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Special collaboration

Functional neuroimaging in the diagnosis of patients with parkinsonism: Update and recommendations for clinical use☆,☆☆

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ABSTRACT

Functional neuroimaging has been traditionally used in research for patients with different parkinsonian syndromes. However, the emergence of commercial radiotracers together with the availability of single photon emission computed tomography (SPECT) and, more recently, positron emission tomography (PET) have made them available for clinical practice. Particularly, the development of clinical evidence achieved by the functional neuroimaging techniques over the past two decades have motivated a progressive inclusion of several biomarkers in the clinical diagnostic criteria for neurodegenerative diseases that occur with parkinsonism. However, the wide range of radiotracers designed to assess the involvement of different pathways in the neurodegenerative process underlying parkinsonian syndromes (dopaminergic nigrostriatal pathway integrity, basal ganglia and cortical neuronal activity, myocardial sympathetic innervation), and the different neuroimaging techniques available (scintigraphy, SPECT and PET), have generated some controversy concerning the best neuroimaging test indicated for the differential diagnosis of parkinsonism. In this article, a panel of nuclear medicine and neurology experts has evaluated the functional neuroimaging techniques emphasizing practical considerations related to the diagnosis of patients with uncertain origin parkinsonism and the assessment of Parkinson's disease progression.

Neuroimagen funcional en el diagnóstico de pacientes con síndrome parkinsoniano: actualización y recomendaciones para el uso clínico

Palabras clave:
Enfermedad de Parkinson
Parkinsonismo

RESUMEN

Las técnicas de neuroimagen funcional se han utilizado tradicionalmente en la investigación de los pacientes que presentan un síndrome parkinsoniano. Sin embargo, la aparición de radiofármacos

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comerciales junto a la disponibilidad de equipos de tomografía por emisión de fotón único (SPECT) y más recientemente de la tomografía por emisión de positrones (PET), han permitido su empleo rutinario en la práctica clínica. Precisamente el desarrollo y grado de evidencia clínica alcanzado por los biomarcadores de neuroimagen durante las 2 últimas décadas ha conllevado que progresivamente se estén incluyendo en los criterios clínicos de diagnóstico de enfermedades neurodegenerativas que cursan con un síndrome parkinsoniano. No obstante, la diversidad de radiofármacos que permiten evaluar la funcionalidad de las vías anatómicas involucradas en la neurodegeneración presente en los diferentes síndromes parkinsonianos (vía nigroestriatal dopaminérgica, actividad neuronal de los ganglios basales y la corteza, inervación simpática miocárdica), junto a las técnicas de neuroimagen (gammagrafía, SPECT y PET) han originado cierta controversia con respecto a la indicación de las pruebas de neuroimagen como exploración complementaria. En esta revisión realizada por un panel de expertos en medicina nuclear y neurología se analizan las técnicas de neuroimagen funcional disponibles haciendo especial énfasis en las consideraciones prácticas del diagnóstico de pacientes con un síndrome parkinsoniano de origen incierto y la valoración de la progresión de la enfermedad de Parkinson.

Introduction to the clinical problem

In recent years there has been a steady inclusion of different neuroimaging biomarkers in the criteria for clinical diagnosis of neurodegenerative diseases. Undoubtedly, this change is due to the notable progress and advances undergone by imaging techniques in the last decade. Specifically, functional techniques in nuclear medicine, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), have greatly contributed to our knowledge regarding the physiopathology of different neurodegenerative diseases and also to diagnosis in the earliest phases of disease, when structural changes are not yet evident.

The diagnosis of neurodegenerative diseases presenting as a parkinsonian syndrome may be complex in the early phases due to the initial overlapping of symptoms between different diseases. Diagnostic accuracy improves with disease progression, when some atypical signs, incompatible with the diagnosis of idiopathic Parkinson's disease (PD), become evident. In this scenario, the possibility of *in vivo* noninvasive evaluation of the integrity of the dopaminergic nigrostriatal pathway, neuronal activity of the basal ganglia and cortex, as well as myocardial sympathetic innervation may be useful to complement the clinical diagnosis, thereby improving the specificity and facilitating decision making.

There is currently a great diversity of functional neuroimaging techniques with common objectives, but there is also a certain degree of controversy regarding the diagnostic capability of each technique. Therefore, it is necessary to determine the utility of each and every technique in order to establish recommendations for their use in the clinical diagnosis of patients with parkinsonism of uncertain origin. This document is the result of the consensus reached by a panel of neuroimaging experts from the Spanish Society of Nuclear Medicine and Molecular Imaging (SEMNIM) and experts in movement disorders from the Spanish Society of Neurology (SEN), following an exhaustive review of the literature.

Clinical characteristics of parkinsonian syndromes

Parkinsonism is defined as a clinical syndrome characterized by a combination of the following cardinal symptoms: resting tremor, rigidity, bradykinesia, loss of postural reflexes, gait impairment, motor blockade or freezing phenomenon. Parkinsonism can be a clinical manifestation of hereditary and nonhereditary neurodegenerative diseases but it can also be secondary to multiple causes including structural, infectious, pharmacological, toxic or traumatic events. The most frequent form of degenerative parkinsonism is PD. In contrast to PD, other types of parkinsonism called Parkinson's plus syndromes or atypical parkinsonism do not respond to conventional levodopa treatment or show mild and transitory response. Atypical parkinsonisms include multiple system atrophy (MSA) with its parkinsonian and cerebellar atrophy variants, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) (Table 1).[1]

Although PD patients may exhibit different clinical manifestations and disease progression, they present some common characteristics that can help in the differential diagnosis of the disease with other degenerative parkinsonisms. PD has an asymmetrical presentation since the beginning of the disease and remains asymmetrical throughout the evolution of the disease. The presence of resting tremor is characteristic. Despite certain differences, depending on the age of onset, progression of PD is slower than atypical parkinsonisms, and gait and balance impairment are usually present in advanced stages of PD. Motor manifestations of PD significantly improve with dopaminergic agents but most develop motor complications (motor fluctuations and dyskinesias) after 5–8 years of levodopa therapy. Non-motor symptoms are very common in PD patients, especially in advanced stages of the diseases being cognitive decline, depression, anxiety, dysautonomia, fatigue and pain the most frequent. The underlying pathology of these symptoms is unknown and, in some cases, these symptoms precede the appearance of the classical motor profile by many years.

MSA usually appears as a parkinsonian syndrome in combination with cerebellar, pyramidal and/or dysautomonic symptoms/signs. The scarce response to levodopa, the prominence and precocity of the dysautonomy, and more rapid and torpid progression differentiates MSA from PD.

PSP classically appears as a rigid-akinetic symmetric syndrome with predominant axial rigidity and early alteration in balance, frequent falls, vertical supranuclear gaze palsy, bulbar syndrome and frontal cognitive dysfunction. In recent years, other phenotypes have been described including parkinsonian-type PSP in which patients initially present a parkinsonism with resting tremor and

Table 1
Classical clinical characteristics of degenerative parkinsonisms.

	EP	AMS	PSP	CBD
Progression	Slow	Rapid	Rapid	Rapid
L-DOPA response	Excellent	Mild and initial	Absent	Absent
Parkinsonism	Mixed	R-A	R-A	R-A
Asymmetry	+	–	–	++
Dysautonomy	Late	Early intense	–	–
Pyramidalism	–	+	+	+/–
Cerebellar syn.	–	+/–	–	–
Oculomotor deficits	–	+	++	+
Apraxia in extremities	–	–	–	+

MSA: multiple system atrophy; CBD: corticobasal degeneration; PD: Parkinson's disease; Mixed: with resting tremor, bradykinesia with/without rigidity; PSP: progressive supranuclear palsy; R-A: parkinsonism with rigidity and bradykinesia.