed type dementia (AD + cerebrovascular lesions of different severity - 28.8%) increased with age from 39 to 48.9% and slightly decreased after age 95 (47.3%), while the relative prevalence of AD + Lewy body pathology slightly increased and Lewy body disease without AD pathology significantly decreased with age (from 8.0 to 1.3%). 95% of the oldest-old patients with "pure" VaD had morphologic signs of hypertension, 85% histories of diabetes, 75% of previous strokes, and 65% recent or old myocardial infarctions. 97% had cerebral hypertensive microangiopathy (associated with cerebral amyloid angiopathy in 23%) and 90% severe atherosclerosis of large cerebral arteries. In postmortem series of elderly individuals the incidence of cerebral amyloid angiopathy (CAA) in AD ranges from 94 to 100% (average 97%), in mixed cases around 90%, in VaD cases around 30% and in non-demented subjects 23-45% (median 33%) [6,13]. Similar autopsy findings were seen in mixed dementia [14,19]. Cerebral microinfarcts are common in various brain regions including cortex and are related to dementia in the oldest-old [20]. Braak NFT stage and severity of cortical microinfarcts usually allow defining of most demented in the oldest-old population [21].

However, a large percentage of non-demented oldest-old individuals with both AD-related and vascular brain pathologies have been reported [13,18], whereas many demented individuals aged 80+ do not meet the diagnostic criteria of either VaD, AD or diffuse Lewy body disease [22]. This is exemplified by the findings among 180 prospectively studied individuals (mean age 85±3.4 yrs), 24% of them had been demented. Autopsy revealed AD in 48, MIX in 19%, VaD in 11% and diffuse Lewy body disease in 9%, whereas 18% did not meet the pathologic criteria of one of these groups [23].

These and other studies confirm the existence of "pure" VaD/VCI in the age group 70+, however, with a moderate decline in centenarians, whereas AD and MIX show a significant increase over age 90, confirming the presence of mixed pathologies in the oldest-old population [11,15,24]. The overlap between vascular and neurodegenerative factors in the pathogenesis of dementia has been critically summarized recently [8,19,25], and the thresholds for vascular and degenerative

lesions for distinguishing "pure" VaD or AD from mixed cases have been critically discussed [26].

Clinical diagnostic criteria of VaD/VCI show moderate sensibility (around 50%) and variable specificity (range 64-98%) [13]. Although several international efforts have been performed and are currently undergoing to define cognitive impairment due to CVD, due to the high variability of underlaying CVLs and of the relevant pathomechanisms, including shared mechanisms with AD, no internationally accepted, reproducible and validated clinical and neuropathological diagnostic criteria are currently available.

Clinical diagnostic criteria for VCDs, have recently been proposed by the VASCOG group and members of the Neurocognitive Disorders Work Group of the fifth revision of the Diagnostic and Statistical Manual (DSM-5) Task Force, providing a coherent approach to the diagnosis of this diverse group of disorders, with a view to stimulating clinical and pathologic validation studies [27]. Recently the VICCCS group presented a new consensus based set of guidelines supported by a large international pool of researchers that may help to facilitate standardization in research [28]. There are several recent proposals to define the pathology of VaD: (1) the Newcastle group introduced a categorization of CVLs associated with cognitive impairment according to six subtypes [29]; (2) the revised NIA-AA guidelines recommend reporting all macroscopic vascular brain injuries and microvascular lesions (microinfarcts/hemorrhages) in standard screening sections, multiple such lesions being associated with increased likelihood of cognitive impairment [30] and (3) another recent staging proposes semiquantitative assessment of CVLs in four brain areas with a score ranging from I to IV/VI. All of them await further validation. The challenge of synthesizing a global 'vascular pathology score' depends on uniform and standardized study criteria [31], and pathological confirmation of a clinical diagnosis of VaD/VCD remains largely subjective in view of the fact of multiple pathologies involving the aged brain.

Recently, scientists from 9 UK centers have developed a set of neuropathologic guidelines to determine the inter-rater reliability for each type of underlying pathologies. 14 different vessel and parenchymal pathologies were assessed in 13 brain regions, and almost perfect agreement was found when the agreed criteria were used for the assessment of cerebral amyloid angiopathy, large and lacunar infarcts, larger and microhemorrhages, fibrinoid necrosis, perivascular space dilatation and hemosiderin leakage, and myelin loss. The preferred model included occipital leptomeningeal amyloid angiopathy, severe atherosclerosis in occipital white matter and at least one large infarct. The presence of 0, 1, 2 or 3 of these features resulted in predicted probabilites of VCI in 16, 43, 73 or 95%, respectively [32].

Conclusions and Future Outlook

"Pure" VCI/VaD is characterized by cognitive impairment of variable types and severity associated with multiple CVLs affecting different brain areas without essential concomittant pathology (Braak neuritic stage ≤ 2.0, no Lewy type or other lesions). In elderly subjects its prevalence averages 10 to 15%, with a tendency to decline after age 90, whereas AD and other dementias, in particular those with mixed pathologies, show considerable age-related increase.

Recent research suggests that neuropathological dissociation between cases with and without dementia narrows as age increases [9,33,34], but these and other problems including the prevalence and incidence of VaD in the oldest-old need further elucidation. To improve the diagnosis and management of VCI at older age, further progress has to be made in understanding the relevant pathomechanisms, including those shared with AD, bringing together international research initiatives, testing known risk factors in prospective clinico-pathologic studies and defining clinical stages and their relation to neuropathology, in particular to CVLs [13,18,35].

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