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Review

Hyperglycaemia as a determinant of cognitive decline in patients with type 1 diabetes

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Abstract

Individuals with type 1 diabetes show mild performance deficits in a range of neuropsychological tests compared to healthy controls, but the mechanisms underlying this cognitive deterioration are still poorly understood. Basically, two diabetes-related mechanisms can be postulated: recurrent severe hypoglycaemia and/or chronic hyperglycaemia. Intensive insulin therapy in type 1 diabetes, resulting in a durable improvement of glycaemic control, has been shown to lower the risk of long-term microvascular and macrovascular complications. The down side of striving for strict glycaemic control is the considerably elevated risk of severe hypoglycaemia, sometimes leading to seizure or coma. While retrospective studies in adult patients with type 1 diabetes have suggested an association between a history of recurrent severe hypoglycaemia and a modest or even severe degree of cognitive impairment, large prospective studies have failed to confirm this association. Only fairly recently, better appreciation of the possible deleterious effects of chronic hyperglycaemia on brain function and structure is emerging. In addition, it can be hypothesized that hyperglycaemia associated microvascular changes in the brain are responsible for the cognitive decline in patients with type 1 diabetes. This review presents various pathophysiological considerations concerning the cognitive decline in patients with type 1 diabetes.

Keywords: Type 1 diabetes; Microvascular disease; Cognitive functioning; Brain structure; Brain function

Contents

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1. Introduction

Type 1 diabetes is characterized by an autoimmune destruction of the beta cells, resulting in an inability of the pancreas to secrete insulin and in turn in a dependency of exogenous insulin treatment. Despite the introduction of various insulin preparations with a wide range of kinetic properties and modern medical technologies as for example insulin pumps, patients with type 1 diabetes experience fluctuations in blood glucose levels throughout the day, ranging from low blood glucose levels (hypoglycaemia) to high blood glucose levels (hyperglycaemia). The primary goal of treatment in type 1 diabetes is to avoid hyperglycaemia, which is responsible for the development of microvascular complications involving the eyes (retinopathy), kidneys (nephropathy) and nerves (neuropathy) and macrovascular complications involving the heart. There is evidence to suggest that the brain is susceptible for the effects of diabetes as well. This was already recognized in 1922 by Miles and Root (Miles and Root, 1922):

> 'Diabetes is well known to exert an important influence on the central nervous system. The diabetic patient on his own part, complains of loss of memory and of poor ability to concentrate the attention. So far as we are aware, there are no objective data which either substantiate or contradict this clinical picture in reference to attention and memory.'

Later, in 1950, the term 'diabetic encephalopathy' was introduced, a term used to describe the impaired ability to process information (De Jong, 1950). In 1965, rather characteristic pathological changes were found in brains of 16 long-term 'juvenile' diabetic patients who had died from vascular complications of diabetes (Reske-Nielsen et al., 1965). The authors stated that the histological pattern they observed justifies the term 'diabetic encephalopathy', because it differs from that seen in any other clinical condition. However, today, there still is no consensus on how to describe the cerebral consequences, if any, of the disease (Mijnhout et al., 2006).

2. Cognition and type 1 diabetes

A recent meta-analysis by Brands et al. (Brands et al., 2005) showed a modest but highly significant difference in cognitive performance between patients with type 1 diabetes and non-diabetic control subjects. The pattern does not suggest an overall impairment of cognitive function, but rather a slowing of mental speed and a diminished 'mental flexibility'. This suggests that patients with type 1 diabetes are less able to flexibly apply acquired knowledge in a new situation. This meta-analysis suggests that on average, the magnitude of most of these cognitive decrements is modest.

3. Possible mechanisms underlying cognitive decline in type 1 diabetes

Both recurrent hypoglycaemia and chronic hyperglycaemia are held responsible for the cognitive decline in patients with type 1 diabetes. In addition, it now has been recognized that the age of onset may modify the effects of these determinants.

3.1. Acute and recurrent episodes of hypoglycaemia

Glucose is the predominant fuel utilized by the central nervous system (Sokoloff, 1977). Because the brain cannot synthesize glucose nor store more than a few minutes' supply as glycogen, the brain requires a continuous supply of glucose from the circulation. Therefore, disruption of the supply of exogenous glucose will rapidly cause functional disturbances.

Several studies have shown that some aspects of cognitive functioning are altered during experimentally induced hypoglycaemia (Cox et al., 1993; Deary et al., 2003; Draelos et al., 1995; Gold et al., 1995; Maran et al., 1995; McAulay et al., 2001; Sommerfield et al., 2003). Tasks which primarily involve higher cognitive processes appear to be more sensitive to neuroglycopenia than motor tasks (Cox et al., 1993; McAulay et al., 2001). Moreover, tasks that involve rapid responses and those which are more cognitively complex and attention demanding tend to show substantial impairment during neuroglycopenia, whereas ability on simple motor and cognitive tasks such as finger-tapping, digit span and simple reaction time are relatively well preserved (Deary et al., 1993). In general, recovery from any acute cognitive decrement after an acute, severe episode of hypoglycaemia was completed by 1.5 days (Strachan et al., 2000).

In the past decades, several studies have addressed the effects of recurrent hypoglycaemia on cognition. Retrospective studies in adult patients with type 1 diabetes have demonstrated an association between a history of recurrent severe hypoglycaemia and a modest degree of cognitive impairment (Deary et al., 1993; Fanelli et al., 1998; Langan et al., 1991; Lincoln et al., 1996; Perros et al., 1997; Wredling et al., 1990). Furthermore, there are numerous case-reports presenting the adverse effects of hypoglycaemia on the central nervous system. In contrast, large prospective studies did not confirm the earlier observations (1996; Jacobson et al., 2007; Reichard et al., 1991). Therefore, recurrent hypoglycaemia does not seem to have a detrimental effect on brain functioning. This is in contrast with the general belief that hyperglycaemia is an important contributor to cognitive decline.

3.2. Chronic hyperglycaemia

Only fairly recently, more appreciation for the possible deleterious effects of chronic hyperglycaemia on brain function

has emerged (Cox et al., 2005). The results of two studies performed by Ryan et al. (Ryan et al., 2003; Ryan et al., 1992) showed that patients with type 1 diabetes with one or more diabetes related complications (distal symmetrical polyneuropathy; advanced background or proliferative retinopathy; overt nephropathy; one or more episodes of severe hypoglycaemia) performed significantly worse on several neurocognitive tests compared with healthy control subjects. Furthermore, it appeared that polyneuropathy and elevated HbA1c levels were associated with an impaired cognitive test performance. Another, retrospective study by Ryan et al. (Ryan et al., 2003) showed that cognitive efficiency may decline over time in diabetic adults, and that this neurocognitive change may be linked to the occurrence of complications like proliferative retinopathy. Two microvascular complications, in particular retinopathy and peripheral neuropathy, have been shown to be predictive of cognitive decline in patients with type 1 diabetes (Ferguson et al., 2003; Ryan et al., 1992). These two complications have a microvascular origin and it can be hypothesized that microvascular changes in the brain, as a result of chronic hyperglycaemia, are responsible for the cognitive decline in patients with type 1 diabetes.

Recently, the DCCT/EDIC Study Research Group reported that (Jacobson et al., 2007) higher glycaeted haemoglobin values were associated with moderate declines in motor speed and psychomotor efficiency. It is important to note that participants with advanced retinopathy, nephropathy or neuropathy were excluded in the original DCCT (1996). Unfortunately, in the current report, no mention is made of the number of participants with advanced (proliferative) diabetic retinopathy. It would be of great interest to learn whether this subgroup suffered a greater decline in cognitive function than those without microvascular complications.

4. Does age of onset modify the adverse effects of hypo- and hyperglycaemia?

Early onset of type 1 diabetes (onset between 4–7 years) has emerged as one of the most consistent risk factors for neurocognitive decline in patients with type 1 diabetes. Children developing the disorder in early childhood are more likely to score relatively poorly on cognitive tests, independent of diabetes duration. Prospective evaluation has confirmed that early onset of diabetes independently influences verbal and nonverbal intelligence, attention, psychomotor speed, and executive functions (Northam et al., 2006; Rovet and Ehrlich, 1999; Schoenle et al., 2002). Notably, these deficits could not be explained by a known history of hypoglycaemic seizures early in life. Unrecognised episodes of hypoglycaemia or chronically elevated or fluctuating glucose levels may alter the structure or function of specific pathways or regions in the brain, with cognitive decline as a result.

A study to quantify regional brain volume differences in a large sample of young patients with diabetes (Perantie et al., 2007), found that a history of hypoglycaemia was associated with smaller grey matter volume in the left superior temporal region, whereas greater exposure to hyperglycaemia was associated with smaller grey matter volume in the right cuneus and precuneus and smaller white matter volume in a right posterior parietal region and larger grey matter volume in a right prefrontal region. Earlier age of onset was not associated with differences in grey matter, but a larger white matter volume was found in the left precuneus region. Adults with an early childhood onset of type 1 diabetes showed mild central brain atrophy and significant differences in intellectual performance (Ferguson et al., 2005), which implies that neurodevelopment may be adversely affected by early onset disease.

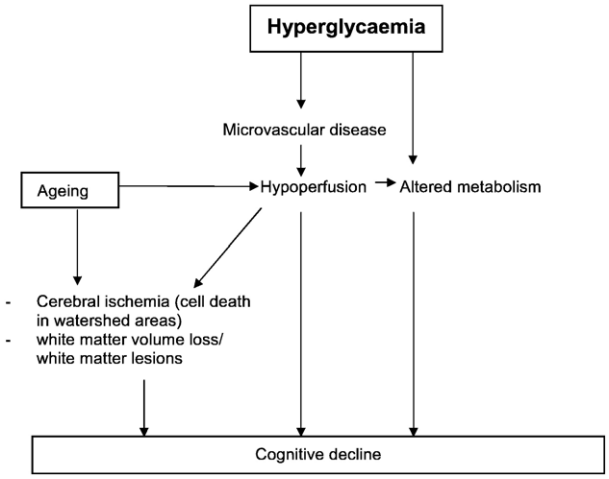

Fig. 1. Possible pathophysiological mechanism underlying cognitive decline in type 1 diabetes.

Ryan (Ryan, 2006) proposes a vulnerability hypothesis and posit that in the very young child diagnosed with diabetes, chronic hyperglycaemia initiates a cascade of structural and functional brain changes that disrupt normal brain development. The resulting alterations in brain organisation induce a predisposition that increases the individual's sensitivity to additional brain insults at any time thereafter. Up to now, this hypothesis has not been tested in practice. Therefore, follow-up studies of well-characterized patients are warranted to determine the course of brain functioning in response to aging and exposure to hypo- and hyperglycaemia.

5. How to study microvascular disease in the brain?

We hypothesize that cognitive decline in type 1 diabetes is the result of hyperglycaemia associated microvascular disease inside the brain. To test this hypothesis, one should study the integrity of the cerebral vessels. Unfortunately, to date, there is no technique available which is able to directly demonstrate the presence of microvascular disease in the brain. Therefore, researchers are dependent on surrogate markers. The retinal vessels and the cerebral microvasculature share common anatomic, embryologic and physiologic characteristics (Wong et al., 2001b). Changes in the retinal vasculature may reflect similar changes in the cerebral vasculature. This forms the basis for using retinal vascular topographical features as a marker of the cerebral microvasculature in cerebrovascular disease. Moreover, retinal microvascular changes seem to reflect

cerebral microvascular changes in ageing, as for example in diseases such as vascular dementia and stroke (Wong et al., 2001a). Until no better or more direct measure is available, retinopathy appears to be the best marker for cerebral microvascular disease available.

6. Pathophysiological mechanisms

The results of our recent research form the basis of the proposed hypothetical chain of events, which possibly can explain the cognitive decline in patients with type 1 diabetes (Fig. 1).

As stated earlier, the most important mechanisms may be hyperglycaemia-induced microvascular disease. Hyperglycaemia results in an increased flux of glucose to the brain that is shunted through the so-called 'polyol pathway', by which excess glucose is converted to sorbitol and fructose (Greene et al., 1987). Elevated glucose levels also enhance the formation of advanced glycation end products. These biochemical changes contribute to functional and structural abnormalities which among others include thickening of capillary basement membranes and decreased capillary density. This has been shown in brain autopsy studies of patients with diabetes (Johnson et al., 1982; Reske-Nielsen et al., 1965). The average age of onset of this population was 7 years and all patients had retinopathy. The retinal lesion in 14 (out of 16) of the patients was severe (proliferative retinopathy) and nine of them had severe visual impairment.

6.1. Microvascular disease and brain activation

The results of our functional MRI study (Wessels et al., 2006a) suggest that patients with severe diabetic retinopathy (as a marker of intracerebral microangiopathy), compared with patients without retinopathy, showed decreased deactivation in the anterior cingulate gyrus and the orbitofrontal cortex during hypoglycaemia (which served as a stressor in this experimental design) as compared with euglycaemia. One possible explanation for these functional differences between the retinopathy and the non-retinopathy group is that microvascular alterations in the retinopathy patient group result in regional abnormalities in the regulation of cerebral blood flow (Fig. 1). Cerebral vasoreactivity and accompanying changes in cerebral blood flow are important compensatory mechanisms in general and especially during hypoglycaemia. Loss of these compensatory mechanisms may therefore result in the changes in blood oxygenation level dependent response as observed.

There are several, to some extent contradictory, reports dealing with cerebrovascular reactivity in patients with type 1 diabetes. Two studies (Fulesdi et al., 1997; Keymeulen et al., 1995) found that the increase in blood flow following administration of a dilatory stimulus, as for example acetazolamide, is impaired. This impairment appeared to be most pronounced in subjects with a long duration of diabetes and in patients with other complications such as retinopathy and nephropathy.

In children and adolescents with type 1 diabetes (mean age 14.7+/−3.4 years), cerebral hypoperfusion, compared with controls, has been demonstrated (Salem et al., 2002). This hypoperfusion was mainly found in the basal ganglia and frontal regions. These changes were not related to the age, sex, diabetes duration, mean blood glucose or HbA1c and no correlation was found between cerebral blood flow changes and cognitive scores.

Increases in cerebral blood flow, primarily to the frontal lobes in response to acute hypoglycaemia, have been demonstrated in studies using single-photon emission tomography (MacLeod et al., 1996; MacLeod et al., 1994; Tallroth et al., 1993). In diabetic patients who have a history of recurrent, severe hypoglycaemia, regional cerebral blood flow changes in the frontal lobes were observed during normoglycaemia and may represent a cerebral adaptation to recurring hypoglycaemic insults (MacLeod et al., 1996; MacLeod et al., 1994). Another single-photon emission tomography study in diabetic patients showed decreased regional cerebral blood flow, but the results may have been biased by atrophy (Sabri et al., 2000). However, none of the currently available studies specifically addresses the role of cerebral microangiopathy in brain perfusion and metabolism in type 1 diabetes. This issue needs to be addressed in future studies.

A decreased cerebral blood flow, lower metabolic rates of glucose and oxygen and a compromised structural integrity of the cerebral microvasculature are degenerative features of the vascular system of the ageing brain (Farkas and Luiten, 2001). The two characteristic parameters of cerebral metabolism are the cerebral metabolic rate for oxygen and cerebral glucose utilisation. From several human studies it is known that cerebral glucose metabolic rates gradually decreases with advancing age (Kuhl et al., 1984; Marchal et al., 1992; Yamaguchi et al., 1986). The parallel, concomitant decline of the cerebral metabolic rate of oxygen, cerebral glucose utilisation and cellular energy substrates in normal ageing probably represents a gradual shift to lower cerebral metabolic activity in general, which likely is a result of a lower cerebral blood flow (Farkas and Luiten, 2001).

Only a few studies employed positron emission tomography (PET) to study cerebral glucose uptake in patients with type 1 diabetes (Chabriat et al., 1994; Cranston et al., 2001) and in healthy volunteers (Segel et al., 2001). These studies primarily focussed on the effect of hypoglycaemia on cerebral glucose uptake. So far, the effect of acute hyperglycaemia on cerebral glucose handling in patients with type 1 diabetes has not been studied yet. The interactive processes of ageing and chronic hyperglycaemia on the morphology and function of cerebral capillaries may affect cerebral metabolism and brain perfusion, thus further contributing to the decline in cognitive performance. Alterations in cerebral glucose metabolism might therefore be an additional explanation for the decreased deactivation in the anterior cingulate and the orbitofrontal gyrus as observed in our functional MRI study. It can be hypothesized that these areas are preferentially affected by reduced cerebral blood flow and decreased glucose metabolism.

6.2. Microvascular disease and brain structure

The possible chain of events (Fig. 1), explaining the occurrence of cognitive decline includes cellular ischemia and

infarctions of the brain. It is well established that so-called vascular watershed zones are the first to be deprived of sufficient blood flow in the event of hypoperfusion (Snowdon et al., 1997). Watershed areas are located peripheral to primary arteries in the vascular systems. Because they are located at the extreme ends of the arterial distribution, they are particularly vulnerable to ischemia and infarction in people with a compromised circulation.

A recent report of our group (Wessels et al., 2006b) showed a decreased grey matter density in patients with diabetic retinopathy (compared with a non-retinopathy patient group and healthy controls) in the inferior frontal gyrus and the occipital lobe. These brain areas are the watershed areas of the medial cerebral artery and the posterior cerebral artery. The diminished grey matter density in the retinopathy patient group may be the result of (recurrent) micro-infarction in the grey matter, due to microvascular disease. Micro-infarction has also been reported to result in dementia (Kaplan et al., 1985; Tomlinson et al., 1970) and is associated with a history of transient ischemic attacks (Munoz, 1991) and contributes significantly to the progression of cognitive deficits in brain ageing (Kovari et al., 2004). The preponderance of cortical micro-infarcts in our population to watershed cortical areas points to cerebral hypoperfusion as the determining factor in their pathogenesis. Another possible contributing mechanism underlying the diminished grey matter density in the retinopathy patient group may be accelerated ageing. The similarities of the events occurring in diabetes and ageing (degeneration of brain capillaries, thickening of basement membranes and reducing vessel elasticity (De la Torre and Mussivand, 1993; Kalaria and Hedera, 1995)), suggest that diabetes and ageing share some, and in particular vascular, pathogenic processes. Since only the retinopathy patient group showed a reduction in grey matter density, it is likely that hyperglycaemia induced changes contribute to an accelerated ageing of the brain, as reflected by increased cortical atrophy.

A study by Musen et al. (Musen et al., 2006) also investigated whether lower grey matter densities in patients with type 1 diabetes were present, and if so, whether they were associated with glycaemic control and/or a history of severe hypoglycaemic events. It was found that, compared with healthy controls, patients with type 1 diabetes showed lower grey matter densities in several brain areas. One or more severe hypoglycaemic events was associated with less grey matter density in the left cerebellar posterior lobe. Moreover, poor glycaemic control was associated with lower grey matter density, including the left posterior cingulate, right parahippocampal gyrus, left hippocampus, left superior temporal gyrus, right occipital cuneus and left thalamus. In an additional (post hoc) analysis, the authors found that retinopathy was associated with grey matter density loss in brain regions used for cognition (frontal and temporal regions). It was concluded that persistent hyperglycaemia may be associated with lower grey matter density in patients with type 1 diabetes and that the superior temporal gyrus is particularly vulnerable. Although this study and our study found a relation between retinopathy and the degree of density reduction, there are important differences in design and patient population that complicate comparison of results.

6.3. Microvascular disease, brain function and structure

We recently reported that cognitive performance in relatively young diabetic patients is worse with regard to tests measuring speed of information processing and visuoconstruction as compared to sex-, age- and education matched nondiabetic controls (Wessels et al., 2007). Notably, patients with a microvascular complication showed a decreased white matter volume compared with nondiabetic controls. Reduced white matter volume was associated with worse performance in the domain of speed of information processing and attention and executive functioning. Our findings corroborate with previous findings suggesting that deficits in speed of information processing and cognitive slowing are the fundamental features of clinical disorders characterized by abnormalities in cerebral white matter (Filley, 2001). For example, a relation between reduced white matter volume and impaired processing speed performance and working memory was found in patients with multiple sclerosis and temporal lobe epilepsy (Dow et al., 2004; Sanfilipo et al., 2006).

As stated earlier, evidence is increasing that psychomotor slowing is a core cognitive deficit associated with diabetes (Ryan, 2005), and studies have demonstrated that the presence of microvascular complications like retinopathy is predictive of mental slowing in adults with type 1 diabetes (Ferguson et al., 2003; Ryan et al., 2003). Furthermore, retinal microvascular abnormalities have been shown to relate to white matter lesions in patients with type 1 diabetes (Ferguson et al., 2003) and in healthy middle-aged men and women (Wong et al., 2002). In this study, we focused on whole grey and white matter volume, rather than lesion burden, since these are more closely related to neuropsychological performance (Sanfilipo et al., 2006; Zivadinov et al., 2001). We found a relation between white matter atrophy and performance in the domain of speed of information processing and attention and executive function. These results are consistent with the notion that temporary storage and manipulation of new information may require rapid communication between different brain regions via white matter tracts, which may become compromised with progression of the disease. This finding indirectly suggests that disruption of centrally located cortical subcortical white matter connections may be responsible for slower processing speed.

White matter hyperintensities have often been reported. Although the pathogenetic mechanism of white matter hyperintensities has not been resolved, they may represent demyelination, axonal loss, changes in glial cell numbers and morphology or some other pathology (Fazekas et al., 1993). Accumulating evidence suggests that the clinical manifestations of white matter hyperintensities include poorer performance in executive functioning, particularly among subjects who were not demented (Bigler et al., 2003; Burton et al., 2004; Gunning-Dixon and Raz, 2003; Tullberg et al., 2004). In the Rotterdam Scan Study, de Groot et al. (De Groot et al., 2000) reported that psychomotor speed was more strongly associated with white matter hyperintensities than was memory.

Whether white matter hyperintensities are associated with white matter volume is still under debate. The results of a study by Wen et al. (Wen et al., 2006) suggest that white matter hyperintensities are associated with loss of brain volume. Another study (Smith et al., 2000) reported that decreased white matter volume measured from MRI was associated with dementia and with lower cognitive test scores, whereas extent of periventricular white matter hyperintensities found on the same images was not. In this study, white matter hyperintensities were not related to white matter volume, stroke, or dementia. One could speculate that deleterious white matter pathology would result in atrophy as suggested by other studies (DeCarli et al., 1995; Ylikoski et al., 1995), but the authors of this study did not find an inverse correlation between hyperintensity rating and white matter volume. Nonetheless, low white matter volume was strongly related to dementia and poor cognitive performance in this sample.

Small white matter hyperintensities have been found in patients with type 1 diabetes with retinopathy (Ferguson et al., 2005). Background diabetic retinopathy was associated with small focal white matter hyperintensities, corresponding to enlarged perivascular spaces, in the basal ganglia. Other studies on structural brain abnormalities in patients with type 1 diabetes have reported conflicting results concerning the presence of white matter lesions and cortical atrophy (Araki et al., 1994; Dejgaard et al., 1991; Ferguson et al., 2003; Lunetta et al., 1994; Perros et al., 1997). These conflicting results may be due to different patient populations.

An early diabetes onset (<7 years) was associated with a higher ventricular volume but not with cortical atrophy or white matter lesion severity (Ferguson et al., 2005). These results indicate that MRI changes in the brain of patients with type 1 diabetes are relatively subtle and may be more pronounced in patients with an early diabetes onset.

Whether type 1 diabetes is indeed characterized by changes in cerebral white matter or whether diabetes can be characterized by global brain atrophy (affecting both grey and white matter) needs to be clarified in future longitudinal studies.

Future longitudinal studies should also utilize newer MRI techniques, such as diffusion tensor imaging, to quantify changes in the integrity of the cerebral white matter and to enhance our understanding of the potential mechanisms underlying structural brain damage and its effect on cognitive performance in patients with type 1 diabetes.

In trying to understand the link between cerebral perfusion, metabolism, integrity of the grey and the white matter and cognitive performance, it can be concluded that a decrease in regional cerebral blood flow and/or regional glucose metabolism in grey as well as in white matter in patients with microangiopathy has been demonstrated in several studies (Kawamura et al., 1991; Kobari et al., 1990; Mielke et al., 1992; Reiche et al., 1991; Yao et al., 1990). Furthermore, in one study neuropsychological deficits correlated with decreased regional cerebral blood flow and regional glucose metabolism, whereas lacunar infarctions and white matter lesions were not associated (Sabri et al., 1999). Another study reported (DeCarli et al., 1995) that white matter hyperintensity volume (which is indicative for cerebral ischemia/brain atrophy) was associated with poorer cognitive function and, when severe, was accompanied by significantly reduced frontal lobe metabolism as measured with PET. The results of our study also suggest a relation between cognitive performance and white matter volume (Wessels et al., 2007).

7. In conclusion

Patients with type 1 diabetes develop cognitive deficits that likely are a consequence of changes within the central nervous system. Numerous neuropsychological studies have delineated the nature and extent of these cognitive changes, but little is known about the underlying mechanism that may explain the cognitive decline. Although several other research groups have assessed brain structure in diabetic patients using MRI, the results are inconsistent across groups, and no efforts have been made to specifically examine brain/behavior relationships and the impact of microvascular disease.

Chronic hyperglycaemia likely plays a key role in the development of the structural and functional changes in the brain: cerebral microvascular pathology in diabetes may result in a decrease of regional cerebral blood flow and an alteration in cerebral metabolism. If this condition persists for long, neuronal disintegration and cell death may follow. This process will be translated, at a behavioral level, in cognitive decline. Developing diabetes within the first 4–7 years of life appears to be a risk factor for cognitive decline: exposure to glycaemic fluctuations may alter the structure and function of specific pathways or regions in the brain that disrupts normal brain development. This makes an individual sensitive to additional brain insults at any time thereafter.

8. Future directions

Future studies should focus on the cerebral vascular changes occurring in diabetes. These may include the investigation of the cerebrovascular reactivity after administration of a vasodilatory stimulus to assess cerebrovascular function in patients with diabetes and microvascular disease. The question whether and how hypoperfusion and altered metabolism precedes cognitive deficits in patients with diabetes should also be resolved. In addition, it is important to find out whether type 1 diabetes can be characterized by changes in cerebral white matter or by global brain atrophy (affecting both grey and white matter), and how these changes are related to cerebral microangiopathy.

Apart from determining whether structural changes in the brain are related to cognition, it is of interest to assess the association between structural brain parameters and disease variables such as chronic hyperglycaemia, diabetes duration and/or microvascular damage and age of onset of the disease.

Future research can contribute to a better understanding of the effects of microvascular disease on brain structure and brain blood flow, in relation to changes in brain functioning. To date, apart from tight glycemic control, no other evidence-based treatments are known to ameliorate or prevent microvascular

complications. A better understanding of the factors determining the effects of microvascular disease on cognitive performance in diabetes may allow us to more accurately tailor our treatment to individual patient characteristics, and to design targeted interventions to halt or prevent cognitive decline.

For the time being, in order to preserve optimal cognitive functioning, the best advice is to maintain strict glycemic control (with attention for episodes of hypoglycaemia) to avoid chronic hyperglycaemia, as is the case for the other vascular complications.

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