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Review

Metabolic Topography of Parkinsonism

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Metabolic Topography of Parkinsonism

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Parkinson's disease is one of the most frequent neurodegenerative diseases, which mainly affects the elderly. Parkinson's disease is often difficult to differentiate from atypical parkinson diorder such as progressive supranuclear palsy, multiple system atrophy, dementia with Lewy body, and corticobasal ganglionic degeneration, based on the clinical findings because of the similarity of phenotypes and lack of diagnostic markers. The accurate diagnosis of Parkinson's disease and atypical Parkinson disorders is not only important for deciding on treatment regimens and providing prognosis, but also it is critical for studies designed to investigate etiology and pathogenesis of parkinsonism and to develop new therapeutic strategies. Although degeneration of the nigrostriatal dopamine system results in marked loss of striatal dopamine content in most of the diseases causing parkinsonism, pathologic studies revealed different topographies of the neuronal cell loss in Parkisonism. Since the regional cerebral glucose metabolism is a marker of integrated local synaptic activity and as such is sensitive to both direct neuronal/synaptic damage and secondary functional disruption at synapses distant from the primary site of pathology, an assessment of the regional cerebral glucose metabolism with F-18 FDG PET is useful in the differential diagnosis of parkinsonism and evaluating the pathophysiology of parkisonism. (Nucl Med Mol Imaging 2007;41(2):141-151)

Key Words : Parkinsonism, F-18 FDG, PET, Metabolism

Introduction

Parkinsonism is described as a symptom complex manifested by any combination of six cardinal features: tremor at rest, rigidity, bradykinesia-hypokinesia, flexed posture, loss of postural reflexes, and the freezing phenomenon. Idiopathic Parkinson's disease (IPD) is the most common neurodegenerative cause of parkinsonism followed by atypical parkinson disorders (APD) such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), dementia with Lewy body (DLB), and corticobasal degeneration (CBD).[1] APD are characterized by generally more rapidly progressive parkinsonism associated with early postural instability, a poor or transient response to dopaminergic therapy, and additional features such as supranuclear gaze palsy, early autonomic failure, pyramidal signs, as well as cerebellar features.[2,3]

IPD is often difficult to differentiate from APD based on the clinical findings because of the similarity of phenotypes and lack of diagnostic markers.[2-15] The major diagnostic errors occur when attempting to differentiate IPD from some of APD early in their disease course. A diagnosis of IPD appears to be challenging with a misdiagnosis rate as high as 20-30% in the early stages.[2,3,14] The accurate diagnosis of IPD and APD is not only important for deciding on treatment regimens and providing prognosis, but also it is critical for studies designed to investigate etiology and pathogenesis of parkinsonism and to develop new therapeutic strategies.[15]

Although a definite diagnosis of the parkinsonism can only be made by a neuropathological examination, functional neuroimaging techniques have been applied and

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studied to distinguish IPD from other parkinsonian disorders. Functional neuroimaging studies may assist in a differential diagnosis of parkinsonism and provide a means to investigate the in vivo neurochemical or metabolic consequences of the degeneration of the nigrostriatal dopaminergic system in IPD. Currently, functional neuroimaging techniques allow imaging of both pre- and postsynaptic components of the dopamine system. Since the core biological pathology in parkinsonism is decreased dopaminergic neurotransmission in the basal ganglia, these techniques have been used to characterize in vivo the different pathologic changes of the parkinsonian disorders in attempts to differentiate between them.[4,13,16-18] Recently, PET studies using dopamine D_2 receptor have shown that a combing approach of dopamine transporter and D_2 receptor imaging may help in the differential diagnosis of parkinsonism.[16] For the clinical practice, however, there are limitations in this approach: It has been shown to significant overlap in striatal dopamine transporter or receptor uptake of individual patient with parkinsonism. It is also uncomfortable for patients to undergo PET scan twice.

F-18 FDG is a most popular and available radiotracer for PET and has become a major tool for investigating the neurodegenerative disease such as Alzheimer's disease and differentiating parkinsonism.[1,19,20] Although degeneration of the nigrostriatal dopamine system results in marked loss of striatal dopamine content in most of the diseases causing parkinsonism, pathologic studies revealed different topographies of the neuronal cell loss.

Studies of the cerebral glucose metabolism with F-18 FDG PET are of considerable interest because the regional cerebral glucose metabolism is a marker of integrated local synaptic activity and as such is sensitive to both direct neuronal/synaptic damage and secondary functional disruption at synapses distant from the primary site of pathology.[21]

Parkinson's Disease

IPD is characterized by progressive death of dopamine neurons in the substantia nigra, especially in the ventrolateral part, resulting in striatal dopamine deficiency most prominent in the putamen.[22] This deficiency results in alterations in the function of cortical-striatal-pallidal-thalamic-cortical circuits that modulate normal movement, resulting in bradykinesia and rigidity.[23]

The change of glucose metabolism in IPD is well known but several controversies according to various conditions are still remained. With respect to subcortical structures, FDG PET studies in patients with early IPD have shown lentiform nucleus hypermetabolism, especially contralateral to the more affected limb.[24] In contrast, another studies reported reduced striatal, especially caudate metabolism in advanced IPD, similar to that reported in progressive supranuclear palsy.[25] This metabolic change are paralleled by changes in striatal D_2 receptor binding, which is increased in early, untreated disease and decreased in the advanced treated state. Reductions in caudate metabolism during the course of IPD probably reflected frontal input due to direct pathological involvement.[26,27]

Regarding cortical metabolism, no significant changes have been reported in early stages of IPD. In contrast, widespread reductions of association cortex glucose metabolism, most prominent in temporoparietal cortex, have been demonstrated in IPD patients with coexisting dementia,[28-30] a complication that has a prevalence of 18% to 44% at later stage of disease.[31,32] This finding of IPD with dementia is similar to that of Alzheimer disease. Studies of non-demented IPD covering ranges of disease duration up to 29 years have produced conflicting findings. Some demonstrated significant cortical hypometabolism,[33,34] while others could not confirm this finding.[35-37] These conflicting findings may result from several factors such as medication, disease duration, and coexisting disease.

Significant relative regional reductions of glucose metabolism in studies of non-demented IPD patients with established disease (mean durations between 6 and 8 years) have been demonstrated in various association cortical regions: occipital,[33,38] parietal,[33,34] frontal,[19,34] and temporal (Fig. 1). In both early disease with a mean duration of 4 years, and in some studies with longer mean durations of disease (between 6 and 7 years), no significant reductions have been reported.[19,24,36,37] The reason for this is likely to reflect inclusion of very early cases in these studies with 1 to 2 years duration of disease, where cortical

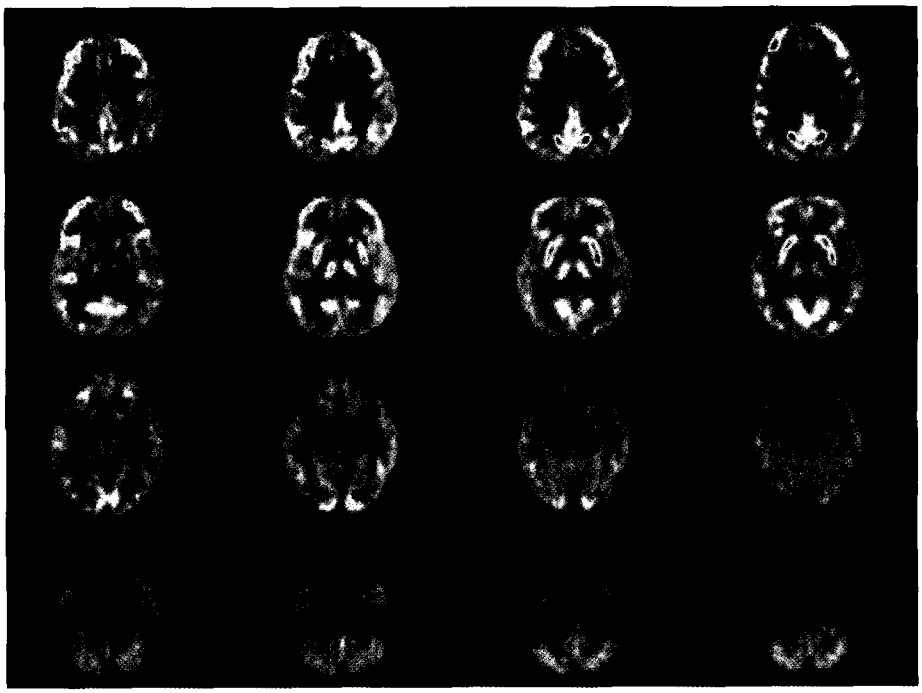

Fig. 1. Seventy-one years old male with Parkinson's disease. Axial image of F-18 FDG shows mild cortical hypometabolism. There is no significant hypometabolism in the striatum.

hypometabolism is unlikely. Combining those reported in the literature suggests that cortical hypometabolism in IPD parallels disease duration even in the absence of dementia. Widespread hypometabolism, which is a pathognomomic feature in IPD with dementia,[28,35] also appears to be common in non-demented patients with advanced IPD.

In particular, frontal hypometabolism seems to be a characteristic of advanced disease, as it was found only in the study[19] with the longest mean duration. Further evidence that frontal lobe dysfunction is a specific finding in advanced disease comes from PET studies of neurotransmission and neuropsychological data. In advanced IPD, reduced dopamine $D_{2/3}$ receptor binding has been demonstrated in the prefrontal cortex,[39] Conversely, higher flurodopa uptake has been reported in the frontal cortex of IPD patients with better performance in cognitive testing.[40] Neuropsychological testing also reveals that frontal lobe functions are specifically impaired at more advanced stages of disease.[41,42]

Another factor that might influence cerebral glucose metabolism in IPD is antiparkinsonian medication. There is evidence that therapy with levodopa (L-dopa) or apomorphine can decrease metabolism in cortical and sub cortical regions by 2% to 9%.[43,44] Furthermore, neuropsychological studies have shown that L-dopa treatment can adversely affect some cognitive functions in IPD.[45,46] Berding et al. reported in IPD, administration of levodopa is associated with hypometabolism in orbitofrontal cortex: an area known to be relevant for reversal learning where perfo-rmance is typically impaired after dopaminergic treatment.[47]

Multiple System Atrophy

MSA is a sporadic adult onset neurodegenerative disease presenting symptoms and signs of extrapyramidal, cerebellar, and autonomic dysfunction in various combinations.[48,49] MSA is characterized by neuronal degeneration and gliosis in the basal ganglia (putamen and globus pallidus), brain stem (substantia nigra, locus ceruleus, dorsal vagal nuclei, vestibular nuclei, inferior olives, and pontine nuclei), cerebellum (cerebellar Purkinje cells), and spinal cord.[50] Several neurological diseases constitute subgroups of MSA, including striatonigral degeneration (SND),[51] Shy-Drager syndrome (SDS),[49] and olivopontocerebellar atrophy (OPCA).[52]

Most patients with MSA manifest cerebellar symptoms

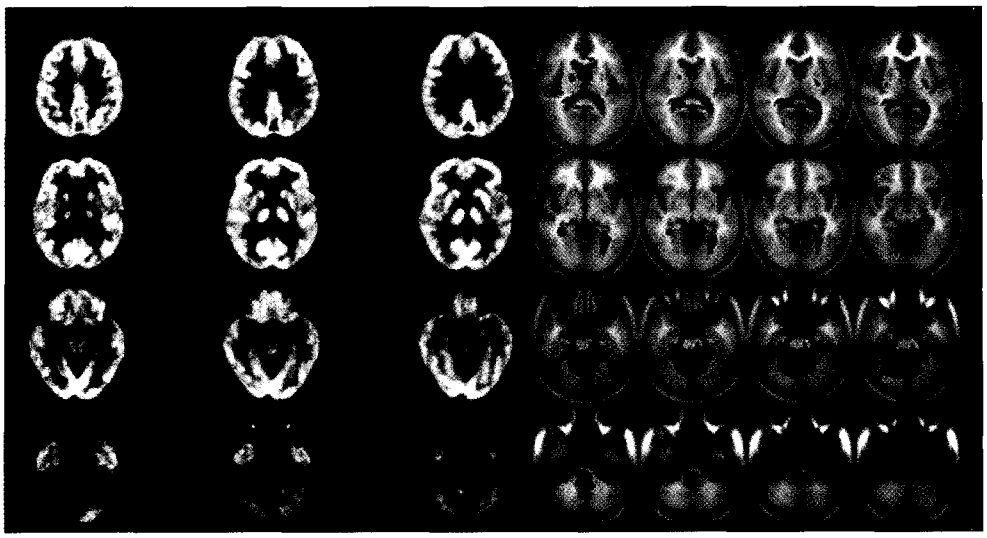

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Fig. 2. Fifty-three years old female with multiple system atrophy (cerebellar type). Axial image of F-18 FDG PET and SPM results comparing with age matched normal controls show significant hypometabolism of pons, cerebellum, medulla and putamens.

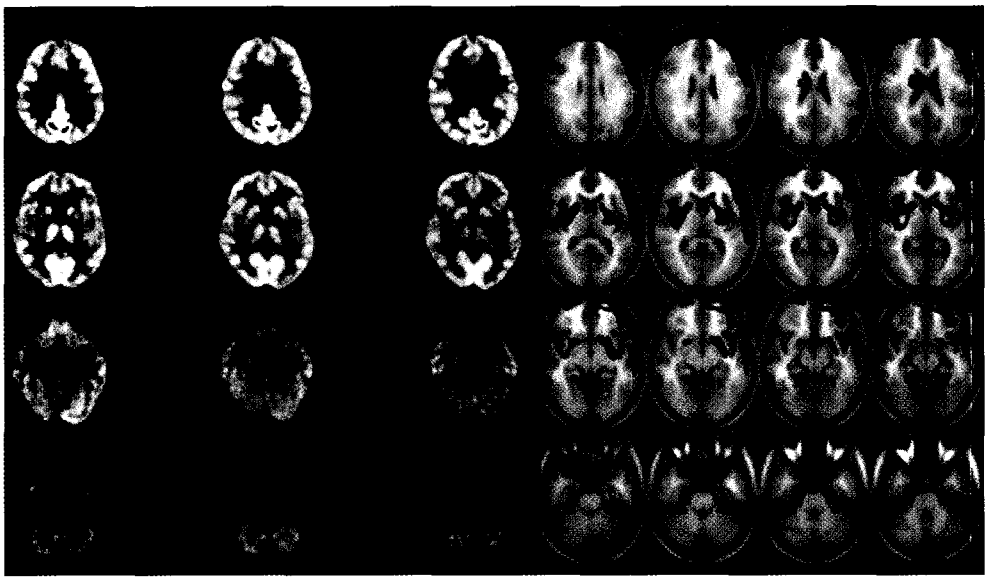

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Fig. 3. Sixty-seven years old female with multiple system atrophy (parkinson type). Axial image of F-18 FDG PET and SPM results comparing with age matched normal controls show significant hypometabolism of bilateral putamens (especially posterior portion).

and then develop autonomic or extrapyramidal symptoms. Some patients with MSA initially develop extrapyramidal symptoms and late accompanying autonomic or cerebellar symptoms or both. Even if some clinical features of MSA are clearly distinctive from IPD, diagnostic errors are not uncommon. Neuropathological studies have shown that about 20% of patients clinically diagnosed with IPD may prove at postmortem to have had another neurodegenerative disorder such as MSA.[53]

Previous PET studies have shown a significant

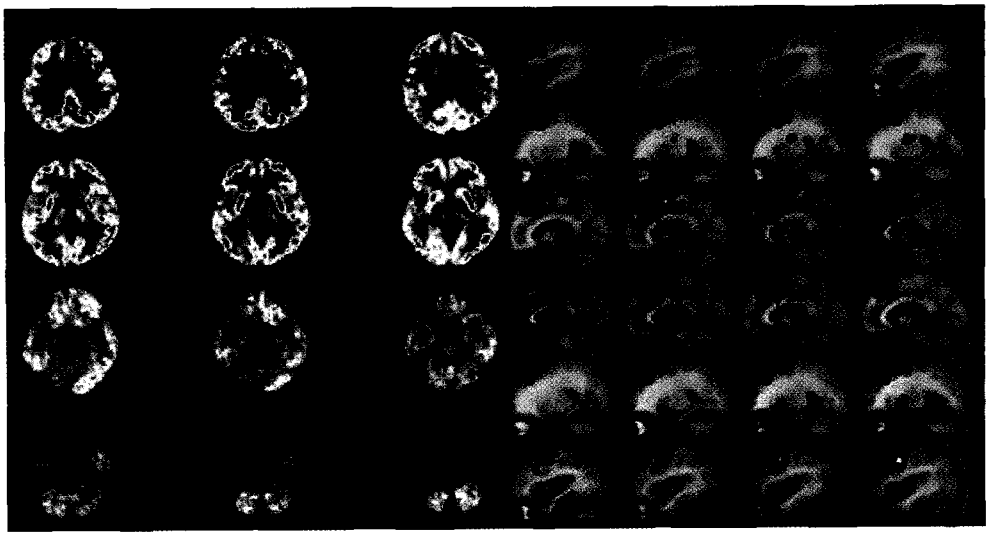

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Fig. 4. Seventy-four years old male with progressive supranuclear palsy. Axial image of F-18 FDG PET and SPM results comparing with age matched normal controls show significant hypometabolism of midbrain, bilateral medial frontal cortices, caudate nuclei, and thalami.

widespread reduction of glucose metabolism in the putamen, cerebellum, and brainstem in not only advanced but also early MSA.[54-56] These findings are consistent with the neuropathological features of MSA.[57] Thus, hypometabolism in the putamen, cerebellum, and brain stem reflects the loss of neurons and synaptic connections in these sites. (Fig. 2 and 3) However, there is controversy in the cortical metabolism in MSA. Most of PET studies on advanced stage of MSA showed the reduction of glucose metabolism in the cerebral cortex as well.[54,55] However, Taniwaki et al. reported no hypometabolism in the cerebral cortex in the early stage of MSA.[56] The cerebral cortices in MSA have been rarely involved on postmortem pathological examinations. These findings suggest that the dysfunction in the cerebral cortex appears in the late stage of MSA.

Several studies have reported a strong correlation between the severity of ataxia and cerebellar hypometabolism in early and advanced stage of MSA.[56-58] These results indicate that the hypometabolism of the cerebellum is tightly linked to the cerebellar ataxia. Taniwaki et al. also reported a strong correlation between the severity of autonomic dysfunction and brainstem hypometabolism in the early stage of MSA.[56] Since autonomic failure was known to be associated with cell loss in the spinal cord and brainstem in the neuropathological study,[59] they suggested that the hypometabolism in the brainstem is indicative of the autonomic dysfunction in the early stage of MSA. However, there is a controversy in the relationship between the severity of parkinsonism and striatal glucose metabolism. Although decreased metabolism in the striatum was closely related to the severity of parkinsonism in advanced MSA,[57,60] the severity of parkinsonism did not correlated with the decline of striatal glucose metabolism in the early stage of MSA.[56]

Progressive Supranuclear Palsy

PSP is a late-onset neurodegenerative disease characterized by supranuclear vertical gaze palsy, postural instability, rigidity, bulbar dysfunction, and dementia with variable presence of pyramidal and cerebellar signs.[61] PSP is pathologically characterized by neuronal loss, gliosis, and neurofibrillary tangles that are most prominent in the basal ganglia (especially globus pallidus), subthalamic nucleus, several brainstem nuclei, and the dentate nucleus of the cerebellum.[61] PSP represents at least 5% of parkisonism. However, this percentage is probably an underestimate due to the difficulties in diagnosing this syndrome.

Several studies using F-18 FDG PET have demonstrated

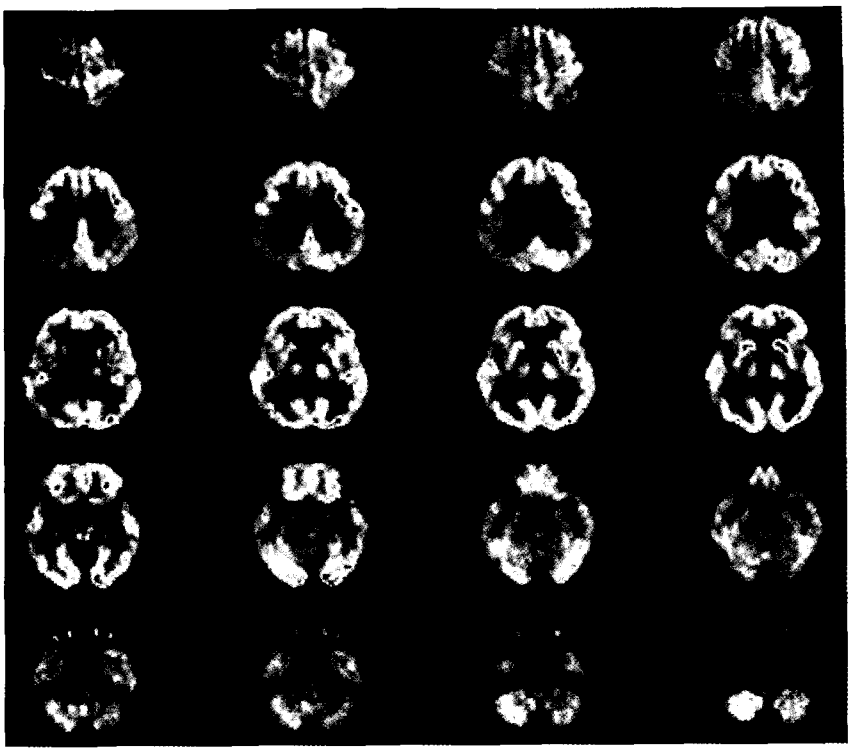

Fig. 5. Seventy-five years old male with corticobasal ganglionic degeneration. Axial image of F-18 FDG PET shows asymmetric hypometabolism of frontoparietal cortex, putamen, thalamus and cerebellum.

decreased glucose metabolism not only in the caudate nucleus, putamen, thalamus, and brainstem, but also in the cerebral cortex,[62-64] particularly in the frontal lobes. This decrease in cerebral cortical glucose metabolism correlates with the severity of dementia.[65] Hosaka et al. reported hypometabolism in the lateral and medial frontal lobes, caudate nucleus, and midbrain as compared with age-matched healthy controls using voxel based analysis of FDG PET imaging.[66] Our experience also confirmed subcortical hypometabolism of caudate nucleus, thalamus, and midbrain and cortical hypometabolism (especially medial frontal cortex) (Fig. 4). These metabolic patterns may help to differentiate PSP from other atypical parkinsonism.

In PSP, the basal ganglia and brain stem are the main loci of pathological changes, while the cortical regions have only a slightly pathological involvement. Therefore, the hypometabolism of the cerebral cortex in PSP has generally been attributed to deafferentiation of the cerebral cortex from subcortical projections.[62] Recent pathologic studies, however, demonstrate neuronal loss and neurofibrillary tangles in the cerebral cortex that could contribute to the cortical hypometabolism by reducing activity of the terminal fields of local interneurons.[67] The current study also suggests that intrinsic neurons containing benzodiazepine/$GABA_A$ receptors are lost, primarily in the anterior cingulated cortex. Foster et al reported that PSP causes loss of benzodiazepine receptors in the cerebral cortex and suggested that both loss of intrinsic neurons containing benzodiazepine receptors and deafferentiation of the cerebral cortex from distant brain regions contribute to cerebral cortical hypometabolism in PSP.

Corticobasal Ganglionic Degeneration

CBD is an adult-onset progressive parkinsonian syndrome with cortical and basal ganglionic dysfunction. The typical clinical features include asymmetric rigidity, bradykinesia, tremor, dystonia, myoclonus, dyspraxia, and cortical sensory loss, along with gait disorder, and dementia.[1] Neuropathology is characterized by cortical neuronal loss and intense astrogliosis with basophilic

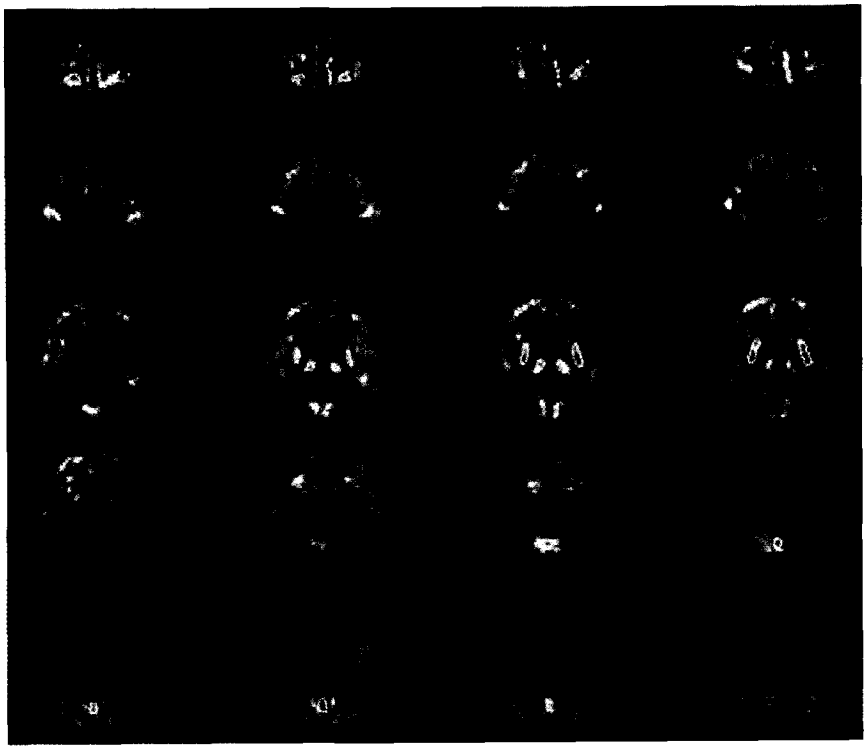

Fig. 6. Sixty-seven years old male with dementia with Lewy body. Axial image of F-18 FDG PET show significant cortical hypometabolism involving bilateral parietotemporal cortex and occipital cortex.

argyrophilic and tau-positive inclusions in the substantia nigra and basal ganglia and sometimes along the dentate-rubro-thalamic tracts.[68]

In CBD, asymmetric cortical hypometabolism has been known as a characteristic pattern of cerebral metabolism Fig. 5). Several studies have reported asymmetric metabolic dysfunctioning in paracentral, posterior frontal, and inferior parietal cortices.[66,69-71] Laureys et al. reported metabolic decrease in premotor, primary motor, supplementary motor, primary sensory, prefrontal, and parietal associative cortices, and in caudate and thalamus contralateral to the side of clinical signs in patient with early stages of CBD.[71] Hosaka et al. also reported asymmetric parietal hypometabolism using a voxel based analysis. However, they failed to find a significant decrease in the thalamus. This difference may be attributable to the normalization process of voxel based analysis.[66]

Dementia with Lewy Body

DLB is a neurodegenerative disease that is characterized by a progressive cognitive decline and the presence of numerous Lewy bodies in the cortical and subcortical brain region with a variable degree of coexisting Alzheimertype pathology.[72] According to a recent report, DLB is considered to be the second most common cause of neurodegenerative dementing disorders following Alzheimer's disease.[73] The clinical criteria for the diagnosis of probable DLB require the presence of dementia combined with at least two of the following core features: fluctuating cognition and levels of consciousness, recurrent visual hallucinations, and motor features of parkinsonism. Neuropathological criteria are based on examination of the following brain regions for the density of Lewy bodies: subtantia nigra; transentorhinal cortex; cingulate gyrus; and midtemporal, midfrontal, and inferior parietal cortices.[73] There are consensus reports on the clinical and pathologic diagnostic criteria for DLB, but the accuracy of the clinical diagnostic criteria has been debated.

Recent studies of F-18 FDG PET have shown the characteristic patterns of hypometabolism in DLB. Albin et al. reported an occipital metabolic reduction with autopsy

confirmed DLB using PET.[74] Minoshima et al. also reported significant metabolic reductions involving parietotemporal association, posterior cingulate, frontal association, and occipital cortices in autopsy confirmed DLB.[75]

Occipital metabolic reduction was observed also in clinically diagnosed PD with dementia.[76-78] These findings have been confirmed independently.[79,80] In contrast, many investigators have observed relatively preserved occipital metabolism with AD.[81,82] These two observations suggest that occipital metabolic reduction may be a metabolic signature specific to DLB and can be used to distinguish the two diseases antemortem (Fig. 6). Occipital metabolic changes, however, did not correlate with parietotemporal changes in DLB, suggesting impairment of distinct neuronal systems.

In DLD, the density of Lewy bodies was reported to be the lowest in the occipital cortex.[83,84] Although precise comparisons between antemortem metabolic changes and postmortem pathological findings are difficult due to the time interval, the expression of Lewy bodies in DLB brains does not appear to correlate with the distribution of metabolic changes. This discordance between metabolic and classical pathologic changes, however, is not unique to DLB.[85] In AD, classical pathologic changes occur initially in the transentorhinal cortex.[86] In contrast, early metabolic changes occur in the posterior cingulate cortex and lateral association cortices,[87] which correlate more closely with synaptic alterations revealed by immunocytochemical analysis.[88] Multivariate analysis showed that occipital metabolic abnormalities were not merely an extension of parietotemporal pathology indicating an impairment of distinct neuronal systems. A similar but milder metabolic reduction in the occipital lobe was observed also in IPD without dementia.[28,33,38] This may or may not indicate preclinical evidence of Lewy body dementia. However, Bohnen et al. reported that occipital reduction correlated with nigrostriatal dopaminergic functions,[33] and indicated a possible pathophysiological relationship in impaired saccade and visual attentional systems.[89] Metabolic reduction in the visual cortex also coincides clinically with a high prevalence of visual hallucinations in DLB.[73] Abnormalities in primary visual processing as evidenced by metabolic reduction in DLB and IPD, may cause a release of higher visual association cortices and result in visual hallucinations.[90] Alternatively, visual hallucinations might be caused by neurochemical changes outside of the primary visual system.[91]

Conclusion

The clinical differential diagnosis of Parkinson's disease and atypical parkinsonism is often complicated by the presence of signs and symptoms common to both groups, although parkinsonism involves different pathophysiology in cortical and subcortical brain structures. Since the regional cerebral glucose metabolism is a marker of integrated local synaptic activity and is sensitive to both direct neuronal/synaptic damage and secondary functional disruption at synapses distant from the primary site of pathology, an assessment of the regional cerebral glucose metabolism with F-18 FDG PET is useful in the differential diagnosis of parkinsonism and evaluating the pathophysiology of parkisonism.

국문초록

파킨슨병은 노년층에 가장 흔한 퇴행성 뇌질환 중의 하나로 진행성핵상마비, 다중계 위축, 루이체 치매 등과 같은 비전형 파킨슨병과 임상적으로 감별이 어려울 수 있다. 파킨슨병과 비전형 파킨슨병의 감별은 치료방침 결정과 예후평가 뿐만 아니라 파킨슨병의 원인과 병태생리를 연구하고 새로운 치료법 개발에 있어서도 매우 중요하다. 파킨슨병과 비전형 파킨슨병과 같이 파킨슨 증후군을 유발하는 질환은 선조체내 도파민 신경의 퇴행성 변화를 흔히 동반하지만 병태생리학적으로 서로 다른 뇌피질 및 피질하 구조물에서의 신경세포 소실을 동반하고 있다. 따라서 국소 시냅스 활성도와 신경 및 시냅스의 손상, 그리고 원발병변과 기능적으로 연결된 원격부위의 기능이상 등을 대변하는 뇌포도당 대사를 F-18FDG PET으로 평가하는 것은 파킨슨 병의 감별진단과 병태생리를 평가하는데 유용하다.

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