Diabetes Mellitus and Dementia

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Abstract

Diabetes mellitus increases the risk for developing dementia...BUT there is inconsistency with the subtypes of dementia...
Diabetes Mellitus (DM)

- defined as a problem of hyperglycemia
  - 366 million people worldwide → 552 million by 2030
- Type 1 DM
  - autoimmune disease: beta cells don’t produce insulin
- Type 2 DM
  - “lifestyle” disorder: due to diet and exercise habits
- DM is a risk factor for vascular dementia and Alzheimer’s
29.1 million Americans have diabetes. 5% have Type 1 and 95% have Type 2.

Source: American Diabetes Association, 2012
Polyuria (Frequent Urination)

Polydipsia (Excessive Thirst)

Polyphagia (Excessive Hunger/Increased Appetite)

Involuntary Weight Loss
So what is dementia?

- “Syndrome that affects memory, thinking, behavior, and the ability to perform everyday activities”
- Two major subtypes
  - Alzheimer’s Disease (AD)
  - Vascular Dementia (VD)
Who has dementia?

- Currently, 35.6 million people worldwide
  - will double by 2030

- Think about the cost associated with it
  - caretakers, meds, etc
  - currently costs $214 billion → projected to $1.2 trillion by 2050
35.5 million people worldwide have dementia

Source - “Dementia: a public health priority” report, World Health Organization and Alzheimer’s Disease International
Most Common Dementia: Alzheimer’s

- Initially only thought of as only neurodegenerative
  - extracellular amyloid beta plaques (AB)
  - intracellular neurofibrillary tangles (tau)
- BUT now insulin might have a huge role
# Dementia vs. Alzheimer's

<table>
<thead>
<tr>
<th></th>
<th>Dementia</th>
<th>Alzheimer’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Definition</strong></td>
<td>A brain related disorder caused by diseases and other conditions.</td>
<td>A type of dementia. But the most common type.</td>
</tr>
<tr>
<td><strong>Cause</strong></td>
<td>Many, including Alzheimer’s disease, stroke, thyroid issues, vitamin deficiencies, reactions to medicines, and brain tumors.</td>
<td>Unknown, but the “amyloid cascade hypothesis” is the most widely discussed and researched hypothesis today.</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Permanent damage that comes in stages.</td>
<td>Average of 8 to 20 years.</td>
</tr>
<tr>
<td><strong>Typical Age of Onset</strong></td>
<td>65 years and older.</td>
<td>65 years but can occur as early as 30.</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Issues with memory, focus and attention, visual perception, reasoning, judgment, and comprehension.</td>
<td>Difficulty remembering newly learned information. With advancement, disorientation, mood and behavior changes may occur.</td>
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</table>
Second most common: Vascular Dementia

- Small vessel disease $\rightarrow$ strokes $\rightarrow$ vascular dementia (VD)
  - causes permanent cognitive damage
<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Vascular Dementia</th>
<th>Alzheimer’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of atherosclerotic</td>
<td>Transient ischemic attack, strokes,</td>
<td>Less common</td>
</tr>
<tr>
<td>diseases</td>
<td>atherosclerotic risk factors e.g., diabetes mellitus,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hypertension</td>
<td></td>
</tr>
<tr>
<td>Onset</td>
<td>Sudden or gradual</td>
<td>Gradual</td>
</tr>
<tr>
<td>Progression</td>
<td>Slow or stepwise progression</td>
<td>Slow, progressive decline</td>
</tr>
<tr>
<td>Neurological examination</td>
<td>Neurological deficits</td>
<td>Normal</td>
</tr>
<tr>
<td>Gait</td>
<td>Often disturbed early</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Memory</td>
<td>Mild impairment in early phase</td>
<td>Prominent in early phase</td>
</tr>
<tr>
<td>Executive function</td>
<td>Marked impairment and early</td>
<td>Impaired later</td>
</tr>
<tr>
<td>Type of dementia</td>
<td>Subcortical</td>
<td>Cortical</td>
</tr>
<tr>
<td>Hachinski Ischemic Score</td>
<td>$\geq 7$</td>
<td>$\leq 4$</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>Infarction or white matter lesions</td>
<td>Normal or hippocampal atrophy</td>
</tr>
</tbody>
</table>

Source: Roman GC, 2003;\textsuperscript{11} Muangpaisan W et al., 2005.\textsuperscript{18}
Epidemiological Evidence

• They used MEDLINE via Ovid computer search (1946-2013)
  ○ keywords used: diabetes mellitus, dementia, epidemiologic studies
• yielded 795 research articles → exclusion requirements → 18 specific articles reviewed
From the 18 studies...

- Most studies in Western countries (US, CAN, Euro) and two in Japan
- diagnosis of DM based on
  - self reports
  - medical records
  - anti-diabetes meds
  - oral glucose tolerance test
Out of the 18 studies...

● 15/18: DM increased risk of all dementia
  ○ about a 1.7x increase

● 14/18: Addressed DM and AD specifically
  ○ so 5/14 demonstrated a significant increased risk
    ▪ 9/14 didn’t show a significant difference because of experimental method differences
Major Correlations

- Risk of AD is 1.6x greater with DM
- Risk of Vascular Dementia is 2.2x greater with DM
- “People with DM have a 1.5-2.5x greater risk of dementia that those without it among community-dwelling elderly people”
Morphologic Changes in the Brain
Hisayama Study

- In Japan, the diabetes diagnosed by glucose tolerance test
  - measured the 2 hour post-load plasma glucose (2PG) and the fasting plasma glucose (FPG)
- 2PG levels linked to increased risk of AD and VD
  - 2PG associated with strokes
Hisayama Study Cont.

- Presence of plaques increased with increases in 2PG levels (not FPG), fasting insulin, and insulin resistance
  - increase in ApoE4 increases these risks
    - ApoE is a gene on chrom. 19 (strong genetic factor for AD)
      - produced by astrocytes, liver, and macrophages
      - 7 receptors → variety of effects
Rotterdam Scan Study

- Based on MRI, hippocampus and amygdala of DM patients was smaller than those without DM.
Honolulu Heart Program Study

- DM + ApoE4 allele increases number of plaques and tangles in the brain (cortex and hippocampus to be specific)
- Risk of cerebral amyloid angiopathy was higher in DM patients and ApoE4 than without it
  - associated with worse cognitive function
Honolulu Heart Program Study Cont.

- Perhaps the link between DM, AD, and ApoE4 is due to an increased risk of cerebral amyloid angiopathy formation
  - cerebral amyloid angiopathy= Amyloid protein builds up in arteries of brain
Potential Biological Mechanisms
Cardiovascular Risk Factors

1) In Type 2 DM
   a) obesity, insulin resistance, atherogenic dyslipidemia, hypertension, proinflammatory states
      i) clustering of these risk factors accelerates stroke, small vessel disease, and subsequent vascular dementia
         (1) increasing exposure to hyperglycemia $\rightarrow$ ruins capillaries $\rightarrow$ decreases oxygen supply to brain $\rightarrow$ physical damage of artery $\rightarrow$ vascular dementia
Cardiovascular Risk Factors Cont.

2) Standard strategies of risk reduction among the elderly are not effective in treating dementia
   a) anti-hypertension meds, anti-platelet therapy, and statin treatment
      i) suggests that maybe there’s more to cardiovascular diseases than just cardiovascular agents
Glucose Toxicity

1) Mediated By:
   a) increase flux of glucose through the polyol and hexosamine pathway
   b) an increased production of oxidative stress
   c) accumulation of advanced glycation end-products (AGEs)
      i) proteins or lipids that become glycated after exposure to sugars
      ii) prevalent in the diabetic vasculature
         (1) believed to play causal role in blood vessel complications in DM
         iii) believed to speed up oxidative damage to cells
Hyperglycemia Increases Flux Through Polyol Pathway
Hyperglycemia Increases Flux Through Hexosamine Pathway
Hypoglycemia

1) In Type 2 Diabetes Patients
   a) 1.5-2.0 times greater risk of the development or deterioration of cognitive impairment
   b) can induce permanent neurologic sequelae:
      i) neuronal cell death
      ii) increase in platelet aggregation and fibrinogen formation
   c) could cause neurological changes that render older patients more susceptible to dementia
Hemodynamic Changes

- ↑ Heart Work Load
- ↑ Contractility
- ↑ Adrenalin
- ↑ Oxygen Consumption

Rhythm Abnormalities

- QTc Prolongation
- Flattening of T wave
- ST Depression
- ECG Changes
- Heart Rate Variability
- Ectopic Activity
- Ventricular Tachycardia
- Atrial Fibrillation

Sympathoadrenal Response

- ↑ Diplopia
- ↓ Retinal Sensitivity
- ↓ Retinal Response
- ↓ Retinal Viability
- ↑ Loss of Vision

HEART

HYPOGLYCEMIA

EYE

BRAIN

OTHER REGULATORY RESPONSES

Inflammation

- ↑ C-Reactive Protein
- ↑ Inter Leukin-6
- ↑ Vascular Endothelial Growth Factor

Endothelial Dysfunction

- ↓ Vasodilation

Blood Coagulation Abnormalities

- ↑ Factor VII
- ↑ Neutrophil Activation
- ↑ Platelet Activation

Neurocognitive Dysfunction

- ↑ Dementia
- ↑ Seizures
- Functional Brain Failure
- Brain Injury
- Prolonged Cerebellar Ataxia
Changes (Disruption) in Insulin Sensitivity

1) Insulin Resistance + Hyperinsulinemia
   a) typical of early type 2 DM
   b) impaired cognitive function

2) Insulin and Insulin Receptors
   a) important roles in cognitive performance via modification of activities of excitatory and inhibitory postsynaptic receptors and activation of specific signaling pathways
Insulin receptor signal transduction with respect to neuronal function: Insulin binds to and activates the insulin receptor (IR). The receptor undergoes a conformational change resulting in the phosphorylation of intracellular insulin receptor substrate (IRS) proteins on tyrosine residues.
Changes (Disruption) in Insulin Sensitivity

3) AD Patients
   a) lower insulin levels in cerebrospinal fluid (CSF)
   b) higher plasma insulin levels
   c) drastically reduced densities of insulin receptor in the brain

4) Amyloid Beta (Aβ) Protein
   a) Higher levels of plasma insulin → limit degradation of Aβ protein
      (via direct competition for the insulin-degrading enzyme) → amyloid accumulation
   b) lower insulin levels in CSF + impaired response to insulin and insulin-like growth factor-1 → inhibit the transportation of Aβ carrier proteins (albumin and transthyretin) → decrease the clearance of Aβ protein
Inflammation

1) DM Patients
   a) type 2 have higher levels of circulating inflammatory markers.
   b) Elevated circulating levels of inflammatory markers were associated with worse cognitive ability

2) AD patients
   a) increase levels of: interleukin-1, interleukin-6, tumor necrosis factor -\(\alpha\)
   b) Macrophage inflammatory protein-1\(\alpha\) in reactive astrocytes nearby A\(\beta\) plaques in the brain

3) Dementia patients
   a) Evidence of activated inflammatory response of microglial cells
Conclusions

1) Diabetes mellitus is a significant risk factor for vascular dementia and Alzheimer’s disease.
2) Good control of cardiovascular risk factors could be expected to reduce the risk of dementia
3) Chronic hyperglycemia may cause cognitive impairments and abnormalities in synaptic plasticity.
4) Hypoglycemia is a risk factor for cognitive impairments
5) Prolonged hyperinsulinemia induces an impaired response to insulin through a decreased expression of insulin receptors at the blood brain barrier and brain and consequently inhibits the insulin transportation into CSF and brain tissues → Aβ protein build up
6) Chronic inflammation may play a role in accelerated cognitive impairment.
Conclusions
THANK YOU