Blood pressure reduction and risk of dementia in patients with stroke: rationale of the dementia assessment in PROGRESS (Perindopril Protection Against Recurrent Stroke Study)

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High blood pressure is a known risk factor for multi-infarct dementia, a subtype of dementia caused by the occurrence of several strokes. However, this form of dementia is relatively uncommon and the influence of blood pressure on the risk of other subtypes of vascular dementia remains to be clarified. Furthermore, recent studies have suggested that vascular risk factors could also play a part in Alzheimer's disease.

One of the aims of Perindopril Protection Against Recurrent Stroke Study (PROGRESS) is to test the hypothesis that blood pressure decreasing treatment based on perindopril would reduce the incidence of dementia among patients with cerebrovascular disease. The dementia procedures in PROGRESS involve a classical two-phase design, with an initial screening phase based mainly on the Mini-Mental State Examination – a simple, brief, and widely used screening test for dementia. The second phase involves a diagnostic assessment for dementia in individuals screened as positive according to the criteria of the American Psychiatric Association's *Diagnostic and statistical manual of mental disorders* (4th ed.).

In this project, two other domains of the relationship between vascular risk factors and cognition are being explored in relation to PROGRESS substudies. The apolipoprotein E polymorphism, a genetic risk factor for Alzheimer's disease, is being determined in each patient, as part of the genetic substudy. This will allow study of the relationship between this polymorphism and blood pressure, and of the effect of blood pressure decreasing treatment on the risk of dementia. The magnetic resistance imaging substudy will improve understanding of the relationship between blood pressure decreasing and the occurrence of cerebral white matter lesions, which are known to be related to cognitive decline and dementia. *J Hypertens* 18 (suppl 1):S21–S24 © 2000 Lippincott Williams & Wilkins.

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Introduction

Increased blood pressure is a major risk factor for cerebrovascular diseases, in particular stroke, and lesions of the white matter of the brain. There is also a link between blood pressure and the occurrence of vascular dementia – that is, dementia related to single or multiple strokes. However, it has not been well established that decreasing the blood pressure reduces the risk of vascular dementia. Dementia, therefore, was included as a major end-point in the Perindopril Protection Againts Recurrent Stroke Study (PROGRESS), a randomized controlled trial of blood pressure decreasing treatment for the prevention of stroke and other vascular events in patients with a history of cerebrovascular disease [1].

Since PROGRESS was initiated in 1995, however, significant advances have occurred with respect to our knowledge of dementia, and specifically of Alzheimer's disease. Evidence has accumulated that provides a strong rationale for various vascular factors, including blood pressure, acting as cofactors in the occurrence (and progression) of dementia, including Alzheimer's disease, in a broad cross-section of patients. In this paper, we review some of this new evidence and its implications in terms of the classification of dementia for epidemiological research, and outline the assessment of dementia in PROGRESS.

Vascular risk factors and dementia

Cerebrovascular disease and Alzheimer's disease are both common conditions in older people. Evidence is accumulating that there is an association between the two, and that cerebrovascular disease may have a role in the aetiology (or time to presentation) of Alzheimer's disease in addition to that of vascular dementia. This evidence can be summarized as follows:

(a) Alzheimer's disease and cardiovascular disease appear to share several key factors that are associated with either a greater or lesser risk of disease. For example, the ApoE

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ε4 allele [2] and angiotensin-converting enzyme polymorphism have been demonstrated to modulate the risk of both coronary disease [3] and dementia [4], whereas the antithrombotic agents, aspirin and nonsteroidal anti-inflammatory drugs [5], and hormone replacement therapy appear to be protective for both vascular dementia [6] and Alzheimer's disease [7].

(b) Patients with the ApoE ε4 allele, one of the few established risk factors for Alzheimer's disease, are at much greater risk of dementia after the onset of stroke than patients without this allele [8,9]. Moreover, the risk of dementia with stroke among those homozygous for ApoE ε4 is three times greater than that for ApoE ε4-heterozygous individuals [8].

(c) Patients with a high cardiovascular risk profile are at increased risk of Alzheimer's disease. In the Rotterdam study [10], for example, patients with evidence of atherosclerosis had a threefold greater risk of Alzheimer's disease, and in the nun study [11], participants who met neuropathological criteria for Alzheimer's disease had a 20 times greater likelihood of dementia during life if they also had evidence of small, asymptomatic, cerebral infarcts.

(d) Perhaps the most persuasive evidence to date has come from the Systolic Hypertension in Europe (Syst-Eur) trial, which suggests that blood pressure lowering treatment may reduce the risk of dementia of all kinds [12,13]. The Syst-Eur trial was a double-blind, placebo-controlled trial of nitrendipine (a calcium-channel-blocking agent), with possible addition of enalapril and hydrochlorothiazide, for isolated systolic hypertension in more than 4000 patients older than 60 years; it included a dementia substudy on a subset of 2418 patients. At the end of the trial, which was stopped prematurely with a median follow-up of 2 years, 21 cases of dementia were diagnosed in the placebo group compared with 11 cases in the treatment group. The treatment not only produced a 50% reduction in the incidence of dementia, but the majority of cases prevented were of Alzheimer's disease rather than vascular dementia. This remarkable finding should, however, be interpreted with caution, as there is uncertainty over the treatment effect because of the small number of outcome events, so that the possible impact of blood pressure lowering could range from no effect to a massive 76% reduction in the rate of dementia. Moreover, the large number of participants who were lost to follow-up further undermines the validity of the observed treatment effect.

It may be concluded that a combination of clinical, epidemiological and neuropathological evidence is consistent with the hypothesis that an interaction between various vascular factors and degenerative changes could determine the time to presentation and rate of progression of dementia.

Potential mechanisms

There are several potential mechanisms by which vascular factors could play a part in the aetiology of dementia in a broad spectrum of patients. A strong hypothesis is that cognitive loss is determined by the deposition of amyloid, and other changes in the brain secondary to cerebral ischaemia in susceptible individuals – those with the ApoE ε4 allele [8,10]. In this way, cognitive function could be altered by strategically placed single lesions or joint effects of different types of ischaemic damage within the brain on a background of neuropathological changes, including the senile plaques and neurofibrillary tangles of Alzheimer's disease that are often present in older people. Support for this mechanism was provided by recent studies in which large numbers of individuals from the general population underwent cerebral magnetic resonance imaging (MRI) [14,15]. These studies show that 'silent stroke' – that is, stroke in the absence of any clinical manifestations but producing lesions of the cerebral parenchyma – is relatively common in the older population. In addition, multiple white matter lesions, or high-intensity signal abnormalities located in the cerebral white matter, are a frequent finding in older people. Although the aetiology of white matter lesions remains largely unknown, it is generally assumed that the lesions are markers of chronic cerebral ischaemia, because of an association with risk factors common to stroke – in particular age and hypertension [16,17] – and a link with impaired cognition [15,18,19].

Dementias or dementia?

These data outlined above reprise the old, and ongoing, debate on the difference between degenerative dementia (principally Alzheimer's disease) and vascular dementia. Unfortunately, the progressive dementia of Alzheimer's disease and so-called stepwise deterioration of multi-infarct dementia as distinct entities have been extremely difficult to define for epidemiological (and clinical) purposes, so that several definitions of vascular dementia currently exist, creating confusion in the field [20–22]. Apart from multi-infarct dementia, other types of vascular dementia with a more insidious evolution could mimic the features of Alzheimer's disease, but the relative contribution of the various types of vascular dementia to cognitive loss in the community is largely unknown.

Despite considerable effort devoted to the development of criteria, to date no acceptable classification system has arisen and no consensus has been achieved that easily define the various types of vascular dementia. As a consequence, there is considerable variability in the prevalence of vascular dementia, with estimates varying from 3% to 30% in the older age groups across studies [23,24].

An alternative view is to consider subtypes of dementia as a continuum from two extremes, with degenerative and vascular dementia at each pole. However, pure forms of these extremes appear uncommon, so that it is likely that the vast majority of cases of dementia in the population can be explained by varying combinations of degenerative and vascular factors. If this hypothesis is true, then the benefits

of correction of vascular risk factors, such as blood pressure, would not be limited to the prevention of vascular dementia, but would also be realized in combatting the vascular component that would be present in many of the dementias, including Alzheimer's disease. If this prevention strategy could postpone the onset of dementia for even just a few months, it would have important consequences for the prevalence of dementia [25].

Dementia is one of the major causes of loss of autonomy and the main cause of institutionalization of the elderly. Epidemiological studies conducted during the past 10 years have shown that the prevalence of dementia is close to 5% in the population older than 65 years and is closely correlated with age. The number of patients with dementia is therefore expected to increase sharply in the next few years in ageing populations. On the basis of demographic trends for those aged 80 years and more, it is anticipated that there may be 10 to 15 million people affected by Alzheimer's disease by the middle of the century in the United States [26]. Moreover, estimates that include the rapidly ageing populations of Japan and other Asian countries give global figures that may exceed 100 million [27].

Assessment of dementia in PROGRESS

One of the main objectives of PROGRESS outlined in the original study protocol was to test the hypothesis that perindopril-based blood pressure lowering treatment would reduce the incidence of dementia among patients with cerebrovascular disease [1]. Measures of cognitive impairment and dependency have been used from the beginning of recruitment of patients into the study, but, in the light of advances described above, an enhanced assessment for the diagnosis of dementia was planned to be introduced in 1999. Therefore, PROGRESS Dementia is not a new substudy *per se*, as the assessment procedures are based on existing measures and are being conducted on the entire study population across all 172 collaborating centres. All assessment procedures were designed to be undertaken double-blind to treatment allocation.

Screening phase

In PROGRESS, data concerning the cognitive function of patients are collected at 6 months, and at each year of follow-up after the random assignment of the participants to study groups. At each visit, patients are assessed using the Mini-Mental State Examination (MMSE) [28] and by the subjective impression of the attending clinical investigator, who asks a simple question 'In your opinion, does this patient have dementia?' All patients who score 25 points or less on the MMSE, or for whom the investigator answers 'yes' to the dementia question, or for whom, for any reason, there is missing information (MMSE scores or response to the dementia question) from the last scheduled visit, are requested to undergo a further diagnostic assessment by a specialist to ascertain the presence of dementia. For deceased patients who had been screened as positive, the same diagnostic evaluation procedures are used, but data are obtained from all available alternative sources, including medical records and interviews with family members.

Dementia diagnosis

The diagnostic assessment is undertaken by a local specialist, ideally a neurologist, geriatrician or psychiatrist, who is experienced in the diagnosis of dementia. This person is required to interview the patient (and informant) and use all available additional information to confirm or refute a diagnosis of dementia. The information is gathered with the aid of a checklist that follows the steps for the diagnosis of dementia according to the criteria of the American Psychiatric Association (DSM-IV) [29]. In addition, questions are asked concerning the onset and progression of cognitive loss, the relationship of stroke to the onset of dementia, and other symptoms to support the diagnosis of dementia.

For both the patients assessed in person and those whose assessment is made from other information, the final diagnosis of dementia is checked by a panel who review all the existing information, blind to treatment allocation.

Statistical analysis

Epidemiological studies and clinical trials indicate that the incidence of dementia in elderly hypertensive patients is between 7 and 10 per 1000 person–years [13,30]. Given that patients with stroke are likely to have at least double the risk of dementia [31], the sample size of 6105 patients in PROGRESS with an average follow-up of 4 years is sufficient to test the two-sided hypothesis of a 30% difference in the incidence of dementia between the active and control groups with a significance level of 5%, and 90% power.

Assessment of relative efficacy will be based on a comparison between the effects of the two treatment regimens on the risk of dementia over time. The main analysis will be on an intention-to-treat basis, in which all patients allocated randomly to study groups are considered at risk to their planned end of the study, irrespective of their compliance with the study procedure. Analyses of the treatment effect will be undertaken using the χ^2 test and logistic regression models, both adjusted and unadjusted for baseline prognostic variables. The effects of treatment on MMSE scores will be investigated by modelling methods for repeated measures, such as the generalized estimating equations approach [32].

Other assessment procedures

Two further domains are being explored during the clinical assessment. The first concerns the importance of focal cognitive deficits (e.g. aphasia) and other neurological abnormalities (e.g. paresis) caused by stroke that could cause a low MMSE score in the absence of dementia. The other relates to the presence of major depressive illness, which is frequent after a stroke and could account for low cognitive scores. The diagnosis of major depression is also being based on DSM-IV criteria [29].

Two current PROGRESS substudies will provide additional information about the relationship between vascular factors and cognition. First, as part of the genetic substudy, the ApoE polymorphism is being determined in each patient, to allow examination of the influence of the relationship between this allele and blood pressure lowering treatment on the risk of dementia. Second, the MRI substudy, performed on a subset of patients in France, should provide insights into the relationship between blood pressure lowering treatment and the occurrence of cerebral white matter lesions, which are known to be related to cognitive decline and dementia.

Conclusion

Dementia is a major public health challenge for this new millennium. At present, there is no proven effective treatment for its prevention. The results of the blood pressure lowering treatment from the Syst-Eur trial are encouraging, but require confirmation. PROGRESS has sufficient power to answer reliably certain questions related to the efficacy of blood pressure lowering treatment for the prevention of cognitive loss in the setting of cerebrovascular disease. If the answers are positive, the results would have a considerable impact on public health.

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