Anatomically standardised $^{99m}$Tc-ECD brain perfusion SPET allows accurate differentiation between healthy volunteers, multiple system atrophy and idiopathic Parkinson’s disease

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Abstract. The clinical differentiation between typical idiopathic Parkinson’s disease (IPD) and atypical parkinsonian disorders such as multiple system atrophy (MSA) is complicated by the presence of signs and symptoms common to both forms. The goal of this study was to re-evaluate the contribution of brain perfusion single-photon emission tomography (SPET) with anatomical standardisation and automated analysis in the differentiation of IPD and MSA. This was achieved by discriminant analysis in comparison with a large set of age- and gender-matched healthy volunteers. Technetium-99m ethyl cysteinate dimer SPET was performed on 140 subjects: 81 IPD patients (age 62.6±10.2 years; disease duration 11.0±6.4 years; 50 males/31 females), 15 MSA patients (61.5±9.2 years; disease duration 3.0±2.2 years; 9 males/6 females) and 44 age- and gender-matched healthy volunteers (age 59.2±11.9 years; 27 males/17 females). Patients were matched for severity (Hoehn and Yahr stage). Automated predefined volume of interest (VOI) analysis was carried out after anatomical standardisation. Stepwise discriminant analysis with cross-validation using the leave-one-out method was used to determine the subgroup of variables giving the highest accuracy for this differential diagnosis. Between MSA and IPD, the only regions with highly significant differences in uptake after Bonferroni correction were the putamen VOIs. Comparing MSA versus normals and IPD, with putamen VOI values as discriminating variables, cross-validated performance showed correct classification of MSA patients with a sensitivity of 73.3%, a specificity of 84% and an accuracy of 83.6%. Additional input from the right caudate head and the left prefrontal and left mesial temporal cortex allowed 100% discrimination even after cross-validation. Discrimination between the IPD group alone and healthy volunteers was accurate in 94% of the cases after cross-validation, with a sensitivity of 91.4% and a specificity of 100%. The three-group classification (MSA, IPD and healthy volunteers) resulted in an overall accuracy of 86% post hoc, with 98% of normals, 78% of IPD and 93% of MSA correctly classified. These values were slightly lower after cross-validation: 96% for healthy volunteers, 77% for IPD and 67% for MSA. In conclusion, using age- and gender-matched healthy volunteer data and anatomical standardisation, it is possible to differentiate between IPD and MSA with high discriminating power in clinically relevant circumstances.

Keywords: $^{99m}$Tc-ECD SPET – Multiple system atrophy – Parkinson’s disease – Discriminant analysis – Anatomical standardisation

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Introduction

Parkinsonism is characterised clinically by deficits in motor function such as tremor, rigidity, bradykinesia, hypokinesia, akinesia and postural abnormalities. However, parkinsonism is a feature of a number of neurodegenerative or metabolic-toxic diseases; among these, idiopathic Parkinson’s disease (IPD) and multiple system atrophy (MSA) are the two most common forms, accounting for more than 90% of cases. Separating parkinsonian syndromes using clinical criteria alone can be difficult, but such differentiation is important for therapy (medication, neurosurgery or neuroprotective clinical trials) and prognosis [1, 2].
The major cause of parkinsonism is IPD, which accounts for approximately 60%–85% of all cases [3]. IPD is characterised neuropathologically by degeneration of the substantia nigra pars compacta in association with the formation of Lewy bodies, leading to functional alterations in basal ganglia activity and accompanying alterations in regional cerebral glucose metabolism and blood flow [4].

MSA includes striatonigral degeneration (SND or MSA-S), sporadic olivopontocerebellar atrophy and Shy-Drager syndrome in its spectrum and may present clinically with any combination of extrapyramidal, pyramidal, autonomic and cerebellar features. The pathology of MSA is quite distinct from that of IPD and is characterised by neuronal degeneration and gliosis in the caudate and putamen, globus pallidus, brain stem, cerebellum and spinal cord. Fifty percent of patients with the akinetic-rigid variant show a good response to levodopa, which makes it difficult to distinguish MSA from IPD on the basis of clinical criteria alone [5]. About 10% of patients thought to have IPD during their lifetime are found to have MSA at autopsy [3, 6]. As in IPD, degeneration of the nigrostriatal dopaminergic pathway has been described. Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) studies have reported reduced levels of striatal, cerebellar and brain stem glucose metabolism [7, 8, 9]. 18F-FDG PET is able to detect the presence of lentiform nucleus hypometabolism in 80% of patients clinically suspected to have MSA of the SND type [10].

As regards functional neurotransmitter measurements, relative levels of tracer uptake in the putamen and caudate employing 18F-dopa, 123I-β-CIT or FP-CIT discriminate at most 70% of SND cases from PD [11], and more recent studies suggest an even lower discrimination rate [12, 13]. Dopamine D2-receptor binding studies using 11C-raclopride [14], 123I-epidepride [15] and 123I-iodobenzamide (IBZM) [16] can aid significantly in differentiating between patients with a good response to levodopa and those with development of motor fluctuation. Although 11C-raclopride studies have shown a very high discriminating capacity [14], dopamine D2 PET tracers are available only in PET centres with an in-house cyclotron. The iodinated single-photon emission tomography (SPECT) ligands are fairly sensitive, but also expensive, and medication (neuroleptics, antidepressants, etc.) exerts a strong influence on their binding properties.

Perfusion imaging at rest is widely available and is used as an indirect marker of neuronal function. The role of perfusion SPET for the pure diagnosis of IPD has been disputed, and its contribution to the differential diagnosis between IPD and MSA is not known [17]. Over recent years, camera resolution characteristics have improved and techniques have become available that allow objective, observer-independent automated analysis of brain SPET data [18, 19]. Based upon anatomical standardisation or spatial normalisation, automated reference can be made to a set of healthy volunteers using predefined volumes of interest (VOIs) or on a voxel-wise basis. With VOI data as input, advanced statistical analysis using neural network analysis [20] or discriminant analysis [21] can then be applied to evaluate clinical studies based on a “training” set of previously acquired data from age- and gender-matched normal volunteers and patient groups.

The aim of this study was to evaluate the contribution of brain perfusion SPET, based on anatomical standardisation and automated analysis, in the detection of and differentiation between IPD and MSA. The a posteriori individual classification accuracy was estimated from cross-validated discriminant analysis of a large set of clinically evaluated patients and compared with the available literature data on 18F-FDG PET as well as dopamine receptor PET and SPET functional imaging.

Materials and methods

Subjects. Eighty-one patients clinically assessed as having probable IPD (age 62.6±10.2 years; disease duration 11±6.4 years; 50 males and 31 females) and 15 patients with probable MSA (61.5±9.2 years; disease duration 3.0±2.2 years; nine males and six females) were included in the study. The mean Hoehn and Yahr stage was 2.4±1.1 for both IPD and MSA. Full clinical data and follow-up information were available at the time of SPET. The data included medication (levodopa, agonists and other medications (levodopa dosage was expressed as equivalent levodopa in mg and agonist dosage was expressed as equivalent of bromocriptine, using the equivalence ratio of 10 mg bromocriptine = 1 mg pergolide = 1 mg pramipexole = 4 mg ropinirole), subscores for the most relevant symptoms (tremor, bradykinesia, autonomic failure, gait pattern and cognitive function) (1= absent to 4= severe) and the results from complementary examinations (EEG, MRI, CT, neuropsychology). The clinical diagnosis of IPD and MSA was made on the basis of the Brain Bank criteria [3] and Quinn criteria [6] respectively. All studies were approved by the local ethical committee.

Forty-four age- and gender-matched healthy volunteers (age 59.2±11.9 years; 27 males and 17 females) were selected. The recruitment, pre-screening and screening procedures and exclusion criteria for the healthy volunteers have been described previously [22]. In short, all included subjects underwent thorough screening for normality, including a complete history, physical and paraclinical examination, full clinical neurological examination by a board-certified neurologist, psychiatric examination and neuropsychological testing by a board-certified psychiatrist. High spatial resolution MRI scan results were normal as assessed by a board-certified neuroradiologist.

Data acquisition and reconstruction. Technetium-99m ethyl cysteinate dimer (ECD) (Neurolite, Bristol-Myers-Squibb/Dupont Pharmaceuticals, Brussels, Belgium) was used to estimate brain perfusion. All subjects received 1.110 MBq (25 mCi) (+5%) of 99mTc-ECD under standard injection circumstances (dimly lit room, eyes closed). Data were acquired with patients in the “on” state. In the first 62 patients, SPET images were acquired by means of a dual-head Helix system (Elscint/GE, Haifa, Israel), while the most recent 34 scans were acquired on a triple-head gamma camera (Toshiba GCA-9300A, Dutoit Medical, Wommelgem, Belgium) equipped with parallel-hole low-energy high-resolution collimators. For the former scans, acquisition was done over 20 min, over 60 angles through 360° in step-and-shoot mode. The triple-head data were acquired over 90 angles through 360° in continuous mode over 20 min. For all patients, data were acquired...