Hyperglycaemia, microangiopathy, diabetes and dementia risk

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Abstract

Brain microangiopathy increases in frequency and severity with older age, with the presence of hypertension and to a lesser extent with diabetes. Magnetic resonance imaging is used to provide anatomical descriptions, but at this time only clinical examination and neuropsychological testing can assess white matter functioning. Clinical correlates of microangiopathy appear as subcortical cognitive alterations, but data are controversial about dementia risk. Brain microangiopathy seems to be however a complication of chronic hyperglycaemia, probably due to similar mechanisms occurring in retinopathy and other microvascular complications. To date, many questions have been raised: How can brain microangiopathy progression be monitored? Is there a reversible stage of brain microangiopathy? Which preventive actions should be implemented in aging patients with diabetes? Finally, what type of care should be provided for people with diabetes and mild cognitive impairment or overt dementia to slow down cognitive worsening?

Keywords: Dementia; Cerebral microangiopathy; Hypertension; Hyperglycaemia; Magnetic resonance imaging; Review

1. Introduction

Many efforts have been made to describe the links between diabetes and dementia due to the importance of any means for decreasing the incidence of dementia, and thus targets for prevention [1]. There is an increasing body of evidence supporting the role of diabetes in vascular dementia (VD) or mixed dementia (MD), rather than in Alzheimer’s disease (AD).

Diabetes is a major cause of microangiopathy, related to hyperglycaemia and hypertension, and leads to renal insufficiency, retinal damage and polyneuropathy. The brain is thus likely a site for microangiopathy, whether or not in association with large-vessel brain pathology. However, the brain is not an easy organ to access, and few non-invasive tools are able to provide an accurate description of its anatomy and functioning. For these purposes, magnetic resonance imaging (MRI) and neuropsychological testing were used, sometimes
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supplemented by neuropathological autopsy studies. These MRI and neuropsychological investigations are however difficult to conduct due to high costs and scarcity of magnetic resonance imaging equipment.

We aim here to review the consequences of brain microangiopathy on cognitive functioning and dementia risk, as well as the role of diabetes and hyperglycaemia with respect to other risk factors.

2. Dementia and diabetes

We previously reviewed the role of insulin resistance and diabetes as risk factors for dementia, AD, VD and dementia of any type [1]. The complexity of the dementia risk factor spectrum makes it difficult to isolate the role of diabetes to the exclusion of other vascular risk factors, mainly the ApoE-ε-4 allele. An increased risk of any dementia type and not only AD or VD seems possible in people with diabetes, but the means of causality remain clinically uncertain [2].

The predominant cognitive deficits in vascular cognitive impairment are subcortical, i.e., frontal and executive functioning alterations [3]. In vascular dementia, diabetes is equally represented in the risk factor profile of small and large vessel diseases [4]. After a stroke, dementia risk increases [5-7] and recovery of cognitive function is less frequent [8] in patients with diabetes.

The effects of diabetes on accelerated cognitive decline may decrease with older age, as it had no effect on cognition in subjects older than 85 years in the Leiden 85-plus study [9]. Another longitudinal community-based study in people older than 75 years showed an increased risk for vascular dementia in subjects with diabetes but no effect on Alzheimer’s disease risk [10]. However, the authors found an increased risk of Alzheimer’s disease in subjects with undiagnosed diabetes and with high blood glucose values; they concluded that there was a hyperglycaemic effect independent of vascular complications, which was involved in the neurodegenerative process. During a 5-6 year follow-up, a population-based study confirmed an increased risk for developing dementia only in subjects with undiagnosed diabetes and with an HbA1c > 7% [11].

3. MRI findings in relation to cognition

White matter lesions, also known as leukoaraiosisisiosis or brain microangiopathy, were first described from brain imaging with some uncertainty about their clinical expression. Extrapyramidal symptoms [12-14], gait disturbance [15,16], falls [13,16] and bladder incontinence [16] are reputed to be clinical features of brain leukoaraiosis. However, these latter studies had some difficulties showing correlations between these symptoms and MRI signs of leukoaraiosis. Microangiopathy in MRI appeared as white matter hyperintensities (WMH) in FLAIR or T2 sequence; lacunae, which are ischemic lesions, appeared as hypointensities in FLAIR sequence and hyperintensities in T2; microbleeds were only seen with gradient-echo T2* MRI due to the paramagnetic effect of hemosiderin.

Subjects with WMH may be either non-symptomatic, have cognitive impairment or be severely demented. It is agreed that the prevalence and severity of lesions increases with age [17]. Hypertension in older people has been shown to be a major risk factor for brain microangiopathy and brain atrophy, which progress independently over time [18]. A cross-sectional study showed that there were significant relationships between WMH and blood pressure, hypertension, and plasma cholesterol in subjects aged 65 to 74 years. After this age, the relationship weakened [19]. In this study, WMH tended to be associated with lower scores on cognitive function tests and were significantly associated with subjective mental decline [19]. Indeed, the influence of older age seems very important. Leukoaraiosis is very common in older subjects [14]. Correlations between the severity of cognitive impairment associated with aging, such as slowed psychomotor speed, alteration of episodic memory and executive dysfunctions with severity of frontal and temporal WMH, have been shown [20]. Another cross-sectional study found a relationship between WMH and cognitive deficits and an association with brain atrophy [21].

Hypertension is well-recognised as a major risk factor for stroke. In the SCOPE trial comparing hypertensive subjects with candesartan or placebo and normotensive subjects, MRI exams explored the rate of brain atrophy and the change in WMH over a 3-year period [18]. The WMH fraction correlated with baseline diastolic blood pressure, and changes were related to baseline MRI WMH, baseline systolic blood pressure and inter-exam diastolic blood pressure. The rate in brain atrophy was independent of WMH fraction or changes. Brain atrophy was related to baseline systolic blood pressure. The comparison between the 3 groups showed that non-hypertensive subjects had a lower rate of brain atrophy compared with subjects treated with candesartan, and that those receiving the drug had a lower rate than those receiving placebo [18].

There is an ongoing debate about the respective role of periventricular leukoaraiosis (PVLA) compared to deep white matter leukoaraiosis (DWMLA) in cognitive impairment. In a small sample of cognitively intact elderly subjects, worsening of non-dementia cognitive impairments were shown to be related to PVLA worsening rather than to baseline PVLA severity [22]. Furthermore, in the Rotterdam study, the 5-year dementia risk increased with the higher severity of PVLA, while the relationship with baseline DWMLA was less significant [23]. PVLA seems to be correlated with age, while DWMLA does not [3].

In a large autopsy study, the presence of subcortical infarcts in Alzheimer’s disease incrementally increased the risk of dementia [24]. However, the brains of demented patients from the Baltimore Longitudinal Aging Study did not exhibit more frequent subcortical infarcts (lacunae) in the autopsy study [3]. On the other side, lacunae and cerebral atrophy were both found to be predictors of mild cognitive impairment in the longitudinal Cardiovascular Health Study [25].
Microbleeds are mainly associated with small vessel lipohyalinose degeneration related to hypertension but are also present in cerebral amyloid angiopathy. Cross-sectional studies, although not all, have shown associations of microbleeds with cognitive alterations [26]. Microbleeds occurred more frequently in Alzheimer’s patients compared to controls; they were predominantly found in the occipital region, were associated with severity of leukoaraiosis, and were not associated with a history of hypertension, suggesting that they might represent amyloid vasculopathy [27].

4. Association of brain vascular pathology with diabetes

In patients with peripheral arterial pathology, type 2 diabetes was associated with more global and subcortical brain atrophy and more lacunar infarcts [28]. In this cross-sectional study in patients with diabetes, high glucose levels and diabetes duration were associated with global brain atrophy.

In the LADIS study, which included non-disabled subjects, 14.4% of them with diabetes, significant mild cognitive deficits were seen only in those with combined medial temporal lobe atrophy and severe WMH on MRI exams [29]. Severity of age-related microangiopathy was correlated with severity of cognitive alterations (general functioning, memory, verbal fluency, executive functions and attention). Patients with diabetes performed worse in these neuropsychological tests independent of age, education and previous stroke [30]. During the 3-year follow-up for 639 patients, white matter changes and diabetes, both together and independently, predicted cognitive decline (including dementia). Diabetes however did not specifically predict VD or AD in this study [31].

The cohort of men in the Honolulu-Asia Aging Study underwent MRI investigation at a single visit. The proportion of men with diabetes in the cohort was high (38%), and more than one in two were undiagnosed. Men with diabetes had a higher rate of lacunae and hippocampal atrophy. Furthermore, those with longer diabetes duration (> 20 years compared to < 5 years) had more lacunae, hippocampal atrophy, infarcts, and WMHs [32]. An increased frequency of lacunae has also been shown to be associated with diabetes elsewhere but in an unadjusted model with a small size population [33]. Another study found a trend for increased frequency of white matter disease with diabetes, but in multivariate analysis the association disappeared and only age, stroke history and the presence of the ApoE-ε-4 allele carriage were found to be predictors [34].

Other cross-sectional studies have shown that type 2 diabetes was associated with hippocampal atrophy specifically [35, 36] or with cortical atrophy [37] but not with white matter lesions.

Neuropathological studies however, which are scarce, had difficulty finding systematic differences in the brains of older patients with type 2 diabetes and others. In non-demented subjects, Nelson et al. showed increased cerebrovascular disease in patients with a history of diabetes, involving both small and large vessels, and less Alzheimer-type pathology compared to controls [38]. A Finnish prospective study in the very elderly found an increased risk of dementia with diabetes, both VD and AD, in fully adjusted analysis including the APO E phenotype [39]. However, the brain of the individuals with diabetes showed more vascular pathology and less Alzheimer’s [39]. Insulin resistance was shown to be negatively associated with right hippocampal volume and with global cognitive functioning in a group of middle-aged women without diabetes [40]. In a longitudinal population-based study, insulin resistance measured in the 5 previous years before death was not associated with significant increases in Alzheimer’s neuropathology in the absence of the ApoE-ε-4 phenotype, but was enhanced in the opposite case [41].

5. Diabetes and the blood brain barrier

One other consequence of brain microangiopathy could be a less effective blood brain barrier (BBB). The CSF albumin/serum albumin ratio increases with the severity of BBB dysfunction. It has been consistently shown that this ratio increases with age in the cognitively intact elderly but also in demented patients. However there were no differences between VD and AD shown in this ratio, nor any relationship with dementia severity [42]. It is likely that these changes were due to associated microangiopathy. Indeed, it has recently been found in a MRI study that older age, hypertension, diabetes and aspirin use were related to increased BBB permeability [43]. In a streptozotocin-induced diabetes rat model, an increase of BBB permeability has been shown via a loss of tight junction proteins dependent on increased matrix metalloproteinase activity. In this animal model the increased BBB permeability in diabetes did not result from hyperglycaemia alone, and the intervention of other metabolic abnormalities (insulin defect, dyslipidaemia) seemed likely [44]. In a similar model, the time consequences of diabetes on BBB were not equal in all brain regions. The midbrain was the first place exhibiting this functional damage, followed by the hippocampus, cortex and basal ganglia [45]. The consequences of permeability aberration of small brain vessels on brain functions remain to be explored.

6. Brain microangiopathy and diabetes-related complications

The severity of WMH was associated with arterial stiffness, arterial thickness and markers of endothelial dysfunction independent of common cardiovascular risk factors in a sample of elderly subjects with memory complaints [46]. Indeed, an MRI study in the general population showed a correlation between WMH or lacunae presence and retinal arterial narrowing and sclerosis [47]. Several reports have described an association between hypertensive retinopathy
and lacunae. In hypertensive subjects free of stroke, age and severity of retinopathy were independent risk factors for lacunae [48].

A meta-analysis reported lower cognitive abilities in patients with type 1 diabetes compared to a control group and an association between lower cognitive functions and the presence of retinopathy, although without relationships with blood glucose or blood pressure control [49].

Advanced retinopathy was used as a marker of microvascular disease and chronic hyperglycaemia in a case-control study for type 1 diabetes. Here MRI was not suitable for the study of white matter changes but showed a relationship between the severity of retinopathy and cortical atrophy [50]. However, in another group of patients with type 1 diabetes younger than 40 years old, no relationship was found between the presence of retinopathy or the quality of the blood glucose control with WMH severity [51]. In subjects with type 2 diabetes (mean age 65 years), multivariate analysis showed that older age increased the risk of any brain MRI changes, and in particular, cortical atrophy increased with the presence of retinopathy and cortical infarcts but decreased with the use of statins. DWMLA was more frequent in subjects with higher insulin levels, and PVL was more frequent with the presence of brain infarcts and less so with the use of statins [52]. The HbA1c value and the measured blood pressure were not related to any of the MRI or cognitive alterations. However, the proportion of subjects with uncontrolled glycaemia or blood pressure was very low in this group. Gold SM et al. found a specific relationship between HbA1c values and hippocampal atrophy in a group of younger subjects with diabetes but no relationship with alterations of cognitive performance [35].

7. The hyperglycaemia hypothesis

Hyperglycaemia has been found to be a risk factor for cognitive decline. Mild cognitive impairment risk increased after 4 years in subjects with HbA1c > 7% in a large female cohort in the general population [53]. Both low and high fasting blood glucose concentrations in middle-aged men with diabetes were associated with lower cognitive functioning in an observational study [54]. An improvement in working memory but not in other cognitive functions in non-demented subjects with diabetes (45-75 years old) was reported after 24 weeks of either rosiglitazone or gliburide and was correlated with better fasting blood glucose control [55]. A randomized controlled trial compared glibenclamide to repaglinide in older people with diabetes (mean age 75 years) for one-year cognitive decline. Executive functions and attention declined in the glibenclamide group but not in the repaglinide one; the difference was attributed to the higher reduction of post-prandial blood glucose [56]. Larger daily blood glucose fluctuations were related to lower levels of cognitive functions in older people with diabetes, independent of fasting and post-prandial blood glucose and HbA1c [57]. Better cognitive performances were consistently seen after taking a low glycaemic index food in elderly subjects with type 2 diabetes [58].

The mechanisms of hyperglycaemia toxicity have been extensively investigated in the pathogenesis of microvascular complications of diabetes [59]. Briefly, hyperglycaemia enhances four interrelated pathways including through increased polyol pathway flux, increased production of advanced glycation end-products, activation of protein kinase C, and increased flux through the hexosamine pathway in endothelial cells. This induces an alteration in blood flow, small and large vessel occlusion, angiogenesis and permeability abnormality due to increased VEGF production, inflammation due to increased NF-κB production, and increased ROS production due to increased level of quinone reduction. Increased production of ROS and NF-κB in endothelial cells also occurs with aging [60], and thus brain microangiopathy could be due to similar mechanisms in diabetes or senescence. The metabolic alterations related to hyperglycaemia seem enhanced in cases of glycaemic fluctuations rather than with constant elevated blood glucose levels. Indeed, transient peaks of hyperglycaemia were shown to induce activation of NF-κB production and epigenetic changes in the promoter of the NF-κB, themselves due to increased ROS production [61]. This could be the basis of what is called “hyperglycaemia memory”, resulting in persistent activation of inflammation even after normalization of blood glucose concentrations.

8. The patient with dementia and diabetes

In a cohort of patients with Alzheimer’s disease (REAL-FR) and with similar dementia severity at baseline, those with diabetes had slower cognitive decline than the others independent of other characteristics of the subjects [62]. The authors hypothesized that subjects with diabetes received drugs more often for vascular protection. However, it has been shown in a randomized controlled trial that an intervention for optimal vascular care compared to usual care did not modify the course of cognitive decline in patients with mixed dementia [63]. Assuming that the rate of cognitive decline in mixed dementia is slower than in Alzheimer’s disease [64], patients with diabetes in the REAL-FR cohort may have been more likely to present the course of mixed dementia. A 12-month longitudinal study in demented subjects with diabetes has shown that cognitive decline was slower among those with insulin therapy compared to those with only hypoglycaemic oral agents [65]. The authors suggested that increased levels of insulin could be beneficial. However, baseline data showed that patients on insulin were older, had longer diabetes duration and had higher levels of fasting glycaemia and lower fasting insulin blood levels than those with oral agents. It is also notable that the rate of complications and hypertension was also higher in patients with insulin. Thus, it seems unlikely that intensification of risk factor control for diabetes and other vascular conditions could modify the course of dementia in people with diabetes.
9. Insights from interventional studies

Indeed, most interventional studies have brought disappointing results. One of the secondary endpoints in the ADVANCE study was the prevention of a 3-point decrease in the Mini-Mental State Examination (MMSE), or lowering the rate of incident dementia in patients with type 2 diabetes. The interventions, either intensive blood glucose control using glycazide [66] or lowering blood pressure with an angiotensin converting inhibitor-diuretic combination [67], had no effect on cognition or incident dementia after a 5-year follow-up. The mean diabetes duration was 8 years before inclusion in the trial, and thus these patients may have suffered from the hyperglycaemia memory phenomenon.

Statins, such as pravastatin, may preserve endothelial function in the presence of hyperglycaemia in patients with diabetes and thus prevent the occurrence of microangiopathy due to decreased activation of NF-κB [68]. However, in the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial, WMH severity increased equally in both groups over time [69]. Furthermore, the long-term brain volume reduction was equivalent in both groups, as was the decline in cerebral blood flow [70].

10. Conclusion

There have been few investigations on brain microangiopathy related to diabetes, probably due to methodological and technical difficulties. Furthermore, its role in dementia risk is still not completely known. However, brain microangiopathy seems to be a diabetes-related complication. Currently, many questions have been raised, namely with regard to monitoring brain microangiopathy progression; whether there is a reversible stage of brain microangiopathy; the preventive actions that should be implemented in aging patients with diabetes; and finally, the best care for people with diabetes and mild cognitive impairment or overt dementia.

11. Conflicts of interest

None of the authors have any conflict of interest concerning this paper.

References


