The effects of donepezil on nicotinic receptor status in dementia: a 123I-5IA-85380 SPECT study

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examing neuropathologist. However, on the basis of the clinical presentation and CSF results, the patient was thought to have a subacute demyelinating polyneuropathy. She was treated with oral steroids and, over the next 6 weeks, made a complete neurological recovery.

Three months later, she was admitted to a gynaecology ward with menorrhagia and fluctuating pyrexia. She was anaemic with raised inflammatory markers and recurrent abnormal liver function tests (γ-CT 259 IU/L). HIV and hepatitis serology (A, B, C) were negative. A CT scan showed evidence of ascites and soft-tissue abnormalities involving the omentum. She underwent a laparoscopy and omental biopsy. This showed a polymorphic cellular infiltrate, including many small mature lymphocytes and histiocytes. It also included frequent medium-sized and large lymphocytes with atypical cytological features, including vesicular nuclei, prominent nucleoli and abundant pale cytoplasm. Immunohistochemistry showed the atypical lymphocytes to be CDS-positive T cells with a cytotoxic phenotype. CD4, CD3, CD57, CD30, ALK and B-cell markers were all negative. In situ hybridisation for EBV was positive in a proportion of large cells and T-cell receptor gamma gene rearrangement PCR demonstrated a clonal T-cell population, confirming that the tumour was of T-cell rather than NK-cell origin. However, because of the perforin and granzyme B positivity, it is still regarded as part of the Extranodal NK/T lymphoma, nasal-type group. A diagnosis of extranodal NK/T-cell lymphoma of nasal type was made.

The prognosis was regarded as poor, so treatment was commenced with the CODOX-M and IVAC schedule. This intensive chemotherapy schedule was originally described for use in Burkitt’s lymphoma, but has also been used in a variety of poor prognosis high-grade lymphomas.

A brisk response to treatment was noted with rapid resolution of the ascites and all other symptoms and signs. A reduced intensity unrelated donor allogeneic transplant was considered but it was not possible to find a full match. An end-of-treatment PET scan demonstrated an excellent response but was equivocal for whether a complete or partial remission had been obtained. MRI and ultrasound scans of the equivocal areas in both ovarian adnexa on the PET scan suggested that complete remission had been obtained. The patient remains well and in remission more than 1 year from diagnosis, with no neurological symptoms.

**DISCUSSION**

Lymphomatous tumours have a propensity to affect the nervous system. Most peripheral nerve complications are due to non-Hodgkin’s lymphoma (NHL) infiltration of nerve roots, leading to a radicular picture affecting spinal and cranial nerve roots. NHL has also been described in association with a predominantly sensory axonal syndrome and the presence of GD1b antibodies or other immunoglobulins with anti-myelin activity. Contrastingly, Hodgkin’s lymphoma (HL) usually damages peripheral nerves by an inflammatory process and may be associated with Guillain–Barre syndrome or chronic inflammatory demyelinating polyneuropathy. Paraneoplastic neuropathies have a heterogeneous phenotype and the classical sensory ganglionopathy may be absent. HL has been reported in association with a sensory neuropathy and various paraneoplastic antibodies, akin to anti-Hu.

Extranodal NK/T-cell lymphoma of nasal type is a rare NHL with male preponderance. The category includes both cytotoxic T-cell and NK-cell lymphomas, which show essentially identical clinical and pathological features, and frequently overlapping immunophenotypes. Although it may affect a wide variety of extranodal sites, the prototypic site of involvement is the nasal cavity, and it is best known as the most common cause of lethal midline granuloma. EBV almost certainly plays a pathogenetic role, clonal episomal integration of EBV being demonstrable in the majority of cases. The tumour has a variable but generally poor prognosis with a 5-year survival rate of only 20%. Systemic dissemination of disease appears to be the most important adverse prognostic factor regardless of the site of primary origin. Some tumours respond well to aggressive anthracycline-containing combination chemotherapy, but histological grade has not been shown to be useful in predicting outcome. Involvement of the central nervous system is extremely rare and, to our knowledge, involvement of peripheral nerves has not previously been described.

We cannot exclude the possibility of sequential presentations of two extremely rare disorders. However, in view of the temporal course of the patient’s illness, as well as the transient disturbance of liver function in the prodromal period (perhaps indicating a precipitating viral infection) and the inflammatory nature of the neuropathy, we feel that the lymphoma was aetiological. It could be argued that the initial neurological symptoms were radical and caused by lymphomatous infiltration, but the CSF results coupled with the complete recovery following steroid treatment, in our view, makes this explanation less likely.

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**REFERENCES**


**The effects of donepezil on nicotinic receptor status in dementia: a 123I-5IA-85380 SPECT study**

Disturbances in the cerebral cholinergic nervous system and subsequent reduction of acetylcholine (ACh) are biochemical features of Alzheimer’s disease (AD) and dementia with Lewy bodies (DLB), and treatments with acetylcholinesterase inhibitors (AChEIs) offer symptomatic improvement in cognitive and non-cognitive symptoms. One important subclass of ACh receptors are nicotinic acetylcholine receptors (nAChRs), which have been shown to be implicated in memory and cognitive processes. The SPECT tracer 123I-5IA-85380 is a radioligand that can visualise in vivo the presynaptic nAChR (α4β2 subtype, the most common subtype in man). In the present study, we assessed the effects of the AChEI donepezil on nicotinic receptor status in AD and DBL using 123I-5IA-85380 SPECT imaging. We hypothesised that relative 123I-5IA-85380 uptake would
increase after administration of donepezil in accordance with previous studies using non-selective nicotinic ligands.²

METHODS

Subjects

We recruited 9 non-smoking patients (for >10 years) with dementia (4 AD and 5 DLB). Patients with AD fulfilled NINCDS/ADRDA criteria for “probable” AD,³ whereas DLB subjects satisfied criteria for “probable” DLB.⁴ The study received ethical and ARSAC approval. All participants and their nearest relative gave informed written consent.

Assessments and study design

Prior to baseline ¹²³I-5IA-85380 imaging, patients underwent physical, neurological and neuropsychiatric assessments. Tests included the Cambridge Cognitive Examination (CAMCOG), the Mini-Mental State Examination (MMSE) and the motor Unified Parkinson’s Disease Rating Scale (UPDRS III). Following baseline scan, all patients were treated with an AChEI (donepezil, 10 mg). After a period of at least 6 months, patients underwent repeated cognitive tests and SPECT scanning.

¹²³I-5IA-85380 synthesis and imaging

Preparation of ¹²³I-5IA-85380 was carried out by the West of Scotland Radionuclide Dispensary, Glasgow University, UK.⁵ Subjects were scanned for 30 minutes using a triple-headed rotating gamma camera (Picker 3000XP) approximately 2 hours after a bolus intravenous injection of 185 MBq of ¹²³I-5IA-85380. The projections were reconstructed using ramp-filtered back-projection and corrected for attenuation using Chang’s method.

Image analyses

Imaging data were assessed for regionally specific effects using SPM2 (Statistical Parametric Mapping program, version 2; http://www.fil.ion.ucl.ac.uk/spm). Initially, each subject underwent the following spatial normalisation procedures:

- Co-registration of repeat scan to baseline scan using rigid body registration.
- Spatial normalisation (12-parameter) of baseline scan to ⁹⁹mTc-exametazime SPECT template in standard MNI space.
- Transformation parameters calculated (as above) applied to repeat scan.
- Spatial smoothing of spatially normalised scans using 10 mm FWHM 3D Gaussian filter.

Prior to smoothing, all spatially normalised images were visually inspected to ensure the accuracy of registrations. Next, a univariate voxel-wise statistical model was used—that is, multi-subject conditions and covariates (paired r-test)—to assess regions of significant alterations in ¹²³I-5IA-85380 uptake in the repeat scan relative to baseline scan in the pooled dementia group (AD and DLB). Images were scaled to their mean global brain activity (counts voxel⁻¹). Regions were reported as significant if multiple-comparison corrected voxel-level was p<0.05.

RESULTS

Table 1 shows demographic data. At baseline, groups were matched for MMSE, CAMCOG and CAMCOGmemory (F₁, ⁷ < 1.3, p=0.5), but not for age and UPDRS III (F₁, ⁷ > 6.5, p<0.04). Gender also slightly differed among groups (χ² = 4.2, df = 1, p = 0.04). Within each group, variables did not significantly alter between baseline and repeat scanning (t score < 1.9, p>0.1), except for CAMCOGmemory in patients with AD, which was of modest significance (t = 3.2, p = 0.05). Patients also received medication over long periods (AD: min–max, 11.7–17.7 months; DLB: 8.3–18.0 months), although the average duration did not significantly vary (F₁, ⁷ = 1.9, p=0.1), except for CAMCOGmemory in patients with AD, which was of modest significance (t = 3.2, p = 0.04). SPM compared the differences in ¹²³I-5IA-85380 uptake between baseline and repeat scans, demonstrating no significant voxels (post-correction). Figure 1 shows individual

![Figure 1](http://www.fil.ion.ucl.ac.uk/spm)

**Figure 1** Scatter plots of individual AD (open squares) and DLB (closed diamonds) mean normalised ¹²³I-5IA-85380 uptake values at baseline and repeat scans in frontal and temporal regions. Also shown are transverse scans of an AD and DLB before and after treatment with donepezil, in which uptake is not significantly affected. AD, Alzheimer’s disease; DLB, dementia with Lewy bodies.

### Table 1 Demographic and neuropsychological data of subjects

<table>
<thead>
<tr>
<th></th>
<th>AD (n = 4)</th>
<th>DLB (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st Scan</td>
<td>2nd Scan</td>
</tr>
<tr>
<td><strong>Sex (M:F)</strong></td>
<td>3:1</td>
<td>5:0</td>
</tr>
<tr>
<td><strong>Age, years (SD)</strong></td>
<td>80.9 (7.4)</td>
<td>82.2 (7.6)</td>
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<tr>
<td><strong>MMSE, max 30 (SD)</strong></td>
<td>21.8 (4.0)</td>
<td>22.5 (6.4)</td>
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<tr>
<td><strong>CAMCOG, max 107 (SD)</strong></td>
<td>75.0 (11.8)</td>
<td>65.3 (17.3)</td>
</tr>
<tr>
<td><strong>CAMCOGmemory, max 24 (SD)</strong></td>
<td>16.0 (5.7)</td>
<td>12.8 (6.9)</td>
</tr>
<tr>
<td><strong>UPDRS III, max 108 (SD)</strong></td>
<td>8.0 (2.5)</td>
<td>4.8 (4.2)</td>
</tr>
<tr>
<td><strong>Time on Donepezil at 2nd scan, months (SD)</strong></td>
<td>15.5 (2.7)</td>
<td>13.6 (4.7)</td>
</tr>
</tbody>
</table>

Values expressed as: Mean ± SD.

AD, Alzheimer’s disease; DLB, dementia with Lewy bodies; M, male; F, female; SD, standard deviation; MMSE, Mini-Mental State Examination; CAMCOG, Cambridge Cognitive Examination; UPDRS III, motor Unified Parkinson’s Disease Rating Scale.
mean normalised regions of interest data at baseline and repeat scans in patients with AD and those with DLB for selected regions (frontal, temporal), as well as typical axial images of a patient with AD and DLB before and after treatment with donepezil. No correlations were observed between cognitive measures and imaging data.

**DISCUSSION**

*In vivo* SPECT was used to investigate the effect of AChEIs on nicotinic receptor binding in dementia. No differences were observed between baseline and repeat scans. Group comparisons were also carried out independently in patients with AD and DLB with similar results. This suggests that administration of AChEIs over the study period was either providing some degree of neuroprotection of the nicotinic cholinergic system, or that treatment did not affect receptor status and 123I-5IA-85380 uptake was unchanged. However, in the absence of a placebo control group, the result is tentative. Another explanation could be that increased levels of ACh after donepezil displaced 123I-5IA-85380 binding on nAChR sites, therefore underestimating the difference between baseline and repeat scans.

Previous imaging studies have investigated the effects of AChEIs on cholinergic receptor function, but these have been exclusively in patients with AD. Nordberg et al. showed an associated increase in nAChR binding in the temporal cortex after a 3-month treatment period with tacrine (an AChEI) using 11C-nicotine and PET imaging. They also demonstrated its positive effect after long-term use of the drug (15–31 months) in three patients with mild AD. Kemp et al. studied the effects of donepezil on muscarinic AChR receptor status in patients with AD using 11C-tacrine and PET SPECT. They reported a greater degree of uptake in their placebo group compared to their treated group, indicating a neuroprotective role, a result that could be interpreted as consistent with findings of the present study.

Pooling of groups was performed in an effort to increase statistical power of SPM analysis, although such an approach may be questionable. Also, as subjects received treatment over a variable timescale (3.5–18.0 months), an attempt was made to adjust for this potential confound and was thus entered into the statistical model as a nuisance variable. However, this did not change the outcome. Spatial normalisation of scans was optimum in our view given the present data set, although co-registration to their MRI (if obtained) may have offered greater registration accuracy. Limitations of the study included: small populations; lack of other imaging data for subjects (rCBF SPECT, MRI); no partial volume effect correction due to lack of MRI information; absence of a placebo control group to confirm with greater confidence the role of donepezil on 123I-5IA-85380 uptake; and—as patients were on medication during the second scan—a direct or indirect pharmacological effect on 123I-5IA-85380 uptake cannot be excluded.

In conclusion, we found no significant change in nAChR assessed using 123I-5IA-85380 SPECT in patients with AD and DLB after donepezil treatment, which may imply a degree of neuroprotection of the nicotinic cholinergic system. Serial 123I-5IA-85380 imaging could be an effective tool in assessing the response of nicotinic receptors to disease-modifying agents in dementia.

**REFERENCES**


**BOOK REVIEWS**

The soul in the brain: the cerebral basis of language, art, and belief


“The soul in the brain: the cerebral basis of language, art, and belief” represents a major project from neuropsychiatrist Michael Trimble. An original and distinguished academic who has focused his research on the behavioural and psychiatric correlates of epilepsy, Dr Trimble has attempted to describe the neuroanatomical substrates that make us uniquely human. Ambitious and broad, the book tackles everything from religion, ethics, philosophy, poetry, music and visual art, while attempting to place the appearance of these uniquely human abilities in a historically temporal schema and understand their neuroanatomical underpinnings. The influence of neurological and psychiatric disorders is explored as they relate to creativity, whether religious, philosophical, literary, musical or visual. Simultaneously, the author attempts to translate these fascinating topics to a large audience, an audience presumably linked together by an interest in the brain and the mind.

Written by a real scholar with an entertaining and rich mind, the book is largely successful at bringing together the widely ranging functions and topics that are addressed.

The book begins with an interesting chapter that outlines the origins of human consciousness, tackling myth, religion and psychology while discussing major historical thinkers on these topics ranging from Descartes to James to Freud. This is followed by a lively and comprehensive chapter on the anatomy of emotion and cortical function, the only part of the book with extensive visual illustrations. These two chapters serve as a template for the rest of the book, in which the discussion moves quickly back and forth between philosophy and anatomy.

In later chapters discuss language; the first emphasises the origins of language in the human cortex, the next a discussion of written language with a particularly compelling section on poetry and, finally, a third chapter tackles the breakdown of language in disorders such as schizophrenia and aphasia. The thoughts of diverse figures ranging from MacDonald Critchley, Michael Corballis, Samuel Coleridge and Noam Chomsky are quoted on the origins of thought and language. On the topic of thought without language there is a remarkable statement from Coleridge, “I believe that the process of thought might be carried on apart from written or spoken language. I do not doubt in the least that if language had been denied or withheld from man, thought would have been a process more simple, more easy, and more perfect than at present.” The mixing of scientific and literary perspectives makes this book particularly fun to read.

Two subsequent chapters on neuroethology weave important themes related to belief, moral reasoning and religious experiences as they relate to epilepsy and other neuropsychiatric syndromes. Dr Trimble has