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COMMENTARY

Cognitive decline associated with dementia and type 2 diabetes: the interplay of risk factors

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The possible association between type 2 diabetes and dementia, Alzheimer's disease in particular, has been shrouded in confusion for some time, with some researchers noting that Alzheimer's patients are rarely diabetic [1] but others suggesting diabetes to be a major risk factor for the disease [2]. Since an earlier review of the evidence [3], a number of things have become clearer. First, histopathological examinations of the brains of type 1 and type 2 diabetic patients have demonstrated that diabetes as such does not produce the amyloid plaques and neurofibrillary tangles considered hallmarks of Alzheimer's disease [4]—a finding supported by a recent extensive post-mortem examination [5]. Second, research has shown that, in non-demented patients with type 2 diabetes, cognitive deficits are relatively mild before the age of 70 years, although they increase in frequency and severity thereafter [6]. Finally, people with type 2 diabetes who maintain less than optimal glycaemic control (i.e. with many occurrences of high blood glucose levels) are more likely to start manifesting cognitive deficits. Interestingly, improving glycaemic control in this population can reduce these cognitive deficits [7], suggesting that cognitive deficits might not be permanent in patients in whom presentation is early.

Unfortunately, for a considerable number of patients, the presence of diabetes increases the impact of other risk factors that also lead to cognitive decline and dementia (see Fig. 1). For example, hypertension [8] and arterial disease [9], which are found in many older people with type 2 diabetes, can contribute alone or in concert to decreased cognitive performance and, eventually, dementia. Another risk factor for cognitive decline in ageing and dementia concerns the gene encoding apolipoprotein E (*APOE*). This gene has three major alleles (*APOE* ε2, ε3 and ε4), which produce three distinct variants of apolipoprotein E. APOE is a glycoprotein attached to lipoprotein particles that acts as a ligand for the receptor-mediated endocytosis (transport) of lipoproteins particles in the brain from which cholesterol is released in the brain. People with two *APOE* ε2 alleles have a higher risk of premature vascular disease but a lower risk of Alzheimer's disease. However, people with one *APOE* ε4 allele have a two- to threefold higher risk of developing Alzheimer's disease, while people with two *APOE* ε4 alleles have a 12-fold higher risk [10]. *APOE* ε4 alleles are also associated with early cognitive decline and early manifestation of Alzheimer's disease pathology [11].

Contrary to some previous reports, the largest histological post-mortem study to date found that type 2 diabetes does not increase amyloid deposition or neurofibrillary tangles in diabetic patients with *APOE* ε4 alleles [5]. Thus, the increased likelihood of cognitive deficits in diabetic patients with *APOE* ε4 alleles is not due to diabetes increasing Alzheimer's disease pathology. Rather, it is more likely that the cerebrovascular lesions associated with diabetes combine synergistically with pathologies associated with Alzheimer's disease to hasten cognitive decline [9].

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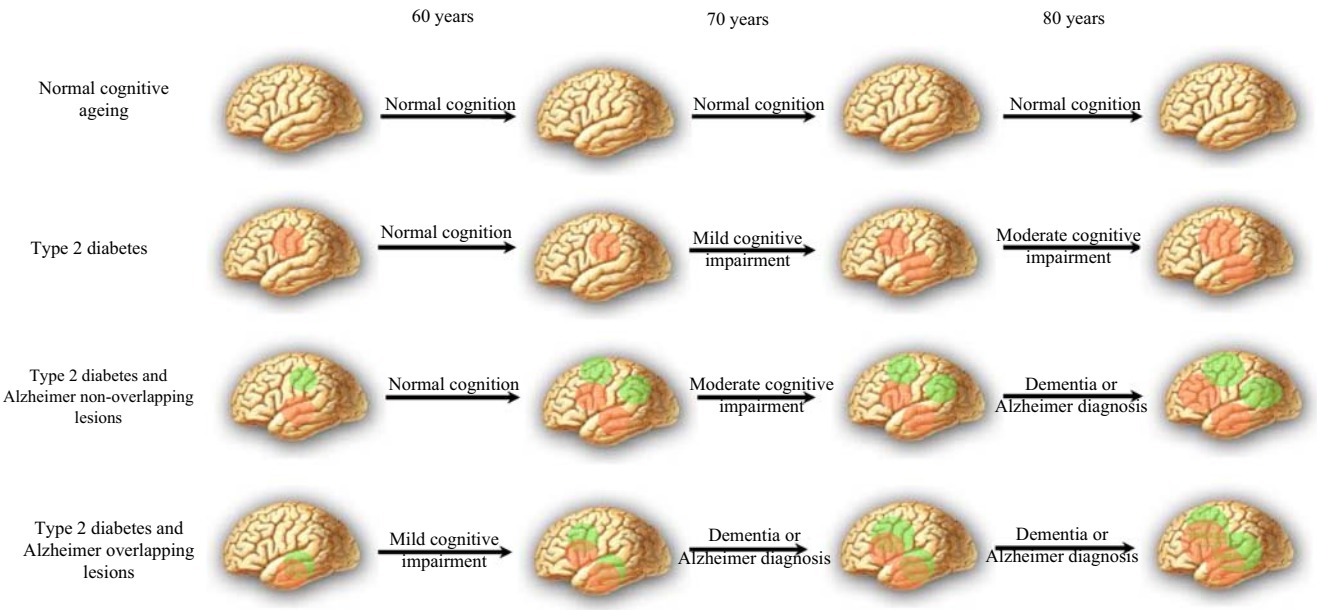

Fig. 1 Progression of cognitive decline as a function of the presence of diabetes and Alzheimer's disease lesions. Diabetes leads to mild cognitive deficits around the seventh decade, probably associated with vascular pathology. Non-overlapping brain lesions due to type 2 diabetes and Alzheimer's disease produce earlier and more pronounced cognitive deficits that progress to dementia. Overlapping lesions produced by type 2 diabetes and Alzheimer's disease produce the greatest and most extensive cognitive deficits and lead to the fastest progression towards dementia. The pink shading indicates vascular lesions and the green shading indicates amyloid and neurofibrillary tangles

Taken together, these observations suggest that while type 2 diabetes as such may not cause large decrements in cognitive function, it may increase the impairing effects of other risk factors, such as hypertension, arterial disease and *APOE* ε4 genotype. Knowing how these different risk factors overlap and how they interplay would be of great help in predicting the course of cognitive changes in people with multiple risk factors for dementia. Moreover, a diabetic person who has one or two *APOE* ε4 alleles would be even more strongly encouraged to engage in the difficult lifestyle changes known to modulate the course of diabetes and vascular disease.

The study by Dore and colleagues [12] presented in this issue of *Diabetologia* was designed to address the question of how the risks of different factors add up to predict early cognitive deficits in type 2 diabetes. Few studies have combined *APOE* genotyping with a measure of diabetes and extensive cognitive testing to evaluate this issue. Dore's large cross-sectional community-based study observed more cognitive deficits in people with diabetes and in carriers of the *APOE* ε4 allele. Interestingly, when present in combination, diabetes and the *APOE* ε4 genotype acted synergistically to produce a cognitive decline that was beyond a simple additive effect of each risk factor alone. The large potentiation produced by the combination of these two risk factors for cognitive decline is likely due to the older age of their cohort and the inclusion of people with mild cognitive impairment. The major limitation of the study by Dore et al. is the cross-sectional nature of the design, which reduces its ability to predict the progression of cognitive decline associated with the presence of risk factors. In addition, the low number of African-American participants may have precluded the observation that, in this subset of the population, type 2 diabetes does not appear to increase the cognitive decline associated with the *APOE* ε4 genotype, as previously reported in a study of a younger cohort (mean age 55 years) [13]. However, a follow-up study of the same cohort did not report such lack of association [14], leaving the question unanswered as to whether *APOE* ε4 genotype in African-Americans has the same consequences for cognitive decline.

The cause of the accelerated cognitive decline in type 2 diabetic patients is still subject to debate. Early hypotheses (i.e. advanced glycation end-products) suggested that brain cells were exposed to high glucose levels. This is unlikely because brain glucose levels are 20–30% of blood levels [15]. An asymmetry in glucose transporters on each side of the blood–brain barrier prevents glucose levels in the brain from reaching those observed in blood that are associated with diabetes pathology in the rest of the body. However, while the brain side of the brain blood vessels is protected from the high glucose levels observed in diabetes, the inner walls of the brain vasculature (on the blood side) are exposed to hyperglycaemia, which can cause vascular damage. Other hypotheses propose that putative changes

in brain insulin levels or sensitivity in the diabetic patients facilitate amyloid deposition and neurofibrillary tangles, but these ideas also appear unlikely at this time [16]. A more likely hypothesis to explain accelerated cognitive decline is the higher prevalence of vascular disease in diabetes, some of which may be caused by high blood glucose levels or by other associated pathologies, such as hypertension and atherosclerosis.

Contrary to the clearer association between diabetes and vascular dementia, the question of whether diabetes increases the likelihood of developing Alzheimer's disease has yet to be answered, with some studies showing that having both diabetes and *APOE* ε4 genotype increases the risk of a diagnosis of probable Alzheimer's disease or mixed dementia [17, 18], while others do not [19, 20]. This lack of consensus is driven on the one hand by the difficulty in interpreting and classifying the observations of vascular damage using imaging techniques or post-mortem examinations [21], and on the other hand by the relative lack of correlation between mild diffuse vascular damage and cognitive deficits. One of the possible ways diabetes might increase the likelihood of a diagnosis of Alzheimer's disease is by creating small-vessel-associated lesions [22]. If, in a given patient, these lesions occur in the brain regions that are most affected by Alzheimer's disease, then larger deficits in the cognitive functions controlled by these regions would be observed. This occurrence would eventually lead to an earlier diagnosis of Alzheimer's disease. A second source of variability might arise from the observation that few deficits are observed before the age of 70 in non-demented diabetic patients [6]. Variation in the mean age of participants in studies might also lead to different conclusions. Finally, not all patients can achieve good glycaemic control, and some studies suggest that worse glycaemic control is associated with worse cognition [9]. Thus, variability in participants' glycaemic control across studies may also lead to different conclusions. Studies that incorporate new in vivo imaging techniques of amyloid deposits and the evaluation of infarcts together with the measure of regional brain volume will likely provide a more definitive picture of the interaction between type 2 diabetes and dementia.

To summarise, type 2 diabetes can lead to cognitive deficits later in life (earlier if there is poor glycaemic control). The most likely cause of cognitive deficits in later life in diabetic patients is vascular disease; if vascular disease damage overlaps with the damage produced by other diseases such as Alzheimer's disease, the cognitive effects will be cumulative and this may hasten the progression of Alzheimer's disease or other dementia. On the positive side, there are indications that exercise, weight control, and glycaemic control can afford protection against cognitive deficits as they do against other diabetic complications. This knowledge may help to motivate patients to make greater efforts to follow these prescriptions.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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