The brain of the elderly diabetic patient

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SUMMARY
All available estimations agree that the French population is aging and that the proportion of diabetics in the elderly population is increasing. The prevalence of diabetes could be about 10% in the over 65 y population. The fact that diabetes has an effect on brain function is widely accepted, but there are very few studies providing pertinent details. Diabetes is known to affect brain function, potential consequences including cognitive decline, dementia, depression, and stroke. These complications are frequently associated, leading to poor quality-of-life with considerable social and economic impact. While the results of different studies can be contradictory, there is an overall trend towards the conclusion that diabetes, often associated with high blood pressure, contributes to cognitive decline in elderly diabetics as well as to an increased frequency and severity of cerebral vascular events. These considerations point out the importance of proper management of diabetes in the elderly population and the need for cooperative studies to determine the role of diabetes and different cardiovascular risk factors in the development of dementia, stroke, and depressive syndromes whose consequences are probably underestimated.

Key-words: Diabetes mellitus · Dementia · Stroke · Depression.


RESUMÉ
Le cerveau du diabétique âgé
Toutes les estimations montrent qu’en France, le vieillissement de la population s’accompagne d’une majoration de la prévalence du diabète qui peut être évaluée à environ 10 % chez les seniors de plus de 65 ans. L’influence du diabète sur les fonctions cérébrales est soulignée par tous, mais peu d’études contrôlées permettent de les préciser. Les conséquences du diabète sur les fonctions cérébrales sont représentées par le déclin cognitif et les démences, les états dépressifs et les accidents vasculaires cérébraux. Ces complications s’associent fréquemment pour handicaper la qualité de vie de ces malades et générer des conséquences socio-économiques considérables. Si les résultats des études sont parfois contradictoires, il est globalement possible de conclure à la responsabilité du diabète souvent associé à l’hypertension artérielle, dans le déclin cognitif de ces malades ainsi que dans la fréquence et de la gravité des accidents vasculaires cérébraux (AVC). Ces considérations invitent à une meilleure prise en charge de ces patients et à la mise en place de travaux coopératifs pour préciser la responsabilité de la maladie diabétique et des différents facteurs de risque cardiovasculaire dans la survenue des démences, des AVC et enfin des syndromes dépressifs dont les conséquences sont probablement sous-estimées.

Mots-clés : Diabète · Démence · Accidents vasculaires cérébraux · Dépression.
According to the most recent estimations, more than 500,000 French people aged over 75 years have diabetes. The PAQUID study demonstrated that the prevalence of diabetes in France is an estimated 10.3% in people aged over 65 years [1]. The fact that diabetes has an effect on brain function is widely accepted, but there are very few studies providing pertinent details. This is not surprising since the age factor is known to play a major role in these cerebral manifestations of diabetes. The deleterious effects of diabetes can however be divided into three categories known to progress in concert and to have mutually stimulating effects. Thus, cognitive decline and dementia, together with depression and stroke constitute a particularly disabling triad deteriorating the quality-of-life of these patients and generating considerable social and economical consequences.

Cognitive decline in diabetics

Large-scale epidemiological studies have emphasized the concomitant increase in the prevalence of diabetes and dementia. In the general population, more than 33% of women and more than 16% of men aged over 65 years will develop a state of dementia leading to total loss of autonomy [2]. Alzheimer’s disease affects 1.5% of persons aged 65-70 years and 30% of those aged over 90 years [3]. As the prevalence of diabetes in the elderly population is an estimated 10%, it is easy to perceive that combined diabetes and dementia is not an uncommon situation. The question is to determine whether there are other links between diabetes and dementia other than these common epidemiological characteristics.

Influence of diabetes on cognitive decline

Epidemiological data emphasize the correlation between the main cardiovascular risk factors and cognitive decline. In their prospective study, Piguet et al. demonstrated that high blood pressure is associated with more pronounced decline in cognitive capacity [4]. This was confirmed in the Framingham Heart Study which pointed out that improved intellectual function is observed in subjects with normal blood pressure levels and normal body weight [5]. The very frequent association between diabetes and high blood pressure makes it difficult to sort out the role of diabetes per se.

The effect of hyperglycaemia on cognitive function is a controversial issue [6]. The vast majority of the cross-sectional studies show that, globally, diabetics display altered cognitive function compared with their disease-free counterparts [7, 8]. The prevalence of altered cerebral function is considerable after the age of 70 years as demonstrated by Bruce et al. in the Fremantle Cognition in Diabetes Study [9] where only 36% of diabetics were found to be free of both cognitive deficit and depressive syndrome. The degradation of cognitive function appears to be related to the duration of diabetes and quality of glucose control [10].

Furthermore, brain function appears to be particularly sensitive to acute changes in glucose level and good glucose control would improve intellectual performance [11, 12].

The available longitudinal studies provide evidence in favor of accelerated degradation of cognitive function in diabetics [13]. In one six-year follow-up study including a cohort of 9,679 women aged over 65 years, 682 who had diabetes for more than 15 years displayed a 57-114% higher risk of cognitive decline [2]. In another two-year follow-up study, Wu et al. found that diabetes was a factor predictive of cognitive impairment [14].

Impaired intellectual performance hinders proper management of diabetes and leads to frequent hospitalizations, emphasizing the importance of early diagnosis of cognitive deficit [15].

All authors are not in agreement with this notion of diabetes as a risk factor for cognitive decline. Using a battery of twelve tests to evaluate cognitive function in 1,509 subjects aged over 55 years, Scott et al. were unable to find a significant difference between controls, patients with glucose intolerance, and diabetics [16]. More recently, Lindeman et al. reach the same conclusion in their cohort of 883 subjects aged over 65 which included 188 diabetics [17].

Influence of diabetes on dementia

Large-scale autopsy studies of elderly subjects have demonstrated that Alzheimer’s disease was the substratum of 80% of the dementia cases. The diagnosis of “pure” vascular dementia was retained in only 7-10% of cases, and only in 3-5% for “mixed” forms with signs of both Alzheimer and vascular dementia.

Diabetes and vascular dementia

The diagnosis of vascular dementia is defined by the clinical criteria described by the National Institute of Neurologic Disorders and Stroke-Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) [18]. The characteristic feature is a sudden decline in cognitive function within three months of a cerebral vascular event. The symptoms must be associated with focal neurological signs compatible with stroke and imaging anomalies showing evidence of multiple infarcts or hemorrhage.

Diabetes as a risk factor for cerebral vascular events could favor the development of vascular dementia. The conclusions of the Rotterdam Study are in line with this notion. In this study which followed 6,370 elderly subjects free of signs of dementia at inclusion, the presence of diabetes increased the risk of developing vascular dementia two-fold [19]. These results were confirmed in later work by Hassing et al. in a population of 702 patients aged more than 80 years [20]. In another study of more than 1,700 subjects aged over 60 years, Haan et al. demonstrated that the association of type 2 diabetes with stroke increases the risk of dementia 8-fold [21]. Posner et al. reported a cohort of 1,259 subjects followed for seven years and emphasized the influence of the association of high blood pressure and diabetes which increased the risk of vascular dementia.
6-fold [22]. The deleterious synergetic effect of diabetes and high blood pressure was also illustrated by the large-scale National Health and Nutrition Examination Survey III (NHANES III). The cognitive function in 3,385 adults aged 30-59 years with no history of stroke was assessed using three distinct tests. After adjustment for a large number of medical or socio-cultural factors, the authors found that neither diabetes nor high blood pressure were independently associated with poor cognitive scores. Conversely, the association of the two conditions had a negative effect which was significant for two tests and close to significance for the third [23].

All of these data confirm the deleterious role of diabetes as a risk factor for the development of vascular dementia.

**Diabetes and Alzheimer’s disease**

Alzheimer’s disease is a degenerative disease of the central nervous system leading to progressive impairment of cognitive function and eventually total loss of autonomy. The neuropathological lesions, neurofibrillar tangles and amyloid plaques, are characteristic. In a prospective study of 1,449 subjects, Kivipelto et al. demonstrated that two cardiovascular risk factors, hypercholesterolemia and elevated systolic blood pressure, were also independent risk factors of Alzheimer’s disease [24]. The responsibility of hypercholesterolemia was recently confirmed in an autopsy study [25]. The involvement of diabetes, as a major cardiovascular risk factor in the development of Alzheimer dementia, would suggest potential prevention via a good glucose control [26, 27]. A body of epidemiological evidence would also suggest that diabetes is a risk factor for Alzheimer’s disease, particularly among patients homozygous for allele E4 and ApoE [28-30]. Diabetes favors the development of Alzheimer’s disease by inducing an increase in amyloid deposits [31]. The most recent work published confirms that insulin resistance plays a role in the development of this type of dementia [32].

All authors do not agree that diabetes is related with the development of dementia. Hassing et al. noted dementia in 187 of 702 patients aged over 80 years and remarked that only 31 of the demented patients had diabetes [20]. The statistical analysis demonstrated that diabetes multiplied the risk of vascular dementia two-fold but did not affect the risk of Alzheimer’s disease. These data were later confirmed by the results of the Canadian Study of Health and Aging [33].

While profound recurrent episodes of hypoglycaemia have a recognized deleterious effect on cognitive performance in diabetics [34], the type of antidiabetic treatment given does not appear to affect Alzheimer’s disease [35].

**Treatment**

In 1999, a panel of ALFEDIAM experts published management guidelines for elderly diabetics [36]. Of course, the usual measures for care of demented patients should be applied for diabetics with dementia. Insulin therapy using a simplified regimen implemented by a caregiver is often a necessary solution for patients with cognitive impairment. The importance of improving glucose control is underscored by the results of several studies which have demonstrated that good glucose control slows down the degradation of cognitive functions [14, 37, 38]. Nevertheless, the objectives set for these patients must remain reasonable and episodes of hypoglycaemia must be avoided.

Statins, which are widely prescribed for patients with cardiovascular risks, might also have a protective effect against Alzheimer’s disease [39], but, due to the lack of clear evidence, there is currently no consensus on the potential efficacy of statins in this indication [40].

**States of depression**

Depression is particularly frequent in elderly subjects. It could be both a confounding factor and an aggravating factor in the early phase of dementia. Screening and early treatment are thus indicated. Diagnosis of depression is often a difficult task in these patients, correct assessment being hindered by misleading presentations and interactions with the cognitive impairment. It can be extremely useful to collect information concerning the subject’s living conditions from the family or caregivers in order to sort out the impact of each parameter. The fluctuating nature of memory disorders, the fact that complaints are often centered on memory problems, the presence of moral suffering, and predominant depressive mood or guilt feelings are all elements suggestive of a depressive syndrome rather than dementia.

While these different considerations are not specific to the diabetic subject, they are of particular importance in this population because of the frequency of depression. In the PAQUID study, 21.3% of diabetics presented depression as a complication of their disease [1]. There are however few data detailing the consequence of depression in elderly diabetics.

The frequency of depression is however probably underestimated in elderly diabetics. In their series of 223 diabetic patients aged over 70 years, Bruce et al. noted severe depression in 14.2% and at least one symptom compatible with depression in 50.2% of the remainder [9]. The presence of a depressive syndrome also appears to be a risk factor for the development of type 2 diabetes as was demonstrated in the Rancho Bernado Study [41]. It was also found, in a cohort of 1,830 Mexican Americans, that diabetes and depression produce a synergetic effect increasing micro- and macroangiopathies complications and mortality [42]. Treatment of depression improves the functional and affective status of diabetics even though the HbA1c level, as demonstrated by William et al. [43], remained stable in their series of elderly subjects with a well controlled baseline glucose.

All of these results emphasize the importance of identifying and treating depression in elderly diabetic patients.

**Stroke**

Stroke is a serious and frequent complication feared by both elderly diabetics and their general practitioner [44]. Unfortunately, scientific evidence concerning elderly diabet-
Epidemiology

Diabetes is generally considered as a major stroke risk factor. Although hemorrhagic events appear to be less frequent among diabetics, the risk of ischemic stroke is globally four-fold higher in diabetics [46, 47] and appears to occur earlier in life [48]. These studies have however included a small proportion of subjects aged over 70 years and diabetes becomes less important as a risk factor compared with age and high blood pressure in very old people. In a study of 3,050 Mexican Americans aged more than 65 years, the frequency and mortality of stroke were significantly higher in the group of 690 diabetics [49]. Thus stroke in diabetics is strongly associated with a high risk of disability [50]. The risk of stroke increases with high blood pressure and atrial fibrillation [47], with carotid stenosis and poor glucose control [51], and with prior history of stroke [52].

Pathogenesis

The site of the causal lesion is a controversial issue although the presence of diabetes is known to increase the frequency of carotid stenosis and the other causes of stroke [48, 53]. Similarly, there is no consensus concerning the responsibility of diabetes in the genesis of lacunar infarcts. These small profound infarcts result from lesions of small intracerebral arteries and appear to be related to diabetes. Thus for certain authors, diabetes would double the risk of lacunar infarcts [54] or silent infarcts recognized on the brain MRI [55]. Other authors however argue that the risk of this type of event would not be any higher in diabetics [48]. Patient age has a predominant effect, lacunar infarcts being observed more frequently in subjects aged over 80 years. The importance of stroke in the genesis of cognitive decline in diabetics was already mentioned above.

Conversely, diabetes appears to protect patients against the development of hemorrhagic events. For subarachnoid hemorrhage the risk is 4- to 10-fold lower and for intracerebral hematoma 1,5- to 6-fold lower [48, 53, 56]. However, the blood glucose level at the time of the accident does not have any impact on the risk of progression from ischemic to hemorrhagic stroke [57].

Prognosis

Although all authors are not in agreement, stroke mortality appears to be higher in diabetics, with either type 1 or type 2 diabetes [58]. Both conditions increase the risk of death 1.8- to 3-fold, particularly during the acute phase [46, 59]. This greater mortality appears to be related to direct consequences of stroke, to the higher rate of recurrence, and to the development of other vascular events, particularly coronary events [46]. The PROGRESS (Perindopril Protection Against Recurrent Stroke Study) study found that the risk of stroke was increased 35% among diabetics [60]. In addition, diabetes has a negative impact on disability assessed three months after the stroke. The role of hyperglycaemia during stroke has been advanced in reference to observations in myocardial infarction. Thus in diabetics, mortality and residual disability are well correlated with blood glucose level and HbA1c at admission for all types of stroke, but particularly for ischemic stroke [51, 57, 61]. The risk of mortality is increased three-fold when fasting blood glucose at admission exceeds 6.1 mmol/l [62].

Treatment

Primary stroke prevention has clearly improved with better control of risk factors and better glucose control [52].

Controlling blood pressure is a crucial element in preventing stroke in all elderly subjects, and particularly in diabetics as has been demonstrated by several primary and secondary prevention studies [63-65]. The only limitations for intervention to control blood pressure are the risk of orthostatic hypotension and the presence of a tight carotid stenosis. In this latter case, lowering blood pressure too much could favor vascular events due to a drop in brain perfusion.

The use of statins has also been found to be very beneficial as was demonstrated by the Heart Protection Study (HPS) where 40 mg simvastatin reduced the incidence of stroke 25% [66]. In the Collaborative Atorvastatin Diabetes Study (CARDs) of 2,838 subjects aged 40-75 years (including 12% aged over 70 years), administration of 10 mg atorvastatin for primary prevention reduced the risk of stroke by 48% [67].

Preventive antiplatelet therapy is also widely used even though the meta-analysis Antiplatelet Trialists’ Collaboration (ATTC) showed that the beneficial effect of a 25% decrease in the overall stroke rate but at the cost of increased rate of hemorrhagic stroke, was only significant for non-diabetics [68]. Despite these results, aspirin is frequently given to elderly diabetics at risk of a vascular accident since there is no evidence that other antiplatelet therapy would have a supplementary benefit in this very precise indication.

Risk factors thus must be controlled very carefully in elderly diabetics to prevent stroke. The benefit has been clearly demonstrated in the STENO 2 study which showed a 53% regression in macroangiopathic accidents after intensive global management of type 2 diabetics while they are relatively young [69]. There is however no evidence to determine at what age and for what indications this triple preventive therapy should be instituted.

Surgical treatment of carotid stenosis is not different than in non-diabetics. The risk of stroke and the operative risk are high, but the potential benefit is greater in diabetics. The indication for surgery must be established on the basis of the patient’s age, the severity of the stenosis, and the presence of symptoms or not.
When materially possible, emergency hospitalization in a specialized center is always advisable for stroke victims. Correct hydration, quality nursing, and early rehabilitation are indispensable elements for effective care.

Since stress-induced hyperglycaemia is an undeniable aggravating factor, glucose control as optimal as possible is indispensable. In this context, use of insulin is advisable.

Use of heparin therapy or thrombolysis should be weighted, keeping in mind the risk of this type of treatment in frail elderly diabetics.

**Conclusion**

The explosive epidemic of diabetes and its brain complications, including stroke, dementia and depression, is an important public health issue. Although some discordant evidence has been produced by different studies, globally, it can be concluded that diabetes contributes to cognitive decline in these patients and to the higher frequency and greater severity of cerebral events. These considerations point out the importance of carefully planned patient care and the need for cooperative studies designed to determine the real role of diabetes and the different cardiovascular risk factors in the development of dementia and stroke, without neglecting probably underestimated depression. These studies could also be used to evaluate treatment of these different factors.

**References**


If you have a question or need further assistance, please let me know!