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Original Research Article

Positive FP-CIT SPECT (DaTSCAN) in Clinical Alzheimer's Disease – An Unexpected Finding?

Verena Bittner[a] Gerhard Ullrich[b] Markus Thormann[b]
Notger G. Müller[c] Christin Friederichs[b] Holger Amthauer[b]
Hans-Jochen Heinze[a, c] Daniel M. Bittner[a]

Departments of [a]Neurology, and [b]Radiology and Nuclear Medicine, University of Magdeburg, and [c]German Center of Neurodegenerative Diseases, Magdeburg, Germany

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Abstract
Clinically, Alzheimer's disease (AD) is by far the most common cause of dementia. Criteria for the diagnosis of dementia with Lewy bodies (DLB) are highly specific but not at all sensitive, which is reflected by the higher number of DLB cases detected histopathologically at autopsy. Imaging of dopamine transporter with FP-CIT SPECT is one possibility to increase sensitivity. Pathological confirmation was also included in the revised consensus criteria for the diagnosis of DLB. However, in the absence of parkinsonism, one of the core features, a clinical diagnosis of AD is more likely. The role of FP-CIT SPECT in DLB diagnosis remains to be clarified. Based on our 3 case reports and a review of the literature, the utility of this imaging method in the differential diagnosis of AD and DLB is highlighted.

Introduction

In postmortem studies, dementia with Lewy bodies (DLB) accounts for 10–20% of all cases of dementia and can therefore be regarded as the second most common cause of dementia after Alzheimer's disease (AD) [1–3]. For a definite diagnosis, autopsy is required.

Daniel M. Bittner, MD
Department of Neurology, University of Magdeburg
Leipziger Strasse 44
DE–39120 Magdeburg (Germany)
E-Mail daniel.bittner@med.ovgu.de

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Table 1. Presence of core symptoms of DLB in the 3 cases

	Dementia	Parkinsonism	Fluctuations	Visual hallucinations
Case 1	+	–	+	–
Case 2	+	–	–	+
Case 3	+	–	(+)	(+)

Table 2. Basic demographic data for the 3 cases

	Case 1	Case 2	Case 3
Age, years	80	82	72
Gender	male	male	male
Clinical symptom duration, years	2	1	1
MMSE	28	24	26
Phosphorylated tau, pg/ml	107	62	–
Tau, pg/ml	404	408	–
$A\beta_{1-42}$, pg/ml	469	577	–

However, confirmation of the diagnosis during the patient's lifetime is both reasonable and important, since patients with DLB respond to acetylcholine esterase inhibitors [4] and furthermore demonstrate a hypersensitivity to antipsychotic treatment [5, 6]. Clinical consensus criteria from 1996 possess a fairly high specificity with 80–90% [7], but only a low sensitivity, decreasing to 30% according to some studies [8–10]. DLB is most commonly misdiagnosed as AD [10, 11]. An improvement in clinical accuracy – particularly when AD is part of the differential diagnosis – seems to be worthwhile.

In postmortem studies, a 57–90% loss of presynaptic dopamine transporters could be demonstrated in DLB but not in AD [12, 13]. The presence a dopaminergic abnormality in DLB including striatal dopaminergic transporter loss was outlined in vivo with positron (PET) [14] and single-photon emission computed tomography (SPECT) [15, 16]. On the grounds of these observations, a positive, i.e. abnormal, FP-CIT-SPECT was included as a feature suggestive of DLB in the revised clinical consensus criteria from 2005 [17]. Sensitivity could thereby be increased up to 81.3% [18, 19]. Moreover, in a follow-up study over a period of 1 year, it was shown that in case of clinical suspicion, an FP-CIT scan may be helpful. Of 19 patients initially diagnosed as having possible and after 1 year as having probable DLB, 12 patients (63.2%) had pathological FP-CIT-SPECT, while the remaining 7 cases that were assessed as non-DLB at the 1-year follow-up had normal DaTSCAN (100% specificity) [19].

Another challenge in differential diagnosis resides in the distinction between Parkinson's disease and dementia (PDD). It is still an open question whether the underlying neurobiological changes result from one and the same mechanism in both entities. FP-CIT-SPECT is abnormal in both DLB and PDD [20, 21], possibly with a lower dopamine transporter uptake in PDD than in DLB [18]. Regarding the current clinical criteria, an agreement was reached that the diagnosis of DLB is not possible when extrapyramidal features are present for >12 months before the diagnosis of dementia [17]. In the following, we describe 3 cases who had no extrapyramidal signs, and thus DLB was the only possible diagnosis (table 1). Basic demographic data are listed in table 2.

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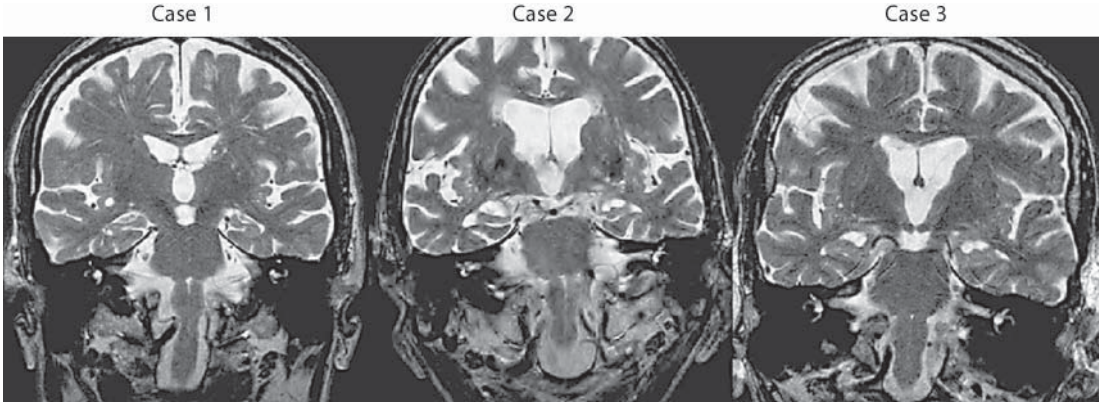

Fig. 1. cMRI of the 3 cases (T_2, coronal plane, including hippocampal area).

Table 3. Neuropsychological profiles of the 3 cases

	Case 1	Case 2	Case 3
MMSE	28	24	26
Attention	↓	↓	
Visuoconstruction	↓	↓	↓
Episodic memory	↓	↓	↓
Short-term/working memory	↓	↓	
Naming	↓	↓	↔
Executive function	↔	↓	↓
Orientation	↔	↔	↔

↓ = 1.5 SD below the median of a control sample (according to the respective test manuals); ↔ = value within the normal range of controls.

Case 1

An 80-year-old male complained of progressively decreasing memory over the previous 2 years. Word finding was particularly difficult. Orientation in time and place was reduced, and he developed difficulties in finding the treatment rooms during hospitalization. Additionally, vision began to be disturbed. He scarcely read anymore due to the effort required. Financial affairs were managed together with his wife. Neurological examination was completely normal, and, in particular, there were no signs of rigidity, hypokinesia or tremor. The UPDRS-III motor score was 0. Clinical chemistry did not reveal any significant abnormality apart from slightly elevated homocysteine (16.1 μmol/l). Mini Mental State Examination (MMSE) was within normal limits (28 of 30 points), but extensive neuropsychological testing revealed significant abnormalities regarding attention, visuospatial capabilities, short-term and working verbal memory, verbal episodic memory and naming. Orientation and executive functions were preserved (table 3). Moreover, during the session massive fluctuations were present. Cerebrospinal fluid (CSF) was normal with respect to basic parameters, but phosphorylated tau at threonine 231 was elevated and β-amyloid ($A\beta_{1-42}$) was decreased. Cerebral magnetic resonance imaging (MRI) revealed no significant vascular lesions, but frontotemporal atrophy was noted, with relative preservation of hippocampal formation (fig. 1).

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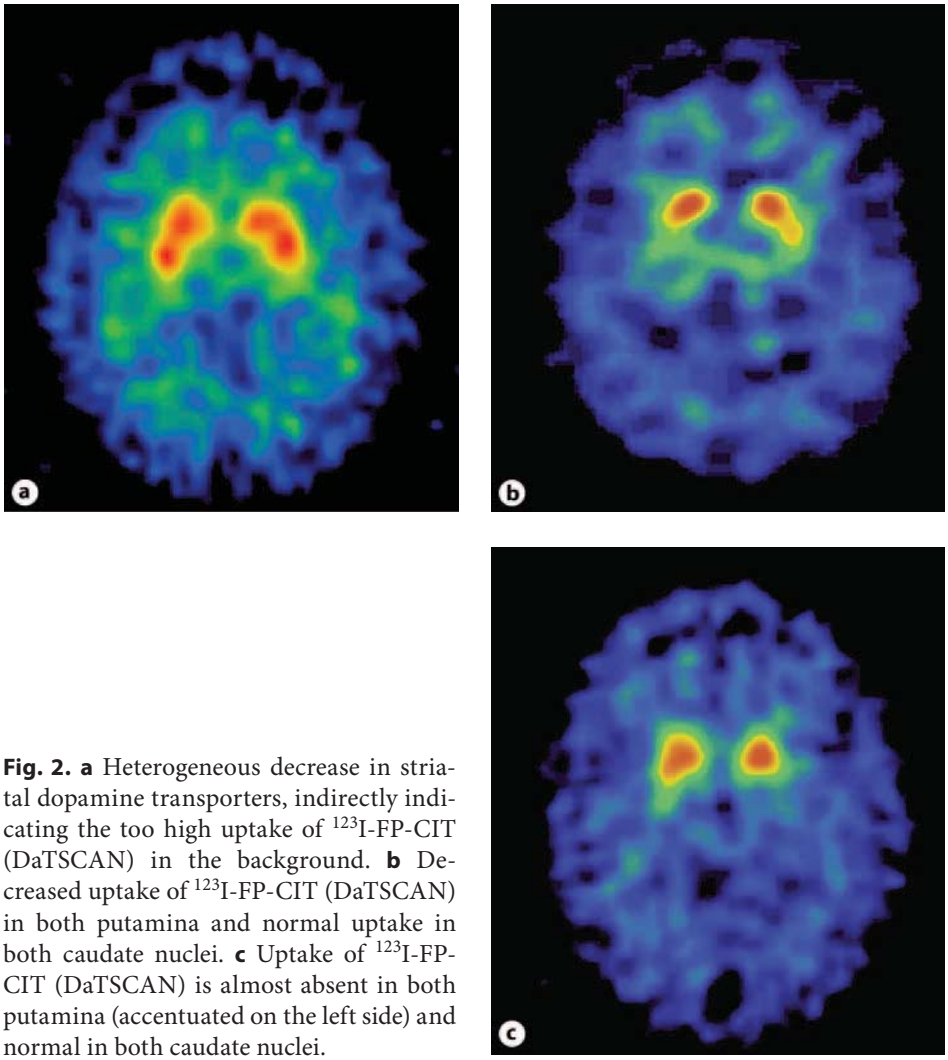

Fig. 2. a Heterogeneous decrease in striatal dopamine transporters, indirectly indicating the too high uptake of ^{123}I-FP-CIT (DaTSCAN) in the background. **b** Decreased uptake of ^{123}I-FP-CIT (DaTSCAN) in both putamina and normal uptake in both caudate nuclei. **c** Uptake of ^{123}I-FP-CIT (DaTSCAN) is almost absent in both putamina (accentuated on the left side) and normal in both caudate nuclei.

According to DSM IV [22] criteria, dementia was diagnosed and according to NINCDS-ADRDA criteria [23] probable dementia of the Alzheimer type was assumed: symptoms were progressive and were demonstrated in more than one cognitive domain. The findings were supported by typical CSF data. Although only one core feature (fluctuation) was present, FP-CIT-SPECT was performed and revealed a diminished dopamine transporter uptake in the basal ganglia (fig. 2a). In conclusion, following the revised consensus criteria for DLB from 2005, probable DLB was diagnosed.

Case 2

An 82-year-old male with AD diagnosed 1 year previously was admitted to the inpatient neurological department due to uncontrolled visual hallucinations. On neurological examination, there were no abnormalities, particularly no extrapyramidal signs. UPDRS-III motor score was 0. No fluctuations were observed or reported. In neuropsychology, MMSE was only slightly decreased (24 of 30 points), but apart from orientation all other cognitive do-

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mains were at least 1.5 SD from age-corrected means (attention, executive function, verbal short-term, working and episodic memory, naming and visuoconstruction; table 3). MRI of the head revealed global atrophy including the mesiotemporal region (fig. 1). CSF analysis was normal (including tau and $A\beta_{1-42}$). Due to the neuropsychological findings and at least one core feature of DLB, a DaTSCAN was performed and bilateral diminished dopamine transporter uptake was found (fig. 2b). On the basis of all the findings, a diagnosis of probable DLB was made.

Case 3

A 72-year-old male was admitted to the neurology outpatient clinic with subjective memory complaints. He had difficulty in remembering names and terms and moreover experienced spatial disorientation. Finally, completion of planned actions, e.g. handling of the coffee machine, were reported to be impaired. Neurological examination showed no abnormality, in particular no extrapyramidal signs. UPDRS-III motor score was 0. Only upon further inquiry, he admitted fluctuations and to some degree visual hallucinations although the latter more resembled misperception, were only of short duration and were not very well formed. Neuropsychologically, MMSE was almost within the normal range with 26 of 30 points, but deficits were found in visuospatial capabilities, executive function and verbal episodic memory, while orientation and naming were spared. Thorough assessment of attention was not performed (table 3). MRI of the head revealed some global atrophy but the mesiotemporal region, including the hippocampus, was spared (fig. 1). No CSF was obtained from this patient. DaTSCAN was performed and again dopamine transporter uptake was diminished (fig. 2c). A diagnosis of probable DLB was made.

Discussion

To be able to offer optimal therapeutic treatment, an accurate diagnosis during a patient's lifetime is important since DLB patients respond to therapy with acetylcholine esterase inhibitors [6, 24]. In addition, in DLB patients the sensitivity to antipsychotics is increased, with a 2- to 3-fold increase in mortality [5]. Treatment with these drugs has to be rational and should be restricted to carefully selected substances. Although the clinical diagnosis offers a high specificity, sensitivity with respect to DLB is only very low, leading to an important role of supplemental imaging techniques. In particular, distinguishing DLB from AD and PD is important.

Differentiating between DLB and PDD does not require further investigation since they are distinguished by an anamnestic criterion: whether or not dementia has developed within 1 year of onset of extrapyramidal signs. Dementia onset during that period suggests a diagnosis of DLB, whereas a later onset of dementia is suggestive of PDD.

Differentiation between DLB and AD is less clear. Since there is a huge overlap of clinical criteria, distinction is not feasible in most cases. Additional diagnostic parameters are inappropriate. Results from biomarkers gained by lumbar puncture are very similar in both diseases. The increase in tau and phosphorylated tau and decrease in $A\beta_{1-42}$ sometimes found in AD is less pronounced in DLB [25, 26]. However in a single case, distinction cannot be made. On MRI, mesiotemporal structures seem to be more affected in AD, whereas in DLB mesencephalic regions are atrophied [27]. Again an evaluation of a single subject is very difficult. Another imaging technique, perfusion scintigraphy of the brain with ^{99m}Tc-bicisate (Neurolite), has been investigated for its possible role as a diagnostic tool. The patterns of

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hypoperfusion slightly deviate between DLB and AD, with more occipital involvement in DLB, while in AD the characteristic finding is a temporoparietal hypoperfusion [28–36], but differences are not sufficient [37] or at least inferior to those found using FP-CIT-SPECT [38]. Hence depiction of the dopaminergic system using ligands such as FP-CIT offers the greatest potential for accurate diagnosis during a patient's lifetime. Neuroimaging is well tolerated by patients, particularly in early stages of the disease. Furthermore, SPECT is readily available, analysis is easily adapted to the diagnosis of DLB, and the procedure is not too time consuming. Reduction in FP-CIT is clearly and evidently associated with a fundamental neurobiological alteration recognized in DLB, namely dopaminergic loss [12, 13]. The above-mentioned reasons explain the increased implementation of FP-CIT-SPECT in routine diagnostics to support a diagnosis of DLB.

The question of the utility of the FP-CIT-SPECT in the distinction between DLB and AD then arises, especially for an early diagnosis. In AD, extrapyramidal signs occur in 20–30%, usually later in the course of the disease. Parkinsonism in early stages of dementia therefore argues against AD and favors DLB. Thus, whether there are extrapyramidal signs or not has a substantial impact on the diagnosis made. Although parkinsonism is one of the core features of DLB and occurs frequently in the course of the disease, in up to 75–80% of cases [39, 40] it is not required for a probable diagnosis of DLB. In a review of histopathologically confirmed cases from a brain bank and the current literature, parkinsonism was only found as a first sign of DLB in about 50% of the 239 study patients [41, 42].

It remains to be clarified how often an FP-CIT-SPECT will be abnormal in the absence of parkinsonism, and what criteria should be met before a DaTSCAN is performed in case extrapyramidal signs are absent. Our 3 case reports indicate that a FP-CIT scan may indeed be abnormal in the absence of extrapyramidal signs. An overview of the current literature is difficult because in most of the cases there are no detailed clinical descriptions of the patients and their association with DaTSCAN findings. From the literature, an abnormal DaTSCAN was obtained in 6 of 7 cases when parkinsonism was absent [18, 43, 44]. Furthermore, an abnormal DaTSCAN was found in the presence of only minor motoric abnormalities in 7–8 of 11 patients (UPDRS < 15) in a further study [45]. In the light of these observations, it is interesting that even when extrapyramidal motor signs are present, an abnormal FP-CIT-SPECT is rarely found in AD [18, 46], possibly pointing to an extrastriatal mechanism in the development of parkinsonism in AD.

Conclusion

We conclude that to increase diagnostic accuracy FP-CIT-SPECT should be readily available once the criteria of possible DLB are met. As demonstrated in our cases, attention should be focused on neuropsychological findings, namely preserved orientation, fluctuating levels of attention and visuoconstructive deficits. The latter two have been shown to be sensitive to and predictive of DLB even in the early stages of mild cognitive impairment [47].

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