J Neural Transm (2010) 117:1111–1114
DOI 10.1007/s00702-010-0459-7

DEMENTIAS - SHORT COMMUNICATION

Confirmation rate of blinded ^{99m}Tc-SPECT compared to neurochemical dementia biomarkers in CSF in patients with Alzheimer disease

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Received: 1 June 2010 / Accepted: 27 July 2010 / Published online: 7 August 2010

Abstract In Alzheimer disease, CSF biomarkers and nuclear imaging are of particular interest. Many studies investigated only one technique, limiting comparison. Here, in 76 patients blinded 99mTc-SPECT was compared to CSF. Sensitivity of CSF was 92%; and 51% for SPECT. Specificity favored SPECT (90 vs. 80%). Both techniques showed no coherence ($p = 0.17$–0.47). Our results confirm that CSF biomarkers show higher sensitivity. SPECT has higher specificity and can also be used for other dementias without established CSF biomarkers.

Keywords Biomarker · Cerebrospinal fluid · Nuclear medicine imaging

Introduction

Diagnosis of Alzheimer disease (AD) shifts towards biomarkers (Fink 2008; Wallesch 2007; Lewczuk et al. 2010). Especially nuclear imaging methods (Rodda et al. 2010) and CSF assays hold promise to improve early AD diagnosis. SPECT can show the typical cortical parieto-temporal pattern of AD, but also frontotemporal dementia and dementia with Lewy-bodies can be differentiated (Jobst et al. 1998; Lobotesis et al. 2001; Dougall et al. 2004). Past studies have often investigated either SPECT or CSF and correlated it to the clinical diagnosis. In the current study we performed a direct head-to-head comparison of both methods.

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Methods

Between 2002 and 2009, 534 Patients were evaluated for memory disorders as described (Weih et al. 2009). According to guidelines, patients received imaging MRI or CT. Diagnosis of probable AD was made using NINCDS-ADRDA criteria. CSF analyses and routine SPECT results were then used to correlate the diagnosis. All other diagnoses were made according to ICD-10. Patients either received AD diagnosis after initial assessment or after a follow-up time of at least 2 years. Of all, 273 had CSF assays and 214 SPECT during a brief hospital admission. 91 patients received both tests, but in 15 cases either CSF or SPECT could not be assessed due to technical reasons. In the current study, 76 patients are summarized. APOE-genotyping was performed after informed consent (INNO-LiPA APOE; Innogenetics, Belgium). The study was approved by the local ethics committee. CSF assays was performed as described elsewhere (Lewczuk et al. 2004a; Lewczuk et al. 2008; Zimmermann et al. 2010).

The reference values are:

1. $A\beta_{1\text{-}42}$: >600 pg/ml (provided by the manufacturer)
2. $A\beta_{x\text{-}42}$: >550 pg/ml (Lewczuk et al. 2004b)

3. Phospho-tau 181 threonine (P-Tau): <60 mg/ml (Lewczuk et al. 2004a)
4. Total-tau (T-Tau): <300 pg/ml (Lewczuk et al. 2004b)

The reference values are subjected to the internal certified quality control system of the department (DIN ISO 9001-2008; LGA/InterCert). Longitudinal stability of the assays was tested with a quality control sample prepared and aliquoted from human CSF and then measured at every analytical run. No issues of assay instability have been observed to date. Due to technical reasons, phospho-tau was determined only in 54 patients. Negative control: 59 random selected patients without AD (19× FTD, 20× Depression, 20× MCI). Tc-99 m SPECT was performed using a Siemens Multispect 3 camera. Data acquisition was started 30 min after 740 MBq Tc-99 m i. v. Transaxial tomograms were reconstructed using back-projection (Butterworth 5th, cut-off 0.3 Nyquist, 1st order attenuation). In plane, resolution of the reconstructed images was 11 mm FWHM, and slice thickness was approximately 5.8 mm. After stereotactic reorientation, normalized 3D surface projections were generated and *Z*-scores were calculated pixel-by-pixel. Images were reinterpreted by two independent blinded observers (TK, DS). 20 Patients without dementia served as a negative control. In cases of differences, a consensus was formed after reassessment. All images were then categorized as either "normal", "AD possible" and "AD probable".

Results

Mean age was 66.8 ± 9.2 years, mean mini-mental status test (MMST) 21.9 ± 5.5. 35 patients were heterozygous for the APOE 4-allele; 4 patients had APOE 4/4. Mean $A\beta_{1\text{-}42}$ level in APOE 4 negative patients was 675 pg/ml and 679 pg/ml in APOE 4 positive patients. Any of the 4 CSF markers were abnormal in 70 of 76 AD patients (sensitivity 92 ± 6%) and normal in of 42 of 59 controls (specifity 71 ± 14%). In 63 of 76 AD cases, total-tau was increased (sensitivity 83 ± 9%) and normal in 43 of 59 controls (specificity 73 ± 14%). P-Tau: 36 of 54 AD (sensitivity 67 ± 11%); controls specificity 80% ± 11%.

$A\beta_{1\text{-}42}$ levels: 64 of 76 reduced in AD (sensitivity 84 ± 9%); controls specificity 80 ± 11%. SPECT was normal in 37 AD cases; 7 cases were possibly related to AD and 32 cases strongly suggestively or probably related to AD (sensitivity for any abnormal result: 51.3 ± 18.0%; sensitivity for probable AD in SPECT 42.1 ± 20.9% 95% CI). 2 of 20 control scans were possible related to AD (specificity 90 ± 13%). The blinded, consented SPECT results did not differ from the previous routine reports. Figure 1 combines CSF and SPECT results. It can be seen that the "probable AD in SPECT" does not cluster with pathological values in CSF (*shaded area*). Multivariate analysis (including age, education, education and APOE genotype) showed no significant coherence (estimated by correlation analysis) between the SPECT and CSF results [for Aβ42 (The Genetics) $p = 0.47$; Aβ42 (Innogenetics) $p = 0.35$; Total-tau $p = 0.10$; Phospho-tau $p = 0.17$].

Discussion

The main result of our study was that CSF and SPECT methods differ in their sensitivity which is in accordance with previous results (Lewczuk et al. 2008, 2009, 2010; Hansson et al. 2006). In contrast to the higher sensitivity of CSF, SPECT often shows no changes in cerebral blood flow in the early stage of the disease but has its advantages due to higher specificity. Also, SPECT has the possibility to detect other dementias like FTD, where there are no established CSF biomarkers (Ashford et al. 2000; Shih et al. 1999). The advantage of our study is that both CSF and SPECT were performed in the same population, under blinded and inter-observer consented reading conditions of the SPECT images allowing direct comparison of the two methods. In clinical routine, the SPECT rater is not blinded and transmission of clinical information might bias the results especially in borderline cases.

Compared with the literature, similar work was performed by Okamura et al. (2002). In their study, however, only 45 patients with mild cognitive impairment or AD were investigated and SPECT was not blinded to the clinical diagnosis. For CSF analysis, only tau-levels, but

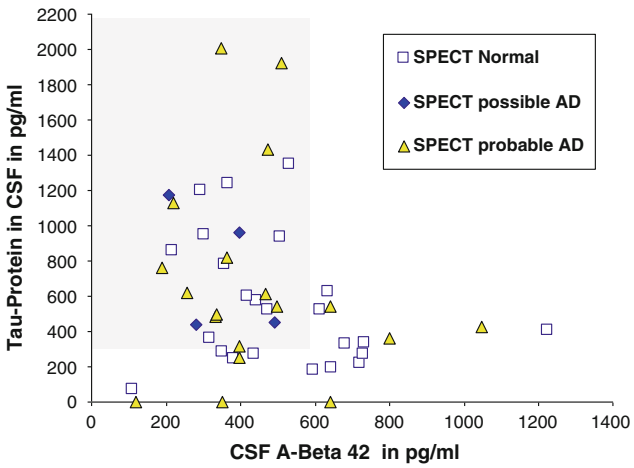

Fig. 1 A-Beta and Tau in CSF compared with ^{99m}Tc-SPECT. A-Beta 42 vs. Tau-Protein; *Squares* normal SPECT; *Diamonds* possible AD; *Triangles* probable AD according to SPECT criteria. *Shaded area* abnormal CSF values of CSF biomarkers

not other CSF biomarkers were examined. The authors suggested a combined CSF (Tau)–CBF (regional to cerebellar) index with a sensitivity of 89%. The combined CSF-CBF index had superior diagnostic value compared to the separated test results of SPECT or CSF alone. Tsolaki et al. (2001) investigated 117 patients with Alzheimer's dementia, but only CSF-Tau as CSF biomarker was tested. No correlation between CSF-Tau and SPECT changes was found. For any SPECT changes suggesting AD, we found a sensitivity of 51%, which is lower than the pooled sensitivity of 77%, as given in a meta-analysis of 13 studies (Dougall et al. 2004). This discrepancy could be due to several reasons: (1) the average age of patients in the meta-analysis was higher (70.1 years) than in the present study (66.8 years). (2) the average mini-mental status in the meta-analysis was 17.6 points, which is much lower than in the present study (21.9), which probably increases the likelihood of a positive SPECT result. (3) In the present study, the SPECT examiners were blinded to the clinical diagnosis and had to reach a consensus for each patient, which could further lower the sensitivity. In our study, the most sensitive CSF biomarkers were the concentrations of total-tau and Aβ42, followed by phospho-tau. In turn, phospho-tau and SPECT is more specific for AD. The main disadvantage of both CSF biomarkers and SPECT is that there are no internationally accepted cut-offs. SPECT images are interpreted by physicians aware of the clinical diagnosis, which can introduce bias. Recently we have shown that sophisticated pre-processing of SPECT data might help to reduce bias due to subjectivity (Merhof et al. 2010). On the other hand, some patients reject CSF collection, which might favor SPECT and leading to bias due to selection or underdiagnosis.

Still we believe that under appropriate quality control, a combination of CSF biomarkers and SPECT might provide the optimal cut-off between diagnostic sensitivity and specificity in the diagnosis of AD.

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