The utility of FDG-PET in the differential diagnosis of Parkinsonism

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ABSTRACT

Introduction: Differential diagnosis of parkinsonian disorders can be difficult on clinical grounds, especially in the early stage. Recent advancements in 18-F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging reveals different patterns of regional glucose metabolism in idiopathic Parkinson’s disease (IPD) and atypical parkinsonian syndromes, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS), which may help differentiating between these conditions.

Purpose: To assess the utility of FDG-PET imaging in differential diagnosis of Parkinsonism in clinical practice.

Methods: FDG-PET was performed in 72 patients with parkinsonism (age 34–80 years) referred to our center by movement disorder specialists. FDG-PET diagnosis was obtained by visual assessment of individual scans combined with voxel-based statistical parametric mapping analysis. FDG-PET diagnosis assigned at the time of imaging was compared with the final clinical diagnosis made by the movement disorder specialists after ≥2 years follow-up.

Results: FDG-PET findings were consistent with IPD in 27, MSA in 18, PSP in 19 and CBS in 2 patients. The final clinical diagnosis was IPD in 29, MSA in 20, PSP in 21 and CBS in 2 patients. Concordance between the FDG-PET and clinical diagnoses was 92% in the overall sample (IPD 93%, MSA 90%, PSP 91% and CBS 100%). The diagnostic accuracy of FDG-PET was 93% for IPD and MSA and 97% for PSP.

Conclusion: FDG-PET may help differentiate between IPD, MSA, PSP and CBS among patients presenting with parkinsonian symptoms, which is important for patient counselling and making early decisions about treatment.

Introduction

Idiopathic Parkinson’s disease (IPD) is the most common age-related neurodegenerative movement disorder presenting with progressive parkinsonism (bradykinesia, rest tremor, muscle rigidity and postural instability) [1]. IPD is a frequent diagnosis in the elderly, but only about 75% of parkinsonian patients have proven IPD at autopsy [2]. The most common alternative diagnosis is one of atypical parkinsonian syndromes, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) [3,4]. The diagnosis is typically made on clinical grounds, but this can be quite challenging even for specialists because of many overlapping symptoms and signs particularly in an early stage of disease [5–9]. In fact, MSA and PSP account for more than 80% of atypical parkinsonian patients initially misdiagnosed as IPD [3]. Despite similarities in early clinical presentation, atypical parkinsonian syndromes have different underlying pathology and carry significantly worse prognosis than classical IPD. Death is common in MSA and PSP 7–9 years after the onset of symptoms [10]. Pathologically, IPD and MSA are characterized by the alpha-synuclein aggregates, whereas PSP and CBS are classified as tauopathies. Regional distribution of pathological changes differs between MSA, PSP, CBS and IPD as do functional changes in neural networks activity [11]. Conventional anatomical imaging techniques, such as MRI and CT, are generally not helpful in early differential diagnosis. A long-term follow-up by a movement disorders specialist is necessary for making more accurate diagnosis based on clinical criteria.

Recent emphasis of research in neurodegenerative disorders has been on the development of biomarkers that could aid clinicians in making earlier and more accurate diagnoses, specifically of IPD and atypical parkinsonian syndromes [12]. Much of the interest in imaging approaches to parkinsonian disorders has
been focused on PET and SPECT imaging using radiouclide scanning or on the novel magnetic resonance techniques [13,14]. SPECT and PET with a variety of specific markers of dopamine transporter (DAT) on presynaptic nerve terminals are objective neuroimaging methods for assessment of nigrostriatal dopaminergic neuronal integrity and degeneration. DAT SPECT is a very useful diagnostic procedure for early detection of neurodegeneration and differentiates neurodegenerative parkinsonism from other forms of parkinsonism. DAT SPECT is unable to differentiate particular form of neurodegenerative parkinsonism (IPD, MSA, PSP and CBD). However, a number of studies have shown different metabolic patterns of regional glucose metabolism using fluorodeoxyglucose positron emission tomography (FDG-PET), reflecting regional changes in neural networks activity in IPD [15], MSA, PSP [16] and CBS [17]. Thus, FDG-PET may increase diagnostic accuracy and aid in distinguishing between these disorders [18–22]. Differential diagnosis of parkinsonian disorders is important because prognosis, treatment options and patient counselling differ between these conditions.

With this in mind, the purpose of this study was to evaluate the diagnostic accuracy of FDG-PET in differential diagnosis of IPD, MSA, PSP and CBS in routine clinical practice. For this purpose, we used ‘visual’ reading and ‘voxel-based’ statistical parametric mapping (SPM) analysis to compare individual patient results to already published patterns of regional glucose metabolism specific to each disease.

Materials and methods

Study overview

Between 2011 and 2015, we prospectively recruited patients with parkinsonism who met the following criteria: diagnosis of parkinsonism made by movement disorder specialists from the Department for Movement Disorders and Neurodegenerative Disorders, Neurology Clinic, Clinical Centre of Serbia; referral to the Centre for Nuclear Medicine, Clinical Centre of Serbia, for FDG-PET imaging of the brain; and absence of structural brain abnormalities on MRI. The final sample included 72 patients (50 men, 22 women, mean age 61 ± 10 years at the time of FDG-PET study). This group of patients represented a subset of a larger group of 97 patients referred for FDG-PET imaging for the differential diagnosis of parkinsonism. Of the total group, 16 patients were excluded for the lack of follow-up and 9 were excluded because of structural abnormalities on MRI and alternative clinical diagnosis. In 18 out of 72 patients finally enrolled in the study, DATSCANT SPECT was performed at the early stage of the disease. Those were the patients with atypical onset of disease and clinical dilemma of neurodegenerative etiology of parkinsonism. DATSCANT pathological findings confirmed the diagnosis of neurodegenerative parkinsonism. All subjects gave written informed consent for the study, which was approved by the Local Ethics Committee.

The referring diagnosis was ‘parkinsonism’, without specifying a suspected disease, in order to mask a nuclear medicine specialist. The same nuclear medicine specialist accepted all referrals, conducted and analysed all imagining studies, and made an imaging diagnosis. The FDG-PET diagnosis was not reported back to the referring movement disorder specialists to keep them also masked. The movement disorder specialists followed up the study patients for at least two years and made a ‘probable’ clinical diagnosis based on the consensus operational clinical diagnostic criteria for IPD [5], MSA [6], PSP [7,8] and CBS [9]. The FDG-PET diagnosis was compared with this final clinical diagnosis for the purposes of this study.

Clinical assessment

The disease stage was assessed with the Hoehn and Yahr stage score and the disease severity with the Unified Parkinson’s Disease Rating Scale. Mini Mental State Examination, Hamilton Depression Rating Scale and neuropsychological assessment were also administered.

FDG-PET imaging

A standard 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) static brain study was performed [23]. After fasting of at least 4 h and after confirming normal blood glucose level just before the study, each patient was injected with 111–185 MBq (3–5 mCi) of F-18-FDG intravenously, while resting supine with eyes closed in a silent, dimly lit room. Antiparkinsonian medication was not withheld prior to the PET study. Images were acquired 45–60 min after FDG injection (3-D mode, 1 bed, 15 min) by PET/CT (Biograph 64, True Point, SIEMENS) with transaxial resolution of 5.9 mm (full width at half maximum). Images were displayed as a series of 35 transaxial slices with standard colour scale according to maximum standardized uptake value (SUV max) after reconstruction using an iterative method (OSEM) and attenuation and scatter corrections. Images were displayed for analysis on a syngo Multimodality Workplace (Siemens AG).

Image analysis: visual and SPM

Qualitative visual assessment of all images was performed by an experienced reader, who specialized in both nuclear medicine and neurology. The activity in the striatal and subcortical structures was compared visually to the activity of the overall cortical strip, cerebellum and occipital cortex. The following criteria [19,20] were used for assigning the specific diagnosis: IPD, increased metabolism in the lentiform nucleus in relation to the
cortex; MSA, decreased metabolism in the basal ganglia-putamen and cerebellum; PSP, medial frontal decrease, especially at superior level; and CBS, marked asymmetric cortical and basal ganglia hypometabolism.

Quantitative voxel-based statistical image analysis was performed using SPM methodology [24–27]. To obtain hypometabolic maps for each patient, single-subject SPM analysis was performed by a voxel-based statistical comparison between patient’s functional images and functional images of cognitively intact controls (20 men, 30 women, mean age 42 ± 12 years) from a database provided by the INLAB SPM web service [24]. This grid-based online service is commonly used for SPM analysis of PET images in multicentre neurodegenerative studies. PET images were functionally normalized by placing the images in the standard Montreal Neurological Institute space using an FDG-PET dementia-specific template for spatial normalization, based on images derived from both neurological patients and age-matched controls [25]. The following parameter settings were included: 12-parameter affine transformation, 7 × 8 × 7 discrete cosine transform basis functions, no template and source weighting; discrete cosine transform cut-off: 25 mm; 16 non-linear iterations and the non-linear regularization term set to 1. No modulation (‘preserve concentrations’) and trilinear interpolation were used during final reslicing. Normalized images were written in the default SPM5 bounding box with an isotropic voxel size of 2 mm. An isotropic 3-D Gaussian kernel of 8 mm was applied to normalized images before starting t-test statistical analysis.

Single-subject analysis was performed using a two-sample t-test provided in the SPM package to test for relative ‘hypometabolism’ detected on each patient’s FDG-PET image in comparison to the control data-set. This method provides regional differences in relative glucose metabolism by means of a t-statistic for each voxel. Only age was included in the statistical model as a covariate because of no significant difference in metabolic activity was measured between males and females [26]. The measurements were assumed to be independent and have unequal variance between levels. Global normalization of voxel values used proportional scaling to a mean voxel value of 6.5 mg/100 ml/min to minimize inter-subject variability, with a threshold at the default 0.8 value. Voxel-wise comparisons were made using an explicit FDG-PET mask, created using SPM masking toolbox. Clusters of decreased metabolism were considered significant providing they reached $p = 0.05$, corrected for multiple comparisons with the family-wise error (FWE) option at the voxel level, and contained more than 100 voxels. Statistical t-maps showing regional differences of relative glucose metabolism in each patient compared to the control group were overlaid onto the T1-weighted MRI template image allowing anatomical location of hypometabolism. Published diagnostic criteria describing characteristic patterns

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pattern</th>
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<tbody>
<tr>
<td>Idiopathic Parkinson’s disease</td>
<td>• Normal or hypermetabolism in nucleus lentiformis on both sides</td>
</tr>
<tr>
<td></td>
<td>• Hypometabolism in dorsolateral prefrontal cortices and parietotemporooccipital cortices</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>• Hypometabolism in dorsolateral putamen on both sides and pons, with or without hypometabolism in bilateral cerebellar hemispheres</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>• Hypometabolism in midline frontal cortex (both anterior cingulate cortices), midbrain and both caudate/basal ganglia</td>
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<tr>
<td>Corticobasal syndrome</td>
<td>• Asymmetric hypometabolism in frontoparietal cortices and basal ganglia contralateral to clinically more affected side</td>
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Results

All 72 recruited patients completed the FDG-PET study and at least 2 years of clinical follow-up by the movement disorder specialists. At that time, the final clinical
diagnosis was IPD in 29 (17 with no cognitive impairment and 12 with dementia), MSA in 20, PSP in 21 and CBS in 2 patients. The respective demographic and clinical characteristics of these patients are presented in Table 2.

FDG-PET findings revealed IPD in 27, MSA in 18, PSP in 19 and CBS in 2 patients. The concordance between the FDG-PET and clinical diagnosis was 92%, kappa 0.88 (95%CI 0.78–0.97) in the overall sample, and, in terms of specific diagnosis, 93% in IPD, 90% in MSA, 91% in PSP and 100% in CBS (Table 3). Across the 3 diagnoses (IPD, MSA, PSP), the sensitivity of FDG-PET ranged from 90 to 93%, the specificity from 93 to 100% and the diagnostic accuracy from 93 to 97% (Table 4).

Two patients with CBS diagnosis were included in the study and correctly classified with FDG-PET imaging (visual and SPM-supported reading).

Features of FDG-PET scans in relation to specific diagnoses

Bilaterally preserved or pronounced glucose metabolism in the nucleus lentiformis was found in FDG-PET scans in 27 of 29 patients with the final clinical diagnosis.
of IPD. Among these 27, 15 patients with dominant motor symptoms and no cognitive impairments showed also slight decrease in the frontal cortical metabolism (Figure 1), whereas 12 patients with dementia additionally presented with hypometabolism in the frontal, parietal, posterior parietotemporal and parietooccipital cortices (Figure 2). Of the two remaining patients, one had decreased metabolism in the striatum and the other one intense bilateral cerebellar hypometabolism. In both cases, FDG-PET diagnosis was MSA.

In the group of 20 patients with the clinical diagnosis of MSA, 16 had a parkinsonian form of MSA (MSA-P) characterized by predominant striatonigral degeneration and 4 had a cerebellar form of MSA (MSA-C) with

![Figure 2. Representative pattern of glucose metabolism in a patient with IPD and dementia: cortical hypometabolism in the frontal, parietal, parietotemporal, parietooccipital regions with normal metabolism in the nucleus lentiformis: (a) FDG-PET, (b) single-subject SPM t-map.](image)

![Figure 3. Representative pattern of glucose metabolism in a patient with MSA: hypometabolism in the bilateral putamen, cerebellum and pons: (a) FDG-PET, (b) single-subject SPM t-map.](image)
predominant olivopontocerebellar degeneration. In 14 of 16 MSA-P patients, FDG-PET showed hypometabolism in the striate (putamen) and brainstem, and most of them also had the cerebellar hypometabolism (Figure 3). The remaining 2 of 16 MSA-P patients had preserved metabolism in the striatum and no evidence of the cerebellar hypometabolism. Thus, their FDG-PET diagnosis was IPD. Although MSA-C patients also had lower metabolism in the striatum, the cerebellar hypometabolism was far more pronounced.

Among 21 patients with the clinical diagnosis of PSP, 16 had the classical Steele–Richardson form of PSP, 4 had parkinsonian form of PSP and 1 had PSP with frontotemporal dementia. In 19 of these 21 patients, FDG-PET showed...
diagnosis of CBS, most notably in the frontoparietal region of the hemisphere contralateral to the predominant clinical symptoms (Figure 5).

The results of group SPM analysis were consistent with the features of regional glucose metabolism in IPD with dominant motor symptoms (Figure 6(a)), IPD with dementia (Figure 6(b)), MSA (Figure 6(c)), and PSP (Figure 6(d)).

![Figure 6. The SPM t-maps of regional glucose hypometabolism based on group analysis overlaid on T1-weighted MRI: (a) IPD with motor symptoms, (b) IPD with dementia, (c) MSA, (d) PSP.](image)

a bilaterally reduced glucose metabolism in the frontal regions (most pronounced in the medial frontal cortex and the lateral premotor cortex), brainstem (midbrain), thalamus and striatum (caudate nucleus) (Figure 4). In the remaining two patients, the FDG-PET diagnosis was IPD and MSA-C, respectively.

The asymmetric cortical and basal ganglia hypometabolism was found in both patients with clinical diagnosis of CBS, most notably in the frontoparietal region of the hemisphere contralateral to the predominant clinical symptoms (Figure 5).

The results of group SPM analysis were consistent with the features of regional glucose metabolism in IPD with dominant motor symptoms (Figure 6(a)), IPD with dementia (Figure 6(b)), MSA (Figure 6(c)), and PSP (Figure 6(d)).
Discussion

This study revealed high diagnostic accuracy of FDG-PET imaging performed 2 or more years before the final clinical diagnosis of the specific parkinsonian syndrome (IPD, MSA, PSP, CBS) was made by the movement disorder specialists. This is supported by the high rate of agreement between the FDG-PET and final clinical diagnosis (Table 3), which, resulted in high sensitivity, specificity and accuracy values (Table 4). Moreover, FDG-PET imagining was able to discern different clinical features of IPD (with vs. without cognitive impairment/dementia) and MSA (parkinsonian vs. cerebellar form). These results re-affirm previous studies and demonstrate utility of FDG-PET imaging as a useful adjunct to neurological examination for differential diagnosis of parkinsonian syndromes in routine clinical practice.

The uniqueness of our study is that it was implemented in the routine clinical practice and used previously published information about FDG-PET patterns specific to different parkinsonian syndromes. The nuclear medicine specialist responsible for conducting and interpreting FDG-PET results was masked for the clinical diagnosis at the time of imaging to eliminate bias. Similarly, the FDG-PET results were withheld from the referring movement disorder specialists to avoid bias when making the final clinical diagnosis. Visual analysis of FDG-PET images was complemented by the more comprehensive single-subject SPM analysis. This approach strengthens the study integrity and validity of results.

The indices of diagnostic utility of FDG-PET in differential diagnosis of parkinsonism reported here (concordance, sensitivity, specificity and accuracy) were 90% and above across IPD, MSA, PSP and CBS. This is in agreement with the studies by Eckert et al. and Tripathi et al. that used similar design and methodology and both reported comparable concordance rates (92%). This confirms the robustness of metabolic information provided by FDG-PET study in distinct populations of parkinsonian patients even when using different PET scanners [19,20]. The successful implementation of Web SPM service for analysis of individual data and high agreement of FDG-PET results with the final clinical diagnosis suggest that this approach may be useful in routine clinical practice when clinicians are faced with diagnostic dilemmas.

Our findings re-affirm that the pattern of regional glucose metabolism revealed by FDG-PET can differentiate typical from atypical parkinsonian syndromes and discriminate among atypical parkinsonian syndromes (MSA, PSP and CBS) with high sensitivity and specificity. This is important because prognosis and treatment options differ for IPD and atypical parkinsonian patients. Our study concurs with the literature that glucose metabolism in the lentiform nucleus is preserved or increased in IPD, whereas it is reduced in most atypical parkinsonian cases [15–21]. In terms of the cortical glucose metabolism, our IPD patients with dementia showed significantly lower metabolism in the posterior regions in contrast to the patients with motor symptoms with hypometabolism in the anterior-frontal regions. In addition, FDG-PET results differed between IPD patients who later did and did not develop cognitive impairment/dementia. These results are consistent with previous findings that posterior hypometabolism in patients with IPD may predict later development of dementia [22].

FDG-PET imaging also accurately classified patients as having IPD or MSA-P. This form of MSA is the most difficult to distinguish from IPD on clinical grounds, because two disorders may have similar clinical presentations (asymmetric parkinsonism) and both may respond to dopaminergic therapy at the disease onset. However, FDG-PET can clearly differentiate between these two forms of parkinsonism; the glucose metabolism in the putamen is preserved or elevated in IPD but significantly decreased in MSA-P in addition to the cerebellar hypometabolism. In our patients with MSA, presenting clinically with an asymmetric parkinsonism, hypometabolism in the putamen was more pronounced contralaterally. PSP is characterized by frontal (medial, lateral premotor), midbrain and striatal-caudate glucose hypometabolism. Since CBS is a rare disorder, we were able to recruit only two patients. Nevertheless, both of them showed characteristic asymmetrical cortical and subcortical glucose hypometabolism, most notable in the frontoparietotemporal regions of the hemisphere contralateral to the clinically more involved side.

Our results have important clinical implications for patient management because evolution, prognosis and treatment options differ between IPD and atypical parkinsonian syndromes, which are more aggressive, less treatable and carry a significantly worse prognosis [4,10]. For example, early recognition that an IPD patient is likely to develop dementia (presence of posterior hypometabolism) may prompt timely introduction of anticholinesterase therapy. Also, IPD, but not atypical parkinsonian patients show a good response to dopaminergic treatment [10]. Whereas deep brain stimulation is a well-established treatment for advanced IPD, patients with atypical parkinsonian syndromes were found to develop serious complications [28]. Arriving to an early and accurate diagnosis of the specific disease becomes even more important considering further development of treatments targeting the underlying pathophysiology of parkinsonian disorders [29,30].

Since the PET/CT diagnostics in recent years became available for clinicians, and Web service SPM analysis is simple to use, it is possible to introduce this imaging method (FDG-PET/CT with computer assisted SPM analysis) in widespread clinical practice for the accurate differential diagnosis of parkinsonian syndromes.
Study limitations

The overall sample of 72 may be perceived as small given variable number of patients within each form of parkinsonism (e.g. CBS). However, such a disproportion is consistent with previous investigations [19,20] and the selection bias is unlikely because our institution is the main referral centre for patients with atypical parkinsonian syndromes. In the absence of real gold standard, the consensus operational clinical diagnostic criteria and at least 2 years of follow-up were used for arriving to the final clinical diagnosis of different parkinsonian syndromes. As such, the study reflects a real clinical practice, which in turn, may also be viewed as the strength of the study.

In conclusion, our results suggest that FDG-PET metabolic imaging in conjunction with the SPM single-subject image analysis provides an objective and useful approach for distinguishing between different forms of neurodegenerative parkinsonian disorders in routine clinical practice.

Contributors

LB: conception, design; data acquisition, analysis, interpretation; wrote the article in whole, final approval of submission. DS-S, VA and VK: conception, design; draft revision; final approval of submission. ES: data acquisition, conception, design; draft revision; final approval of submission. AJ and MS: data acquisition, analysis, interpretation; drafting the manuscript; final approval of submission. MJ-L and SO: data acquisition, analysis, final approval of submission. BR: data acquisition, analysis, drafting the manuscript; final approval of submission. FG: statistical analysis, drafting the manuscript; final approval of submission. IC: statistical analysis, draft revision; final approval of submission. GT: statistical analysis, final approval of submission.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Serbian Ministry of Education and Science.

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