Editorial

Cardiovascular factors in Alzheimer's disease

The traditional assumption that there are two distinct forms of dementia—vascular dementia and Alzheimer's disease—respectively with and without evidence of vascular disease as a presumed causative factor, has been called into question by recent epidemiological evidence which raises the possibility that vascular risk factors may be important in the aetiology not only of dementia in general but also specifically for Alzheimer's disease. This editorial summarises these epidemiological findings and considers possible methods of pathogenesis.

Methodological issues

The historical distinction between the vascular dementias and Alzheimer's disease is a major obstacle in assessing the role of vascular disease as a risk factor for Alzheimer's disease. Defining a condition according to its presumed aetiology can preclude a critical examination of risk factors included or excluded by that definition. Research criteria such as NINCDS-ADRDA,¹ emphasise Alzheimer's disease as a diagnosis of exclusion particularly with regard to vascular disease, therefore any association between the two will be underestimated through selective classification. The increased use of imaging techniques may cause additional confusion—namely, what bearing should evidence of subclinical cerebrovascular disease (known to be common in older populations) have on the diagnosis? However, failing to assess subclinical cerebrovascular disease in this way limits the conclusions that can be drawn from any association found between vascular risk factors and clinical Alzheimer's disease, an important issue being whether such an association is mediated by an effect on Alzheimer's pathology or by cognitive impairment secondary to increased cerebrovascular disease in the context of “mixed dementia”. Given high rates of mixed Alzheimer's and cerebrovascular pathology at postmortem examination,² a diagnostic system which attempts to subdivide dementia into mutually exclusive categories is of limited usefulness in assessing the role of disease processes which may affect both.

The problem of subclinical disease complicates the assessment not only of dementia as the outcome variable but also of vascular disease as the exposure. A history or not of cardiovascular events is an inadequate reflection of underlying vascular disease just as reported hypertension or diabetes may not reflect measured blood pressure or glucose tolerance and studies which rely on reported diagnoses in unscreened populations may underestimate associations between Alzheimer's disease and covert vascular disease. This situation is compounded by the important proportion of subjects who will die from vascular disease before dementia becomes apparent.

An association between cardiovascular status and Alzheimer's disease?

Cognitive impairment has been found to be associated in population studies with cardiovascular disease and atherosclerotic indices,³ and with cardiovascular risk factors such as non-insulin dependent diabetes mellitus,^{4,5} and hypertension.^{6,7} More recent work has focused on possible associations with Alzheimer's disease specifically. In the Rotterdam study, 284 subjects with dementia of less than 3 years duration were compared with 1698 without dementia. Atherosclerotic disease was quantified by carotid wall thickness or plaques on ultrasound and by ankle-brachial systolic blood pressure ratios, and was graded in severity on a four point scale. Dementia was identified with a three phase screening process with the mini mental state examination (MMSE)⁸ and CAMDEX,⁹ assessment leading on to neurological and neuropsychological assessment and MRI. Diagnosis of dementia was according to DSM-III-R criteria,¹⁰ and categorisation according to NINCDS-ADRDA.¹ All indices of atherosclerosis were associated with both vascular dementia and Alzheimer's disease and the prevalence of both increased with the severity of atherosclerotic disease.¹¹ This study also found atrial fibrillation to be associated with Alzheimer's disease, the association being most strong in the group with Alzheimer's disease and cerebrovascular disease. An association was also suggested in those without cerebrovascular disease although after adjustment for potential confounding factors, this fell just below conventional levels of significance.¹²

The association between hypertension and dementia has been examined in the Göteborg study, a longitudinal population based examination of a cohort of 382 subjects without dementia at age 70, finding that the 18 participants who developed dementia at ages between 79 and 85 had had significantly higher systolic blood pressures at 70 and higher diastolic pressures at 70 and 75 than those who did not develop dementia.¹³ In addition higher diastolic blood pressure at age 70 was also associated with development of Alzheimer's disease specifically in 10 of these subjects. Dementia was screened for by using a semistructured telephone interview with a close informant and then diagnosed by psychiatric assessment using DSM-III-R and NINCDS-ADRDA criteria. Interestingly a decline in blood pressure was seen before the diagnosis of both vascular dementia and Alzheimer's disease although the 5 year examination intervals and the difficulty in accurately estimating onset of dementia do not permit a conclusion as to cause or effect. Reported cross sectional associations of lower blood pressure with dementia, particularly in older subjects,¹⁴ may be because metabolic disturbances in dementia cause hypotension, because lower blood pressure contributes to preferential survival in certain decades and

an increased risk and duration of dementia in later life, or because by the time hypertensive disease has begun to cause cognitive impairment, associated physical morbidity and diminished vascular reactivity have caused blood pressure to fall. The third possibility is supported by the finding that higher systolic pressures continued to be associated with lower MMSE scores in a selected group of physically healthy subjects aged over 70.¹⁵ It is important to bear in mind that hypertension clusters heavily with other vascular risk factors and is found in isolation only in a minority.¹⁶ Antihypertensive medication seems to have little or no role in any association with cognitive impairment,¹⁷ favouring the importance of underlying or related pathology rather than a direct effect of blood pressure itself on cognitive decline.

Some case-control studies have reported a negative association between non-insulin dependent diabetes mellitus and Alzheimer's disease,^{18,19} but have been of small size and have used referred patients with Alzheimer's disease, open to selection bias. The Rochester study retrospectively examined case notes of 1455 subjects with adult onset diabetes mellitus followed up over a period of 9981 person-years and found an increased incidence of Alzheimer's disease, particularly in men, compared with general population estimates.²⁰ The Hisayama study, a 7 year follow up of 828 residents aged 65 and over and without dementia, found an increased risk of Alzheimer's disease associated with a diagnosis of diabetes close to significance.²¹ Recent findings from the Rotterdam study support this association²²; diabetes mellitus (the use of antidiabetic medication or a random or post-load serum glucose >11 mmol/l) was found to be associated with an increased risk both of incident dementia and Alzheimer's disease for 6370 subjects aged 55 and over followed up over 2 years. Risk of dementia was lowest in those on no medication and highest in those receiving insulin. Interestingly, adjustment for other vascular factors made little difference to the associations seen, possibly implying non-vascular mechanisms of pathogenesis.

The relation between smoking and Alzheimer's disease has been examined in numerous studies but there remains some dispute as to whether there is a positive or negative association. A meta-analysis of 11 case-control studies found an inverse association between the two with a strong trend towards decreasing risk of Alzheimer's disease with increasing use of tobacco.²³ However, none of the studies had adequate statistical power individually, most were based on outpatient samples with potential for selection bias, and ages of onset were heterogeneous. In addition, classification and mortality biases, as suggested earlier, may underestimate any association. In the opposite direction, an association between smoking and incident Alzheimer's disease approached significance in participants in an anti-hypertensive treatment trial who lacked a family history of dementia,²⁴ and the Rotterdam Study has found current smoking to be a significant risk factor for incident Alzheimer's disease over a 2 year period.²⁵

Possible mechanisms of association

The epidemiological findings summarised above have suggested that cardiovascular disease is an important risk factor for clinically diagnosed Alzheimer's disease. However, they are limited in the conclusions that can be drawn concerning mechanisms of association. Predominantly clinical criteria were used for the diagnosis of Alzheimer's disease with a dichotomous division into Alzheimer's disease and vascular dementia without a "mixed dementia" category apart from the Rotterdam study, in which overt cerebrovascular disease occurring in the presence of Alzheimer's disease but which was not considered to be causative

received a separate category. Magnetic resonance imaging was performed in the Rotterdam study and CT in the Göteborg study but it is not clear how these were used in diagnosis. It cannot therefore be concluded whether the associations found with Alzheimer's disease are due to effects on Alzheimer's pathology itself or due to increased subclinical cerebrovascular pathology in the context of "mixed dementia". The findings from the Washington Heights study of a fivefold increased risk of dementia in the 4 years after an ischaemic stroke but in the absence of further stroke or depression in 75% of cases,²⁶ questions "multi-infarct dementia" as a common entity and suggests either that subclinical cerebrovascular disease is itself responsible for a steadily progressive dementia or that it is exacerbating Alzheimer's processes. The rarity of isolated cerebrovascular pathology associated with dementia at postmortem examination,²⁷ supports the second possibility. If cerebrovascular disease exacerbates Alzheimer's disease, this may be through direct interactions between the two pathological processes or through cognitive impairment secondary to cerebrovascular disease "unmasking" Alzheimer's disease at an earlier stage than it would otherwise become apparent.

DIRECT EFFECTS OF VASCULAR DISEASE ON THE PATHOLOGY OF ALZHEIMER'S DISEASE

Severe coronary artery disease has been associated with increased senile plaque counts and hypertension with increased plaque and neurofibrillary tangle densities in a necropsy series of subjects without dementia,²⁸ suggesting that the burden of Alzheimer's pathology may be increased by systemic vascular disease, possibly to a threshold beyond which it becomes progressive and self generating. Increased amyloid precursor protein activity and β -amyloid production have been found in the hippocampi of rodents after severe but transient ischaemia,²⁹ a process which is probably a non-specific response to cerebral trauma³⁰ (head injury is also known to be associated with amyloid deposition,³¹ and may be activated by more mild episodes of ischaemia). These subclinical processes may involve small areas of cortical or subcortical infarction or may be related to disturbances in cerebral perfusion possibly exacerbated by pre-existing microvascular abnormalities associated with Alzheimer's disease.³² One means of ascertaining whether the origin of amyloid in Alzheimer's disease is neuronal or vascular has been to examine its distribution relative to neurons or blood vessels. The complex anatomy of these structures in the cortex, however, has limited the conclusions that can be drawn. A recent study attempting to resolve this problem by examining amyloid deposition in white matter has reported distributions of amyloid to be particularly related to blood vessels, suggesting a vascular rather than neuronal source.³³

The relevance of vascular amyloid deposition (cerebral amyloid angiopathy) in the pathogenesis of Alzheimer's disease remains uncertain but may play a part in interactions with cerebrovascular pathology. Cerebral amyloid angiopathy is common in Alzheimer's disease and is associated with cerebral arteriosclerosis.³⁴ It has also been reported to be associated with cerebral infarction seen postmortem and this association was increased in those with a history of hypertension.³⁵ Cerebral amyloid angiopathy may be a consequence of cerebrovascular disease via effects of ischaemia and secondary amyloid deposition or, on the other hand, it may cause vascular disease through toxic effects (possibly mediated by free radical damage) of β -amyloid on the vascular endothelium.³⁶ Vascular risk factors such as hypertension may potentially mediate this association in either direction. A role for vascular amyloid deposition in causing lesions in white matter

is possible and the two disorders are seen to coexist in the rare disorder of hereditary cerebral haemorrhage with amyloidosis-Dutch type,³⁷ but changes in white matter were not associated with vascular amyloid in one study which examined this possible association in the context of both Alzheimer's disease and vascular dementia,³⁸ and the cerebral infarctions found to be associated with cerebral amyloid angiopathy have been reported to be predominantly cortical rather than subcortical.³⁴ Increased permeability of the blood-brain barrier has been found to occur secondary to transient ischaemia,³⁹ and this process may underlie both perivascular amyloid deposition and white matter lesions.⁴⁰

It has been mentioned earlier that the increased risk of Alzheimer's disease associated with type 2 diabetes may be mediated to a large extent by non-vascular mechanisms. These may include hyperglycaemia compounding the ischaemic burden of pre-existing vascular disease by increasing anaerobic metabolism and lactic acidosis,⁴¹ associations with insulin resistance as outlined below, or the exacerbation of β -amyloid neurotoxicity by advanced glycation end products.⁴² In addition, decreased cholinergic transport across the blood-brain barrier has been reported,⁴³ which may be potentially important in exacerbating cognitive impairment in the presence of subclinical Alzheimer's disease.

VASCULAR DISEASE UNMASKING SUBCLINICAL ALZHEIMER'S DISEASE

Although theoretical mechanisms exist by which cerebrovascular and Alzheimer's pathologies may interact, it is also possible that the two processes may be parallel and unrelated at a pathological level but interacting in their clinical effects. The Nun study examined 678 female subjects aged 75–102 years with a cognitive battery and dementia screen and reported necropsy findings on 102 subjects who had died 2 to 4 years later.² Of those who met neuropathological criteria for Alzheimer's disease, 39% had evidence of infarction. This was associated with increased prevalence of dementia and with worse cognitive performance in those with Alzheimer's disease although not with worse cognitive performance in those without dementia. Counts of neurofibrillary tangles in the neocortex were found to correlate strongly with cognitive performance. However, in those with infarcts the effects of tangle counts on cognitive performance were enhanced and less tangles were seen in association with Alzheimer's disease than in those without infarction. Infarcts were not associated with increased Alzheimer's disease pathology in the whole group examined. These findings suggest that the two processes may be independent but that cerebrovascular disease acts to precipitate clinical Alzheimer's disease at pathological stages where it would not otherwise become clinically apparent.

Related to this is the issue of white matter pathology. Population based studies have shown that changes in white matter on imaging are common with increased age and are associated with vascular risk factors,⁴⁴ although their pathological basis is heterogeneous and unclear. Periventricular hyperintensities on MRI have been cited as being more common in Alzheimer's disease, particularly in older comparison groups.⁴⁵ Studies that have failed to show any association have tended to be those adjusting for or excluding vascular risk factors,⁴⁶ and little association has been shown so far between the presence of hyperintensities and the severity or course of the dementia. It is possible that Alzheimer's disease and vascular disease affect parallel cognitive functions which, when impaired, interact to manifest as dementia. Memory impairment secondary to hippocampal damage in Alzheimer's disease may in itself

not be sufficient to present as dementia until a relatively advanced stage is reached, but dementia may be precipitated at an earlier stage in the presence of impaired executive function secondary to vascular disease and related frontosubcortical disruption.

INSULIN RESISTANCE: A COMMON UNDERLYING FACTOR?

Peripheral insulin resistance has been hypothesised as mediating the noted clustering of vascular risk factors such as hypertension, type 2 diabetes, dyslipidaemia, and obesity.⁴⁷ The possibility that it may underlie an association with Alzheimer's disease has been raised by findings from the Kuopio population study of 980 subjects between ages of 69 and 78, reporting hyperinsulinaemia to be associated with recent onset Alzheimer's disease in non-diabetic subjects.⁴⁸ The cross sectional nature of the study does not permit firm conclusions as to hyperinsulinaemia being a cause or effect of Alzheimer's disease but insulin receptors are known to be dense in the rat hippocampus,⁴⁹ and insulin itself has been shown to inhibit synaptic activity at excessively high or low levels,⁵⁰ and down regulate choline acetyltransferase,⁵¹ *in vitro*. In addition, recent research has suggested a role for insulin and insulin growth factor 1 in the regulation of tau protein phosphorylation,⁵² the process underlying the formation of neurofibrillary tangles. Processes which regulate tau phosphorylation may be affected by a state of decreased insulin sensitivity resulting in a predisposition to Alzheimer's disease as well as to vascular disease or a common genetic abnormality affecting insulin dependent pathways may result in Alzheimer's disease and insulin resistance independently, hyperinsulinaemia possibly further compounding cognitive impairment through effects on synaptic activity and cholinergic transport.

THE ROLE OF THE $\epsilon 4$ ALLELE

The $\epsilon 4$ allele of apolipoprotein E (apoE) is known to be a risk factor for cardiovascular disease,⁵³ as well as for Alzheimer's and possibly also vascular⁵⁴ dementias. However, increased cholesterol concentrations, thought to be important in mediating the former association have generally not been found to be associated with Alzheimer's disease,²¹ and the Kuopio study reported a cross sectional association between Alzheimer's disease and lower cholesterol.⁴⁸ Findings from the Rotterdam study suggest an important interaction between atherosclerotic disease and the $\epsilon 4$ allele¹¹: the associations found between Alzheimer's disease and the severity of atherosclerosis were only significant in subjects with one or more $\epsilon 4$ allele. In addition, the association of the $\epsilon 4$ allele with Alzheimer's disease was only significant in those subjects with more severe atherosclerosis. Other studies examining head injury,⁵⁵ and herpes simplex exposure,⁵⁶ have also found $\epsilon 4$ interactions suggesting that its role in Alzheimer's disease may be as a modifier of environmental risk factors, possibly through cell repair mechanisms. Another possibility is raised by research examining the response of rodent hippocampal cells to transient ischaemia. As well as the amyloidogenic response described above, apoE has also been reported to accumulate in the CA1 pyramidal cell layer after such trauma.²⁹ Possession of the $\epsilon 4$ allele in conjunction with increased β -amyloid and apoE expression in response to cerebral ischaemia or other environmental insults may predispose to the formation of the insoluble deposits seen in Alzheimer's disease, predicting the genetic-environmental interactions reported by epidemiological research.

Conclusion

Cardiovascular disease and Alzheimer's disease are both common with increasing age but evidence is accumulating that there is more than a chance association and that the

first could play an important part in the aetiology or time of presentation of the second. What has not been established is the mechanism of association. Alzheimer's disease may magnify coexisting cardiovascular disease as cognitive decline leads to worsening self care although studies have attempted to reduce the issue of reverse causality through focusing on new dementia cases. Alzheimer's disease and cardiovascular disease may share common risk factors (such as insulin resistance) and therefore show an association without causation. Vascular disease may have a direct impact on Alzheimer's pathology through amyloidogenesis secondary to cerebral ischaemia in the presence of the apoE ϵ 4 allele or its effect may be one of cognitive impairment (through white matter pathology and disrupted executive function) unmasking unrelated Alzheimer's disease.⁵⁷

The possibility of vascular disease as an environmental risk factor for Alzheimer's disease naturally raises the issue of prevention and treatment. Evidence is accumulating concerning the protective role of non-steroidal anti-inflammatory drugs (NSAIDs) in Alzheimer's disease. A recent meta-analysis of 17 studies found significant negative associations between Alzheimer's disease and both NSAID and steroid use,⁵⁸ findings supported by other work showing less cognitive decline in patients with Alzheimer's disease taking NSAIDs,⁵⁹ and a reduced relative risk of Alzheimer's disease associated with increased duration of use,⁶⁰ the second study also suggesting that the effect is related to anti-inflammatory action rather than that on free radicals,⁶¹ or platelet aggregation given that no benefit was seen in those subjects taking (low dose) aspirin. What remains to be established is whether inflammatory processes which may be reduced by these agents are related to Alzheimer's pathology or associated with subclinical cerebrovascular disease in the context of mixed dementia.

The study of vascular factors in Alzheimer's disease raises a serious issue with the current system of dementia classification. Requiring that Alzheimer's disease can only be diagnosed in the absence of cerebrovascular disease is prejudicial to a meaningful examination of links between the two. However, failing fully to identify cerebrovascular disease in diagnosing Alzheimer's disease means that the effect of vascular risk factors on Alzheimer's pathology cannot be assumed. The reality is that both situations, being categorical, cannot reflect the frequent co-occurrence of two pathological processes increasingly common with age. A classification system which started with a "diagnosis" purely of dementia and which then allowed dimensional rather than categorical estimates of the contributions of Alzheimer's disease, cerebrovascular disease, Lewy body disease etc to that diagnosis would allow less biased examination of the aetiology of each of the disease processes. Further research into links between atherosclerotic disease and neurodegenerative processes may well provide avenues for prevention and treatment in the future but it will be necessary to question certain preconceived ideas concerning the classification of dementia. Should we continue to refer to two pathological processes but recognise that mixed cases are in fact common or should we abandon the dichotomy and consider the two to be interconnected?

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