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COMMENTARY

Diabetes and brain damage: more (or less) than meets the eye?

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Brain damage is now a well-established complication of diabetes, but its pathophysiological basis remains controversial. Until very recently, most research on this topic was devoted to demonstrating that hypoglycaemic events are the primary cause of neurocognitive dysfunction. This was a plausible hypothesis because the central nervous system (CNS) has very limited stores of glucose and other substrates, but neurons have a very high rate of glucose utilisation; any reduction in glucose availability would probably induce neuroglycopenia, ultimately leading to significant neuronal damage. Support for this view came from research demonstrating that profound hypoglycaemia could produce neuronal necrosis [1] and induce distinctive patterns of neuropathological [2] and neurocognitive [3] impairment in humans who had experienced very low blood glucose levels over an extended period of time. Fortunately, most diabetic patients never experience profound hypoglycaemia. Although some writers have speculated that recurrent episodes of moderately severe hypoglycaemia could induce a less severe degree of neurocognitive dysfunction [4, 5], most recent studies of children [6] and adults [7, 8] have failed to find compelling evidence for that possibility. Taken together, these findings suggest that there is not a linear relationship between falling blood glucose levels and permanent brain dysfunction. Rather, necrotising neuronal damage occurs only after the threshold for cerebral energy failure is reached—most typically when blood glucose values fall below 1.5 mmol, and the electroencephalogram has reached an isoelectric (flat) state [9].

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Retinopathy predicts neurocognitive dysfunction

If moderately low blood glucose levels are not sufficient to induce detectable brain damage, and if profound hypoglycaemia is a rare event, to what can we attribute the modest, but consistently reported, brain dysfunction found in many diabetic patients? A growing literature now suggests that functional and structural CNS changes may have a vascular basis, and reflect the occurrence of cerebral microangiopathy that is secondary to chronic hyperglycaemia and indicated by the presence of retinopathy. For example, when adults with type 1 diabetes were followed for 7 years, a significant decline in mental efficiency was found over time, but this was limited to those who either had clinically significant diabetic proliferative retinopathy when they entered the study or who subsequently developed diabetic proliferative retinopathy during the follow-up period; those without retinopathy showed no cognitive changes. The magnitude of cognitive decline was further, and independently, influenced by elevated systolic blood pressure and by duration of diabetes [10]. The presence of retinopathy—even relatively early retinopathy—has also been associated with cerebral white matter lesions [11] in otherwise healthy diabetic adults, and a recent exploratory analysis has suggested that increasing severity of retinopathy is related to reductions in cortical grey matter density [8].

Of perhaps even greater significance is the discovery that these effects are not limited to diabetic patients. Data from the Atherosclerosis Risk in Communities Study have now

demonstrated that retinal microvascular abnormalities (particularly microaneurysms) are associated with exactly the same pattern of neurocognitive dysfunction—namely, psychomotor slowing—in middle-aged adults without diabetes [12]. Retinal abnormalities are also predictive of MRI-defined evidence of cerebral atrophy [13] and subclinical cerebral infarcts [14], and are especially pronounced in non-diabetic individuals with elevated blood pressure. Those associations, given the close anatomical and physiological relationships between the retinal and cerebral vascular networks [15], suggest that digitised fundus photography of retinal vessel diameters can provide a non-invasive assessment of the integrity of the cerebral microcirculation [16, 17].

Cortical atrophy, cerebral hypoperfusion and diabetic proliferative retinopathy

If chronic hyperglycaemia induces cerebral microangiopathy, and if the resulting vascular abnormalities lead to cerebral hypoperfusion, then diabetic patients with clinically significant retinopathy should show a greater degree of structural brain damage than those without retinopathy. In an elegant test of this hypothesis, Wessels and her colleagues employed a case-control design and found exactly that. As described in the present issue of *Diabetologia* [18], normotensive adults with advanced diabetic proliferative retinopathy had reduced grey matter density compared with a demographically similar group of childhood-onset diabetic adults with no clinically significant microvascular complications. Most noteworthy is the regional distribution of the grey matter density reductions. Rather than being spread diffusely across the cortex, these changes were limited to only a few areas, which tended to be in the more extreme, or 'watershed', areas of the distribution of the medial and posterior cerebral arteries. This is just what one would have predicted if cerebral hypoperfusion was a major factor contributing to the reduction in grey matter density seen in the diabetic patients with retinopathy, since these watershed areas are a prime site for cortical microinfarcts in other patient populations experiencing cerebrovascular insufficiency [19].

Structural changes of this sort ought to affect brain function as well, and in a separate report that included many of the same subjects, Wessels' group was able to demonstrate the existence of differences in brain activation during a cognitively demanding working memory task [20]. Normally, a deactivation of certain brain regions occurs during working memory, and this can be measured using functional MRI techniques. When brain activity was assessed twice—once during euglycaemia and once during a hypoglycaemic clamp—those with diabetic proliferative retinopathy showed significantly less activation (indicative of subtle brain pathology) than those without retinopathy. Nevertheless, despite functional MRI evidence of changes in brain function during hypoglycaemia, cognitive function remained unaffected: those with diabetic proliferative retinopathy performed the working memory task as well as those without microangiopathy. It remains to be determined whether this preservation of cognitive performance is secondary to possible compensatory changes in cerebral blood flow [21] or in other neural or cerebrovascular processes that might develop over time in response to slowly evolving microvascular damage. Alternatively, it could merely reflect an insensitivity of the working memory task to very subtle alterations in CNS function.

Is diabetes-related brain dysfunction a 'vasocognopathy'?

For many reasons, it should not be particularly surprising to find a vascular basis for diabetes-related brain dysfunction. Blood pressure elevations, particularly increases in systolic blood pressure, are frequently found in patients with type 1 or type 2 diabetes. Such elevations are strongly associated with neurocognitive impairments [10] and cortical atrophy [22], and appear to have a synergistic effect insofar as individuals with both diabetes and elevated blood pressure tend to have the poorest neurocognitive outcomes [22–24]. Similarly, cerebral blood flow, especially in the frontal and frontotemporal brain regions, is reduced in diabetic patients [25, 26] as is cerebrovascular reactivity, with this latter effect being most pronounced in those with retinopathy [27] or hypertension [28]. Cerebral metabolism, as measured by proton magnetic resonance spectroscopy, has also been found to be significantly affected in diabetic patients and again, this is linked to the presence of hypertension [28] and retinopathy [29], with abnormalities being greatest among those with the poorest long-term metabolic control.

The development of degenerative dementias, such as Alzheimer's disease, has also been attributed to chronic brain hypoperfusion [30]. In a series of compelling theoretical papers, de La Torre [31, 32] has suggested that Alzheimer's disease may best be conceptualised as a 'vasocognopathy' ('vaso': vessel/blood flow; 'cogno': relating to cognition) that results from a cascade of haemodynamic abnormalities, including reduced cerebral flood flow, that lead to a decline in cerebral perfusion. According to that model, the resultant reduction in the delivery of glucose and oxygen initiates a neuroglial

'energy crisis' that eventuates in mild cognitive impairment, more serious neurodegeneration and ultimately, in clinically significant dementia.

Many of the risk factors for Alzheimer's disease identified by de la Torre (e.g., hypertension, atherosclerosis, elevated cholesterol, ischaemic stroke, haemodynamic abnormalities, depression) are also co-morbid conditions associated with diabetes of long duration. Reasoning by analogy, one would predict that if diabetes-related cognitive impairment is primarily vascular in origin, then individuals with a childhood onset of diabetes ought to manifest a marked neurocognitive deterioration over a time period similar to that seen in adults who go on to develop Alzheimer's disease. Yet cross-sectional studies comparing cognitive functioning in diabetic and non-diabetic individuals [7] and longitudinal studies measuring cognitive decline over time in adults with type 1 diabetes [10] have typically found quite modest deficits that have never met criteria for 'clinically significance'. Although a number of studies have reported a somewhat greater risk of dementia among diabetic patients, these risks are also relatively small, and in the order of a 1.5-fold increased risk [33, 34].

Indeed, during the past 40 years there has been only one compelling report of profound neuropathological and neurological damage in type 1 diabetic patients, and that focused on 16 poorly controlled, middle-aged adults, who came to autopsy after 17–36 years of diabetes [35]. These patients showed evidence of cerebral angiopathy with enormously thickened walls in the arterioles and in the basement membrane of capillaries, accompanied by gross, diffusely distributed reductions in cortical grey matter, as well as white matter changes characterised by degeneration of myelin sheaths and axon cylinders. All were blind, or nearly blind, and all had neurological abnormalities that ranged from reflex abnormalities to profound dementia. Reske-Nielson and her associates aptly described their findings as evidence of 'diabetic encephalopathy', but while their work is consistent with the vasocognopathy model, there have been no other reports of such profound brain damage associated with type 1 diabetes in young and middle-aged adults. To some extent this may be a consequence of the dramatic improvements made in treating diabetes and reducing its micro- and macrovascular complications, but it may also reflect a failure, on the part of modern researchers, to enrol their most poorly controlled patients into research studies.

Absence of progressive neurocognitive deterioration in older diabetic adults

Because cerebral hypoperfusion and other vascular changes become more prominent during the course of normal ageing [36, 37], one might also expect to find evidence of clinically significant impairment in older adults who have had type 1 diabetes for many years. Somewhat surprisingly, however, a recent report provides very little support for that possibility. Despite an average disease duration of 34 years and a high prevalence of microvascular complications, this group of older (52–77 years) diabetic individuals performed significantly more poorly than their demographically similar non-diabetic peers only on a single cognitive measure (speed of information processing), and the magnitude of that effect was small and not clinically significant [38]. Further, there were no between-group differences in MRI measures of cortical atrophy, white matter abnormalities or cerebral infarcts. This study suggests that diabetic patients have a remarkable level of what might be best conceptualised as 'neurocognitive resilience', and is inconsistent with a diabetic vasocognopathy model that predicts a gradual but apparently relentless decline over time as duration of hypoperfusion increases.

Also at variance with that model are results from an analysis of participants in the Leiden 85-Plus Study. Following older adults with and without type 2 diabetes over a 5-year period, van den Berg and associates (present issue of *Diabetologia*) [39] failed to find a faster rate of cognitive deterioration in diabetic patients over time, although at baseline (age: 85 years), diabetic patients performed more slowly on several speed tests, but this was largely attributable to their history of macrovascular disease (stroke). A greater degree of learning and memory dysfunction, generally considered to be a predictor of progression to dementia [40], was also not evident within the diabetic group. Other investigators, following somewhat younger (mean age: 75 years) adults for up to 9 years, have noted a similar pattern of results: no evidence of an accelerated decline attributable specifically to diabetes [41].

A need for new research paradigms

The absence of serious and progressive global cognitive impairment in virtually all modern studies of diabetic adults, despite the presence of clinically significant vascular complications in those samples, presents an interesting dilemma to anyone struggling to identify underlying pathophysiological mechanisms. If there is no inexorable neurocognitive deterioration in the vast majority of diabetic patients, what is it that protects the brain from further vascular (and non-vascular) damage?

Answering that question will require a number of changes in the design and conduct of neurocognitive research studies. To map the trajectory of brain changes and to differentiate age-related effects from disease duration better, longitudinal studies are needed that include both

adults and children with carefully ascertained diabetes. Given the apparently close linkages between cognition, micro- and macrovascular diabetic complications, and diabetes-related co-morbid conditions such as hypertension, it behoves researchers studying brain function to include patients with a variety of complications rather than to exclude them, as is so often the case. This, of course, requires the use of more sophisticated and comprehensive medical (and laboratory) assessments rather than a reliance on medical record information that may be out of date or incomplete. The availability of sophisticated, non-invasive techniques to estimate the magnitude of microvascular changes within the brain, such as digital retinal imaging [15], as well as the demonstrated relationship between retinal abnormalities and brain dysfunction, make it imperative that researchers measure the retinal microvasculature at the same time a neurocognitive assessment is undertaken.

Do diabetic patients manifest a classic 'diabetic encephalopathy', as described by Reske-Nielson and implied by many other writers? From this review of the recent literature, there is no evidence to support that view. Neurocognitive dysfunction does exist, but for most diabetic patients, it is likely to be quite subtle and to be manifested primarily as mental slowing, similar to the reduction in mental efficiency that occurs during the normal ageing process. Retinopathy is very clearly a marker of diabetes-associated changes in brain structure and function, and while this is consistent with a vascular pathology, the underlying mechanisms remain to be determined. Vascular and neuronal protective processes must contribute to the relative preservation of neurocognitive function, but exactly what those are remains unknown, largely because of the continuing—and perhaps misplaced—focus of diabetes researchers on brain pathology, rather than on brain protection.

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