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Original

Impact of CT based attenuation correction on quantitative assessment of DaTSCAN (^{123}I–Ioflupane) imaging in diagnosis of extrapyramidal diseases

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Abstract

The quality of visually and semi-quantitatively assessed DaTSCAN images is crucial for differential diagnostics of extrapyramidal diseases. Neuroimaging with the use of presynaptic tracers of the dopaminergic system provides evidence of nigrostriatal degeneration and may support the clinical diagnosis of Parkinsonism. During the last two years (2007–2008) we tried to elaborate the optimal methodology of SPECT/CT examination with the use of DaTSCAN (^{123}I-Ioflupane), and we sought to evaluate the effect of the reconstruction and attenuation correction method on semi-quantitative measures of relative uptake in the striatum.

In a present study, we retrospectively studied DaTSCAN scans of 44 consecutive patients with clinical indications of Parkinson's disease or uncertain Parkinsonian syndromes.

The quality of DaTSCAN images reconstructed with the use of ordered-subset expectation maximization reconstruction technique (OSEM) with attenuation correction based on CT maps was found to be superior to that provided by the commonly applied filtered backprojection method (FBP) with Chang attenuation correction. OSEM reconstructed transverse slices were more legible for clinical interpretation because of increased contrast and improved delineation between striatum structures.

Semi-quantitative assessments of relative striatum uptake for OSEM reconstructed slices secured better intra-operator reproducibility than that obtained by FBP method.

Key words: SPECT/CT DaTSCAN imaging, Parkinson disease, striatal dopamine transporter activity, iterative reconstruction technique

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Introduction

Differential diagnostics of extrapyramidal diseases remains an important challenge for clinicians. Many conditions mimic Parkinsonian syndromes, making diagnosis difficult, particularly during the early clinical stages when the signs and symptoms are subtle.

Functional investigations of the dopaminergic system with the use of nuclear medicine methods create a new possibility of differentiation between the involvement of the pre- and postsynaptic parts of the system [1, 2]. Research has shown that in patients with clinically uncertain Parkinsonian syndromes, DaTSCAN may provide physicians with greater diagnostic confidence in differentiating between pre-synaptic or non pre-synaptic Parkinsonism, leading to changes in the clinical management of the majority of patients [3–5].

The differentiation between a normal and abnormal distribution of radiotracer is primarily based on visual assessment of shape

and intensity that reflects differences of uptake. In normal cases, a transverse slice through the striatum shows a "comma" shaped putamen and a circular "full stop" shaped caudate on both hemispheres. Loss of uptake in the putamen is regarded as abnormal. Uptake in the caudate is initially preserved leaving just a circular image. In case of any abnormality, semi-quantitative evaluation is helpful in assessing asymmetry or lack of uptake [6].

In two years experience (2007–2008) of our department in diagnostics with the use of DaTSCAN (^{123}I-Ioflupane), we tried to elaborate the optimal methodology of SPECT/CT acquisition and processing technique [7, 8]. The aim of our present study was to evaluate the effect of iterative reconstruction algorithm OSEM with scatter correction and attenuation correction based on CT maps upon semi-quantitative measures of the relative uptake in the striatum [9–11].

Material and methods

We retrospectively analyzed records of the DaTSCAN examinations of 44 patients with clinical findings indicative of Parkinson's disease or clinically uncertain parkinsonian syndromes (atypical parkinsonism, secondary parkinsonism) or essential tremor. There were 25 females with an average age of 59 ± 12 years (range 29––79 years) and 19 men with an average age of 56 ± 21 years (range 19–84 years).

SPECT/CT acquisitions were performed with double-head hybrid gamma-camera Infinia Hawkeye GE, 4 h after intravenous administration of 185 MBq of ^{123}I–DaTSCAN (prior to radiotracer injection, patients received 3 times 10 drops of Lugol solution to prevent uptake of iodides by the thyroid gland).

Data were acquired with use of low-energy high-resolution (LEHR) collimators in a dual energy window: 159 keV ± 10% (scatter: 130 keV ± 10%), in a 128 × 128 matrix. In a step-and-shoot method, 120 projections for 45 seconds each were registered using 1.5 zoom.

Immediately after SPECT acquisition, CT scans (140 kV; 2.5 mA) of the patient's head were acquired. The entire acquisition procedure lasted about 50 minutes and it was generally well tolerated by the patients.

The patient's head was positioned on the head support usually used for brain imaging and was lightly restrained with special stretchers. For patients with slight tremor of the body, additional stretchers were used to immobilise the trunk. In one patient with pronounced tremor of the head caused by uncontrolled body movements, a short-term pharmacological sedation (Dormicum) was applied.

X-Ray data processed on the acquisition station gave high-resolution transversal slices of fixed 10 mm thickness. SPECT and X-Ray data were further processed and fused on a Xeleris workstation.

To optimise image processing the SPECT images were reconstructed independently by two technologists and with use of two different methods:

— analytical method of filtered backprojection FBP (Butterworth 0.45/10) with commonly used correction for attenuation according to the Chang method (attenuation coefficient: 0.11/cm);
— iterative method of ordered-subset expectation maximization reconstruction technique OSEM (2 iter.,10 sub., postfilter: Butterworth 0.50/10) with scatter correction and attenuation correction based on CT attenuation maps.

Both reconstruction procedures were performed in the orbitomeatal plane.

The obtained images of striatum were evaluated qualitatively by visual inspection and semiquantitatively by measurement of the relative uptake of DaTSCAN in the structures of striatum. Intensity and symmetry of uptake in the striatum was assessed visually by a nuclear medicine specialist on transversal slices obtained by both methods of reconstruction and on fused images (Figure 1).

In the visual assessment, the striatal uptake of the radiotracer was graded as normal or abnormal, and the abnormal images were

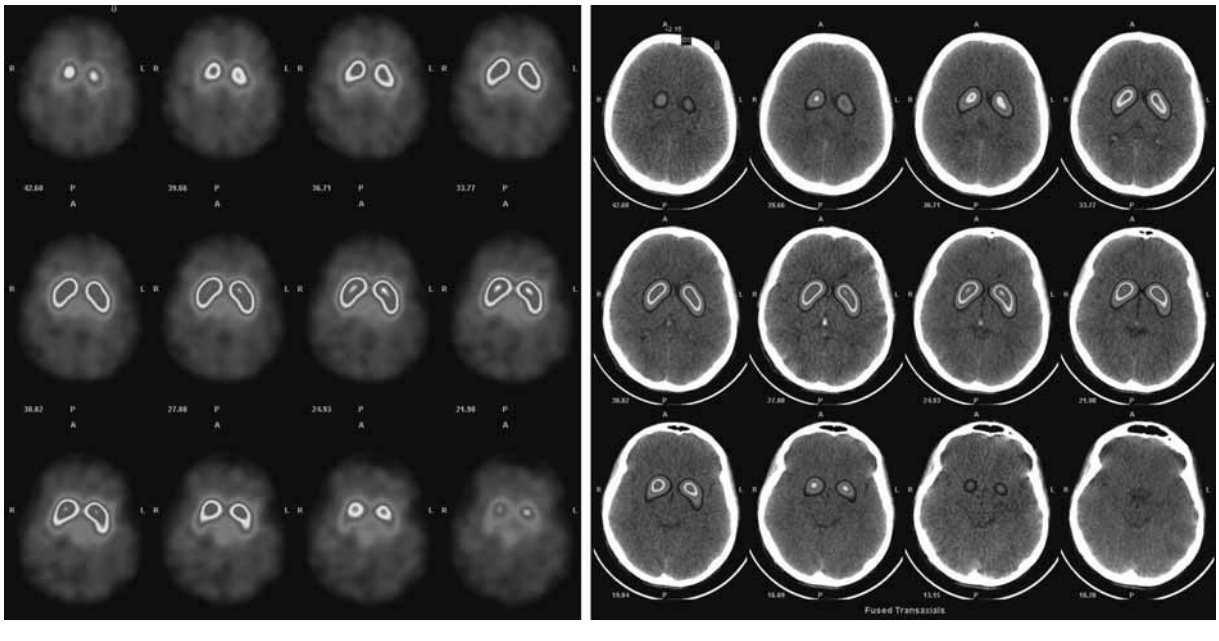


Figure 1. Transversal slices and fused images of DaTSCAN SPECT/CT acquisition.

further graded into three levels of severity: 1 — asymmetrical uptake with reduced putamen activity in one hemisphere; 2 — clear symmetrical reduction of putamen uptake in both hemispheres; 3 — absence of uptake in both putamens and reduced caudate activity in one hemisphere; 4 — bilateral absence of uptake in putamen and caudate nucleus with visualization of background activity (grading developed by A.M.Catafou in 2004 [5]).

In semi-quantitative assessment, binding potential was measured by indices of relative uptake in structures of the striatum to nonspecific uptake in the occipital cortex. Striatum structures were delineated with use of a semi-automatic procedure with fixed templates of putamen and caudate ROIs (manually adjusted by shift and rotation to match the respective striatum structure; ROI size was not affected) — on the 3 consecutive transversal slices with the most intense striatal uptake. Background ROI of fixed size and shape was placed on the occipital cortex in approximately the same manner on each slice.

Striatal binding indices given by the formula:

$$SBI = S/B$$

where S stands for the mean number of counts per pixel in the striatum, and B, the mean number of counts per pixel of background ROI of the occipital cortex) were calculated for each striatal structure in both cerebral hemispheres: caudate (CBI), putamen (PBI), and for the whole striatum (SBI) — for both reconstruction methods (Figures 2A, 2B).

For assessment of asymmetry of uptake, Striatal Asymmetry Indices expressed by the ratio of binding indices for left and right hemisphere (always taken as the ratio of a larger value to a smaller one) were calculated for each striatum structure: caudate (CAI), putamen (PAI), and the whole striatum (SAI).

For both reconstruction methods, processing was performed independently by 2 technologists — to evaluate intra- and inter-technologist variabilities.

Statistical analysis of measurements of relative uptake obtained for both methods of reconstruction and both technologists was performed by means of simple descriptive statistics (mean ± standard deviation) and nonparametric methods of testing the differences between analyzed variables (Mann-Whitney's or paired Wilcoxon's test) — with use of Statistica 8.0 software. The association between qualitative variables was assessed by Pearson correlation coefficient. Statistical significance was considered achieved for a value of $p \leq 0.05$.

Results

In the visual interpretation of the images by nuclear medicine specialists, among 44 cases 17 were reported as normal and 27 as having abnormal uptake in the basal ganglia. OSEM reconstructed transverse slices were found to be clearer for clinical interpretation because of increased contrast and improved delineation between striatum structures (Figure 3); however, there was no difference in visual assessment between the images reconstructed by different methods.

Among the abnormal DaTSCAN images, 6 were graded 1 (reduced uptake in putamen of one hemisphere), 17 were rated 2 (reduced uptake in putamen of both hemispheres), 2 had grade 3 (lack of uptake in putamens and in one caudate), and 2 images that were unreadable were graded 4 (Catafou scale).

Visual rates were highly consistent with results of semiquantitative analysis of specific to nonspecific caudate and putamen uptake.

In 17 patients, the results were visually classified as normal: striatal uptake was nearly equally intensive and symmetric, and mean indices were equal, respectively (Figure 4):

FBP: **CBI: 4.67 ± 0.88** (CAI: 1.04 ± 0.03);
PBI: 4.10 ± 0.84 (CAI: 1.05 ± 0.04);
OSEM: **CBI: 5.97 ± 1.21** (CAI: 1.06 ± 0.03);
PBI: 5.24 ± 1.11 (CAI: 1.08 ± 0.05).

For the whole area of the striatum, the appropriate indices were:

FBP: **SBI: 4.32 ± 0.83** (SAI: 1.03 ± 0.03);
OSEM: **SBI: 5.52 ± 1.12** (SAI: 1.04 ± 0.03);

In 25 cases, the images were classified as abnormal with visible deficits of uptake in the striatum structures, mostly in the putamen: grade 1 — 6 cases, grade 2 — 17 cases, grade 3 — 2 cases, and grade 4 — 2 cases with deficit of uptake in putamen and caudate (quantitative assessment was not possible because of total lack of uptake in striatum structures and very high unspecific cortical uptake).

Mean indices of uptake for 25 cases of abnormal scans were equal, respectively:

FBP: **CBI: 2.79 ± 0.78** (CAI: 1.08 ± 0.08);
PBI: 1.89 ± 0.53 (PAI: 1.14 ± 0.09);
OSEM: **CBI: 3.53 ± 1.31** (CAI: 1.10 ± 0.10);
PBI: 2.23 ± 0.77 (PAI: 1.21 ± 0.16).

For the whole area of the striatum, the appropriate indices were:

FBP: **SBI: 2.24 ± 0.61** (SAI: 1.09 ± 0.08);
OSEM: **SBI: 2.73 ± 0.95** (SAI: 1.14 ± 0.12);

Despite significantly higher values of OSEM indices, the ratios of relative uptake in the putamen and caudate (PBI/CBI) for both methods were almost equal (0.76 ± 0.12 for FBP and 0.75 ± 0.15 for OSEM), the last being due to the fact that there was a very good linear correlation between indices calculated by the same technologist for both methods ($r = 0.97$ for putamen and $r = 0.95$ for whole striatum).

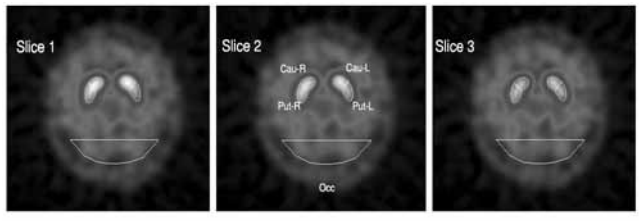
The above-presented mean values of striatal uptake for caudate, putamen, and the whole striatum were significantly lower in abnormal cases than in cases visually evaluated as normal — for both methods of image reconstruction, with approximately equal, very high levels of significance of testing ($p < 0.00001$).

We took into account the fact that in our study the patients with abnormal striatum uptake were significantly older than were those with normal DaTSCAN (62 ± 14 *vs.* 51 ±18; $p = 0.03$), because it is well known that the degree of uptake declines with age [13]. In our data intercorrelation between age and category of radiopharmaceutical uptake (normal/abnormal) cleared to be not significant ($p = 0.29$).

In 17 persons with physiological uptake there was a significant negative correlation between the uptake index in the striatum and the age ($r = –0.78$; $p < 0.001$).

The regression line approximated for our data had the form: SBI = 8.0–0.048·age, which anticipates a decrease of the binding index of about 0.5 in each decade of life. That relation was not statistically significant ($r = –0.39$; $p = 0.06$) in the group of 25 pa-

A

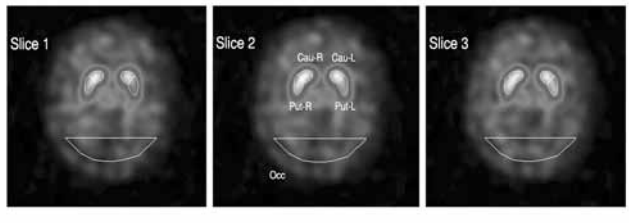


Mean Counts	Cau-R	Cau-L	Put-R	Put-L	Occ
Slice 1	509.21	482.52	402.36	455.35	109.76
Slice 2	480.21	448.31	410.04	453.23	109.01
Slice 3	437.66	403.83	397.32	423.32	106.47
Average	475.7	444.9	403.2	444.0	108.4

Ratios			
Striatum Total/Occ:			4.08
Caud-L/Occ:	4.39	>	4.25
Caud-R/Occ:	4.10		
Put-L/Occ:	3.72	>	3.91
Put-R/Occ:	4.10		
Putamen/Nucleus Caudatus:			0.92

Acquistion/Recons Params	
Dataset Name:	FBPAC_Transversal Obl
Acquisation Zoom:	1.50
Slice Thickness:	2.94 mm
Filter:	Butterworth 0.45/10.0
Attenuation corrected:	YES
Attenuation Corr Type:	CHANG
AttenuationCoeff:	0.11

B



Mean Counts	Cau-R	Cau-L	Put-R	Put-L	Occ
Slice 1	129.47	132.48	106.23	120.74	20.71
Slice 2	138.80	137.31	117.14	133.03	22.92
Slice 3	136.07	134.10	121.74	131.88	24.34
Average	134.4	134.6	115.0	128.5	22.7

Ratios			
Striatum Total/Occ:			5.66
Caud-L/Occ:	5.93	>	5.94
Caud-R/Occ:	5.94		
Put-L/Occ:	5.08	>	5.38
Put-R/Occ:	5.67		
Putamen/Nucleus Caudatus:			0.91

Acquistion/Recons Params	
Dataset Name:	IRACSC_Transversal Obl
Acquisation Zoom:	1.50
Slice Thickness:	2.94 mm
Filter:	Butterworth 0.50/10.0
Attenuation corrected:	YES

Figure 2. Exemplary reports of semiquantitative analysis of 3 selected transversal slices of DaTSCAN images. **A.** Reconstructed by FBP method. **B.** Reconstructed by OSEM method.

tients with abnormal uptake who were at very different stages of significant nigrostriatal degeneration (Figure 5).

Indices of asymmetry for putamen in 25 cases with abnormal DaTSCAN scan were significantly higher than in normal images, for both methods, but the difference of striatum asymmetry was most pronounced in the OSEM method (significance of testing of the difference was $p = 0.001$ *vs*. $p = 0.01$ for FBP method).

Indices of uptake calculated independently by two technologists demonstrated very good concordance ($r = 0.96$ for FBP and 0.97 for OSEM reconstructed slices); however, the mean difference in uptake indices calculated independently was lower for the OSEM method (OSEM: 0.18 ± 0.10 *vs.* FBP: 0.27 ± 0.14; $p = 0.03$).

Discussion

Quantitative methods are known to be a significant support for visual analysis of nuclear medicine images. They are especially useful with the range of normative values for the applied proce-

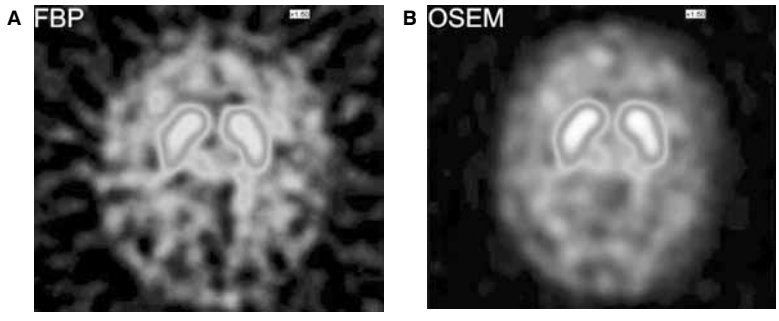


Figure 3. Transversal slices. **A.** Reconstructed by FBP method. **B.** Reconstructed by OSEM method.

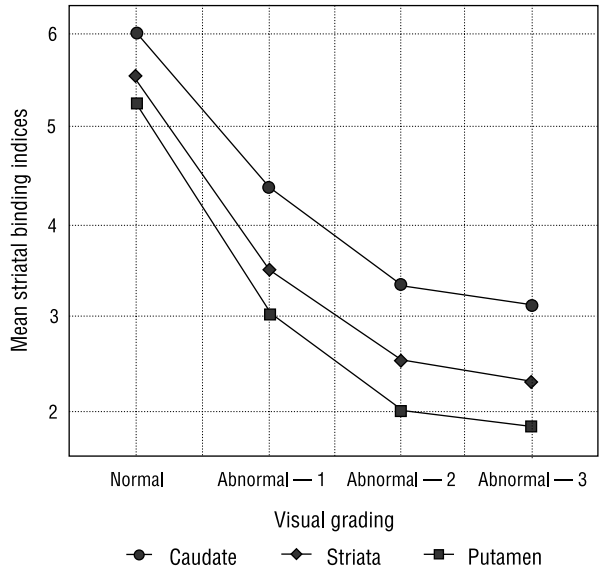


Figure 4. Mean striatal binding indices *vs.* visual assessment grades for OSEM reconstructed DaTSCAN slices of 42 patients.

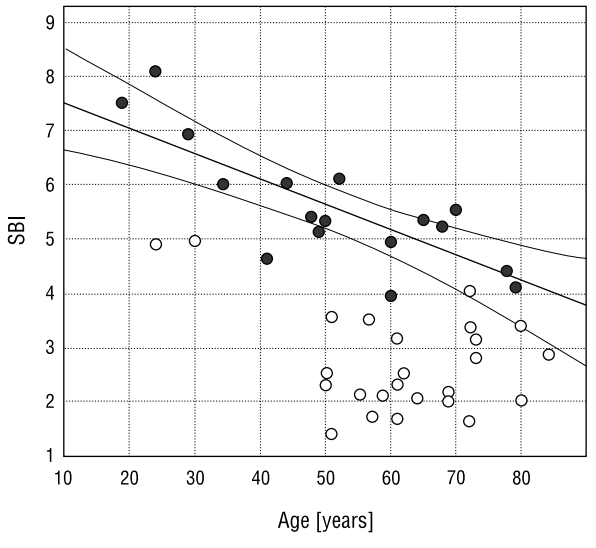


Figure 5. Association between relative striatal uptake and age — in patients with normal and abnormal DaTSCAN SPECT images. SBI — striatal binding index.

dure. Reference values given in the form of indices of relative uptake should be derived independently by each department because of statistical errors connected with the physical features of the given imaging device (partial volume effect, counting statistics, nonuniformity) [12]. In the lack of that kind of reference, data obtained for a control group of healthy volunteers; in some nuclear medicine units normative values for DaTSCAN uptake are evaluated from a patient population of visually normal striatal dopamine transporter activity [13, 14]. In our study we had only 17 normal scans, so we need to continue our experience in DaTSCAN imaging to have more subjects for generating DaTSCAN reference values for different age groups.

Analysis of the association between patient's age and the value of DaTSCAN uptake in the striatum confirmed that in patients with normal DaTSCAN binding the rate of uptake declines with age [13]. In our data the average decrement in the rate of uptake was approximately 0.5 per decade.

Relative measures of striatal uptake calculated on OSEM reconstructed slices seem to guarantee better possibilities of differentiation between normal and abnormal uptake.

The mean asymmetry observed between hemispheres in striatum uptake of normal DaTSCAN scans was about 5% (SAI: 1.04 $\pm$ 0.03). In abnormal cases, the mean difference observed on OSEM slices was ca 15% (SAI: 1.14 $\pm$ 0.12), while mean asymmetry registered with FBP method was only about 10% (SAI: 1.09 $\pm$ 0.08).

OSEM reconstructed images were assessed to have lower inter- and intra-technologist variability, so we decided to introduce that method of processing of DaTSCAN records to everyday practice and to continue research for the optimization of reconstruction parameters of that procedure (number of subsets and iterations).

Conclusions

The quality of OSEM reconstructed DATSCAN images with attenuation correction based on CT maps was found to be superior to images obtained by the commonly used FBP method.

OSEM reconstructed transverse slices cleared to be more legible for clinical interpretation because of increased contrast and improved delineation between the striatum structures.

Semi-quantitative assessment of relative striatum uptake for OSEM reconstructed transversal slices secured better intra-operator reproducibility than for slices obtained by the analytical method of reconstruction.

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