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Cerebral blood flow changes in patients with dementia with Lewy Bodies (DLB). A study of 6 cases

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Abstract

BACKGROUND: The aim of this study was to show the application of cerebral blood flow SPECT (rCBF SPECT) study in dementia with Lewy bodies (DLB).
MATERIAL AND METHODS: ^{99m}Tc-ECD regional cerebral blood flow SPECT scanning was performed using a triple head, high resolution gamma camera on a group of six patients who full-filled criteria for clinical diagnosis of DLB. All patients were examined neurologically by a neurologist specialized in movement disorders. Detailed neuropsychological examination was performed on each patient with a psychological tests battery by an experienced neuropsychologist. Qualitative and quantitative analysis was performed utilizing an asymmetry index for unilateral perfusion deficits and a comparison to cerebellar perfusion to assess regional cerebral perfusion. A control group of 20 patients was studied to assess normal values, utilizing an asymmetry index for unilateral perfusion deficits, and a comparison to cerebellar perfusion was performed to assess regional cerebral perfusion.
RESULTS: In four cases rCBF SPECT images showed patterns of bilateral hypoperfusion of the temporal, parietal and occipital lobes. In two other cases parietal deficits were observed.
CONCLUSIONS: Functional neuroimaging with the use of CBF SPECT may contribute to clinical diagnosis of DLB.
Key words: dementia with Lewy bodies, single photon emission computed tomography, cerebral blood flow

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Introduction

Dementia with Lewy bodies (DLB) is the second most common type of degenerative dementia after Alzheimer's disease (AD) and accounts for 15–20% of all autopsy-confirmed dementias in old age [1]. The mean age of the onset of the disease ranges from 60 to 68 years. The male gender prevails; disease duration is 6-8 years. The differential diagnosis of DLB involves excluding dementia of Alzheimer type, Parkinson's disease with dementia (PDD) or vascular dementia (VaD), and also rare neurodegenerative disorders with parkinsonian features and cognitive decline, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and, in rare cases, Creutzfeldt-Jacob disease [2]. Core clinical features of DLB are: progressive cognitive impairment with temporal fluctuations, visual hallucinations and parkinsonian symptoms and signs. The currently accepted diagnostic criteria for DLB were published in 1996 [3] and improved new recommendations and revised version were proposed in the third report of the DLB Consortium in 2005 [4] (Table 1).

One of those core features has to be present for a diagnosis of possible DLB, and two for probable DLB. Supportive features may increase diagnostic sensitivity and exclusion criteria have to be considered [5]. Following these Consensus guidelines: dementia with Lewy bodies is the preferred term as opposed to "Lewy body variant of Alzheimer's disease" [3].

Early diagnosis of DLB is important, because neuroleptic treatment could be dangerous to patients, resulting in deterioration of

Table 1. Consensus Criteria for clinical diagnosis of probable and possible DLB [5]

Central features
Progressive cognitive decline of sufficient magnitude to interfere with normal social and occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits in tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent.
Core features (two of which are essential for the diagnosis of probable DLB and one of which is essential for the diagnosis of possible DLB)
Fluctuations in cognition with pronounced variations in attention and alertness
Recurrent visual hallucinations that are typically well formed and detailed
Spontaneous motor features of parkinsonism
Supportive features
Repeated falls
Syncope
Transient loss of consciousness
Neuroleptic sensitivity
Systematized delusions
Hallucinations in other modalities

neuropsychiatric symptoms and signs and may be associated with increased mortality.

Dementia with Lewy bodies shows clinical and pathological features which often overlap with AD and PD, especially the variant of PD with dementia (PDD) [3, 6, 7]. The main clinical differences between early stages of PD, DLB and AD are: no parkinsonian symptoms (rigidity, tremor, akinesia) and no effects of L-dopa treatment in patients with AD. Only 20–30% of patients with PD have dementia. Visual hallucinations occur almost solely in patients with DLB [2].

In advanced stages the differentiation might be more difficult, and DLB may be diagnosed retrospectively if memory deficits and hallucinations preceded or appeared within the first year along with parkinsonian symptoms.

Pathologically, Lewy bodies (LB) are rounded eosinophilic intracellular inclusions, containing a-synuclein as a main component, named after Friedrich Lewy, the German pathologist who first described them in 1912 [8]. As well as DLB, LB are classically associated with Parkinson's disease [9], and therefore the whole spectrum of disorders with this pathological hallmark are sometimes known as Lewy Bodies Diseases.

Diagnosis of DLB is difficult and is based on clinical criteria. The aim of this study was to show if there are any characteristic patterns of change in rCBF SPECT which may help to differentiate between AD and PDD.

Material and methods

Brain SPECT study was performed approximately 30 min after intravenous injection of ^{99m}Tc-ECD, activity 740 MBq (20 mCi), produced by FAM, Łódź, Poland. Scanning was performed on a triple-head gamma camera Multispect-3 (Siemens, Erlangen, Germany) using a low-energy, ultrahigh resolution parallel-hole collimator. Regional cerebral blood flow was assessed semi-quantitatively on transverse slices using the cerebellum region as reference. Focal perfusion deficits were assessed using an asymmetry index (AI):

$$AI = R - L/(R + L)/2 \times 100\%,$$

where R and L are mean counts/pixel values in the respective ROIs of the right and left hemispheres. All patients were examined neurologically by a neurologist who specialized in movements disorders (J.S.). Motor functions were assessed using the Hoehn and Yahr disease stage (H-Y) and the Unified Parkinson's Disease Rating Scale (UPDRS): part II - activities of daily living, part III — motor examination, part IV — complications of therapy and the Schwab and England Activities of Daily Living Scale (SE). Detailed neuropsychological examination was performed in each patient with test battery by clinical neuropsychologist (D.W.).

All studied patients had the diagnosis of DLB according to Consensus Criteria [3, 4].

Results

Case 1

Patient: male, age 72, 6 years from disease onset, carpenter, 11 years of education, right-handed:

— neuropsychological presentation and outcome — severe dementia (MMSE score: 10), with fluctuations of cognition. Deficiencies in executive functions, semantic fluency and phonological fluency. Disturbed orientation in time. The motor problems (shuffling gait and bradykinesia) started along with memory problems and visual hallucinations. Moderate response to rivastigmine treatment (2 × 3.0 mg daily) and mild improvement after L-dopa with benserazide (3 × 250 mg daily) were noticed;
— neurological examination — severely stooped posture, bradykinesia, dysarthria and rigidity, Hoehn-Yahr stage: IV, Schwab-England: 40%, UPDRS (II, III, IV): 81;
— magnetic resonance imaging (MRI) — diffused white matter T2 hyperintensities and dilatation of ventricles;
— rCBF SPECT imaging — presents bilateral hypoperfusion of temporal lobes in the range of 71–74%, parietal 73–76% and occipital 76–79% regions of perfusion of cerebellum.

Case 2

Patient: female, age 69, 5 years from disease onset, housewife, 12 years of education, right-handed:

— neuropsychological presentation and outcome — mild dementia (MMSE score: 18), moderate deficits in executive functions and semantic and phonological fluency, acalculia. Memory deficits and depression along with visual hallucinations were present since the year 2000, and motor problems started insidiously later on. Moderate deficit in executive functions as measured by semantic and phonological fluency. After promazine administration she was agitated. There was good response to L-dopa with benserazide (4 × 125 mg daily) and moderate response to rivastigmine (2 × 3.0 mg daily);

— neurological examination — predominantly left side resting tremor and rigidity, slightly stooped posture and mild bradykinesia. Hoehn-Yahr stage: 2.5, Schwab-England: 70%, UPDRS (II < III, IV) score: 34.
— MRI — slight dilatation of ventricles and small diffused white matter T2 hyperintensities;
— rCBF SPECT imaging — presents hypoperfusion of entire brain in the range of 68–79% of reference region, mostly expressed in temporal 74–79%, parietal 68–75% and parieto-occipital 74–77% regions. Hypoperfusion of left thalamus AI = 20%.

Case 3

Patient: male, 74-years-old, 2 years from disease onset, locksmith, 9 years of education, right handed:

— neuropsychological presentation and outcome — severe dementia (MMSE = 9) with fluctuations of cognition. Cognitive dysfunction (memory disturbances) started 2 years previously. Executive functions in fluency tests showed moderate deficit. There was very limited understanding, severe alexia, signs of agraphia and acalculia. He was administered L-dopa with benserazide (3 × 125 mg) daily with good response and rivastigmine (2 × 3.0 mg) daily with neither improvement nor deterioration during the 6 months observation;
— neurological examination — mild bradykinesia, rigidity (P ≥ L), stooped posture, retropulsion and hypomimia. Hoehn-Yahr stage: 2, Schwab-England score: 70% and UPDRS (II, III, IV) score: 30;
— computed tomography (CT) scans (MRI scan was not performed because of pacemaker implantation) — cortical atrophy (parietal, frontal and temporal);
— rCBF SPECT imaging — presents pattern of predominantly decreased cerebral blood flow within posterior temporal region in the range of 74–76% of reference region, parietal 69–73% and parieto-occipital region of 69–80%. Hypoperfusion of right thalamus AI = 13%.

Case 4

Patient: male, 62-years-old, farmer/wholesaler, 10 years of education, right handed, 2 years from disease onset:

— neuropsychological presentation and outcome — MMSE score (21) suggested mild dementia. Fluctuations of cognition were observed. Fluency and phonological tests were both impaired. Verbal paralexias with normal reading. Acalculia. He was administered rivastigmine (6 mg/d), L-dopa with benserazide (3 × 62.5 mg) daily and sertraline (50 mg daily) and after 3 months follow up his memory and mood, as well as motor state, were slightly improved and visual hallucinations disappeared;
— neurological examination: mild bradykinesia. In UPDRS the total score of parts II, III and IV was 23, Hoehn-Yahr stage 2, and Schwab-England — 70%;
— MRI — scans were normal;
— rCBF SPECT imaging — decreased cerebral blood flow within parietal superior region: more on right side. Hypoperfusion of left thalamus AI = 29%.

Case 5

Patient: female, 78-years-old, housewife, 8 years of education, right handed, 2 years from disease onset:

— neuropsychological presentation and outcome — global cognitive testing revealed severe dementia (MMSE — 8). Verbal fluency was low. Fluency and phonological tests were both impaired. No arithmetic operations were possible as a result of severe acalculia. She was administered rivastigmine (6 mg daily), sertraline (50 mg/d), L-dopa with benserazide (3 × 375 mg daily) and clozapine (6.25 mg/night) with good response: the frequency of hallucinations decreased, motor performance was better (no falls) and memory did not deteriorate during the follow up of 12 months;
— neurological examination — gait problems, bradykinesia, fluctuating memory problems and visual hallucinations started 2 years ago. In UPDRS the total score of parts II, III and IV was 30, Hoehn-Yahr stage: 2, Schwab-England 60%;
— MRI — Small diffused white matter T2 hyperintensities and slight dilatation of cerebral sulci and ventricles;
— rCBF SPECT imaging — hypoperfusion of entire brain in the range of 69–79% of reference region, mostly expressed in parietal superior region 70–77%. Single focal perfusion deficit in left anterior parietal region, AI = 13%.

Case 6

Male, 70-years-old, technician in a factory, 12.5 years of education, 5 years from the onset of cognitive symptoms:

— neuropsychological presentation and outcome — Mini Mental State results suggested mild dementia (MMSE — 21). Semantic fluency was close to normal, but phonological fluency was impaired. Immediate verbal memory was low. He was administered rivastigmine (7.5 mg/d), sertraline (50 mg/d), L-dopa with benserazide (3 × 125 mg/d) with good response (10 months follow up, no visual hallucinations, stabilization of progression of memory deficits and improved motor performance);
— neurological examination — motor problems (slight bradykinesia and resting tremor, hypokinesia of both upper extremities with predominance of left side). In UPDRS the total score of parts II, III and IV was 25, Hoehn-Yahr stage: 2 and Schwab-England — 90%;
— MRI — small diffused white matter T2 hyperintensities;
— rCBF SPECT imaging — showed hypoperfusion of entire brain in the range of 68–78% of the reference region, mostly expressed in temporo-parietal and parietal superior region 70–77%. Additionally single focal perfusion deficit in left posterior frontal region AI = 14%. Left thalamus hypoperfusion — 17%.

Discussion

Dementia with Lewy bodies AD and PD, especially the variant of PD with dementia (PDD), show clinical and pathological overlapping features [3, 6, 7]. Functional imaging such as rCBF SPECT or PET can provide important information to help clinicians in the diagnosis of these disorders (Figure 1). Unfortunately, access to PET scanning is still very rare and the examination is also rather expensive. Although DLB was described in the early '60s, it became renowned again in the beginning of the '90s. Therefore, the number of PET and SPECT studies in DLB, when compared with PD and/or AD, is rather limited.

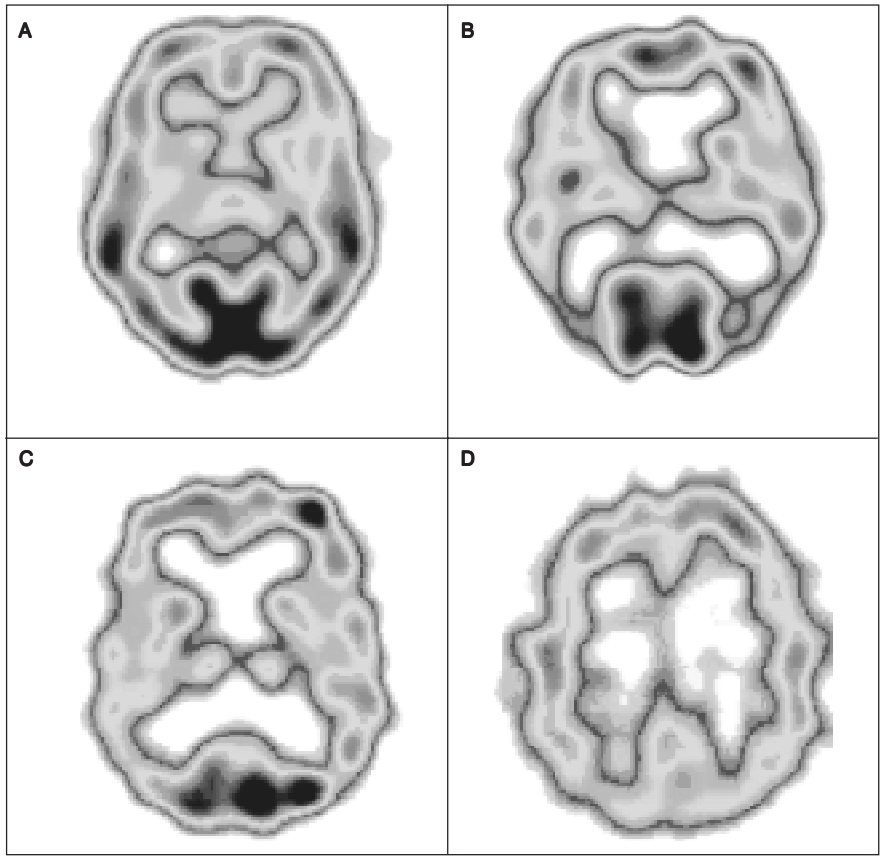

Figure 1. Examples of patterns of cerebral blood flow abnormalities: **A.** Normal image; **B.** Parkinson disease with dementia (PDD); **C.** Alzheimer disease (AD); **D.** Dementia with Lewy bodies (DLB).

Varma et al., in the first known rCBF SPECT study with ^{99m}Tc-HMPAO conducted on a group of patients fulfilling clinical criteria for DLB, have shown bilateral posterior cortical (parieto-temporal) blood-flow hypoperfusion, a pattern strikingly similar to that encountered in AD [10]. So this study contributes relatively little to clinical differentiation of DLB and AD because of the similarity of blood-flow deficit pattern.

The rCBF SPECT study performed by Lobotesis et al on patients with DLB, , showed significantly reduced rCBF in parietal and temporal regions in both: DLB and AD subjects with respect to AD and the control group. Nevertheless, in the AD group, a significant reduction in rCBF in the frontal and medial temporal regions was shown, whereas the DLB group showed prominent reduction of occipital perfusion. Therefore, those two groups differed only in terms of occipital perfusion [11]. A similar pattern of cerebral blood-flow within occipital lobes was also found in studies of Donnemiller [12], Pasquier [13] and Ishii [14], along with well preserved medial temporal perfusion. Similarly, in one of the latest studies of patients with DLB, AD, PDD and PD without dementia, a new means of analysis was performed using three-dimensional stereotactic surface projection (3D-SSP) analysis. SPECT images of the brain with N-isopropyl-p[123I] (^{123}J-IMP SPECT) showed similar cerebral perfusion reduction patterns in DLB and PDD patients at the lateral parietal association and lateral temporal association and precuneus on SPECT by pixel-by-pixel comparison, greater perfusion reduction was observed in DLB than in PDD. Cerebral perfusion was decreased at the occipital lobe of the DLB patients compared with the AD patients [15]. Colloby et al found frontal and parietal hypoperfusion in both AD and DLB, while temporal perfusion deficits were observed exclusively in AD and parieto-occipital deficits in DLB [16].

Different patterns of perfusion were found in both groups, AD and DLB, by Defebvre et al. They showed a hypoperfusion in all frontal regions in the DLB group as the most sensitive region for distinguishing DLB and AD *in vivo* [17].

This great variability of SPECT study results might be explained by the small numbers of subjects included at different clinical stages and differences in both imaging equipment and methods of analysis. It is interesting that DLB patients did not differ from controls in terms of mean subcortical blood-flow, and patients with asymmetrical signs of parkinsonism did not show corresponding left-right subcortical blood-flow asymmetries [10]. This was probably due to poor resolution of the current systems and difficulties in measuring ^{99m}Tc-HMPAO or ECD uptake in regions of small volume (thalamus and lenticular nucleus), but not the complete absence of subcortical abnormalities.

Another technique, which is more widely available than PET and especially useful to differentiate AD and DLB, is the visualizing of dopamine transporter systems by means of specific ligands. Using tracers for presynaptic dopamine transporters, such as I^{123}-β-CIT or I^{123}-FP-CIT (DaTSCAN), recent studies have shown severely impaired dopaminergic function in DLB, similar to PD, which

is not present in AD [18–21]. Another technique which may show the differences between DLB and AD is scintigraphy with ^{123}J-meta-iodo-benzyl-guanidine (^{123}J-MIBG). It enables the assessment of postganglionic sympathetic cardiac innervation. The ^{123}J-MIBG uptake in all patients with DLB was significantly lower than in patients with AD and control subjects [22, 23].

In four of the presented rCBF SPECT images of six cases with clinical diagnosis of DLB a similar pattern of hypoperfusion (with predominance of occipital and parietal lobes) to that shown in most of the studies mentioned above was noticed [11–16]. In three patients, hypoperfusion of the entire brain was shown, and in one of them hypoperfusion was mostly expressed in the parieto-occipital region. One patient presented hypoperfusion mostly expressed in the parietal superior region (more on the right side) and one patient presented with parietal superior along with hypoperfusion of the entire brain. In four patients perfusion deficit of the thalamus was noticed as well.

Practical conclusions

Despite the number of validation studies of diagnostic criteria for DLB and clearly defined core features (progressive cognitive impairment with temporal fluctuations, visual hallucinations and parkinsonian symptoms) it is still a challenge for practicing clinicians to diagnose DLB.

In the third report of the DLB Consortium the list of supportive features for DLB diagnosis has been extended to include radionuclide procedures such as SPECT/PET: hypoperfusion of the whole brain with profound reduction of uptake within occipital lobes- which was observed in most of our cases and low activity of the dopamine uptake site in the basal ganglia or abnormal uptake on MIBG.

The presented cases and the review of current literature reveal that functional imaging studies of brain perfusion with SPECT provide support to the clinician in the differential diagnosis of DLB.

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