Despite growing knowledge of pathophysiological mechanisms and improved characterization of clinical syndromes, the classification of dementia remains conflicting and confused; and there is inconsistency in applying commonly used classification systems for the diagnosis. In a study of 1879 subjects, aged 65 years or older (Erkinjuntti et al., 1997) the highest prevalence was found when using the Diagnostic and Statistical Manual of Mental Disorders-III criteria (DSM-III), being 10 times more than the lowest prevalence, based on the International Classification of Diseases-10 (ICD-10) (29.1% versus 3.1%; Erkinjuntti et al., 1997). A similar level of inconsistency exists when trying to group cognitive disorders into different categories such as ‘vascular dementia’ and ‘Alzheimer’s disease’. Sensitivity for the clinical diagnosis of ‘Alzheimer’s disease’ can be as high as 90% when using autopsy reports as the gold standard (Galasko et al., 1994). However, these numbers may be biased. In a prospective clinicopathological study comprising 163 controls and 307 cases from a university hospital clinic, two sources of bias were identified (Bowler et al., 1998). First, a verification bias in that the proportion of deaths of patients undergoing autopsy differed substantially from those who were not autopsied (Bowler et al., 1998). Among those patients with an initial clinical diagnosis of ‘Alzheimer’s disease’, ‘vascular dementia’ or ‘mixed dementia’ who did not have an autopsy, 22% had not progressed after a median follow-up of 2.6 years (range 0–11.6 years). This means that at least 22% of these patients potentially had conditions other than ‘Alzheimer’s disease’, ‘vascular dementia’ or ‘mixed dementia’, as the explanation for their cognitive impairment; and as they did not die, they were not included in the denominator of the autopsy series (Bowler et al., 1998). The authors conclude that progressive dementia is over-represented in autopsy-based data. The second source of bias is a ‘dual diagnosis fallacy’ related to the role of cerebrovascular pathology identified in autopsies of patients originally categorized as having pure ‘Alzheimer’s disease’ (Bowler et al., 1998). Using standard clinical and pathological criteria, the positive predictive value of the clinical diagnosis of ‘Alzheimer’s disease’ is 81%. However, after reclassifying cases with any extent of infarction as ‘mixed dementia’ if they are accompanied by pathological changes of ‘Alzheimer’s disease’, and after re-categorizing cases with ‘Alzheimer’s disease’ with other co-existing diagnoses (other than ‘mixed dementia’) as ‘other dementia’, the positive predictive value of a diagnosis of ‘Alzheimer’s disease’ falls to 44% (Bowler et al., 1998). Furthermore, the combined effect of the dual diagnosis fallacy and the verification bias leads to further reduction in the positive predictive value to 38% (Bowler et al., 1998).

‘Alzheimer’s disease’ and ‘vascular dementia’ are thought to be the most common causes of dementia. Thus, the incorrect diagnoses and lack of adequate pathophysiological characterization of dementing disorders likely results in missed opportunities for identifying treatable and preventable causes, such as vascular disease. Recognizing the vascular component of dementias is imperative from a prevention standpoint. The Hachinski Ischaemic Score was designed for and serves as a useful clinical instrument for identifying this vascular component (Knopman et al., 2001). However, there is still much to learn about the pathophysiological reciprocal interaction of cerebrovascular disease and neurodegenerative disorders. In this issue of Brain, Toledo et al. (2013) report on the prevalence of cerebrovascular disease (vascular pathology considered as a primary or contributing neuropathology), vascular pathology (vascular findings reaching or not a threshold sufficient enough to contribute to clinical status), and vascular risk factors among autopsy samples of patients with single neurodegenerative diseases, including ‘Alzheimer’s disease’, frontotemporal lobar degeneration due to tau accumulation, and TAR DNA binding protein 43 immunoreactive deposits, α-synucleinopathies, hippocampal sclerosis and prion disease (Toledo et al., 2013). The study comprises 6205 autopsy cases from the National Alzheimer’s Coordinating Centre Database; 5715 with neurodegenerative diseases, 210 samples of unremarkable brains, and 280 brains with cerebrovascular disease. The prevalence of vascular pathology is higher in ‘Alzheimer’s disease’ than in α-synucleinopathy, frontotemporal lobar degeneration-tau and -TAR DNA binding protein associated disease, prion disorders, and unremarkable brains. The prevalence of cerebrovascular disease is also higher in ‘Alzheimer’s disease’ than in α-synucleinopathy, frontotemporal lobar degeneration-tau and -TAR DNA-binding protein disorders, and prion disease. As expected, this is more prevalent in younger patients. Another important finding is that the presence of cerebrovascular disease in cases with α-synucleinopathy is associated with an increased risk of dementia in addition to the increased risk in ‘Alzheimer’s disease’. Interestingly, with the exception of prion...
disease and hippocampal sclerosis, vascular pathology is present in ~60–80% of degenerative diseases. Together, these findings support the hypothesis of neurovascular processes as key targets for preventing or reducing the pace not only of ‘vascular dementia’, but also degenerative dementias.

Neuropathological studies have greatly contributed to the understanding of different types of dementias, but they are limited to description of consequences of the dementing processes, rather than being able to identify the pathophysiological mechanisms occurring during the presymptomatic stage. Newer in vivo approaches, such as novel neuroimaging techniques including PET and MRI, genetic and epigenetic studies, and the use of biomarkers with the potential to identify patients at risk, have led to a new era in exploration of the presymptomatic pathophysiology of dementias. In vivo PET scanning can detect amyloid-β deposition in the human brain and is beginning to be used as a clinical diagnostic tool in strictly defined subsets of cognitively impaired patients (Johnson et al., 2013). Developments are underway to identify specific components of amyloid plaques (i.e. cathepsin D) with the use of new MRI contrast agents (Ta et al., 2013). The role of some genetic factors (e.g. amyloid precursor protein gene, presenilins 1 and 2, and ApoE) in the genesis of dementia has been widely demonstrated (Paulson et al., 2011); and epigenetic studies are shedding light on the impact of gene expression on brain ageing (Akbarian et al., 2013). There is growing interest in the role of biomarkers (i.e. plasma and CSF amyloid-β and total or hyperphosphorylated tau) in the diagnosis of dementia (Noel-Storr et al., 2013). The association between elevated homocysteine and dementia turns plasmatic hyperhomocystinaemia into an attractive biomarker candidate (Wald et al., 2011). Hooshmand et al. (2013) report the results of their investigation on the association of baseline plasma homocysteine determinations and neuropathological and neuroimaging findings in 265 subjects from the population-based cohort of Vantaa 85+ study (Hooshmand et al., 2013). The authors found an independent association between elevated baseline plasma homocysteine and increased burden of neurofibrillary tangles at the time of death. In the group of 103 subjects who had post-mortem MRI, higher homocysteine levels are independently associated with periventricular white matter hyperintensities and more severe medial temporal lobe atrophy. These findings have at least two important implications. First, hyperhomocystinaemia could be considered as a potential biomarker for dementia. Second, and perhaps most important, elevated plasmatic homocysteine detected during early life could potentially become a new target for the prevention or the delay of dementia.

Evidence of shared risk factors for cerebrovascular disease and degenerative dementias continues to accrue (Akinyemi et al., 2013). There are also mounting data supporting the idea of mutually influencing and closely interacting cerebrovascular and neurodegenerative processes (Zlokovic, 2011). The studies of Toledo et al. (2013) and Hooshmand et al. (2013) strongly contribute to this vision. A worldwide ageing population means that the burden of dementia is rising. On the basis of current evidence, and in the face of the failure to mitigate this healthcare problem, we can now argue that classifying dementias into vascular, mixed and degenerative disorders is, at best, strained and does not offer significant improvements in the treatment of patients. It is crucial to build better profiles based on clinical, neuropsychological, imaging, genetic, pathological, epidemiological, and experimental evidence for defining cognitive impairment by using minimum common standards (Hachinski et al., 2006). If the same standard descriptions are used, we can begin to build evidence-based provisional criteria, refined by every new study. Better criteria and in vivo studies of interactive mechanisms of disease will likely result in new approaches and new results. Meanwhile, we propose: (i) making available a simple and reliable tool for diagnosing cognitive impairment; (ii) generating awareness about the importance of the screening and detection of the vascular component; (iii) offering the best available prevention options for those patients in whom a vascular component is identified; and (iv) evaluating this approach. This would be the first step in closing the gap between the promise and the proof of treating vascular cognitive impairment (Hachinski, 1994). Toledo et al. (2013) and Hooshmand et al. (2013) provide a strong rationale for shifting our emphasis from muddled diagnoses to treatable mechanisms.

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References

Akbarian S, Beeri MS, Haroutunian V. Epigenetic determinants of healthy and diseased brain aging and cognition. JAMA Neurol 2013; 70: 711–18.


Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Henscivitch P, et al. Update on appropriate use criteria for amyloid


Inflammation in Alzheimer’s disease: insights from immunotherapy

More than 20 years after its initial formulation, the amyloid cascade hypothesis—which postulates that build-up of toxic amyloid-β species initiates a series of events that culminates in neurodegeneration and symptoms (Hardy and Higgins, 1992)—continues to dominate thinking on the pathogenesis of Alzheimer’s disease. Although the exact sequence of events linking amyloid-β accumulation to aggregation of hyperphosphorylated tau in different neuronal compartments, neuronal loss, synaptic dysfunction and symptoms remains unknown, there is now a substantial body of evidence implicating neuroinflammation in the pathogenesis of Alzheimer’s disease. Thus activated microglia accumulate around amyloid plaques both in the brains of individuals with Alzheimer’s disease and in transgenic mice, and have been implicated in promoting neurodegeneration (Akiyama et al., 2000). Imaging studies using the $^{11}$C-R-PK11195 PET ligand provide evidence that activated microglial accumulate in the vicinity of amyloid plaque pathology, and that activated microglial burden correlates with declining cognition (Edison et al., 2008). Genome-wide association studies have identified a number of risk variants for Alzheimer’s disease implicated in inflammatory responses (Bettens et al., 2013); exome sequencing has revealed polymorphisms in the microglial receptor TREM2 gene as a rare but significant risk for Alzheimer’s disease (Guerreiro et al., 2013; Jonsson et al., 2013); and recently, the $CD33$ risk allele has been shown to inhibit microglial clearance of amyloid-β (Bradshaw et al., 2013; Griciuc et al., 2013). Finally, an integrative network-based genetic analysis of Alzheimer’s disease brain has implicated disturbance in immune/microglial networks in the pathogenesis of the disease (Zhang et al., 2013).

If inflammation, and microglial activation in particular, are core features of Alzheimer’s disease, the exact mechanisms involved, and the roles of the different inflammatory components are far less clear. Microglia—the predominant macrophage species within the brain—can express different cell-surface receptors and change morphology in response to changes in local environment thus becoming ‘activated’ in numerous ways (Perry et al., 2010). It is likely that in the Alzheimer’s disease brain some activated microglial species may, in certain circumstances, adopt a proinflammatory profile with deleterious effects, promoting neuronal and synaptic damage. Conversely, a microglial reaction initiated in response to, and promoting clearance of toxic amyloid-β species may confer protection. Given evidence that reductions in the rate of clearance of amyloid-β$_{42}$ are seen in sporadic Alzheimer’s disease (Mawuenyega et al., 2010), it may be that subtle alterations in normal inflammatory-mediated clearance of fibrillar or perhaps oligomeric amyloid-β (Frenkel et al., 2013) play important roles in the earliest stages of Alzheimer’s disease pathogenesis.

Targeting the inflammatory cascade in Alzheimer’s disease either to attenuate harmful effects or promote clearance of abnormal proteins is an attractive therapeutic option. To date, clinical trials of ‘anti-inflammatory’ drugs including non-steroidals and aspirin have yet to show definite benefits in Alzheimer’s disease (Jaturapatporn et al., 2012). After the remarkable demonstration that peripheral, active vaccination against amyloid-β$_{42}$ leads to clearance of brain amyloid from the brains of transgenic mice carrying human Alzheimer’s disease mutations (Schenk et al., 1999) immunotherapy-based approaches aimed at promoting amyloid clearance have dominated attempts to modify the course of human Alzheimer’s disease over the last decade or so. The first such study in man (AN1792) was halted after 6% of those on active therapy developed significant brain oedema/effusions (ARIA-E) or haemosiderin deposition.