Diabetes-related dementia is associated with tau pathology rather than amyloid pathology

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Background and Purpose

Type 2 diabetes mellitus (DM) has been shown to increase the risk for cognitive decline and dementia, such as Alzheimer disease (AD) and vascular dementia (VaD). Additionally, there may be a dementia subgroup associated with specific DM-related metabolic abnormalities rather than with AD pathology or cerebrovascular diseases in patients with dementia associated with DM, referred to as "diabetes-related dementia (DrD)."

We studied amyloid (PiB) and Tau (PBB3) PET in subjects with DrD to investigate underlying neuropathological conditions.

Classification of dementia associated with type 2 DM

- Alzheimer’s disease
- Vascular dementia
- Diabetes-related dementia?

- DM ⇒ Dementia
- old age, high HbA1c level, long duration of diabetes, high frequency of insulin therapy, low frequency of ApoE 4 carriers, less severe medial temporal lobe atrophy, more impaired attention and executive function, less impaired word recall, and slow progression of cognitive decline.

Subjects

AD+DM: probable AD with type 2 DM (n=5)
DrD: Diabetes-related dementia (n=27)

Guidelines for the clinical diagnosis of diabetes-related dementia

1. Type 2 diabetes mellitus: long duration and less well-controlled glycemia
2. Dementia: impaired attention but less impaired word recall, slow progression of cognitive impairment
3. CT/MRI: no evidence of vascular lesions, diffuse cortical atrophy but less severe medial temporal lobe atrophy
4. SPECT/PET: no decreased hypoperfusion/hypometabolism in the posterior cerebral lobe
5. CSF: normal (or slightly elevated) p-tau and normal Aβ1-42 levels
6. ApoE4 carrier: low frequency
7. Exclusion of other dementia causes: i.e., hypothyroidism, vitamin B1, B12 deficiency, head trauma, chronic alcoholism, cerebrovascular disease or other neurodegenerative diseases

Methods (Amyloid and Tau PET)

PET: SET-2400W(Shimadzu, Kyoto, Japan)
Positron Medical Center, Tokyo Metropolitan Institute of Gerontology

Amyloid PET: 600 MBq of [11C]-Pittsburgh compound-B (PiB)
Tau PET: 400 MBq of [11C]-Pyridinyl-Butadienyl-Benzothiazole 3 (PBB3)

Clinical characteristics of AD and DrD

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<thead>
<tr>
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<th>AD</th>
<th>DrD</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>Age (years)</td>
<td>79.8 ± 6.6</td>
<td>79.7 ± 6.2</td>
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<tr>
<td>Gender (men/women)</td>
<td>3/2</td>
<td>9/18</td>
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<tr>
<td>Duration of dementia (years)</td>
<td>3.0 ± 1.1</td>
<td>3.1 ± 0.8</td>
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<tr>
<td>Education (years)</td>
<td>12.2 ± 2.5</td>
<td>12.0 ± 2.7</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.1 ± 0.8</td>
<td>8.1 ± 1.2</td>
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<tr>
<td>Duration of diabetes (years)</td>
<td>13.6 ± 11.2</td>
<td>19.4 ± 10.4</td>
</tr>
<tr>
<td>Treatment of diabetes (Insulin/oral)</td>
<td>0/5</td>
<td>9/18</td>
</tr>
<tr>
<td>MMSE score</td>
<td>22.2 ± 3.7</td>
<td>22.0 ± 2.1</td>
</tr>
<tr>
<td>ApoE4 carrier/noncarrier</td>
<td>3/2</td>
<td>7/20</td>
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Positive rate of PiB and PBB3 PET studies

<table>
<thead>
<tr>
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<th>PiB (Amyloid)</th>
<th>PBB3 (Tau)</th>
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<tr>
<td>AD(+DM)</td>
<td>100% (5/5)</td>
<td>100% (3/3)</td>
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<tr>
<td>Diabetes-related dementia</td>
<td>37% (10/27)</td>
<td>83% (15/18)</td>
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Classification of DrD depending on positivity of PiB and PBB3

PiB(amyloid)
- (-) 17% (3/18) ⇒ Nonspecific neuronal damage?
- (+) 61% (11/18) ⇒ Tauopathy
- 0% (0/18) ⇒ AD pathology

PBB3(tau)
- (-) 22% (4/18) ⇒ Alzheimers-related dementia
- (+) 61% (11/18) ⇒ Tauopathy
- 0% (0/18) ⇒ Nonspecific neuronal damage

Representative PiB and PBB3 PET images

Diabetes-related dementia ⇒ Tauopathy
AD pathology
Nonspecific neuronal damage

Conclusion

We found that DrD showed variable amyloid and tau accumulation patterns in the brain, different from AD. Although DrD seems to be a heterogeneous condition, DrD may be more associated with tau pathology rather than with amyloid pathology, in addition to AD pathology and neuronal damage due to DM-related metabolic abnormalities.

There are no conflicts of interest related to this study.