Cognitive function and diabetes

- Chairmen: M. Khattab (Egypt), J.F. Raposo (Portugal)
Cognition and diabetes in older individuals: a complex interplay

S. Maggi (Italy)
COGNITION AND DIABETES IN OLDER INDIVIDUALS: A COMPLEX INTERPLAY

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Aging Branch-Padua
Hypothesized model of the origins and life course of brain aging

Muller et al, Pediatrics 2014
One of the hallmarks of Alzheimer's disease is the accumulation of amyloid plaques between nerve cells (neurons) in the brain. Amyloid is a general term for protein fragments that the body produces normally. Beta-amyloid is a fragment of a protein that is snipped from another protein called amyloid precursor protein (APP). In a healthy brain, these protein fragments would be broken down and eliminated. In Alzheimer's disease, the fragments accumulate to form hard, insoluble plaques.
Neurofibrillary tangles consist of insoluble twisted fibers that are found inside of the brain's cells. They primarily consist of a protein called tau, which forms part of a structure called a microtubule. The microtubule helps transport nutrients and other important substances from one part of the nerve cell to another. In Alzheimer's disease, however, the tau protein is abnormal and the microtubule structures collapse.
Genoma-wide association studies have shown that the Insulin-degrading enzyme (IDE) gene links to both late-onset AD and T2DM.
Diabetes as a risk factor for AD

The evolving concept that diabetes is a risk factor for developing Alzheimer disease is supported by scientific evidence and by the common features of the two conditions, such as:

1. increased prevalence with aging
2. a genetic predisposition, and
3. comparable pathological features in the islet and brain (amyloid derived from amyloid beta protein in the brain in Alzheimer disease and islet amyloid derived from islet amyloid polypeptide in the pancreas in type 2 diabetes).
T2DM and cognitive functioning

T2DM is associated with increased risk of dementia

Xu et al., *Diabetes* 2009; 58:71-7

Midlife diabetes doubles the risk of dementia

Xu et al, Diabetes 2010
Diabetes and cognition

Adapted from Strachan et al., *Nat Rev Endocrinol.* 2011

Glycemic control (hyper- & hypoglycemia)

Hyperinsulinemia

Depression

Beta amyloid

Microvascular diseases

Macrovascular diseases

Hypertension

Genetic predisposition

Inflammation
<table>
<thead>
<tr>
<th>Reference</th>
<th>Mechanism</th>
<th>Synopsis</th>
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<tbody>
<tr>
<td>Munch et al., 1998 [135]</td>
<td>AGE</td>
<td>In diabetes, accelerated AGE formation is caused primarily by a higher level of plasma glucose.</td>
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<td>Janson et al., 2004 [89]</td>
<td>Amyloid deposition in islet and brain cells</td>
<td>More islet amyloid in AD patients than control subjects. No greater brain amyloid in diabetic patients compared with control subjects. In cases of T2DM patients with brain amyloid, the extent of amyloid increased with longer duration of diabetes.</td>
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<td>Rivera et al., 2005 [75]</td>
<td>Low insulin and a decrease in ChAT</td>
<td>Low insulin levels and low insulin sensitivity can contribute to a decrease in acetylcholine synthesis, leading to AD.</td>
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<td>Razay et al., 2007 [128]</td>
<td>Metabolic syndrome</td>
<td>AD patients, compared with healthy, normal patients, had a greater waist circumference, higher triglyceride and glucose levels, and lower HDL cholesterol.</td>
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<td>Beydoun et al., 2008 [126]</td>
<td>Weight gain and obesity</td>
<td>Baltimore Longitudinal Study of Aging. Obesity, central obesity and weight loss among women seem to play a role in AD, while underweight and weight gain among men increase the risk.</td>
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<td>Vilalta-Franch et al., 2008 [129]</td>
<td>Metabolic syndrome</td>
<td>Patients with metabolic syndrome are diagnosed with AD at a younger age than AD patients without metabolic syndrome.</td>
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<td>Miklossy et al., 2010 [87]</td>
<td>Amyloid and hyperphosphorylated tau</td>
<td>Islet amyloid polypeptide and hyperphosphorylated tau were found in islet cells of the pancreas in T2DM patients (on autopsy).</td>
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<td>Beeler et al., 2009 [84]</td>
<td>JNK, IB1 and hyperphosphorylated tau with amyloid deposits</td>
<td>Both DM and AD involve co-localization of JNK, IB1 and hyperphosphorylated tau with amyloid deposits.</td>
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</table>
Figure 4: Cerebral changes underlying cognitive trajectories in type 2 diabetes
Slight cognitive decrements are related to subtle cerebral alterations including slight atrophy, disturbed white matter integrity, and vascular lesions (the picture shows two MRI scans and a segmentation of different brain tissues). These changes progress slowly, from midlife onwards, drawing on the reserve capacity of the brain. This progress increases vulnerability to the consequences of further incidents later in life, particularly (silent) stroke (the picture shows a left thalamic infarct on CT perfusion) and Alzheimer’s-type abnormalities (the picture shows a PIB-PET amyloid scan, reproduced from Jack and colleagues, by permission of Elsevier.) Individuals with such a combined burden of multiple abnormalities will have accelerated cognitive decline. Blue arrows indicate hypothetical cognitive trajectories of individual patients with multiple abnormalities.
T2DM are at increased risk of brain structural and functional impairments

Figure 2 Probability map of location of grey matter atrophy attributable to type 2 diabetes Voxel-based morphometric analysis was used to create a probability map of areas of grey matter atrophy attributable to type 2 diabetes, when adjusted for age, sex,...

Paula S Koekkoek, L Jaap Kappelle, Esther van den Berg, Guy E H M Rutten, Geert Jan Biessels

Cognitive function in patients with diabetes mellitus: guidance for daily care


http://dx.doi.org/10.1016/S1474-4422(14)70249-2
Risk factors for late-life cognitive decline in diabetes

Biessels et al, Lancet Diabetes Endocrinol 2014, 2: 246-255
Risk score for prediction of 10-year dementia risk in patients with T2D aged >60 yrs

- 60-64 years: 0 points
- 65-69 years: 3 points
- 70-74 years: 5 points
- 75-79 years: 7 points
- 80-84 years: 8 points
- ≥85 years: 10 points

- Acute metabolic event: 2 points
- Microvascular disease: 1 point
- Diabetic foot: 1 point
- Cerebrovascular disease: 2 points
- Cardiovascular disease: 1 point
- Depression: 2 points

Up to high-school education (≤12 years): 0 points
College or higher education (>12 years): -1 point

Add up points and look up predicted 10-year risk of dementia:

Predicted 10-year risk of dementia (%)

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<th>Risk (%)</th>
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<td>12-19</td>
<td>73</td>
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Diabetes and cognition

N=153 cognitively intact patients from the *Diabetic Foot Patients-Cognition and Depression* (DFP-CoDe) project

Marseglia et al., *J Diabetes Complications*. 2014
Insulin and IGF I are significantly reduced in the frontal cortex, hippocampus and hypothalamus – all areas that are affected by the progression of AD. ‘Type 3 diabetes’, accurately reflects the fact that AD represents a form of diabetes that selectively involves the brain and has molecular and biochemical features that overlaps with T2DM.

Figure 1: Summary of the effects of antidiabetic drugs on the periphery and brain

Type 2 diabetes affects brain cells in several ways, with mainly negative effects on cell metabolism, neuronal viability, and behaviour. GLP-1R agonists, metformin, and thiazolidinediones can improve glycaemic control in the periphery and counteract organ complications in type 2 diabetes. These drugs also have favourable effects on the CNS. The mechanisms for the actions of these drugs in the brain are being investigated—they could involve direct effects on brain cells (figure 2) or they could act indirectly by positively affecting general whole-body metabolism and the vascular system in the brain.
Conclusions

• Type 2 Diabetes is associated to AD

• Although further research is clearly needed to clarify how insulin resistance in the neurons in the brain interacts with other genetic and biochemical abnormalities in the development of Alzheimer's disease, there are plausible mechanisms explaining a biochemical link between the two conditions.

• Understanding and developing treatments for diabetes may have impact not only in diabetes, but in many other common chronic diseases."