Brain MRI Correlates of Cognitive Dysfunction in Type 2 Diabetes: The Needle Recovered From the Haystack?

The risk of dementia is increased by approximately 50% in people with type 2 diabetes (1,2). Assuming a prevalence of type 2 diabetes of approximately 15–25% in people aged over 65 years (3), this translates into a diabetes attributable risk of dementia of 7–11% at the population level. In light of these numbers, better understanding of the links between diabetes and dementia is of great importance. This understanding starts by acknowledging that diabetes is a risk factor rather than a cause for dementia: Diabetes by itself is neither sufficient nor required for dementia to develop. Therefore, the increased dementia risk in diabetes is most likely to be due to added or synergistic effects of processes related to diabetes and its comorbidities on top of other more generic, causative mechanisms for dementia. Identifying these processes is important because this may provide leads for dementia prevention in people with diabetes and possibly also in those without. This has, however, proven to be complex. The key mechanisms thought to be involved in the etiology of dementia are Alzheimer-type processes, in which amyloid β peptides are considered to play a central role (4), and vascular brain damage (5). Importantly, in most cases Alzheimer-type and vascular pathologies co-occur (6). These mixed pathologies evolve on a background of aging-related changes in the brain. The total burden of cerebral pathologies, in interaction with structural and functional compensatory processes, also referred to as brain reserve or cognitive reserve (7), determine when cognitive dysfunction becomes clinically manifest. Where does diabetes come into this picture? It is certainly a challenge to pick up diabetes-related processes among these other pathological processes and the innate interindividual variation in brain structure and cognitive performance.

Over the past decade several studies have tried to pinpoint type 2 diabetes-related brain changes using magnetic resonance imaging (MRI). An example of this approach is the elegant work of Moran et al. (8), which appears in this issue. In a cross-sectional study of 350 people with type 2 diabetes and 363 control subjects, they performed a cognitive assessment and an MRI scan of the brain, aiming to define the regional distribution of brain atrophy and to assess if atrophy or cerebrovascular lesions may mediate the link between type 2 diabetes and impaired cognition. In line with previous studies (9–12), the investigators observed that type 2 diabetes was associated with more cerebral infarcts and lower total gray, white, and hippocampal volumes. Microbleeds were not more common in the study participants with diabetes and the volumes of white matter hyperintensities were not increased. In people with type 2 diabetes, gray matter loss was most evident in medial temporal, anterior cingulate, and medial frontal lobes, and white matter loss in frontal and temporal regions, compared with control subjects. On cognitive testing, visuospatial skills and speed were slightly, but significantly, impaired in the diabetic group. The magnitude of these diabetes-associated cognitive decrements was attenuated by almost half when adjusted for hippocampal and total gray volumes, but was unchanged by adjustment for cerebrovascular lesions or white matter volume. Based on these observations, the authors conclude that cortical atrophy in type 2 diabetes resembles patterns seen in preclinical Alzheimer disease and that neurodegeneration, rather than cerebrovascular lesions, may play a key role in type 2 diabetes-related cognitive impairment (8).

The results from this interesting study clearly speak for themselves. Nevertheless, the conclusion as put forward by the authors merits some reflection. In my view, key issues that should be considered are how the cognitive and MRI changes in patients with type 2 diabetes, as observed in this study, relate to the earliest stages of dementia and how the MRI findings relate to specific etiological processes. The magnitude of diabetes-associated cognitive decrements in individuals without dementia is relatively small, which was also true in the study by Moran et al. Systematic reviews report that effect sizes on affected domains, mainly information-processing speed, executive functioning, and memory, are typically around 0.3 to 0.4 SD (13), representing a 10–15% reduction in normalized test performance relative to people without diabetes. Such effect sizes have been reported in populations of patients with type 2 diabetes aged mid-40 up to 80 years (13). By contrast, in dementia and predementia stages, such as mild cognitive impairment, effect sizes of cognitive deficits, by definition, exceed 1.5 to 2 SD. Such deficits are mainly observed in people above the age of 65, also in people with diabetes (14). Unlike the cognitive decrements that occur in the early stages of dementia, the diabetes-associated cognitive decrements show limited progression over time (15,16). Moreover, unlike early Alzheimer disease, the decrements that are associated with diabetes do not center on disturbances of episodic memory (14). Along these same lines, the magnitude of diabetes-associated reductions in brain volume appears to be modest. In correspondence with the current study, most studies report reductions of 0.5–1.5% relative to control subjects, the equivalent of 2–5 years of normal aging (10–12,17). Just like cognition, these changes in brain volume in people with diabetes evolve only slowly over time relative to control subjects (10,17). In contrast, in people with Alzheimer disease, the rates of cognitive decline and brain atrophy clearly deviate from those of normal aging (18). This deviation of atrophy rates only becomes detectable several years prior to diagnosis (19). Hence, despite the observation by Moran et al. (8) that the pattern of cortical atrophy in type 2 diabetes resembles that seen in preclinical Alzheimer disease, we should be very careful in suggesting that the imaging abnormalities and cognitive decrements that are associated with type 2 diabetes reflect an early stage of a neurodegenerative process, let alone Alzheimer disease. As pointed out above, there are

fundamental differences between diabetes-related cognitive and MRI changes with regard to affected age-groups, the magnitude of the changes, and their progression over time.

Nevertheless, the findings from Moran et al. do show that cognitive decrements in people with diabetes appear to be attributable to structural changes on MRI. These changes may very well contribute to the increased dementia risk in people with diabetes, but what is their etiology? In the current study cortical and hippocampal atrophy appeared to be the main determinants of diabetes-associated cognitive decrements. Should we therefore rule out vascular damage as a causative factor? Probably not. Atrophy has proven to be a very consistent MRI correlate of diabetes (20). Diabetes is also linked to vascular lesions like lacunes (20), but because these lesions are much less common, the a priori likelihood of these lesions to explain the diabetes-associated cognitive decrements is much smaller. The point is that current MRI markers may not fully capture the burden of vascular brain lesions (21). Sensitive markers of white matter disturbances, which will be at least partially caused by vascular damage, are also clearly linked to impaired cognition in type 2 diabetes (22). Moreover, autopsy studies point to vascular damage rather than Alzheimer-type pathology as a major source of the increased dementia risk in people with diabetes (23). So then what is the etiological significance of diabetes-associated brain atrophy? The point is that cerebral atrophy can be a feature of many conditions. The pathological changes that underlie atrophy are heterogeneous and do not necessarily reflect neuronal loss (24). Neuropathological correlates of loss of cortical gray matter volume on MRI, in the context of aging, vascular disease, and dementia, include subcortical vascular pathology, arteriosclerosis, and Alzheimer-type pathologies (25).

In conclusion, the atrophy observed by Moran et al. (8) clearly reflects a fingerprint of diabetes in the brain. Their findings should initiate further research into underlying mechanisms.

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