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Review Article

Radiographic Anatomy in Parkinson Disease - A Mini Review in the Service of Early Diagnosis

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Abstract

Background: Parkinson's disease (PD) is a neurodegenerative disorder affecting the autonomic, limbic and somatomotor system. The most common damages in PD are neocortical, mesolimbic and tuberoinfundibular. Non-motor features include depression, urinary incontinence, hypotension, anosmia, erectile dysfunction, constipation, sleep disorders, and fatigue. However, this cluster of symptoms is rarely used to diagnose PD at an early stage, as differential diagnosis seems rather difficult. The etiology of PD remains unclear and most cases are sporadic. Nevertheless, genetic mutations of at least 20 proteins such as TDP-43, amyloid-β alpha-synuclein at S129, have been demonstrated to cause inherited forms of the disease. The process of neurodegeneration in PD begins long before the onset of clinical symptoms and lacks of specific clinical phenotype, resulting in untimely diagnosis and treatment. Imaging studies such as DAT-SPECT, PET-CT and MRI establish their true value in diagnosing prodromal neurodegeneration. Method: This bibliographic review aims to summarize research findings regarding the value of various imaging methods, in the diagnostic work-up of PD. Manuscripts included in the databases PubMed/Medline and Scopus were included in the review.

Results: PET and SPECT ligands can demonstrate the presence of terminal dopamine dysfunction in early and preclinical disease. Moreover, MRI imaging has enhanced diagnostic accuracy in the differential diagnosis of neurodegenerative parkinsonism. PD imaging detects a possible alternative diagnoses, while its landmark includes the identification of early, new-onset, and even prodromal PD and may alter the therapeutic approach.

Conclusion: Imaging modalities present an essential role in PD early detection and diagnosis.

Keywords: *DAT-SPECT; PET-CT; MRI; Parkinsonism; Neuroimaging*

Introduction

Parkinson's disease (PD) is one of the most common neurological disorder characterized by loss of dopaminergic neurons in the nigrostriatal pathway of the brain with unknown etiology sporadic cases. More than 20 proteins have been shown to cause inherited forms of PD, while many are linked to mitochondrial function [1]. Progressive dopaminergic death in the nigrostriatal system has been regarded as the pathogenic crucial pillar of motor features in PD. Lots of ergot mechanisms have been listed to be the cause for the neural loss, with inflammation presented as central and peripheral. Inflammatory processes, which still today believed that cause afterclap of neuronal death, are being present since the early stages of PD. Genetic predisposition which includes genes such as IL-1β, TNF-α, HLA-DBQ1, HLA-DRA and HLA-DRB1 is associated with increased susceptibility to PD. Nonsteroidal anti-inflammatory drugs can in the long term diminish the risk of PD [2]. It is important to underline that Idiopathic PD is the most common variant. PD clinical symptoms are associated with

lesions in the substantia nigra. Typically, depression, urinary incontinence, hypotension, anosmia, erectile dysfunction, constipation, sleep disorders, and fatigue are present. Atypical parkinsonian disorders, such as multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy and dementia with Lewy bodies, also account for a large percentage of parkinsonian disorder cases [3].

Both early detection and differential diagnosis appear to be rather tricky due to common symptomatology. The group of visual examinations concerning the accuracy of differential diagnosis of PD disease include studies with positron emission computed tomography (^{18}F-FDG PET/CT), SPECT, ^{18}F-FP-CIT PET/CT and diffuse MRI, these include studies on 2-deoxy-2-[^{18}F]-fluoro-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), dual-radionuclide dopamine transporter (DAT) and brain perfusion single-photon emission computed tomography (SPECT) and diffusion-weighted magnetic resonance imaging (MRI) [3].

DAT-SPECT

Even to this day no modifying treatments for PD have been identified effectively. Dopamine transporter DAT-SPECT imaging is widely used for a diagnostic and prognostic biomarker for diagnosing PD [4]. PET and SPECT ligands can exhibit the presence of dopamine terminal dysfunction in the early and preclinical stage of the disease. Also, they can show an abnormal covariance pattern among levels of resting brain blood flow metabolism in cortical and subcortical regions [5].

One sensitive technique to detect presynaptic dopamine neuronal dysfunction is DAT imaging, which can help clinicians to measure the loss of striatal dopamine nerve terminal function, a very specific characteristic clinical symptom of neurodegenerative parkinsonism, which is strongly related to decreases of DAT density [6,7]. Diagnosis of Parkinson disease or tremor disorders can be achieved with high degrees of accuracy in cases with full expression of classical clinical features; nonetheless, diagnosis sometimes it's not so easy, since there is a fundamental clinical overlap, especial in monosymptomatic tremor, such as dystonic tremor, essential tremor, Parkinson tremor. DAT-SPECT could prove or exclude with high sensitivity nigrostriatal dysfunction in those cases, and normal DAT-SPECT it's able to help to distinguish diagnosis of drug-induced, psychogenic and vascular parkinsonism by excluding underlying true nigrostriatal dysfunction [6]. To assist in the evaluation of adult patients with suspected parkinsonian syndromes we use single-photon emission computed tomography brain imaging with one specific radiopharmaceutical-DaTscan. DaTscan is indicated for striatal dopamine transporter visualization using. In these patients, it can be used to help differentiate ET from tremor due to idiopathic Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy [8].

Due to the fact that a series of studies have proposed high clinical diagnostic false for PD and essential tremor, Ioflupane-DaTSCAN or DaTscan or FP-CIT may help in the clinical decision by visualizing the dopamine transporters in parkinsonian cases. SPECT imaging with I-123 Ioflupane is useful to diagnose, to help guide prognosis and treatment in some patients with unconfirmed parkinsonian syndromes. We note that I-123 Ioflupane should be used in the patients with uncertain diagnose and for whom the result image would make a diagnostic difference. Moreover, I-123 Ioflupane scans can be useful in clinicians to choose among the available medications, in cases with uncertain Parkinsonian syndromes (PS) and at the same time can be a prize beneficial diagnostic tool, avoiding costs associated with treatment with no benefits in non-PD cases [8]. DAT-SPECT scan studies' results were correlated with clinical assessment and treatment changes. DAT-SPECT findings impacted treatment decisions in 44.7% [9]. The sensitivity and specificity are reported to be more than 90% with I-123-FP-CIT SPECT for PD diagnosis, and equivalent with other DAT SPECT methods. Soon, the clinical indications of DAT imaging are expected to be figurated; including treatment response, disease progression monitoring, and early diagnosis of premotor PD [10].

DAT-SPECT may show early diagnosis and differentiation from other non-degenerative parkinsonian disorders. DAT-SPECT presents limited value in differentiating between the degenerative types of parkinsonism. The sensitivity should not exclude clinical diagnosis (false negative scans occur and highlight the need for clinical follow-up). As DAT-SPECT is a sensitive modality to detect nigrostriatal degeneration, the clinical assessment remains still today the high aspect in evaluating of these diseases [11].

PET-CT

Movement disorders in Parkinsonian patients are frequent and play a catalytic role in diagnosis and treatment. The authors review the most common MRI and molecular imaging patterns of idiopathic Parkinson's disease and atypical PS. The authors analyzed the clinical available molecular imaging studies beside the fact that imaging test is not always diagnostic, but a combination of tests may help the differential diagnosis. Molecular imaging studies such as the assessment of cerebral metabolism with FDG-PET (2-[fluorine-18]fluoro-2-deoxy-d-glucose Positron Emission Tomography), cortical amyloid deposition with Carbon-11 Pittsburgh compound B and Fluorine-18 PET (18-Florbetapir), and dopaminergic activity with Iodine-123 SPECT (Ioflupane Single-Photon Emission Computed Tomography) are available in today's practice. Findings at Iodine-123 SPECT may confirm the loss of dopaminergic neurons in cases with parkinsonism and help distinguish these syndromes from treatable conditions, including essential tremor and drug-induced parkinsonism. FDG-PET uptake can demonstrate patterns of neuronal dysfunction that are specific to a parkinsonian syndrome. Moreover, positive amyloid-binding PET findings can support the diagnosis of dementia with Lewy bodies. Combined with a thorough clinical evaluation, multimodality imaging information can afford accurate diagnosis, allow selection of appropriate therapy, and provide important prognostic information [12].

Neuroimaging indicators of Parkinson disease have been developed and applied in clinical practices. Dopaminergic imaging presents nigrostriatal dopaminergic dysfunction. Metabolic network imaging provides disease-related metabolic alteration at a system level. Striatal DAT binding connected with akinesia-rigidity except tremor; the metabolic PET imaging, unspecific to the dopaminergic dysfunction, reveal a set of brain regions associating with the cardinal symptoms, containing tremor [13]. PD shows exhibited analogous cerebral patterns characterized by a metabolic increase in the putamen, globus pallidus, thalamus, pons, sensorimotor cortex, and cerebellum, along with a metabolic decrease in parieto-occipital areas during PET examinations [14]. DAT imaging may depicts presynaptic dopaminergic neuronal loss in PD, but is usually not so easy to differentiate the atypical parkinsonism (APD) from PD. in those cases dual-phase F-18 FP-CIT positron emission tomography is proposed [15].

Protein Leucine-rich repeat kinase 2 (LRRK2) is connected with the pathogenesis of PD, as it has been demonstrated that PD is mainly conferred by LRRK2 mutations. Those mutations increase kinase activity. Selective inhibition of LRRK2 may reprocess the normal functions of LRRK2, hopefully, to have one alternative treatment for patients with PD. The mapping of LRRK2 by PET studies allows to understand the mechanism for PD from another LRRK2-related disorders and validate and translate novel LRRK2 inhibitors. However, no LRRK2 PET probes have yet been reported in the primary literature. Subsequent whole-body biodistribution studies indicated limited brain uptake and urinary and hepatobiliary elimination of this radioligand. Further development of a new generation of LRRK2 PET probes is needed [16]. Some studies note that [11C]DTBZ PET is an excellent choice for differentiating idiopathic PD from other disorders [17].

MRI

PD is characterized by the abnormal intraneuronal accumulation of misfolded α-Synuclein into Lewy bodies and Lewy neurites. They are differentiated in section by the temporal relationship among the onset of parkinsonism versus cognitive signs, with the former taking place earlier in PD and the latest generally occurring earlier in dementia-Lewy bodies (DLB). Clinical criteria, history, and exams are necessary to elucidate diagnosis, but the definitive diagnosis can only be assured by autopsy. Currently, several techniques of brain imaging has been utilized to augment diagnosis are being studied as possible to monitor progression and to provide early diagnostic biomarkers for PD. New imaging techniques such as structural magnetic resonance imaging (MRI) can help in differentiating PD from other causes of parkinsonism. Furthermore, molecular and metabolic brain imaging modalities demonstrate promise; clarifying possible diagnostic biomarkers and offering clinical points into pathogenesis for patients with PD [18].

Diagnosis, differential diagnosis, and error rates are challenging in neurology in the field of parkinsonian syndromes. During the past three decades, MRI has increased the diagnostic accuracy in the differential diagnosis of neurodegenerative parkinsonism [19]. Brain MRI is the most frequently modality used in the diagnostic of parkinsonism. MRI techniques increase the clinicians' capacity to unveil

cerebrovascular damage for the diagnosis of vascular parkinsonism and to exclude other possible but more rare causes of parkinsonism such as multiple sclerosis. They can also depict abnormalities which are suggestive of neurodegenerative APS. For example, atrophy and T2 hypo-intensity of the putamen, which may be noticed in the parkinsonian form of multiple system atrophy (MSA-P). On the pons (hot cross bun sign) or pontocerebellar atrophy may point up towards the cerebellar form of MSA (MSA-C), all demonstrated with signal intensity changes. Atrophy of the midbrain (hummingbird sign) or signal intensity changes in the superior cerebellar peduncles are suggestive of progressive supranuclear palsy (PSP). Asymmetrical cortical atrophy is the hallmark of corticobasal degeneration (CBD). Conventional brain MRI is usually normal or will show age-related changes in early stage PD, which is the most frequent cause of parkinsonism. In later stages, cortical atrophy of the frontal or temporal lobe may be seen in PD [20].

Various studies had proven that the value of conventional brain MRI in the diagnosis of parkinsonism is greater in conditions when brain imaging should confirm clinical evaluation and alleviate physicians' doubt. New MRI methods have been issued for clinical practice, techniques involving diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI). Diffusion MRI measures the random movement of water molecules and seems to reproduce a quantitative image of microstructural shifts in neurodegenerative pathology, even when no malfunctions are seen on conventional MRI sequences. Fractional anisotropy (FA) can calculate the degree of anisotropy, i.e. restriction of the random motion of water molecules by the normal architecture of glial tissue and fiber tracts, while mean diffusivity (MD) calculates the average diffusivity. Losing the microstructural integrity of brain tissue is somewhat reflected by diminution in FA and increase in MD. These two quantitative analyses for diffusion MRI involve the region of interest (ROI) method and the automated voxel-based methods [20]. Nonetheless, those methods present high specificity and limited sensitivity for patients with atypical parkinsonian syndromes in comparison with the technique of conventional brain MR imaging [21]. Brain MRI is a practical, helpful and appropriate tool for the differential diagnosis of Parkinson's disease. Conventional MRI can depict PD and may demonstrate idiosyncratic brain alterations in the case of atypical PS. Moreover, advanced MRI techniques are able to obtain quantitative parameters to enhance further the diagnostic accuracy. At the moment, a lot of MR studies are exhibit the underlying neuropathological pattern of the various degenerative parkinsonian syndromes, with qualitative and quantitative findings. Specific radiologic phenotypes can be identified, even though clinicians are in disagreement for which technique is the cold standard. Qualitative/quantitative MRI changes in the substantia nigra do not discriminate between different parkinsonism [22].

Peculiar patterns of microstructural changes can be identified by DTI in PD, patterns which seem to be connected with characteristic histopathologic changes. For instance, we may see an increase in MD and decrease in FA of the putamen or pontocerebellar structures in MSA, and diffusional changes of the midbrain and superior cerebellar peduncles in PSP. By using those calculations we may identify PD with DTI measures of the basal ganglia, brainstem, and cerebellum. Due to the lack of diagnostic criteria in DTI, and no clear guidelines y quantitative diffusional data for one patient is currently difficult to be evaluated. Moreover, only a few studies evaluated brain MRI and DTI in early PD stages, when the added value of brain MRI is mostly clinically relevant [20]. Nonetheless, MRI can show atrophy or signal changes in several parts of the brain with fairly high specificity for particular forms of AP, but the overall diagnostic value of routine brain MRI is limited, conserved only for PD cases [23].

Due to its high spatial and contrast resolution, cMRI with the assessment of T1, T2, proton density-weighted as well as T2 fluid-attenuated inversion recovery (FLAIR) sequences offers in vivo visualization of regional, disease-specific tissue alterations and certain cMRI patterns that are typical for APDs. Atrophy patterns are better optical viewed by T1-weighted images, demonstrating anatomical details and given an excellent contrast with grey and white shades. Currently, T1 sequences were progressive to enhance finds of nigral changes in PD subject. Neuromelanin acts as a paramagnetic agent because of its iron-binding potential in NM-MRI. Neuromelanin-containing tissues seem as areas of high signal intensity. These images with high signal intensity give us measurements of volume and concentration of neuromelanin in the substantia nigra (SN) and locus coeruleus (LC). Also, it appears that visual inspection of NM-MRI sequences gives us results equal to quantitative analyses for the different diagnosis PD in early stages, with SN changes. T2-weighted sequences are more sensitive to changes in tissue properties; increased T2-signal shows one degeneration, demyelination, or another gliosis of the impacted white matter, while an increased T2-signal is commonly restricted to the subcortical grey matter nuclei and might point a deposit of para-

magnetic substances. In fact, increased T2-signal appears to be better identified at higher field strengths as can be seen in a test using brain MRI at 0.35, 1.5 and 3.0 T in cases with MSA or PD. With increasing field strength, the occurrence of hypointensity at the dorsolateral putaminal margin increased in patients with MSA. Therefore, signal abnormalities appear to be affected by the applied magnetic field strength. Despite that, field strength-related changes could result in false-positive points [19].

Furthermore, in the literature there is an Increasing evidence which suggests a connection between imaging biomarkers of small vessel disease and future cognitive decline in PD. Lately, as an imaging biomarker of small vessel disorder has been deemed magnetic resonance imaging-visible perivascular space (PVS) [24].

Conclusion

PD is a highly heterogeneous disorder, which probably consists of multiple subtypes. Therefore, preventative treatments depend on PD being detected in a prodromal phase. PD brings two main issues to the spotlight. The first one has to do with the fact that it differs from one patient to another. The second one has to do with imaging. When it comes to diagnosis radiology depiction, it appears that there are various modalities for achieving it, Yet, clinicians are not aware which one is the most effective. The final choice is usually determined based upon the experience and expertise of the managing physician. Patient's history is also taken into account for that matter. Although PD diagnosis is predominantly clinical, imaging offers great promise for the study of disease pathogenesis and evolution, for staging, as well as factors contributing to the complications of the disease and its treatment. With the advent of technology in imaging methods, we are allowed to understand more about the functions and abnormalities of the brain, while an early diagnosis may be achieved so that a more proper personalized drug administration would ameliorate therapeutic results.

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