CSF biomarkers and the diagnosis of variant forms of Alzheimer’s disease

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The differential diagnosis of progressive neurodegenerative disorders may sometimes be challenging, despite longitudinal assessment and access to traditional modalities of structural and functional neuroimaging. In this article, the authors describe a patient tentatively diagnosed with corticobasal syndrome in whom investigation with cerebrospinal fluid biomarkers led to diagnostic revision and new therapeutic options.

Modern diagnostic criteria for Alzheimer’s disease (AD) have incorporated the use of disease biomarkers, specifically amyloid positron emission tomography (PET) and studies of cerebrospinal fluid (CSF) Aβ and tau proteins. Although some of these criteria were developed largely for use in the research community, for the purposes of therapeutic trials where high diagnostic specificity (exclusion of false positives) is most desirable, nevertheless, use of these sophisticated biomarker investigations may be valuable in day-to-day clinical practice.

Although AD most usually presents as a progressive amnestic syndrome in later life, presenting little diagnostic difficulty to clinicians familiar with the condition, a number of well-recognised AD variants may present a greater diagnostic challenge. The AD diagnostic criteria developed by the International Working Group encompassed AD variants characterised by deficits that principally affect functions other than memory, namely linguistic (logopenic progressive aphasia), visuospatial (posterior cortical atrophy; visual variant of AD), and executive functions (frontal AD). In addition to these variants, there have been occasional reports of AD cases resembling corticobasal degeneration, a rare condition that typically presents with asymmetrical parkinsonism and cognitive dysfunction.

We present a case in which AD CSF biomarkers proved essential in the differential diagnosis of a progressive neurodegenerative disorder of uncertain cause.

Presentation and history
A 64 year-old left-handed woman presented to old age psychiatry services with a 12–18 month history of cognitive dysfunction. These included problems with speech, characterised by word finding difficulties and hesitancy, and with numbers, evident when matching digits with written numbers, for example when writing cheques. She was disoriented around the house and had difficulty reading clock faces. Her memory was subjectively reported to be normal. Limb jerkiness, occasional falls, and tripping were also reported. There was no family history of cognitive disorder.

Initial magnetic resonance (MR) imaging of the brain showed some small vessel ischaemic change. Formal neuropsychological assessment showed a generalised and significant degree of impairment, affecting attentional processes, immediate memory more than delayed memory, language, visuospatial / constructional function, and executive function. The findings were interpreted as a generalised reduction in the efficiency of cognitive processing associated with small vessel disease.

On subsequent referral to the cognitive neurology clinic, salient findings on examination were of apraxia with difficulties in sequencing limb movements. The patient was slow, with some gegenhalten evident but otherwise normal limb tone. There were some myoclonic jerks in the upper limbs. There was some gaze impersistence and visual disorientation. Gait was hesitant because of jerkiness, for which reason she preferred to use a wheelchair.

Cognitive screening tests showed impairment: on the Mini-Mental State Examination (MMSE) she scored 15/30, and on the mini-Adenbrooke’s Cognitive Examination 13/30 with points lost in all domains (see Box).

Repeat MR brain imaging showed volume loss with parietal predominance – left more than right – with relative preservation of hippocampal volumes, as well as the previously observed vascular changes, which were unaltered. MR spectroscopy showed no definite abnormality, with no reduction in frontal lobe N-acetyl aspartate:creatinine (NAA/Cr) ratio compared with the occipital lobe. Functional imaging using 99mTc hexamethylpropylene amine oxime single photon emission computed tomography (99mTc HMPAO-SPECT) showed biparietal hypoperfusion.
Case notes | CSF biomarkers and AD

Box: Patient scores on MMSE and MACE at time of presentation to the cognitive neurology clinic

<table>
<thead>
<tr>
<th>MMSE</th>
<th>MACE</th>
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<tbody>
<tr>
<td>Orientation: Time</td>
<td>2/5</td>
</tr>
<tr>
<td>Orientation: Place</td>
<td>3/5</td>
</tr>
<tr>
<td>Registration: 3 items</td>
<td>3/3</td>
</tr>
<tr>
<td>Attention/Concentration: serial 7s, DLROW</td>
<td>0/5</td>
</tr>
<tr>
<td>Memory: Recall</td>
<td>0/3</td>
</tr>
<tr>
<td>Memory: Registration and recall of 7-item name and address</td>
<td>-</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>-</td>
</tr>
<tr>
<td>Language: Naming</td>
<td>2/2</td>
</tr>
<tr>
<td>Language: Comprehension of written and 3-step commands</td>
<td>4/4</td>
</tr>
<tr>
<td>Language: Repetition</td>
<td>0/1</td>
</tr>
<tr>
<td>Language: Writing</td>
<td>1/1</td>
</tr>
<tr>
<td>Visuospatial abilities: Intersecting pentagons</td>
<td>0/1</td>
</tr>
<tr>
<td>Visuospatial abilities: Clock drawing</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td><strong>15/30</strong></td>
</tr>
</tbody>
</table>

In light of the apraxia, myoclonus, cognitive decline, and parietal brain atrophy and hypoperfusion with relative sparing of the medial temporal lobe volume and perfusion, vascular cognitive impairment was thought an unlikely diagnostic explanation and a provisional diagnosis of corticobasal syndrome (CBS) was made.

Over the next two years, the patient continued to deteriorate slowly, requiring increasing assistance with activities of daily living such as washing and dressing and she was no longer able to cook. Because of the apparent absence of treatment options, a further opinion was sought. MMSE had dropped to 5/30. It was noted that, alongside worsening of the previously documented cognitive impairment, there was now much more marked impairment of memory and speech; and although she could pronounce individual phonemes, words and short sentences without difficulty, this broke down when trying to repeat longer sentences. MR imaging showed mild progression of parietal atrophy, and there was now atrophy involving the hippocampi as well.

Based on the logopenic pattern of speech impairment, the more evident memory issues, and the progression of atrophy to involve the hippocampi, the possibility of variant AD, rather than CBS, was raised. To further investigate this possibility the patient underwent lumbar puncture for cerebrospinal fluid (CSF) analysis, specifically for measurement of Aβ1-42 and tau proteins, CSF biomarkers as recommended for use in AD diagnostic criteria.1,2 These showed depressed CSF Aβ1-42 (400pg/mL; normal range [NR] 627–1322) with very elevated tau (1274pg/mL; NR 146–595) and phospho-tau (102pg/mL; NR 24–68) levels, as typically found in AD.

In light of the revised diagnosis, the patient was treated with cholinesterase inhibitors with some subjective improvement in awareness. Jerkiness settled with a small dose of clonazepam such that she now had more confidence in walking.

**Discussion**

This case illustrates the value of AD CSF biomarkers in the differential diagnosis of neurodegenerative disorders. It endorses the view that ‘in early-onset disease with atypical presentation, diagnostic biomarkers can … guide management and decision making’.3

Corticobasal degeneration (CBD) is a progressive neurodegenerative disorder that typically presents with an asymmetrical parkinsonian syndrome and cognitive dysfunction and is characterised pathologically by the widespread deposition of hyperphosphorylated 4-repeat tau protein in neurons and glia, the latter as astrocytic plaques.4 There are currently no specific treatment options available for CBD. Current diagnostic criteria for CBD recognise the variability of presentation, which complicates clinical diagnosis,5 such that definitive diagnosis can usually be made only at post-mortem.

Cases of clinically suspected CBD that are eventually found to have other pathological substrates are well recognised.6,7 In 2003, Boeve et al.8 and Doran et al.7 independently suggested the terminology of ‘corticobasal syndrome’ or ‘CBS’ be used for suspected cases of CBD but without pathological confirmation, in order to emphasise the pathological heterogeneity of this syndrome.

AD as one of the pathological substrates of CBS is well-described,6,7,9,10 even with signs thought typical of CBD such as the alien limb phenomenon.8 In one recent pathological series of 21 cases with ante-mortem clinical diagnosis of CBD, only five patients had CBD pathology and another five had AD.11 Although there are occasional reports of depressed CSF Aβ1-42 and elevated tau in ‘CBD’ these lack pathological confirmation,12 so it is still to be determined whether the biomarker changes predict pathology with high sensitivity and specificity.

Hence, AD features in the differential diagnosis of CBS and, as this case demonstrates, this is one of the scenarios where molecular investigations to confirm or refute the presence of AD pathology – using CSF biomarkers and / or amyloid PET – should be considered.

In summary, rare presentations of common diseases may be more common than rare diseases, and in the case of the corticobasal syndrome
both atypical presentations of AD and corticobasal degeneration need to be considered. Analysis of AD CSF biomarkers may establish the diagnosis in such atypical presentations, opening up therapeutic options that otherwise may not be considered.

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**Conflicts of interest**
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**References**