Hypertension and cognitive decline

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Significant associations have been reported between cognitive decline, dementia and measures of cardiovascular and cerebrovascular disease. Such findings raise important possibilities for prevention of dementia through reducing the burden of vascular pathology. However, given the long prodromal periods for both clinical vascular disease and dementia, the most fruitful way forward may lie in investigating the effects of risk factors for vascular disease, rather than clinical vascular disease itself. Hypertension has received considerable attention in this respect although it is only recently, thanks to findings from prospective population-based research, that the complex interrelationship between blood pressure levels and cognitive decline has begun to be clarified.

METHODOLOGICAL ISSUES

Study design

The majority of studies examining the relationship between blood pressure and cognitive impairment/dementia have been of cross-sectional case–control design with 'cases' being either hypertensive subjects (measuring cognitive function compared with control subjects) or subjects with dementia (investigating blood pressure levels or a history or not of hypertension compared with control subjects). However, high levels of unrecognised disease in the general population mean that known cases of hypertension or dementia represent a potentially biased and unrepresentative subgroup. Some studies have sought to overcome this difficulty by screening large populations for both hypertension and cognitive status and are more robust in this respect. However, any cross-sectional study is limited in that the direction of causality cannot be assumed. More seriously, any study using prevalent cases of dementia will underestimate associations with disorders which reduce case survival. Prospective studies are less likely to be influenced by these effects and provide an opportunity to examine the longitudinal and potentially changing relationships between blood pressure levels and cognitive function over time. However, the size of the cohort and length of follow-up required to identify incident cases of dementia in adequate numbers have meant that such studies are relatively few and results have only emerged relatively recently.

Measuring exposure and outcome

An additional issue with regard to research in this area has been what to measure. The investigation of blood pressure as the 'exposure' can potentially involve a considerable range of assessments (from a history or not of hypertension through single or multiple blood pressure measurements to more invasive studies of ambulatory levels and orthostatic effects) reflecting its complexity as a physiological variable. Common comorbid conditions such as Type 2 diabetes and dyslipidaemia must also be taken into account if an independent effect of hypertension is to be concluded.

Outcome measures also vary in their utility for investigation of this relationship. Dementia as an outcome is complicated by the current categorical division into Alzheimer's disease and vascular dementia used in clinical research. Since vascular dementia requires evidence of cerebrovascular disease by definition and since Alzheimer's disease tends to be treated as a diagnosis of exclusion with regard to vascular disease, the rates of comorbid hypertension in these diagnostic groups relative to control subjects will be strongly influenced by classification bias. A broad diagnosis of dementia is less problematic in this respect, but still represents a relatively late stage of cognitive decline where functional status has become impaired, and may not be adequate to examine associations with early decline. An alternative strategy has been to use psychometric test performance, which has the advantage of being feasible at younger ages where clinical dementia is too rare an outcome. This may be examined cross-sectionally, identifying individuals with relative impairment or, more satisfactorily, longitudinally, identifying those with declining performance. However, both designs require relatively large sample sizes, the former to allow adjustment for the dominating effects of educational background on relative performance and the latter to see beyond random fluctuations in an individual's test scores over time and detect true cognitive decline.

CROSS-SECTIONAL EVIDENCE

Cross-sectional findings from population studies have been difficult to evaluate because the direction of association between cognitive function and blood pressure appears to change with age. In younger subjects the expected association between high blood pressure and relative cognitive impairment is observed, but in older subjects (broadly speaking, over 75 years old) it is low rather than high blood pressure which is associated with impairment (Breteler *et al*, 1993). Similar findings have been reported from dementia studies – in two studies using populations screened for dementia, elevated blood pressure was found to be associated with Alzheimer's disease in subjects aged 69–78 years (Kuusisto *et al*, 1997) and lower blood pressure was associated with both Alzheimer's disease and vascular dementia in subjects aged 75–101 years (Guo *et al*, 1996). Low blood pressure is recognised to be associated with increased morbidity in older age groups, although factors mediating its association with cognitive impairment and dementia remain unclear. The Rotterdam study (Breteler *et al*, 1993) suggested that low blood pressure in older subjects was more closely associated with cognitive impairment in those who had peripheral arterial disease, suggesting that comorbid disorders are important in mediating some of this reversal of association. No association was seen between antihypertensive medication and cognitive decline in one placebo-controlled trial (Prince *et al*, 1996).

PROSPECTIVE RESEARCH

Although cross-sectional studies have been conflicting in their findings with regard to blood pressure and cognitive performance, clear patterns of association have emerged from prospective research. In particular, high mid-life blood pressure has been

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repeatedly shown to be a strong and independent predictor of later cognitive impairment. The Framingham study (Elias *et al*, 1997) found that mid-life blood pressure levels and hypertension chronicity were both associated with impairment on the composite score of a psychometric battery administered 20 years later, and particularly with impairment on memory and attention sub-scales. This association persisted after controlling for the effect of Type 2 diabetes, but the two conditions showed strong interactions as risk factors.

The situation with regard to dementia appears to depend on the duration of follow-up. While elevated blood pressure is associated with an increased risk of future vascular dementia (Yoshitake *et al*, 1995), studies investigating dementia within the first few months following an ischaemic stroke have suggested that, if anything, it is low rather than high blood pressure which is a risk factor (Pohjasvaara *et al*, 1998). The Göteborg population study, following a cohort of 382 subjects over 15 years, has helped to clarify this issue: subjects who developed Alzheimer's disease aged 80–85 years had higher systolic blood pressures at the age of 75, but lower readings at the time of diagnosis compared with the rest of the cohort (Skoog *et al*, 1996). The number of incident cases was relatively small and the possibility of misclassified vascular dementia accounting for some of the Alzheimer's disease cases cannot be absolutely ruled out. However, this study is the first to demonstrate in one cohort the crossing-over of association suggested by other research.

MECHANISMS OF ASSOCIATION

Strong evidence now exists that elevated blood pressure in mid-life is associated with an increased risk of dementia 15–20 years later. The question of the 'type' of dementia associated with hypertension cannot easily be answered from current epidemiological research because neuroimaging has not been routinely used to quantify coexisting cerebrovascular disease in Alzheimer's disease cases. In addition, categorical diagnostic systems, which divide dementia into vascular dementia and Alzheimer's disease according to an assumption of vascular or non-vascular causation, are over-simplistic and do not take into account the substantial degree of mixed disease seen at post-mortem.

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Arteriosclerotic pathology can be assumed to be an important mediating factor in the association between hypertension and dementia. However, the relative rarity of isolated vascular pathology associated with dementia in post-mortem series and the finding that most dementia after ischaemic stroke occurs in the absence of further infarction (Tatemichi *et al*, 1994) challenge the usefulness of the 'multi-infarct' concept for dementia related to vascular disease. Increased amyloid plaques and neurofibrillary tangles have been reported in hypertensive subjects at post-mortem (Sparks *et al*, 1995) and plausible, but hypothetical, mechanisms exist for direct effects on Alzheimer's processes through blood–brain barrier disturbance or through amyloidogenesis in response to ischaemia. An alternative and not mutually exclusive possibility is that cerebrovascular disease secondary to hypertension accelerates the onset of dementia in the presence of coexisting Alzheimer's pathology. As well as a known risk factor for stroke, hypertension is also strongly implicated in the aetiology of white matter abnormalities seen on magnetic resonance imaging. Periventricular lesions have been reported to be increased in Alzheimer's disease and may mediate observed associations with hypertension, the clinical picture of dementia simply varying according to the relative preponderance of cortical or subcortical damage, rather than reflecting distinct Alzheimer's disease/vascular dementia disease entities.

IMPLICATIONS

Clear prospective associations between raised blood pressure and later dementia indicate a potentially important avenue for preventive intervention. However, further research is required into the apparent decline in blood pressure around the onset and during the course of dementia before conclusions can be drawn about therapeutic options after clinical presentation. The current system of dementia classification is inadequate for investigation of potential vascular risk factors because of implicit aetiological assumptions. This area of research would be better served either through abandoning classification altogether (using measures such as 'dementia' or those based on psychometric assessment) or through the development of an axial rather than categorical classification reflecting the underlying mixed and overlapping pathological processes.

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