PAPER

Increased cortical atrophy in patients with Alzheimer's disease and type 2 diabetes mellitus

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Background: The risk of Alzheimer's disease (AD) is increased in type 2 diabetes (DM2). This increased risk has been attributed to vascular comorbidity, but other mechanisms, such as accelerated ageing of the brain, have also been implicated.
Objective: To determine whether AD in patients with DM2 is associated with an increased occurrence of vascular lesions in the brain, by increased cerebral atrophy, or a combination of both.
Methods: In total, 29 patients with AD and DM2 and 58 patients with AD and without DM2 were included in the study. Clinical characteristics were recorded, and a neuropsychological examination and magnetic resonance imaging (MRI) scan were performed. MRI scans were rated for cortical and subcortical atrophy, medial temporal lobe atrophy, white matter lesions, and infarcts.
Results: The neuropsychological profiles of the two groups were identical. Patients with AD and DM2 had increased cortical atrophy on MRI ($p<0.05$) compared with the non-DM2 group. In addition, infarcts were more common (odds ratio 2.4; 95% CI 0.8 to 7.8), but this effect did not account for the increased atrophy. The other MR measures did not differ between the groups.
Conclusion: The results suggest that non-vascular mechanisms, leading to increased cortical atrophy, are also involved in the increased risk of AD in DM2.

The incidence of Alzheimer's disease (AD) is increased in people with type 2 diabetes mellitus (DM2).[1 2] This increased risk has been attributed to vascular risk factors such as hypertension, dyslipidaemia, and atherosclerosis, but adjustment for these factors has little effect on the relative risk of AD in patients with DM2.[1 2] Alternative explanations have also been put forward. DM may accelerate the ageing process of the brain,[3] as reflected in increased cerebral atrophy, thus reducing the threshold for the development of AD symptoms. In addition, DM may interfere with cerebral amyloid and tau metabolism.[4] A limitation of previous population based surveys on the association between diabetes and AD is that these studies have provided no detailed data on the clinical features of the dementia syndrome or on brain magnetic resonance imaging (MRI) findings in patients with AD and DM compared with those without. This hampers the identification of mechanisms underlying the association between DM and AD.

The aim of the present study was therefore to compare the neuropsychological profile and MRI characteristics of patients with a clinical diagnosis of AD with or without DM2, in order to determine whether AD in subjects with DM2 is associated with an increased occurrence of vascular lesions in the brain, increased cerebral atrophy, or a combination of both.

METHODS

Study population

The memory clinic of the Alzheimer Center serves as a university hospital based secondary/tertiary referral outpatient clinic for dementia. All patients who visit the memory clinic receive a standardised diagnostic investigation including a neurological examination, neuropsychological testing, a computed tomography (CT) or MRI scan of the brain, and blood tests.

For each patient, the diagnosis is made at a multidisciplinary consensus meeting where all relevant data are reviewed. AD is diagnosed according to the NINCDS-ADRDA criteria.[5] Other dementia subtypes are also diagnosed according to established diagnostic criteria, such as the NINDS-AIREN criteria for vascular dementia.[6] The presence or absence of diabetes does not influence the final diagnosis according to these criteria.

The records of all patients diagnosed with AD at the clinic between January 1997 and May 2004 (n = 356) were reviewed. AD was diagnosed according to the NINCDS-ADRDA criteria.[5] From these 356 patients, all patients with DM2 were selected (n = 29), based on the medical history or medication use (n = 28), or on a random blood glucose level >11 mmol/l (n = 1). Of these subjects with DM2, 20 were on oral anti-hyperglycaemic drugs, and 4 of these were also on insulin. Mean (SD) duration of DM2 was 11 (13) years. Random blood glucose values were available for 80% of the patients with AD and without a known history of DM. From the patients with a random blood glucose level <7.0 mmol/l, we selected 58 controls (twice the number of patients with DM2, to increase statistical power). Controls were selected randomly, only taking into account age, sex, and level of education, in order to match the two groups for these variables. We thus obtained a study population of 29 patients with AD and DM2, and 58 patients with AD and without DM2. The clinical characteristics of all subjects were recorded, the results of the Mini-Mental State Examination (MMSE) and neuropsychological tests assessed, and the available MRI scans rated.

Vascular disease

Arterial hypertension was defined as a systolic blood pressure >160 mmHg, a diastolic blood pressure >95 mmHg, or the use of antihypertensive medication. A history of cerebrovascular disease was defined as a previous ischaemic or haemorrhagic stroke. Transient ischaemic attacks were not

Abbreviations: AD, Alzheimer's disease; CT, computed tomography; DM2, diabetes mellitus type 2; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; WML, white matter lesions

taken into account. A vascular intervention was defined as surgical or endovascular treatment for ischaemic vascular disease.

Neuropsychological examination

A neuropsychological examination was performed at the memory clinic for 26 patients with diabetes and 47 without. The clinical characteristics (age, blood pressure, vascular medical history) of these patients were comparable with the whole study population. The cognitive test battery was not exactly the same in all subjects. The following tests were available for at least two thirds of the subjects. (*a*) Attention and concentration: digit span forward and backward and Trailmaking A; (*b*) episodic memory: a visual association test (naming and recalling pictures of interacting objects[7]); (*c*) semantic memory: a verbal fluency task (number of animals named in 60 s); (*d*) executive functions: Trailmaking B; (*e*) praxis and visuoconstruction: Luria's meander (completing a curve consisting of alternating components), and a figure copy test, both of which had been previously validated in dementia patients.[8]

Rating of MRI scans

In the diagnostic process a CT or MRI scan was performed in all subjects, either at the referring clinic, or at our clinic. Only MRI scans that were performed at our clinic were used in the analysis (patients with diabetes n = 17, patients without diabetes n = 45). The clinical characteristics of the subjects with MRI (age, MMSE, blood pressure, vascular medical history) were similar to those of the whole study population. The MRI raters were blinded to the diabetic status.

The MRI protocol included coronal T1 weighted and transverse proton density or fluid attenuated inversion recovery images on a 1.0 T scanner (Impact; Siemens AG, Erlangen, Germany). Cortical atrophy was rated as absent (0), slight (1), moderate (2), or severe (3) in the frontal, parieto-occipital, and temporal regions on left and right (sum score 0–18).[9] Ventricular widening was also rated on a 0–3 scale, including the frontal, occipital, and temporal horns of the lateral ventricles bilaterally, and the third ventricle (sum score 0–21).[9] Medial temporal lobe atrophy was rated on both sides (sum score 0–8).[10] White matter lesions (WML) were rated as described previously:[11] periventricular WML 0–6, lobar deep WML 0–24, basal ganglia lesions 0–30, and infratentorial WML 0–24. Lacunes and cortical infarcts were also identified.

Statistics

Differences between the AD/DM2 and the AD/non-DM group were assessed with linear or logistic regression analyses, allowing adjustment for the effects of age and comorbid conditions, and expressed as estimated mean difference or odds ratios (OR) with 95% confidence intervals. A significance level of $p<0.05$ was used.

RESULTS

Subject characteristics are presented in table 1. As expected, a history of vascular disease was more common in the AD/DM2 group.

The findings of the neuropsychological examination are presented in table 2 (AD/DM2: n = 26; AD/non-DM n = 47). Performance on the neuropsychological tests was similar in both groups. Across the two groups, performance on the visual association task was severely impaired in relation to reference values, and there was a modest impairment on the trailmaking B. This pattern is compatible with early AD.

The MRI data are presented in table 3 (AD/DM2: n = 17; AD/non-DM n = 45). Cortical atrophy was significantly more pronounced in the AD/DM2 than the AD/non-DM group (estimated mean difference sum score cortical atrophy 1.5 (0 to 3); $p<0.05$). In post hoc analyses this between group difference was not due to atrophy in one specific region (mean difference frontal: 0.5 (0 to 1); parieto-occipital 0.5 (−0.5 to 1); temporal 0.5 (0 to 1.5)). Adjustment for age (mean difference sum score cortical atrophy: 1.5 (0 to 3)), the presence of hypertension (mean difference 1.5 (0 to 3)) or a history of vascular intervention (mean difference 1.5 (−0.5 to 3)) had no apparent effects. Nevertheless, the relation between DM and cortical atrophy appeared to be most pronounced in hypertensive subjects (non-hypertensive AD/DM2 versus non-hypertensive AD/non-DM: mean difference 0.5 (−1.5 to 3); p = 0.55; hypertensive AD/DM2 versus hypertensive AD/non-DM: mean difference 2 (0 to 4.5); p = 0.06). Diabetes was not associated with increased medial temporal lobe atrophy, ventricular widening, or higher WML scores. Infarcts were more common in the AD/DM2 group, but not statistically significant OR 2.4 (0.8 to 7.8). The presence of infarcts was associated with cortical atrophy (mean difference sum score cortical atrophy in all patients with AD with infarcts versus patients without infarcts, adjusted for age was 1.5 (0 to 3), $p<0.05$). However, if the effect of DM2 on cortical atrophy was adjusted for the occurrence of infarcts, this had only a limited effects on the mean group difference (mean difference sum score cortical atrophy AD/DM2 versus AD/non-DM was 1.0 (−0.5 to 3))

Age and MR abnormalities were strongly related across the two groups, (regression analyses: medial temporal lobe atrophy $p<0.01$; ventricular widening $p<0.05$; periventricular WML $p<0.01$; deep lobar WML $p<0.01$), as would be expected.

Table 1 Characteristics of the study population

	AD/DM2 (n = 29)	AD/non-DM (n = 58)	OR (95% CI)
Age at initial visit clinic	75.0 (8.6)	74.1 (7.4)	—
Male/female (n)	10/19	20/38	—
MMSE	20.6 (6.6)	20.4 (5.0)	—
Age at AD diagnosis	75.1 (8.4)	74.2 (7.4)	—
DBP (mmHg)	84 (9)	87 (11)	—
SBP (mmHg)	154 (19)	155 (22)	—
Hypertension	63%	51%	1.6 (0.6 to 4.3)
History of MI	17%	5%	3.8 (0.8 to 17.3)
History of VI	17%	3%*	5.8 (1.1 to 32.2)*
History of stroke	3%	5%	0.7 (0.1 to 6.6)

Data are mean (SD) or proportions. OR for AD/DM2 relative to AD/non-DM; *p<0.05. DBP, diastolic blood pressure; SBP, systolic blood pressure; MI, myocardial infarction; VI, vascular intervention.

Table 2 Neuropsychological examination

	AD/DM2 (n = 26)	AD/non-DM (n = 47)
MMSE	20.8 (6.4)	21.6 (4.2)
Digit span forward	5.1 (1.1)	5.2 (1.1)
Digit span backward	3.7 (1.1)	3.8 (1.1)
Trailmaking A (s)	89 (68 to 137)	72 (58 to 86)
Visual association task	4.6 (3.7)	3.8 (3.2)
Verbal fluency	10.6 (3.8)	12.5 (5.0)
Trailmaking B (s)	370 (283 to 600)	282 (192 to 600)
Meander	3.3 (1.0)	3.1 (1.3)
Figures copy test	11.8 (1.4)	11.6 (1.1)

For each test, data for at least two thirds of the population were available. Data are mean (SD), except for the Trailmaking test, which is presented as median (quartiles) in seconds. No statistically significant differences were seen between the groups.

DISCUSSION

We found that patients with AD with DM2 had significantly more cortical atrophy than those without DM2, while their

Table 3 MRI rating

	AD/DM2 (n = 17)	AD/non-DM (n = 45)	Mean difference
Cortical atrophy (0–18)	10 (8 to 11)	8 (6 to 10.5)	1.5 (0 to 3)*
Ventricular widening (0 –21)	12 (8 to 14)	10 (8 to 14)	1.5 (−1 to 4)
Medial temporal lobe atrophy (0–8)	4 (2 to 5.5)	3 (2 to 4)	0.5 (−0.5 to 1.5)
Periventricular white matter lesions (0–6)	4 (3 to 5)	3 (3 to 4.5)	0 (−1 to 1)
Lobar deep white matter lesions (0–24)	4 (1.5 to 10)	4 (2 to 9)	0 (−3 to 3)
White matter lesions basal ganglia (0–30)	0 (0 to 3)	0 (0 to 1)	0.5 (−0.5 to 1.5)
Infratentorial white matter lesions (0–24)	0 (0 to 0)	0 (0 to 0)	0 (−0.5 to 0)
Lacunes	41%	24%	OR 2.2 (0.7 to 7.0)
Lacunes and/or cortical infarcts	47%	27%	OR 2.4 (0.8 to 7.8)

Mean difference is the unadjusted between group difference (diabetes minus no diabetes) in the linear regression analysis, with 95% confidence interval in brackets. OR for AD/DM2 relative to AD/non-DM. Adjustment for age or hypertension did not affect the results. Data are median (quartiles), or proportions. *$p<0.05$.

neuropsychological profiles were identical. Vascular risk factors were more prevalent in the diabetic AD subjects, and the proportion of diabetic AD subjects with infarcts on MRI was higher, although this latter effect was not statistically significant. WML severity was similar in both groups.

A strength of the present study is that all AD subjects that were included received a detailed diagnostic investigation. In the majority of the subjects, a full neuropsychological examination and an MRI scan of the brain were performed at our clinic and thus were available for this study. The limitations of our study relate to its retrospective design, which leads to some missing data. In addition, despite the fact that the total population of patients with AD that attended our clinic over the study period was large (n = 356), the actual number of identified patients with DM2 was limited (n = 29), thus limiting the statistical power of the study. For this reason, the post hoc analyses on the association between cortical atrophy and vascular comorbidity need to be interpreted with some caution. It may also be argued that a patient population attending a tertiary referral centre may be subject to selection bias. Nevertheless, it should be noted that a diagnosis of diabetes as such did not affect the likelihood of receiving a diagnosis of AD at our clinic.[12] Additional information could be gained in prospectively designed clinic and population based studies, including a detailed standardised diagnostic investigation. This would also allow the prospective evaluation of individual patients, which could answer the question whether the rate of cognitive decline differs between AD subjects with or without DM2.

The present MRI findings indicate that the increased risk of AD in DM2 patients may be attributed to dual pathology; increased cortical atrophy on the one hand and an increased occurrence of brain infarcts on the other. This latter observation is not surprising, as diabetes is a well known risk factor for ischaemic cerebrovascular disease,[13] and both symptomatic and asymptomatic ischaemic lesions are relatively more common among diabetic patients.[14] These ischaemic lesions are known to increase the risk of AD.[15] Pathological studies suggest that this association between vascular lesions and the risk of dementia is due to a lowered threshold of developing clinical signs of dementia in subjects with vascular lesions, rather than an interaction between vascular lesions and the actual AD neuropathology.[16 17] The increase in cortical atrophy suggests that diabetes may also have global, non-vascular effects on the brain. Such an effect of diabetes on cortical atrophy has also been reported in elderly individuals without dementia.[18] Moreover, a recent population based study, which included neuropathological data from a proportion of the participants, supports the hypothesis that mechanisms other than vascular disease are involved in the increased risk of AD in diabetic patients.[2] Diabetes, in interaction with an ApoE e4 genotype, was associated with an increased risk of neuritic plaques and neurofibrillary tangles in the cerebral cortex and hippocampus.

The mechanisms underlying increased cortical atrophy and AD pathology in diabetic patients have not been clarified yet, but previous clinical and preclinical studies do provide important clues.[3 4] Several processes that have been implicated in brain ageing, including oxidative stress, accumulation of so called advanced glycosylation end products, microvascular dysfunction, and alterations in cerebral glucose and insulin metabolism may be accelerated by DM.[3] Accelerated brain ageing in DM2, as reflected in increased cerebral atrophy, may thus increase the likelihood of developing clinical signs of AD. Nevertheless, diabetes may also interfere more directly with AD pathology. In subjects with AD, age related changes in cerebral glucose and insulin metabolism are accompanied by malfunctioning of cerebral insulin receptors, which has been provocatively classified as ''cerebral insulin resistance''.[19] Insulin also affects the metabolism of amyloid-β and tau, the building blocks of amyloid plaques and neurofibrillary tangles, the neuropathological hallmarks of AD.[4] These processes could certainly account for part of the association between AD and DM2. If cerebral insulin resistance is indeed a feature of AD, DM2 may accentuate this process, as peripheral insulin resistance is its metabolic hallmark. In addition, hyperinsulinaemia in DM2 subjects may interfere with tau and amyloid metabolism.

CONCLUSIONS

Our study indicates that the association between DM2 and AD should not only be viewed from a vascular perspective. Accelerated brain ageing or disturbances of insulin metabolism in the brain may be additional factors that link DM2 and AD. This hypothesis should be tested in prospective studies that include measures of amyloid and tau metabolism.

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