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Abstract

The cerebral neuropathology of Type 2 diabetes (CNDM2) has not been positively defined. This review includes a description of CNDM2 research from before the 'Pubmed Era'. Recent neuroimaging studies have focused on cerebrovascular and white matter pathology. These and prior studies about cerebrovascular histopathology in diabetes are reviewed. Evidence is also described for and against the link between CNDM2 and Alzheimer's disease pathogenesis. To study this matter directly, we evaluated data from University of Kentucky Alzheimer's Disease Center (UK ADC) patients recruited while non-demented and followed longitudinally. Of patients who had come to autopsy (*N*=234), 139 met inclusion criteria. These patients provided the basis for comparing the prevalence of pathological and clinical indices between well-characterized cases with (*N*=50) or without (*N*=89) the premortem diagnosis of diabetes. In diabetics, cerebrovascular pathology was more frequent and Alzheimer-type pathology was less frequent than in non-diabetics. Finally, a series of photomicrographs demonstrates histopathological features (including clinical–radiographical correlation) observed in brains of persons that died after a history of diabetes. These preliminary, correlative, and descriptive studies may help develop new hypotheses about CNDM2. We conclude that more work should be performed on human material in the context of CNDM2.

Keywords

Diabetes; Alzheimer's; Cerebrovascular; Stroke; Cognition; Clinicopathological; Radiographical; Pathology; Review

1. Introduction

More than 90% of diabetes mellitus cases in Western countries correspond to Type 2 diabetes ("non-insulin dependent", or DM2) [1]. Although technically a misnomer, the term "diabetes"

is used herein to encompass clinical signs and symptoms relating to DM2. The central focus of this review is the cerebral neuropathology of DM2 (CNDM2). We will review briefly the scientific literature from studies in epidemiology, neuropsychology, neuroimaging, and histopathology research that are relevant to human CNDM2. Correlative and descriptive data will be analyzed from the University of Kentucky Alzheimer's Disease Center (UK ADC) autopsy cohort. These studies include a case–control series depicting clinical and pathological indices stratified by the antemortem diagnosis of diabetes. Our study also includes a series of photomicrographs from diabetics' brains that help depict some of the vascular and white matter changes along with radiographical–neuropathological correlation. A central conclusion is that direct pathological studies of human tissues, despite all their technical challenges, are an important experimental component to the study of CNDM2.

2. Potential confounds

Prior studies have been unable to demonstrate pathognomonic changes that discriminate the brains of humans with diabetes from "non-diabetic" brains. This may reflect the formidable obstacles or potential confounds in studying diabetic brain disease. Below we describe five of the most important potential confounds relevant to research on DM2 and the human brain.

2.1. Cohort effect, case–control pitfalls, and other potential biases

In a historical sense, "diabetes" is a moving target. New treatments emerge each year. Environmental challenges, including dietary changes [2] and medications for other diseases, evolve also. These produce changes that impact entire generations and may affect different groups or cohorts distinctly. Thus, there is no guarantee that a human study performed in 2008 will be relevant directly to diabetics in 2028. Another problem is that in any "case–control" study, most individuals identified as diabetics will have been treated for diabetes, whereas some that were not identified as diabetics will be in fact untreated diabetics. This potential confound can be minimized by stringent inclusion/exclusion criteria and monitoring patients. However, in a study with rigorous clinical documentation and careful case selection, the diabetics may be even better controlled in their medical and diet regimens and their case–control outcome differences may change commensurately. Age effects are also difficult to determine without rigorous controls–the findings of the effects of hyperglycemia on brain tissue in a 30-year old are impossible to project onto those in an 80-year old.

2.2. Distinct group characteristics—comorbidities, environmental factors, and genetic factors

DM2 cases are nonrandomly distributed in populations. Rather, the disease is associated strongly with indices related to medical comorbidities, socioeconomic factors, and genetic factors. Many studies on diabetics have noted systematic abnormalities in blood pressure, atherosclerosis, and blood values for pH, urate, lipids, ketones, and clotting factors [3–7]. Diabetics also tend to have concomitant environmental risks such as obesity (presumably reflecting an altered diet) and smoking [1,2,8,9]. Other potential confounds in diabetes studies are the socioeconomic factors that may induce case-versus-control systematic biases in patients' trust of, and willingness to participate in, clinical trials [10–12] much less autopsy-based research. Finally, there are hypothesized genetic risk factors that may relate both to the metabolic syndrome and to neurodegeneration, such as the apolipoprotein E allele [13–17]. In summary, it is a challenge to detect whether a brain change is specific to CNDM2 – hyperglycemia and/or insulin resistance per se – rather than a combination of other medical, environmental, and genetic factors, that disproportionately accompany CNDM2. This consideration amounts to multiple potential confounds that are extremely challenging to eliminate completely, irrespective of study design.

2.3. Hypoglycemia and other treatment effects

Insulin or other agents can induce hypoglycemia iatrogenically. Hypoglycemia induces seizures, coma, and widespread cerebral cortical neuronal loss when glucose levels fall below ~1–1. 5 mM (18–27 mg/dl) [18–24]. The neuropathology that is associated with this devastating condition is not identical to that of widespread ischemia or hypoxia [23,24]. The mechanism of this special type of neuropathology is apparently excitotoxicity via the neurotransmitter aspartate [23,24]. More relevant to many diabetics are the effects of episodic, short stretches of hypoglycemia, aggravated perhaps by chronic recurrence with cycles of hyperglycemia and/or respiratory depression [25]. Depending on many factors, the net effects may be subtle and idiosyncratic. In human studies, teasing out the specific importance of hypoglycemia, versus hyperglycemia, is not a trivial challenge. Further, hypoglycemic agents have effects on the brain other than those that are involved in glucose regulation [26,27]. Medicinal preparations intended to lower blood glucose differentially affect albumin binding, inflammation, blood-brain transport, and other brain and liver indices [26–29]. Additional treatment effects may also be important. Most diabetics take many drugs concomitantly, many of which relate to metabolism, electrolytes, lipids, platelets, hormones, immunomodulation, and/or blood pressure. For example, in the data presented below, the diabetic patients (*N*=50, average age at death, 84 years) had an average intake of over 12 different medications daily. The biological effects of these drugs, in isolation or together, may alter observed brain pathology.

2.4. Glucose—one sugar, many pathways, and complicated curves

Most organisms use glucose as a transportable energy source. Glucose is also a moiety that can be attached – enzymatically or non-enzymatically – to proteins, nucleic acids, and lipids [30–32]. Highly amenable to molecular modifications itself, glucose is a potential "player" in many biochemical pathways [30]. Exactly how these pathways are stimulated and inhibited *in vivo* is currently poorly understood; there is still debate about the basic fundamentals of cellular glucose metabolism in the brain [33–37]. The brain glucose and insulin pathways involve complicated, interacting ripples of effects and counter-effects. The impact on blood vessels by hyperglycemia is thought to be partly mediated through the polyol sorbitol pathway, myoinositol depletion, diacylglycerol pathway, platelet regulation, and many others [18,20, 38–49]. Furthermore, cardiovascular factors can have complicated and non-linear dynamics. For example, in compelling mammalian models of cerebral infarction, hyperglycemia can be either neuroprotective, or by contrast neurotoxic, depending on the model parameters [50–54]. An additional example of complex non-linear cerebrovascular dynamics in humans is the well-documented but unexplained epidemiological "J-shaped curve" effect of alcohol intake upon stroke risk [55–61]. Given these considerations, data can be difficult to extrapolate from an experimental model to the human brain. For example, how can we know if the effects of hyperglycemia at blood levels of 100 mg/dl, 200 mg/dl, and 300 mg/dl on a given brain cell parameter are linear, exponential, or opposite from each other?

2.5. Pitfalls of animal models and comparative disease-related neurobiology

Historically, diabetes research provides outstanding examples of how animal models can be used to inform and improve treatment of human diseases [62,63]. In the context of CNDM2, a number of hypotheses have been developed and tested based largely on animal models [64–70]. On the other hand, there are also drawbacks in using animals to model human cognition and human-specific pathology. Because there is not a known, specific cerebral pathological substrate for diabetes in humans, it is instructive to review the experience in animal models of diabetic kidney disease. A pathognomonic diabetic nephropathy lesion is known, so a mouse model should theoretically help to understand the disease mechanisms and work toward a cure. Unfortunately, although kidney failure is commonplace in humans [71–73], this change has

been extremely difficult to reproduce in mouse diabetes models [74,75]. There is considerable mouse strain-specific variation in diabetes-related nephropathy [74,75]. Commonly used strains such as C57BL/6 are almost entirely resistant to diabetic changes in the kidney, and in fact less than 5% of mouse strains have reported such pathology [74,75].

What about rodent models of human brain disease in diabetes? The human brain is unique, and there are crucial differences between rodent and human aging trajectories. As such it is not surprising that rodent models of CNDM2 have shortcomings [68,76]. Transgenic or treated rodents have been unable to model the best-established substrate for cognitive loss in diabetic humans, namely atherogenic cerebrovascular changes [64,68,76]. Models of other diabetes-related changes on cognition also have varied results. These studies are compounded by the challenges to test subtypes of cognitive domains in rodents. Some diabetes-related studies have produced no cognitive changes in the presence of hyperglycemia, and others show abnormalities in rodent cognitive/behavioral indices even without hyperglycemia [64]. Furthermore, the perturbations that accompany diabetes studies in animals bear consideration. For example, intracerebral or intraperitoneal injection of streptozotocin (SZT) leads to pathological changes analogous to Alzheimer's disease (AD), namely increased phosphorylated tau [69,77–81]. It should be borne in mind that SZT has direct CNS toxicity beyond the known effects of diabetes per se [82–84], and some of the effect of SZT on tau proteins is mediated through hypothermia [69]. The animal studies are biologically interesting and may prove their relevance to humans. However, reciprocal validation is important because animal research and human studies have both complementary strengths as well as complementary weaknesses.

3. Effects of diabetes on cognition

Due partly to the challenges described above, there has been some variability in the results of studies about changes in cognition linked to diabetes. The neurological dysfunction associated with this disease has been designated "diabetic encephalopathy" [45,85,86], yet this term has not been rigorously defined by a consensus of experts. Specific cognitive disturbances associated with diabetes have been described (for reviews see [5,17,46,87–90]). Deficits have been repeatedly observed in particular cognitive domains, including memory and psychomotor speed [46,91]. There is some overlap between the findings of cognitive changes in DM1 and DM2 [43,46,92–94] and an increased risk for dementia or mild cognitive impairment in DM2 and some of this literature is described below.

Research about cognitive changes in diabetics demonstrates the importance of study design. Many experiments assessing the effects of diabetes on cognition and/or pathology (including the research described below) have employed a case–control research design. This study format has important advantages in that cases and controls can be carefully monitored, compared, and described; however, these studies are prone to selection and recruitment biases. A study design involving fewer such biases is a population-based study. These studies typically have more patients and are more representative of a large and heterogeneous cohort. Almost one-half of the published population studies have been interpreted to show no effect of diabetes on cognition [17]. However, these results also may have methodological problems including difficulty with accurate identification of cases and controls.

Future studies may overcome the many confounds and discriminate in fine details which specific aspects of DM2 correspond to which subdomains of cognitive dysfunction. In the meantime, the literature on the cognitive deficits related to diabetic encephalopathy produces a general consensus that multiple cognitive domains are affected adversely in diabetics. There is general, but by no means universal, agreement about "direction of effect"–hyperglycemia is associated with mild cognitive dysfunction in many studies. However, there is uncertainty

about the precise relationships to biological mechanisms. Thus, specific aspects of prior studies should be interpreted with critical scrutiny.

4. Recent neuroimaging studies related to diabetes-linked anatomic and cognitive changes

To the extent that diabetes can be documented to affect cognition, neuroimaging can correlate structural brain parameters with cognitive changes. Unlike neuropathological studies, brain scans can be used to monitor quantitatively the three dimensional effects of a disease over time in an individual. Further, MRIs can assess neuroanatomical areas suspected of involvement in the diabetic brain, namely the cerebrovascular and white matter disease, which are problematic to study routinely in the context of tissue-based neuropathology. For these reasons, neuroimaging studies are practically tailor-made to surmount many of the obstacles in assessing the cerebral neuropathology of diabetes.

Van Harten et al. (2006) provided an outstanding meta-analysis summarizing critically the literature on neuroimaging of diabetes [95]. This study included formal analysis of 46 studies (including population-based, case–control, and clinical studies with various vascular risk factors) using MRI and/or CT. All of these included at least 20 diabetics with specified criteria for diabetes. According to this meta-analysis, the following three structural changes are described consistently in the brains of diabetic patients:

1. White matter lesions (WMLs; 27 studies analyzed) – Some but not all studies show a positive correlation between the presence of WMLs and DM2. When studying cohorts with many vascular risk factors in addition to diabetes, there were weak or no correlations between diabetes and WMLs. In outpatient case–control studies, there was a weak association between WMLs and DM2. A typical depiction of WMLs in the brain of a diabetic is shown (Fig. 1).

2. Lacunar infarcts (LIs; 20 studies analyzed) – A significant association was found between the presence of lacunar infarcts and DM2 across different study designs.

3. Cortical atrophy (CA; 10 studies analyzed) – Studies assessing cortical atrophy were too heterogeneous methodologically to summarize; however, nine of the ten publications in the meta-analysis showed a positive correlation.

Studies performed since the meta-analysis of Van Harten (2006) have further explored the correlation of radiographical changes with the severity of cognitive dysfunction in diabetics [90,93,96–100]. The results of some of these studies are shown in Table 1. Note that the importance and specificity of WMLs appears to be more accentuated in these later studies. Thus, neuroimaging studies help to focus the question with some hope of success, by showing that there are specific anatomical substrates for the cognitive decline seen in diabetics: WMLs, LIs, and CA. Of these three, the two least well understood are WMLs and CA. In the future, technology that probes both functional and structural parameters (fMRI) should provide further insights into diabetes-related brain changes.

5. Human cerebral neuropathology of diabetes

Histopathological studies may complement epidemiological, neuropsychological, and neuroradiographical research regarding the effects of diabetes in the human brain. The discovery of a specific anatomical substrate for CNDM2 would provide needed traction for other experimental systems and for developing therapies. Human CNDM2 data will be described in subsections: first, an overview of human studies on lesions described in diabetics' brains, including a review of the literature concerning specifically whether or not diabetes is linked to AD pathology; second, studies from the UK ADC autopsy cohort include a case–

control study on material from the UK ADC Brain Bank to describe our experiences regarding neuropathological findings in the brains of diabetics, with a series of photomicrographs to demonstrate findings in diabetics' brains including radiographical–pathological correlations; and finally, a summary and conclusions.

6. Peripheral and autonomic nervous system pathology of diabetes

Details about the manifestations of diabetes in the peripheral and autonomic nervous systems are outside the scope of this review. Briefly, peripheral and autonomic neuropathic changes are prevalent, occurring in ~15–25% of diabetic patients [101–107]. Hyperglycemia itself is the main risk factor [103,104]. The often painful "glove and stocking" (long-fiber) sensorimotor polyneuropathy is the most common neuropathic syndrome in Western countries [105,106]. Autonomic neuropathy is selective but affects many systems, and cranial neuropathy (worst in the oculomotor nerve) is also quite prevalent [108,109]. The histopathology for these changes is relatively nonspecific. Nerves show demyelination and remyelination, a dropout of small and large axons, impaired axonal regeneration, Schwann cell dropout, and/or neuritic dystrophy, often with nearby microangiopathy [104,109–117]. The pathological changes may be caused or exacerbated by the polyol sorbital pathways, glycation reactions, oxidative/inflammatory mechanisms, and other pathways [109,110,118–120]. The prevalent but unspecific peripheral nervous system diabetes-related pathology may be relevant biologically to changes in the brain. However, those who have carefully evaluated both in parallel have found the brain pathology far more difficult to discern [85] and/or often disproportionate in degree with the PNS pathology in individual patients [97].

Ultimately, the conclusions from the *Pathology of Diabetes*, 4th Edition (1966) still holds true: "there is still no agreement on the pathogenesis or basic mechanism of diabetic peripheral neuropathy" (p.273) [121].

7. Histopathology of diabetes in the brain: literature review

7.1. Historical note

Much of the work on diabetes pathology dates from before the advent of the 'Pubmed Era'. Naturally, these "classical" studies could only localize diabetes-related brain changes using techniques that are somewhat crude by modern standards. However, it is significant that highly observant researchers, superbly trained in anatomic pathology, and in an era with widespread un-controlled diabetes, could find meager evidence of specific changes in the brains of diabetics.

In the *Pathology of Diabetes*, 4th Edition (1966) [121], the authors designate a chapter to the CNS pathology of diabetes. Here are some relevant excerpts:

"From the brains which we have examined, and from the reports in the literature, there are no changes distinctive of diabetes other than the abnormal glycogen deposits reported in certain cases of diabetic coma…" [121] (p. 279) "…findings of Vonderahe [122] and of Morgan et al. [123] of a reduced number of ganglion cells in the paraventricular regions have not been confirmed…Hagen [124] has described granular inclusions in nerve cells of the hypothalamic region…" [121] (p.280)

Throughout the human body, according to these authors, diabetes affects all blood vessels from the largest to the smallest. However, special focus was merited for arterioles and capillaries:

"Ever since the distinguished studies of Bell [125–127] it has been recognized that arteriolosclerosis is likely to be more severe and extensive in the diabetic, even in the absence of hypertension." [121] (p.313) "The capillaries have frequently been

regarded as the site of 'diabetic microangiopathy', largely because of the importance attributed to the nodular glomerular lesion of Kimmelsteil and Wilson as the one specific lesion of diabetes and the popularity of the common, though nonspecific micro-aneurysms of the retinal capillaries." [121] (p.317)

In the specific context of brain disease, "minor changes are difficult to evaluate since a number follow vascular damage and vascular change is very frequent in the diabetic…" [121] (p.280). Forty-two years after this final edition of *The Pathology of Diabetes*, pathologists still only appreciate two relatively specific diabetes-related lesions outside the pancreas–Kimmelstiel–Wilson nodules in the kidney and diabetic retinopathy (Fig. 2).

7.2. Recent work on cerebral neuropathology of DM2

With regard to more recent 'conventional' cerebral histopathological studies, the scientific literature on diabetes/hyperglycemia in human brains has been nearly mute for several decades. A survey of four popular, comprehensive clinical atlases on neuropathology [85,128–130] provides little information about diabetes-related pathology. Only the *Textbook in Neuropathology*, 3rd Ed (Davis and Robertson Eds, 1997) [85] has a section dedicated to describing the histopathology of diabetic encephalopathy. This section begins: "Most clinicians regard the cerebral manifestations in diabetes to be due to cerebrovascular disease." [85] (p. 590).

The same neuropathology atlas [85] goes on to enumerate several other histopathological findings associated with diabetic encephalopathy: thickening of cerebral cortical capillary basement membrane; possible abnormality in blood-brain barrier; diffuse degeneration of "ganglion cells" and nerve fibers throughout the brain (attributed to Reske-Nielsen and Lundbaek [86]) or diffuse degeneration of cortical neurons similar to those seen in anoxia and ischemia (attributed to Olsson et al. [131]), with poor correlation to hypertension or uremia. Since these are the only authors with a relatively recent summary of the human neuropathology of diabetic encephalopathy, it is worth quoting their conclusions–.

"Although it is conceivable that the primary ganglion cell abnormalities in diabetic encephalopathy may be related to microangiopathy and increased vascular permeability, many aspects in its pathogenesis are still unknown." [85] (p.591)

In addition to neuropathology atlases, there have been individual studies about the pathology in diabetics' brains. Some autopsy series have included evaluations of cerebral pathology in relation to diabetes [86,132–138]; however, there have been few such studies published during the past several decades. Hypothesis-based studies have sought to confirm in human tissues features seen in animal or other models [139–141]. Various findings have been reported, none definitive, except that there is a positive association between diabetes and various strokes [88,132,142–144]. Of the issues pertinent to brain pathology in diabetes that have received most attention, two are conspicuous: the role of cerebrovascular diseases in diabetics, and the pathogenetic connection to AD.

Relatively few recent studies have described in detail the cerebrovascular histopathology linked to diabetes. The scarcity of recent studies stands in contrast to the impressive epidemiological and neuroimaging evidence indicating that diabetic brain dysfunction is mediated at least partly via cerebrovascular disease [88,90,98,132,142–145] (and see below). The lack of human histopathological studies is also remarkable since there are few animal models of diabetes-linked atheromatous brain infarcts [76]. Furthermore, there is cause to re-examine the older autopsy series, because in one study more than a third of patients with cerebral infarcts had an elevated glycosylated hemoglobin although they were not known previously to be diabetics [146,147]. There have been few large human autopsy series performed since that of Aronson (1973) [136]. This study included 4802 non-diabetics and 677 diabetics from consecutive,

complete autopsies performed at Kings County Hospital in Providence, RI. In this study, the frequency of encephalomalacia –softening of the brain, often with rarefaction of white matter – was far more frequent in the diabetics. The author concluded that this pathology reflected small-vessel disease that was "presumably not lethal and frequently subclinical, which is distinctly greater" in diabetics [136]. The correlation of diabetes with small-vessel disease is important and has been repeatedly described [90,96,99,148,149]. This type of pathology is associated with clinical manifestations in sharp contrast to the "stroke" syndromes that are characterized by acute, catastrophic neurological deficits that often culminate in severe disability or death. Instead, the neurological deficits referent to small-vessel disease can be subtle but progressive over time [150,151]. The exact mechanisms that underlie small-vessel disease are not well understood.

Although diabetes is most specifically linked to small-vessel disease, it should be underscored that a connection is also firmly established between diabetes and other subtypes of cerebrovascular disease [6,132,145,152–157]. This pertains to large vessel atherosclerosis, lacunar infarcts, thromboembolic stroke, hemorrhagic stroke, and aneurismal subarachnoid infarcts [15,158–167], all of which can produce a spectrum of clinical syndromes. The relative risk for clinically detectable stroke overall in diabetics is in the range of 1.7 to 5.5 (see review in ref. [146]). This is a devastating disease with an incidence of ~760,000/year in the U.S. [168–170], and it is estimated that 11 million more Americans have clinically "silent" strokes per year [169]. Any additional hypotheses about the effects of DM2 on cognition must include the much higher cerebrovascular risk in diabetics as a scientific fact. If additional types of pathological or clinical manifestations are to be suggested, then diabetes-related cerebrovascular disease is also a strong potential experimental confound.

In contrast to the literature concerning cerebrovascular pathology related to diabetes, the association of DM2 with AD pathology is more controversial but has attracted intense scientific attention [171]. This topic is challenging to address from a neutral perspective because the results of the studies are mixed and sometimes seem mutually contradictory. We describe below some of the data and hypotheses –both "pro" and "con"– pertaining to the possibility that AD is pathogenetically linked to DM2.

7.2.1. Data/hypotheses that suggest that AD is linked specifically to DM2

1. Numerous epidemiological and clinical–pathological studies have reported an increased risk in DM2 patients for developing AD, possibly in connection with ApoE allele 4 [16,154,172–180].

2. Neuroimaging studies show shrinkage of mesial temporal structures (hippocampus and amygdala) in DM2 patients linked to loss of cognition; these are also areas affected by AD [91,181–183].

3. The diabetic pancreas contains amyloid substance, similar histologically to that found in AD brain [184,185].

4. There are inter-related pathways linked to the metabolic syndrome and to dyslipidemia (including cholesterol transport and ApoE alleles) that may credibly affect both DM2 and AD [15,183,186–189].

5. PET neuroimaging studies have shown brain glucose regulatory deficits even in young adults at risk for developing AD decades later (finding not linked to DM2 per se) [190–193].

6. AD is linked to hyperglycemia by the hypothesized importance of insulin/IGF-1 regulated pathways, RAGE, PPAR-gamma, and other advanced glycation end-products in AD brain [48,49,66,79,[139],140,182,194–197].

7. DM2 may potentiate in the brain AD-stimulating pathways that are pertinent to dysfunction in blood-brain barrier, reactive oxygen species, proteases, and leptin or other metabolism-regulatory molecules [48,65,67,69,70,198–201].

8. Survival bias is an important potential confound that may lead to artificially decreased diagnoses of DM2 and AD [202,203]. Persons with DM2 are at increased risk to die of cardiovascular causes and this risk renders them less likely to die of AD, all other things being equal. This effect may bias studies away from recognizing a positive link between DM2 and AD (this does not explain why DM2 patients are found consistently to have higher risk for stroke, however).

9. A number of rodent models including therapy-relevant strategies show linkage between DM2-related effects on the rodent brain and AD-relevant pathways [65,66, 69,199,204,205].

7.2.2. Data/hypotheses that suggest that AD is not linked specifically to DM2

1. Numerous epidemiological and clinical–pathological studies have reported that risk for decreased cognition in DM2 patients is not mediated through AD, but through cerebrovascular disease instead [13,14,47,153,206–216].

2. Confounds related to the metabolic syndrome (hypertension, dyslipidemia, smoking, obesity, genetic factors, and inflammatory mechanisms) also favor brain infarctions, so DM2 may be a strong surrogate for stroke risk and/or low socioeconomic status [8,9,142,143,152,217–220].

3. Most published neuroimaging findings in DM2 are apparently referent to cerebrovascular disease [90,95–99,144,221,222].

4. Whatever the mechanism of DM2-related cognitive decline, the presence of that additive dysfunction in someone developing AD would "lower the threshold" to detection, independent of a specific contribution by DM2. This phenomenon was previously demonstrated in AD pathology [223]. This may help explain epidemiological data linking DM2 to AD.

5. If hyperglycemia and/or poor glycemic control induces AD, then longer-lived juvenile-onset diabetes might be expected to lead to AD, and there is no evidence for this. Several studies have reported that juvenile-onset diabetes patients do not show hippocampal atrophy [224,225].

6. Whereas advanced glycation products are increased in AD brains, there is not compelling evidence for these markers being elevated in the brains of human DM2 patients [196].

7. To date, no therapies have been described in humans connected to the hypothesis of DM2–AD link that have worked independently of stroke risk.

8. In a microenvironment with abundant neuronal death and secondary changes such as the AD brain, there are intuitively good reasons for there to be associations, irrespective of DM2, with deficits in blood-brain barrier, reactive oxygen species, advanced glycation end-products and other inflammatory molecules, and other biochemical perturbations.

9. Findings in cell culture and rodent models must be scrutinized critically before relevance to the aged human brain – much less to AD pathology – is accepted.

8. The UK ADC experience: a retrospective case–control study from an autopsy convenience sample stratified by identified diagnosis of diabetes, and photomicrographs showing histopathology from select diabetic and non-diabetic cases with clinical–radiographical correlation

8.1. Rationale

8.1.1. Database analyses—Analysis of data about volunteers in a UK ADC research cohort may provide evidence relevant to the controversy about the hypothetical associations between DM2 and cerebrovascular or AD pathology. Our autopsy series includes a group of longitudinally followed individuals who were recruited while non-demented and followed for years. The UK ADC database can be queried to indicate the clinical and pathological indices are associated with DM2 before the advent of severe, debilitating dementia. We hypothesized that pathology in patients with DM2 would reflect their differential vulnerabilities to cerebrovascular disease and/or to AD-type pathology.

8.1.2. Photomicrographs from selected diabetics' brains—Few recent studies have described histopathological features in aged diabetics' brains. Some pathological–radiographical studies exist on small-vessel brain disease [226–235], but are not related to diabetes per se. We performed this preliminary experiment in the context of the UK ADC older adult research cohort. These studies include participants who underwent premortem MRI scans to enable radiographical–pathological correlation. This strategy may provide the basis for developing novel hypotheses about mechanism(s) of diabetic encephalopathy.

8.2. Methods: patients, assessments, neuropathology, and analyses

Research protocols were approved by the UK IRB. Details of inclusion criteria and recruitment have been described previously [223]. Patients who had come to autopsy from the UK normal volunteer cohorts were the basis for the study (total *N*=234 patients), with some patients excluded for a variety of factors including tumors, large contusions, missing clinical data, etc., as described previously (*N*=95 excluded) [223]. These patients were relatively intact cognitively, having been recruited as non-demented persons and followed for years. Their pathology (if any) was presumed to represent the earlier phases of cognitive decline. Only patients who had come to autopsy with either "Yes" (*N*=50) or "No" (*N*=89) in the UK ADC database for a diagnosis of diabetes were used (total *N*=139). These diagnoses were derived from medical examinations during life, which included blood evaluations, as well as from extensive evaluations of medical charts as part of the UK ADC database management. Demographic characteristics and particular clinical indices from these groups are shown in Table 2. All initially normal individuals were contacted at 6-month intervals, had detailed mental status testing, and had neurological and physical examinations at least annually. Mental status testing and neuropathological assessments were described in detail previously [223]. Simple means were obtained from each group for the clinical and pathological indices shown (Table 3). Significance was tested via Student's *t* test (unpaired, two-tailed).

A sample of convenience was selected for photomicroscopy:

- Diabetes Case 1 (male) died at the age of 88 with history of DM2. Last MMSE score was 26 out of a possible 30 (mild cognitive decline).

- Diabetes Case 2 (male) died at the age of 87 with history of DM2. Last MMSE score was 21 out of a possible 30 (moderate-to-severe cognitive decline). MRI was obtained within 4 months of patient's death.

- Diabetes Case 3 (female) died at the age of 81 with history of DM2. Last MMSE score was 29. MRI was obtained within a year before patient's death.

- Diabetes Case 4 (female) died at age 82 with history of DM2 and diagnosed clinically with AD. Last MMSE score was 19 (severe cognitive decline). MRI was obtained 5 years before patient's death.

- Diabetes Case 5 (male) died at age 75 with history of DM2. Last MMSE score was 28 (non-demented). MRI was obtained four years before patient's death.

- Diabetic Case 6 (female) died at age 72 years with history of poorly controlled DM2, last MMSE score 29 (non-demented).

- Control Case 1 (male) died at age 78 years with no history of diabetes, last MMSE score of 28 (non-demented).

- Control Case 2 (male) died at age 99 years no history of diabetes but with a history of hypertension, last MMSE score of 26 (mild cognitive impairment).

8.3. Results

This retrospective case–control study from an autopsy convenience sample includes patients that are relatively well matched with regard to levels of formal education and ApoE alleles (Table 2). However, the diabetics died at a slightly younger age (84 years versus 88 years, $p<0.02$ by two-tailed Student's t test), and tended to have a slightly higher final MMSE scores (26 versus 24, $p<0.1$ by two-tailed Student's t test). In terms of pathological parameters, the diabetics tended to have more small infarcts but a slightly less degree of AD-type lesions (Table 3). AD lesions (NFTs and neuritic plaques) are directly quantified by counting or defined according to Consortium to Establish a Registry for AD staging and Braak staging, which are based on consensus criteria for staging AD pathological severity [236,237] (Table 3).

Photomicrographs portray a spectrum of changes in these older persons with differing cognitive changes. The photomicrographs show hematoxylin and eosin (H and E)-stained sections with a special focus on changes in blood vessels and white matter. Histology of cerebral blood vessels and the surrounding Virchow–Robin spaces are shown in Fig. 3 (from Control Case 1 and Diabetes Case 1). Fig. 4 depicts a patient (Diabetes Case 2) with an MRI obtained just prior to a significant decline in cognition as reflected in a drop in MMSE scores (down to 21 near death). In this patient, there were moderate changes referent to Alzheimer's pathology (Braak stage 3), but the predominant pathological changes were related to the cerebral vasculature. In Diabetes Case 3 (Fig. 5), there were also cerebrovascular disease changes including frank infarctions in the frontal cortices bilaterally. There were small infarcts in the temporal lobe including the hippocampal formation, where there was also minimal Alzheimer's-type pathology. By contrast, in Diabetes Case 4 (Fig. 6), there was both dementia clinically as well as advanced AD pathologically. Still, even in this case, notable small-vessel cerebrovascular disease was present. Diabetes Case 5 (Fig. 7) had no dementia, no Alzheimer-type pathology, but had subtle white matter pathology including some periventricular enhancement near the basal ganglia. The photomicrograph shows the corresponding region that contained expanded Virchow–Robin spaces and many corpora amylacea. In Diabetes Case 6 (Fig. 8), a patient with poorly controlled DM2 and mild cognitive decline, there were many corpora amylacea within the cornu ammonis of the hippocampal formation, as well as near the inferior horn of the lateral ventricle.

8.4. Discussion

This study focused on persons who were recruited without cognitive impairment and followed longitudinally in a research clinic. This is an important strength of the study because long-term

medical and neuropsychological studies could be performed on each patient. It also allowed us to minimize various recruitment biases related to already-demented subjects. However, there are several caveats that are germane to these data. Most importantly, the degree of glycemic control was not thoroughly documented by an endocrinologist in all patients. This is only a study of the association of a clinical diagnosis of diabetes, rather than an association that is related to glycemic control per se. The importance of the age difference (average age at death 84 for diabetics, 88 for non-diabetics, *p*<0.02) may constitute an important confound to this analysis. However, note that the cerebrovascular pathology, despite the age difference, was more severe in the diabetics. There are other trends, including a trend to increased hypertension, in the diabetics that may be contributory to the different prevalence of cerebrovascular disease. In summary, results from our database are in agreement with prior studies indicating that DM2 is associated with increased risk for cerebrovascular disease, and yet there is no positive association between the diagnosis of DM2 and the development of AD pathology [13,14,47, 153,206–216].

We also performed a study of a subset of patients including pathological–radiographical correlation. This preliminary, descriptive study underscores our impression from the research literature: cerebrovascular pathology, including extensive small-vessel disease, is an important component of CNDM2. This type of pathology can exist in relative isolation, or together with other diseases such as AD. It is hoped that the pathological–radiographical correlation will help some clinicians to "visualize" at a cellular and sub-cellular level the radiographical changes that have been recorded in the brains of DM2 patients.

In this limited sample, there were relatively many corpora amylacea in the brains of the diabetic patients. By contrast, in the non-diabetics (Control Case 1 and Case 2) there were few or no corpora amylacea in this location. The presence of corporal amylacea in the brains of older patients is generally considered a nonspecific sign of tissue damage or cell loss. However, since these lesions are indeed aberrant, ubiquitinated intracellular deposits of glycated material [238,239], it is possible that their presence in the brains of diabetics may have specific and pathogenetic implications.

These results are neither intended, nor statistically powered, to make comparative assessments. They offer a preliminary, and purely descriptive, portrayal of some of the histopathological features in a limited subset of patients with DM2. However, we hope that these photomicrographs may help demonstrate the potential value of evaluating the histopathological features in human brains with well-documented antemortem characteristics.

9. Summary and conclusions

In the absence of a known pathognomonic anatomic substrate for cognitive dysfunction in diabetics, the question arises–perhaps there are no definitive histopathological changes in diabetic brains? Many metabolic disorders induce mental changes, or *delirium*, out of proportion to known neuropathological changes [240,241]. Such may be induced by fluxes in blood levels of insulin, glucose, and other metabolic parameters in DM2. Other diseases such as hypoxia can produce brain atrophy and cell death in the absence of a pathognomonic change [85,128]. Hence, delirium or a disease with entirely nonspecific pathology may partly contribute to diabetic encephalopathy.

With the above caveat about the specificity of CNDM2, several associations between DM2 and brain pathology appear to exist (Fig. 9). Neuropsychological studies have indicated that there is enduring cognitive deficits in DM2 patients. There is compelling evidence from neuroimaging studies in humans that there are changes in brain parenchyma that are present disproportionately in the brains of diabetics. The specificity of these changes cannot be reliably

ruled out because relatively few studies have tackled the histopathology of diabetes in the brain over the past few decades. This is unfortunate because the changing times have produced new tools available to neuropathologists. There is also increased prevalence of DM2 in Western populations [1] and it would be helpful to evaluate brains in the context of current trends in comorbidities and treatments.

As with many other past studies, we are unable to supply new and definitive answers about CNDM2 based on our illustrative cases and analyses. It is somewhat surprising that there have been so few studies specifically addressing the neuropathology of small-vessel disease in DM2. Moreover, a few questions may be worthy of being addressed. These questions derive from a synthesis of the known scientific literature and the preliminary and descriptive studies that are presented above.

- Are corpora amylacea really benign and/or nonspecific in DM2 brains? Perhaps these structures, comprising glycated material [130,239], may cause or reflect a more specific disease process than previously thought. Corpora amylacea have previously been noted in the context of brain pathology [238,242–244], but not correlated to the diagnosis of diabetes per se.

- Are there specific markers for microangiopathy in DM2?

- Is there a specific process involving Virchow–Robin spaces in DM2?

- Why do the results of studies about the relationship between AD and DM2 vary so much?

Future studies are needed to address these and the other many outstanding questions regarding CNDM2. This field is increasingly topical as the number of DM2 patients increase, and as the average age and longevities of Western populations increase. Many experimental systems should be brought to bear in studying this widespread disease, including the direct evaluation of human brain tissue.

Acknowledgments

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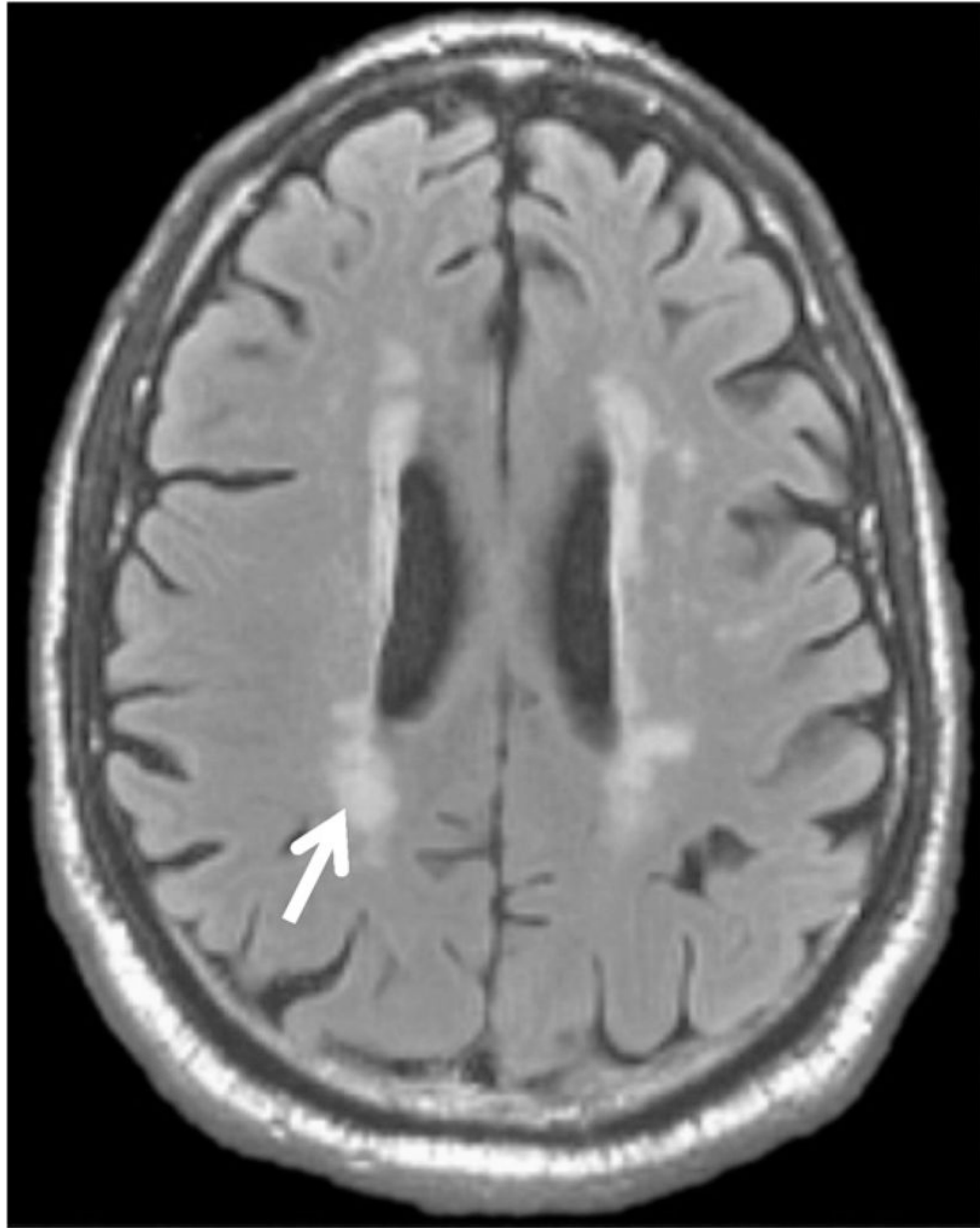
Fig. 1.
There are no neuroimaging findings entirely specific to diabetes per se, i.e. effects of hyperglycemia. Shown is an axial FLAIR image from a 67-year old diabetic man. It shows typical periventricular hyperintensities ("WMLs") seen with diabetes (arrow). These lesions are compounded by other factors: age, hypertension, hypercholesterolemia, and homocysteinemia. In a meta-analysis of MRI findings linked to diabetes, population studies found an odds ratio of ~2 for MRI-detected WMLs in diabetes.
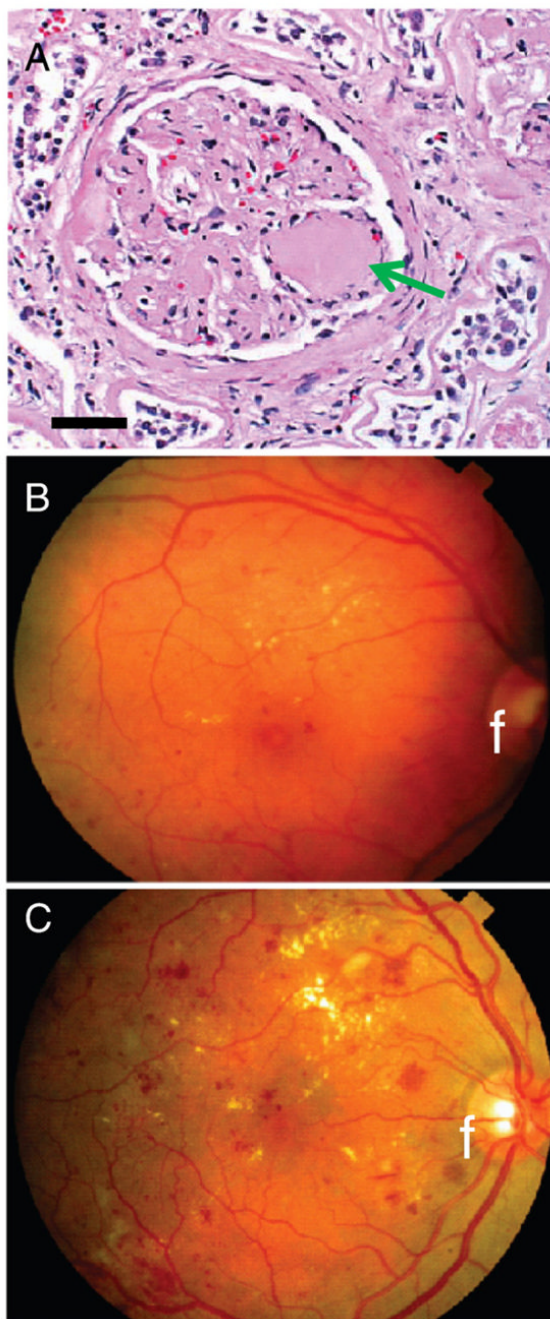
Fig. 2.
Universally recognized diabetes-related histopathology outside the brain is referent to vascular complications in the kidney and eye. Because of prior studies, these lesions are "pathognomonic" in the sense of indicating diabetes in a patient independent of whether or not the clinical history is well-documented. Diabetic nephropathy involves glomerular vascular lesions termed Kimmelstiel–Wilson nodules (arrow in A). Thin-walled blood vessels in the roughly-spherical glomerulus comprise the anatomical substrate for plasma filtration. With diabetes over a decade in duration, a nodular glomerulosclerosis may develop heralded by albuminuria that can lead to kidney failure. Diabetic retinopathy (B and C) is evaluated using fundus microscopy (fundus indicated by an "f"). The pathology can be parsed into two

subtypes: non-proliferative (B) and proliferative (C) retinopathy. Non-proliferative changes (B) are less severe with small capillary micro-aneurysms, dot-type hemorrhages, and microinfarcts ("cotton-wool" spots). This change is associated with gradual but generalized visual dysfunction. Proliferative changes (C) involve neovascularization, fibrosis, and hemorrhages, which can be extensive. Sudden vision loss can occur with vitreous hemorrhage and/or retinal detachment.
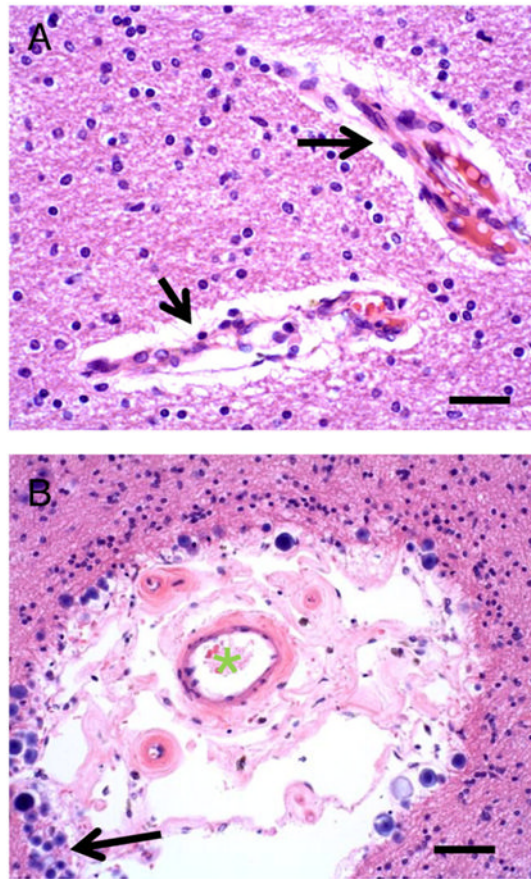
Fig. 3.
Control Case 1 (A) shows normal appearance of small arteries in white matter (arrows). Surrounding the blood vessels, partly as an artifact of fixation, is a space without cells or parenchyma (Virchow–Robin space). Scale bar=150 μm. (B) in some cases, such as this person (Diabetes Case 1, an 88-year old male with mild cognitive impairment), the Virchow–Robin space is enlarged. The lumen of the blood vessel is shown with a green "*". Note that in the Virchow–Robin space are extra blood vessels, and the tissue surrounding has many corpora amylacea (arrow). Scale bar=100 μm.
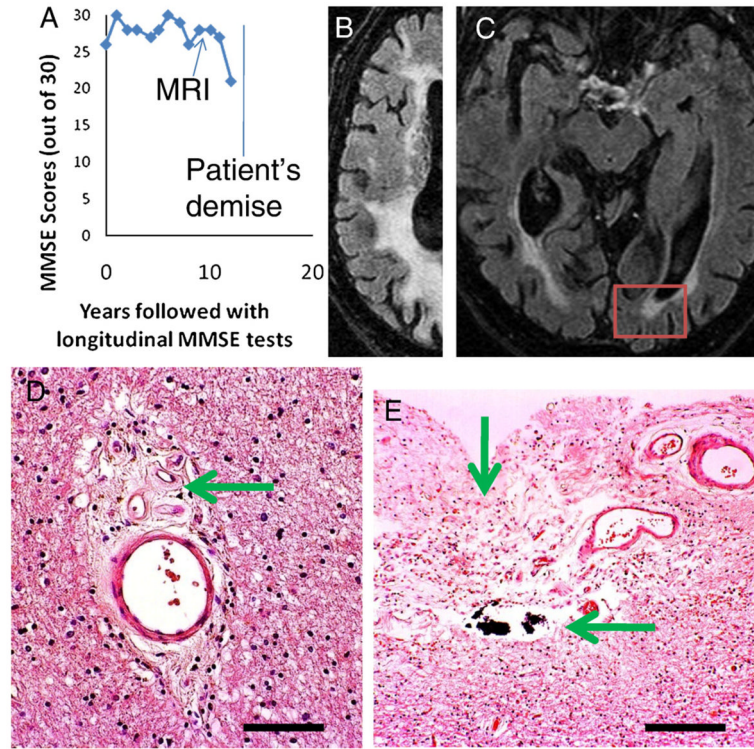
Fig. 4.
Diabetes Case 2–87-year old male with dementia and predominantly cerebrovascular disease by pathology. A shows a chart that depicts the MMSE scores by this patient. Note that the MRI was obtained prior to a significant decrease in the patient's MMSE score (final score =21). B and C show MRI scans that show hydrocephalus ex vacuo and extensive pathological white matter enhancement. The red box in C shows the area depicted in photomicrographs D and E. D shows a small blood vessel in the white matter of visual cortex away from the ventricle. This vascular profile shows expansion of the Virchow–Robin space with organizing cellular material that includes new small blood vessels (arrow). E shows the area immediately subjacent to the ventricle with frank necrosis (vertical arrow) and calcification (horizontal arrow). Scale bars=150 μm in D and 300 μm in E.
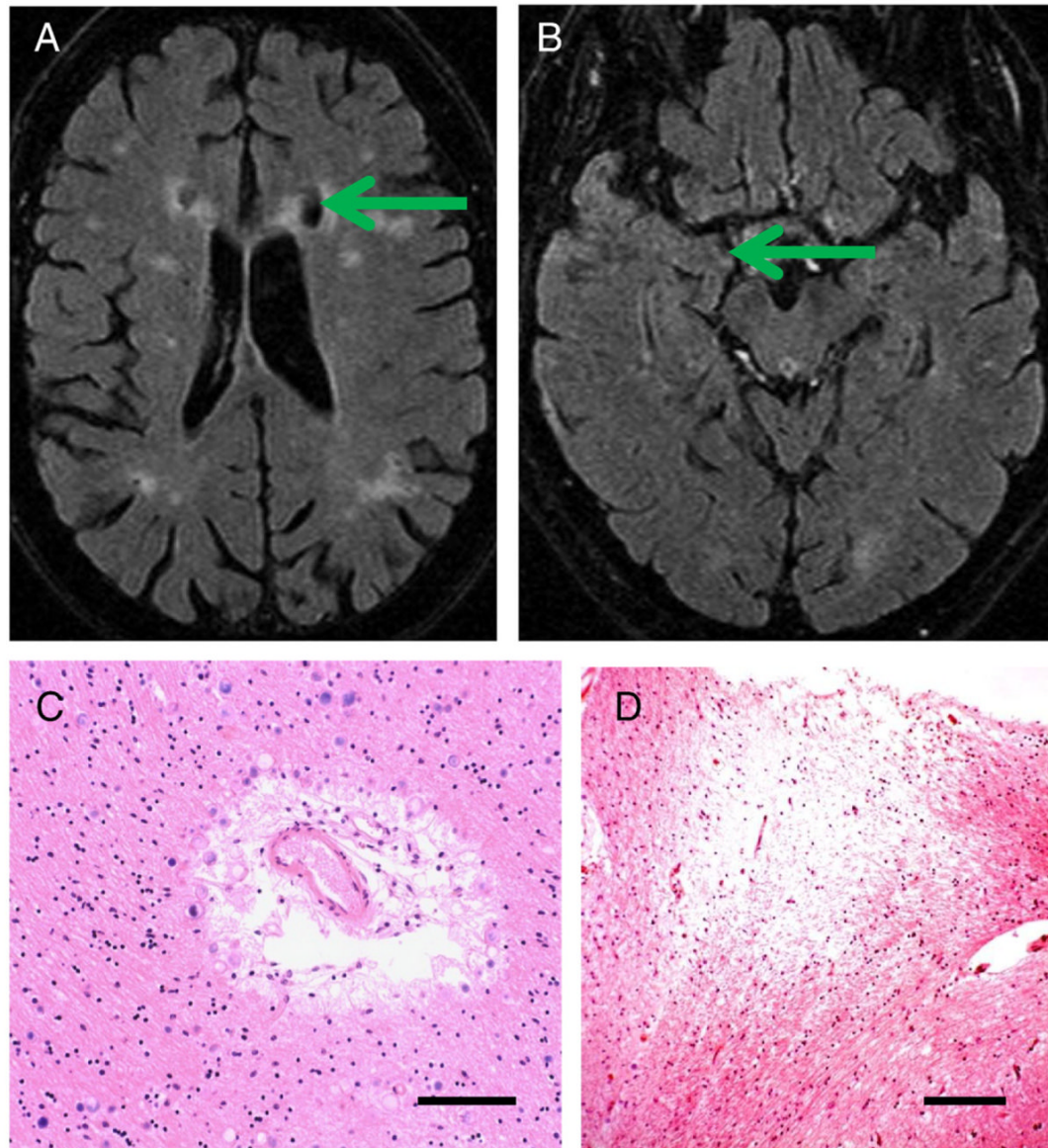
Fig. 5.
Diabetes Case 3–81-year old female with mild cognitive impairment and with predominantly cerebrovascular pathology (final MMSE score=29). (A and B) MRIs show the infarctions in the frontal cortices (arrow in A) and the subtle hippocampal atrophy (B). Histopathology confirmed the presence of frontal cortex infarcts (not shown). C and D show hippocampal histopathology. In this patient, there were blood vessel profiles with expanded Virchow–Robin spaces with many corpora amylacea (C) and there were small infarcts and areas of white matter rarefaction in the fimbria fornix (D), however, Alzheimer's-type pathology in CA1 of the hippocampus was mild (not shown). Scale bar=150 μm in C, 250 μm in D.
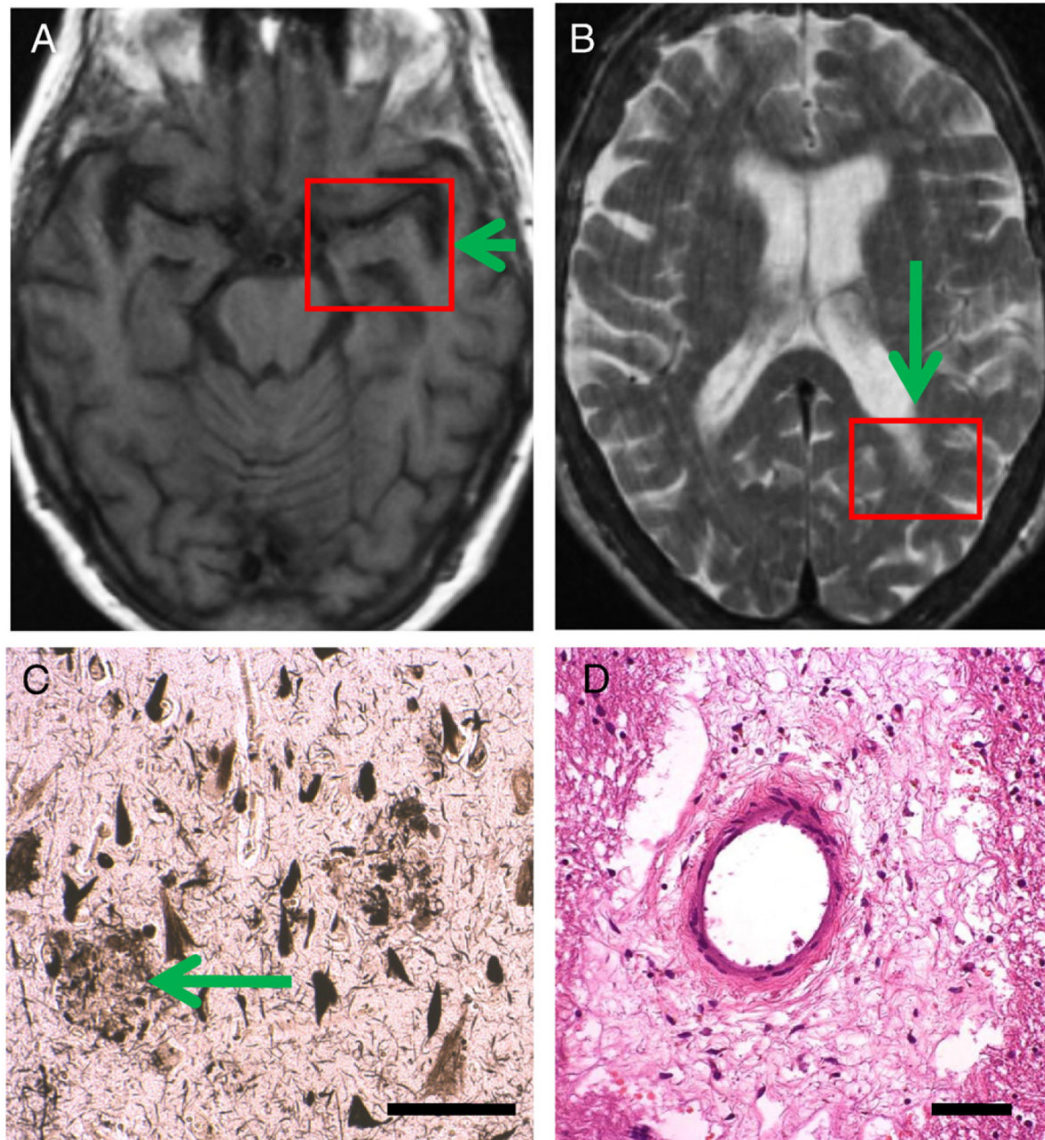
Fig. 6.
Diabetes Case 4–82-year old female diabetic patient with dementia and Alzheimer's disease diagnosis during life (last MMSE score=19). A and B show the final MRI that was obtained 4 years prior to the patient's demise. This already showed hippocampal atrophy (arrow in A) but also some periventricular white matter lesions (such as in arrow in B). Photomicrographs show the histopathological features from the red boxes. C depicts a section from CA1 field of the hippocampus stained with the Gallyas silver impregnation technique and shows severe involvement by Alzheimer's-type neuritic plaques (arrow) and many NFTs. This patient had Braak stage 6 and satisfied CERAD criteria for "Definite Alzheimer's disease" by pathology. In addition to the AD pathology, there was also some cerebrovascular disease including areas with rarefaction of white matter. D is a section from the left parietal lobe (box in B) which shows an expanded Virchow–Robin space with organized cellular and acellular material. In an 82-year old patient such as this, some degree of concomitant pathology is the rule and not the exception. Scale bars=150 μm in C, 100 μm in D.
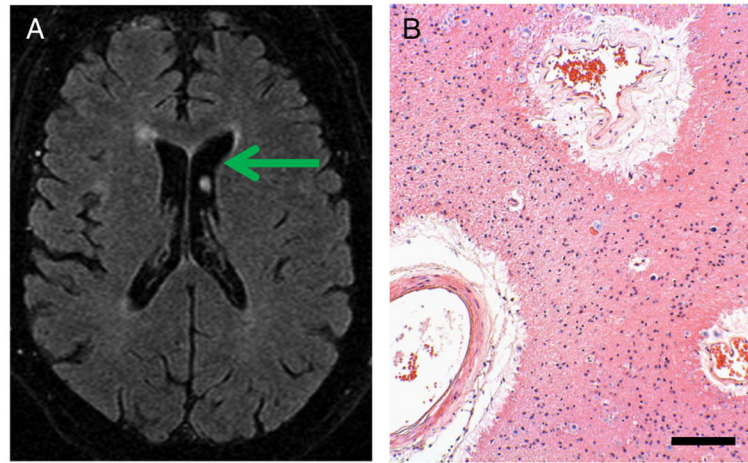
Fig. 7.
Diabetes Case 5–75-year old male diabetic patient with no dementia and with subtle changes on MRI (last MMSE score 29). A shows the MRI with mild periventricular white matter changes including some enhancement near in the subependymal basal ganglia. B depicts a photomicrograph from the same area, which includes pathology surrounding medium-sized blood vessels with expanded Virchow–Robin spaces. Surrounding the vessels are many corpora amylacea and gliosis. Scale bar=150 μm.
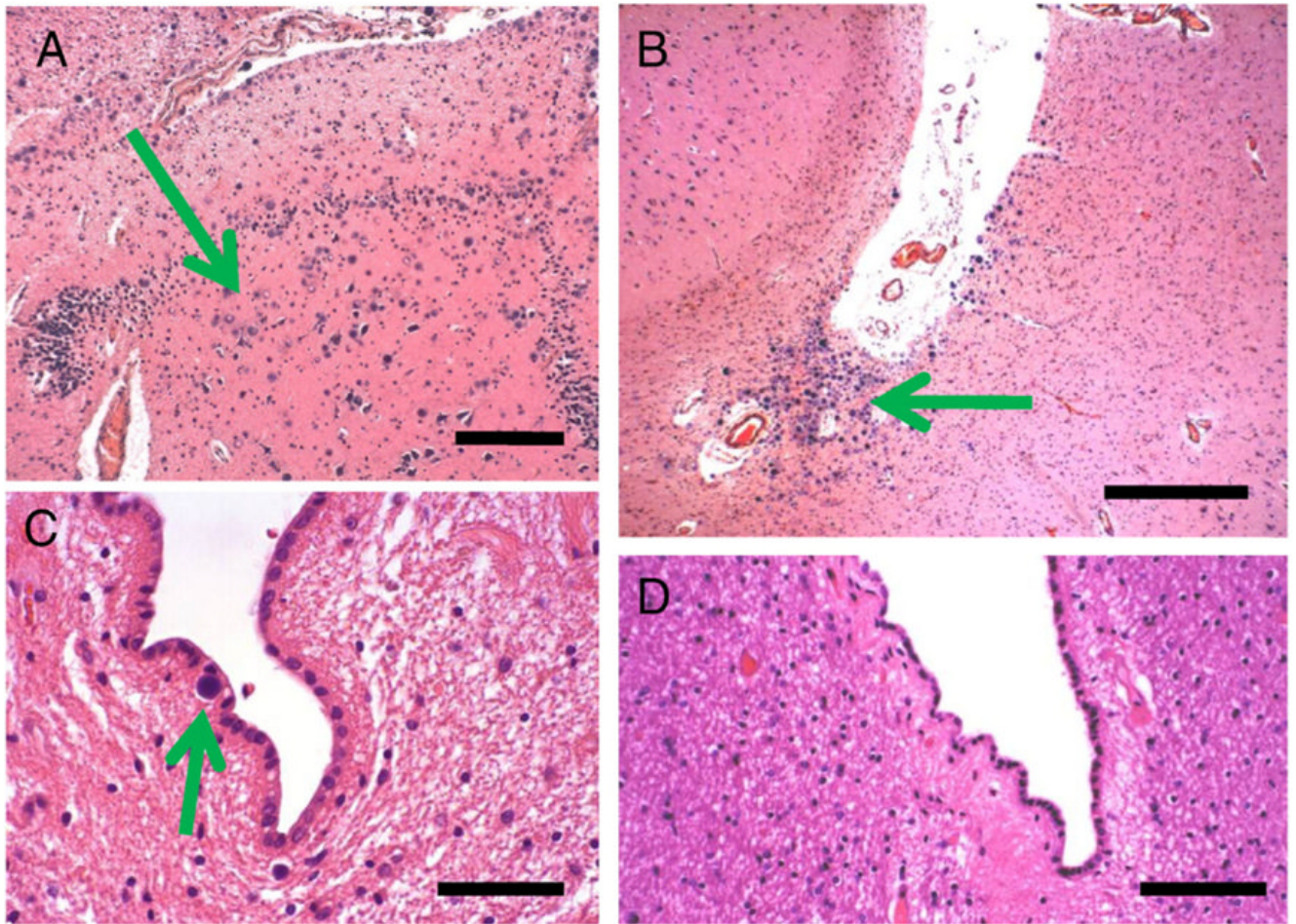
Fig. 8.
Diabetes Case 6–72-year old female patient with poorly controlled diabetes (two confirmed readings in excess of 150 mg/dl) and mild cognitive decline. In this case, the hippocampal formation showed many corpora amylacea including in the cornu ammonis subfields. These are shown in the CA4/dentate gyrus area, where there is some effacement of the normal cytoarchitecture in association with the presence of many corpora amylacea. B shows the crux of the inferior horn of the lateral ventricle, which also contained many corpora amylacea. By contrast, in Control Cases 1 and 2, there were few (arrow in C) or no corpora amylacea there. Scale bars: 300 μm in A and B, 150 μm in C and D.
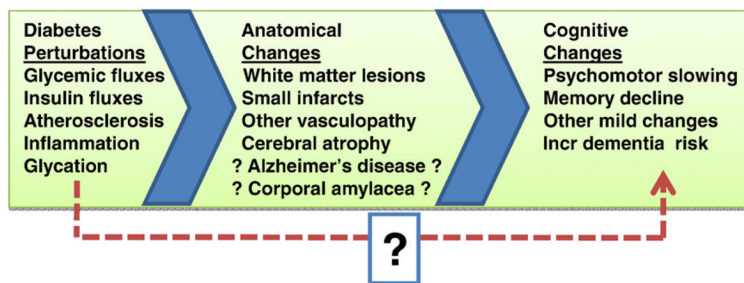
Fig. 9.
Research has provided insights into diabetes-related cognitive dysfunction. However, the specifics are unclear about how the chemical perturbations of diabetes correlate to the hypothesized anatomic substrates associated with "diabetic encephalopathy". In turn, the contribution to cognitive changes from the pathological lesions is poorly understood. The dashed arrow and question mark at the bottom indicate the possibility that metabolic perturbations in diabetes may produce cognitive changes in the absence of detectable anatomic pathology.

Table 1

Recent MRI studies that correlate anatomical changes with cognitive dysfunction

Ref.	Patients	MRI findings in association with Type 2 diabetes	Notes
[98]	113 DM2 51 controls	WMLs, cortical and subcortical atrophy are associated with cognitive decline	Cognitive dysfunction correlated to WMLs and brain atrophy. A1C was 6.9% (moderately well-controlled)
[96]	122 DM2 56 controls	WMLs, atrophy are associated with cognitive decline; pathology and other factors show interactions	Cognitive dysfunction correlated with WMLs, atrophy, hypertension, hyperinsulinemia, and "vascular events"; statin use was associated with improved WMLs and with improved cognition
[90]	92 DM2 44 controls	PVH, WMLs, lacunar infarcts, and cerebral atrophy observed; only PVH was associated with "motor slowing"	MRI findings less well associated with cognitive dysfunction in relation to HbA1C and duration of diabetes, which showed stronger correlation with cognitive dysfunction
[93]	40 DM1 40 DM2	DM2 patients have more WMLs and cortical atrophy in comparison to DM1 patients with much longer disease duration	DM2 patients had more cognitive dysfunction but also more of other metabolic aspects including more hypertension, lipid disorders, etc.
[97]	122 DM2 56 controls	WMLs, atrophy, which were not correlated with peripheral neuropathy within given patients	Authors conclude that CNS and PNS pathology of DM2 may be unrelated because of discrepancies within individuals
[100]	95 DM2	"White matter hyperintensities" in various areas correlated with declines in cognitive domains	Memory and "mental speed" deficits were associated most strongly with white matter hyperintensities in parietal lobe and thalamus

Table 2

UK ADC: demographics and clinical indices

	Diabetics	Non-diabetics	*p*-value
Demographics			
N	50	89	–
Age at death, yrs (mean±SD)	84.7±8.0	88.2±6.7	<0.01[1]
Sex (%F)	54	63	NS[2]
Formal education, yrs (mean±SD)	15.6±2.6	16.0±2.0	NS[1]
ApoE alleles (2/3/4), %	4/84/12	11/76/13	NS[3]
Last MMSE score (mean±SD)	26.4±5.1	24.4±7.4	NS[1]
Interval between last evaluation and death, yrs (mean±SD)	0.64	0.96	NS[1]
Clinical parameters			
Depression, %	20	20	NS[2]
CABG, %	14	7	NS[3]
Peripheral vascular disease, %	26	15	NS[2]
TIA, %	14	8	NS[2]
Hypertension, %	64	55	NS[2]
Daily intake of drugs/meds (mean±SD)	12.2±7.7	19.8±8.5	<0.0001[1]

The demographic and clinical characteristics between diabetics (*N*=50) and non-diabetics (*N*=89) in the BRAiNS program at the UK ADC. This group, which was recruited from non-demented individuals, has been described previously [245]. The demographic and clinical indices are similar between diabetics and non-diabetics. The clinical parameters were dichotomous (0 or 1) except for "Number of drugs" (range: 2–39). Definitions: ApoE = Apolipoprotein E; MMSE = Mini-mental status examination (0–30 scale); CABG = coronary artery bypass graft operation; TIA = history of transient ischemic attack(s).

Statistical tests:

[1] Two-tailed Student's *t* test

[2] Chi-square

[3] Fisher's exact test.

Table 3

UK ADC: pathological indices

	Diabetics	Non-diabetics	*p*-value
Pathological parameters, non-Alzheimer's type			
Lacunar infarcts, %	14	7	NS[2]
Micro-infarcts, %	52	30	0.01[2]
Large infarcts, %	2	10	NS[2]
Hemorrhagic infarcts, %	8	4	NS[2]
Any infarcts, %	56	37	0.03[2]
Hippocampal sclerosis, %	9	6	NS[2]
Argyrophilic grains, %	22	26	NS[2]
Lewy bodies in isocortex, %	6	11	NS[2]
Brain wgt, g (mean±SD)	1196±134	1193±139	NS[1]
Pathological parameters, Alzheimer's type			
Braak stage (median, range)	2 (0–6)	3 (0–6)	NS[3]
CERAD score (median, range)	0 (0–3)	2 (0–3)	0.02[3]
NIARI score (median, range)	0 (0–3)	1 (0–3)	0.03[3]
Probable or definite AD, %	24	22	NS[2]
NFT counts (mean±SD)			
Temporal lobe	1.9±4.62	3.4±8.8	NS[1]
Frontal lobe	0.6±1.9	1.3±3.4	NS[1]
Parietal lobe	0.8±2.3	1.8±4.8	NS[1]
Hippocampal CA1	9.5±15.2	12.1±21.4	NS[1]
Subiculum	10.9±16.8	25.3±40.0	0.004[1]
Neuritic plaque counts (mean±SD)			
Temporal lobe	3.9±5.9	6.4±7.4	0.04[1]
Frontal lobe	4.6±6.9	6.6±7.3	NS[1]
Parietal lobe	5.3±7.6	7.5±8.3	NS[1]
Hippocampal CA1	1.5±3.0	1.1±2.4	NS[1]
Subiculum	1.9±3.9	1.9±3.6	NS[1]

Pathological indices stratified by diabetics (*N*=50) and non-diabetics (*N*=89) in the BRAiNS program at the UK ADC. Note that small infarcts tended to be present more often in diabetics, but AD-related pathology tended to be slightly more abundant in non-diabetics.

Statistical tests:

[1] Two-tailed Student's *t* test

[2] Chi-square

[3] Wilcoxon Rank Sum.