Alzheimer’s disease and frontotemporal dementia are differentiated by discriminant analysis applied to $^{99m}$Tc HmPAO SPECT data

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Abstract

Objective—Alzheimer’s disease (AD) and frontotemporal dementia (FTD) are the most frequent neurodegenerative cognitive disorders. However, FTD remains poorly recognised clinically. The use of $^{99m}$Tc HmPAO-single photon emission computed tomography (SPECT) has been demonstrated in the differentiation of AD and FTD. Nevertheless, there are very few comparative studies designed to assess its precise value in this differential diagnosis. The aim was to determine a simple decision rule, deduced from statistical analysis, which, if applied to regions of interest (ROIs) and mini mental state examination (MMSE), could improve the predictive value of SPECT in differential diagnosis between AD and FTD.

Methods—Forty patients, 20 with probable AD and 20 with probable FTD were included. All patients underwent brain SPECT imaging, after an intravenous injection of $^{99m}$Tc HmPAO ($555$ mBq). For each patient, 20 ROIs were determined on the Fleishig’s slice and their activity was normalised to the mean cerebellar activity. Bivariate analysis (Wilcoxon rank tests) and multivariate analysis (stepwise discriminant analysis) were performed to determine the subgroup of variables able to give the highest predictive value for this differential diagnosis. A simple decision rule was built from a predictive score derived by factorial discriminant analysis.

Results—As previously described, the fixation defect was found in frontal regions of interest (ROIs) in FTD and in the left temporoparietal-occipital ROIs in AD. Among the 21 variables, five were finally selected: right median frontal, left lateral frontal, left temporoparietal, left temporoparietal-occipital areas, and MMSE. One hundred per cent of patients with FTD were correctly classified by the decision rule (20/20 patients) and 90% of patients with AD (18/20).

Conclusion—AD and FTD are differentiated by SPECT. Automatic classification based on a decision rule deduced from factorial discriminant analysis could enhance its performance.

Keywords: Alzheimer’s disease; frontotemporal degeneration; SPECT; discriminant analysis

The frontotemporal dementia (FTD) concept still needs clinical and non-clinical tools to enable better discrimination. The main differential diagnosis remains Alzheimer’s disease (AD). According to the Lund and Manchester criteria, FTD is a clinical designation, applied to a progressive behavioural disorder associated with primary degeneration of the frontal and the temporal lobes. Decreasing regional perfusion shown by SPECT indicates impaired function in specific cortical areas, and this correlates with clinical, neuropsychological, and histopathological findings. Usually, the perfusion pattern is assessed qualitatively by visual inspection and by semiquantitative analysis. Moreover, the studies are usually designed to clarify the functional pattern and not to compare specifically the regional cerebral blood flow (rCBF) in AD versus FTD. However, this approach seems to be necessary to establish the statistical value of the SPECT data in differential diagnosis.

The aim of this study was (1) to specify the contribution of $^{99m}$Tc HmPAO SPECT in the differential diagnosis between FTD and AD by using statistical analysis; (2) to search for a possible decision rule leading to a differential classification of these two types of dementias, deduced from multivariate analysis applied to SPECT data and mini mental state examination (MMSE) score.

Patients and methods

Patients

We included 40 patients in this study, 20 with probable FTD and 20 with probable AD. They were selected and followed up in the Memory Clinic Centre. The Lund and Manchester criteria were fulfilled by patients with FTD and NINCDS-ADRDA criteria by patients with AD. Patients were excluded when other chronic neurological or non-neurological disorder was detected, and CT or MRI was performed for all of them. Patients with strokes
Fixation index (mean (SD)) of each region of interest in the two groups (AD v FTD)

<table>
<thead>
<tr>
<th>ROI</th>
<th>L Med-Fr (0.067)</th>
<th>L Lat-Fr (0.074)</th>
<th>L Post-Fr (0.004)</th>
<th>L Temp-Ins (0.011)</th>
<th>L Temp-Par (0.012)</th>
<th>L Temp-Par-Occ (0.01)</th>
<th>L Par-Occ (0.011)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>0.828 (0.074)</td>
<td>0.871 (0.07)</td>
<td>0.842 (0.011)</td>
<td>0.975 (0.075)</td>
<td>0.775 (0.012)</td>
<td>0.794 (0.011)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.835]</td>
<td>[0.85]</td>
<td>[0.85]</td>
<td>[0.839]</td>
<td>[0.839]</td>
<td>[0.859]</td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td>0.003</td>
<td>0.006</td>
<td>0.14</td>
<td>0.14</td>
<td>0.014</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>FTD</td>
<td>0.795 (0.066)</td>
<td>0.822 (0.062)</td>
<td>0.881 (0.045)</td>
<td>0.839 (0.053)</td>
<td>0.875 (0.056)</td>
<td>0.862 (0.078)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.786]</td>
<td>[0.839]</td>
<td>[0.873]</td>
<td>[0.839]</td>
<td>[0.839]</td>
<td>[0.859]</td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td>0.0003</td>
<td>0.014</td>
<td>0.14</td>
<td>0.14</td>
<td>0.014</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>L Oocc</td>
<td>97.4 (7.2)</td>
<td>0.948 (0.067)</td>
<td>0.879 (0.064)</td>
<td>0.835 (0.073)</td>
<td>0.836 (0.065)</td>
<td>0.878 (0.057)</td>
<td>0.889 (0.083)</td>
</tr>
<tr>
<td></td>
<td>[0.965]</td>
<td>[0.933]</td>
<td>[0.93]</td>
<td>[0.85]</td>
<td>[0.84]</td>
<td>[0.87]</td>
<td>[0.899]</td>
</tr>
<tr>
<td></td>
<td>[0.989]</td>
<td>[0.919]</td>
<td>[0.879]</td>
<td>[0.754]</td>
<td>[0.781]</td>
<td>[0.821]</td>
<td>[0.91]</td>
</tr>
<tr>
<td>p Value</td>
<td>NS</td>
<td>NS</td>
<td>0.003</td>
<td>0.003</td>
<td>0.008</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R Temp-Par</td>
<td>R Par-Occ</td>
<td>R L Thal</td>
<td>R Med-Fr</td>
<td>R Lat-Fr</td>
<td>R Post-Flr</td>
<td>R Temp-Ins</td>
</tr>
<tr>
<td></td>
<td>0.884 (0.06)</td>
<td>0.981 (0.011)</td>
<td>0.968 (0.074)</td>
<td>0.956 (0.061)</td>
<td>0.88 (0.066)</td>
<td>0.88 (0.06)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.875]</td>
<td>[0.979]</td>
<td>[0.98]</td>
<td>[0.915]</td>
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<tr>
<td></td>
<td>[0.851]</td>
<td>[0.872]</td>
<td>[0.997]</td>
<td>[0.891]</td>
<td>[0.921]</td>
<td>[0.874]</td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td>0.013</td>
<td>0.02</td>
<td>NS</td>
<td>NS</td>
<td>0.02</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

Fixation index is defined as a fraction of mean cerebellar fixation. Median (M) and significance after Wilcoxon’s rank test (p) are calculated for each region of interest. The p value is considered significant at p<0.15. Five non-discriminative (NS) variables were eliminated after the initial bivariate analysis.

L=Left; R=Right; Med-Fr=medial-frontal; Lat-Fr=lateral-frontal; Post-Fr=posterior-frontal; Temp-Ins=temporal and insular; Temp-Par=temporal and parietal; Temp-Par-Occ=temporoparieto-occipital junction; Par-Occ=parieto-occipital; Occ=occipital; Lent-Nuc=lenticular nucleus; Thal=thalamus.

RESULTS

The table gives the result of the group comparison. For the multivariate analysis, five ROIs were excluded because p was greater than 0.15 (L Lent-Nuc, R Occ, L Occ, L Thal, and R Thal) leading to the selection of 16 variables.

In a first step, the FDA was performed on these 16 variables (MMSE score and 15 indexes). All of them showed a very good separation between the two groups by means of the discriminant score (r² ratio 0.78). Among the 40 patients, 38 (95%) were correctly classified. After the stepwise discriminant analysis, the following predictor variables were definitively retained: R Med-Fr, MMSE, L Temp-Par-Occ, L Post-Flr, and L Temp-Ins. A second FDA was performed on these five remaining variables. The final score was calculated as follows:

S=6.1×(R Med-Fr)−9.8×(MMSE/100)−12.3×(L Temp-Par-Occ)+9.6×(L Lat-Fr)+9.6×(L Temp-Par)−9.1

The figure represents the distribution of the discriminant score by status (AD or FLD). This graphic demonstrates that the subset of five variables seemed to be relevant for predicting diagnosis. Then, from the figure a decision rule was derived: if S<0, then diagnosis proposed is FTD, and if S≥0, the diagnosis proposed is AD.

Using this decision rule, 100% (20/20) of patients with FLD and 90% (18/20) of patients with AD were classified in the correct group.
This “automatic” method is as efficient as a study based on the selected 16 ROIs.

Discussion

By studying two groups of patients with probable AD and with probable FTD in SPECT with an original statistical approach, we showed that visual analysis can be completed by a decision rule, which provides statistically controlled and safe information.

Clinical possibilities of overlapping are seen at the beginning of the illness and in patients with FTD usually fulfill the NINCDS-ADRDA criteria of AD.10 Other criteria are necessary for the differential diagnosis.

Since the end of the 1980s, many studies have confirmed the usefulness of 99mTc-HmPAO-SPECT in these diseases.11–12 Between FTD and AD, frontal anterior and parieto-occipital hypoperusions are known to be easily distinguishable and to constitute a reliable paraclinical tool for identifying these diseases. In a multivariate correlate study derived from OPTIMA, Jobst et al reported a good correlation between clinical, 99mTc-HmPAO-SPECT, and neuropathological findings in AD. A close coupling between reduced rCBF and specific neuropathological deficits in AD13 and FTD14 was also shown. In our study, in agreement with these previous data, the lateral and internal frontal ROIs were hypoperfused in cases of FTD, at a high significance level.

Pickut et al have applied discriminant analysis to the differential diagnosis between AD and FTD with SPECT.15 They also proposed an algorithm which gives the probability for AD or FTD, but in their approach frontal hypoperfusion was the only SPECT data kept in the final decision rule. Miller et al, using the SPECT data as the gold standard for the diagnosis of FTD,16 identified the best items of the Lund and Manchester criteria by applying a stepwise logistic regression analysis to these criteria for DFT diagnosis. They suggested that only five clinical criteria selected from among those of Lund and Manchester were as efficient as all of them for positive diagnosis of FTD. Although the clinical definition of FTD seems to be well established, it does not exclude disorders that may also affect frontotemporal structures such as AD. In our study, two patients with AD were wrongly classified in the FTD group, but clinical possibilities of overlap are possible at the beginning of the illness.17 Our two wrongly classified patients could belong to this group. Patients with FTD usually fulfill the NINCDS-ADRDA criteria of AD18 and other clinical and neuropsychological criteria are necessary to distinguish these patients. Nevertheless, relatively low fixation levels predominating in frontal, temporal, and limbic areas and basal ganglia are found in normal elderly people compared with younger people.17 This infers that a slight frontal defect may not have pathological significance in AD as a frontal defect seen in AD could be linked to this “physiological” phenomenon. In other words, the emerging concept of dementia with Lewy bodies could lead to a blackballing of the usual approach based on binary differential diagnosis between FTD and AD. Finally, our proposition of an algorithm deduced from stepwise logistic regression could be used as a road to diagnosis when the precise question is: “Is this disease AD or FTD?”. Visual analysis, which is subjective and depends on the examiner, is usually not completed by a decision rule deduced from discriminant analysis for differential diagnosis of AD and FTD. We conclude that discriminant analysis can provide objective information which helps the examiner to establish the final positive diagnosis. Nevertheless, further studies are required to validate this tool.