Brief practical clinical diagnostic criteria for the neurodegenerative diseases in the elderly

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Abstract

In the literature there is need of clinical and instrumental characterization of all neurodegenerative diseases. Particular attention deserves the timing of the onset of motor or cognitive symptoms, which is extremely useful issue giving the frequent overlapping between neurodegenerative diseases. Aim of this review is to provide a description of typical clinical and imaging features of all neurodegenerative diseases, especially idiopathic. Parkinson’s disease (PD) and Alzheimer’s disease (AD). Particular attention will be devoted to the cluster of symptoms at the moment of the diagnosis. Based on early starting symptoms (cognitive or extrapiramidal) we will introduce criteria to differentiate AD from fronto-Temporal Dementia (FTD), Lewy bodies dementia (DLB) and Vascular dementia (VaD), and between PD, Vascular Parkinsonism (VP) and DLB. All these diseases are characterized by cognitive deficits. PD will be suspected if cognitive impairment occurs at least one year after the onset of the motor symptoms while VP and DLB, if cognitive deficits and motor symptoms appear simultaneously. Another scenario is the identification at the time of the diagnosis of parkinsonian signs plus other motor symptoms, as for example cerebellar or pyramidal signs, with falls and autonomic dysfunction, with or without cognitive deficits. In this case, the diagnostic goal includes atypical Parkinsonism together with the differential diagnosis between Cortical-basal degeneration (CBD), Multiple system atrophy (MSA) and Progressive supranuclear palsy (PSP). Finally, we will describe clinical and imaging features of these diseases, by differentiating them on the basis of symptoms at the time of diagnosis.

Typical clinical features and neuropathological findings of the neurodegenerative disorders

When cognitive deficits are the most important features observed at the moment of diagnosis, the differential diagnosis should be made between Mild Cognitive Impairment (MCI), AD, LDB, FTD and VaD. Clinical features allow to exclude PD and other atypical parkinsonism with exception of the CBD (Table 1). Mild cognitive impairment (MCI) is characterized by subjective memory complaints, with objective evidence of non-age related memory impairment from standardized tests, normal mental status with no evidence of global dementia and normal activities of daily living. Among individuals with MCI, the rate of transition to dementia (typically AD) is about 10-15% per year. The early neuropathological findings of early AD can be sometimes detected.

The most prevalent form of dementia is AD, which is characterized by an insidious onset and gradual progression of cognitive impairment along with associated social and/or vocational functional impairment. Typical findings of AD include the amyloid-beta plaques, neurofibrillary tau-protein tangles, and cerebral neuronal loss. The greatest density of plaques and tangles are found in the frontoparietal cortex, hippocampus, amygdala, locus ceruleus, and dorsal raphe nucleus. A progressive loss of cholinergic neurons of the nucleus basalis, noradrenergic neurons of the locus coeruleus, and serotonergic neurons of the dorsal raphe nucleus can also occur. These changes are likely to explain the reduction in cortical concentrations of the neurotransmitters acetylcholine (ACh), norepinephrine, and serotonin. The most profound biochemical abnormality found in AD is the reduction of temporoparietal and hippocampal cortical activity of choline acetyltransferase (CAT). The enzyme CAT is present only in cholinergic neurons, where it catalyzes the synthesis of ACh. There is recent evidence that a clinical diagnosis of AD is supported by the presence of one or more...
of the following biomarkers: i) decreased concentrations of amyloid-beta and increased concentrations of tau-protein in cerebrospinal fluid; ii) identifying specific amyloid-related binding of Pittsburgh compound B (PiB) with the use of PET scanning; iii) medial temporal lobe atrophy with the use of MRI scanning; and/or iv) temporal/parietal hypometabolism with the use of PET scanning.2

The second most common form of dementia is VaD, which is characterized by clinical or laboratory evidence of cerebrovascular disease that is associated with the onset and progression of dementia.3 In contrast to AD, VaD is often characterized by an abrupt onset and step-wise deterioration of cognitive impairment. Multiple small cortical and/or subcortical infarctions are believed to have a cumulative adverse effect on brain function resulting in dementia. The specific cognitive deficits depend on the location of the vascular lesions.3

Two related forms of dementia are DLB and Parkinson’s Disease-Dementia (PDD).4,6 DLB has clinical and pathological features that overlap with those of AD and Parkinson’s disease. In DLB, the progressive decline in cognitive function is eventually accompanied by the development of parkinsonian symptoms (i.e., bradykinesia, rigidity, resting tremors, and abnormalities of balance, gait, and posture).

Table 1. Typical clinical and imaging features of the neuro-degenerative diseases in the elderly.

<table>
<thead>
<tr>
<th>Cognitive Impairment at the moment of the diagnosis</th>
<th>Clinical features</th>
<th>Imaging features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>MCI plus at least one of the imaging features2</td>
<td>MRI: temporal atrophy27 18F-FDG PET study: uptake reduction in the temporo-parietal cortex40</td>
</tr>
<tr>
<td></td>
<td>Semantic dementia</td>
<td>MRI: anterior (often asymmetrical) temporal lobe atrophy27  MRI: left perisylvian loss27</td>
</tr>
<tr>
<td></td>
<td>Progressive non fluent aphasia</td>
<td>MRI: frontal atrophy27</td>
</tr>
<tr>
<td>FTD</td>
<td>Fronto-temporal variant</td>
<td>Focal or asymmetrical frontal or temporal atrophy reduce the likelihood of a diagnosis of AD on both MRI and FDG-PET27</td>
</tr>
<tr>
<td>Motor deficits + cognitive deficits at the moment of the diagnosis</td>
<td>Cognitive impairment with fluctuating cognition and hallucinations plus parkinsonism4</td>
<td>MRI: relative preservation of medial temporal lobe structures27</td>
</tr>
<tr>
<td>LBD</td>
<td>Cognitive impairment with mixed subtle neurological signs, such as extrapiramidal, pyramidal cerebellar signs, and in particular primitive reflexes: snout, grasp, glabellar, and palmo-mental reflexes3</td>
<td>MRI: evidence of vascular changes or white matter changes or one or more lacunes on T2-weighted MRI images27</td>
</tr>
<tr>
<td>VaD</td>
<td>Cognitive impairment with fluctuating cognition and hallucinations plus parkinsonism4</td>
<td>MRI: relative preservation of medial temporal lobe structures27</td>
</tr>
<tr>
<td>Motor deficits at the moment of the diagnosis</td>
<td>Parkinsonism that should be directly related to cerebrovascular disease on MR122 Normal SPECT tracer uptake28</td>
<td></td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Bradykinesia plus at least one of the following criteria: rigidity or 4-6 Hz rest tremor or Postural instability31</td>
<td>[123I] FP-CIT SPECT: low putamen/caudate ratio, expressed by a pre-sinaptic reduction tracer uptake49  18F-DOPA-PET study: at early stage reduced tracer uptake in the posterior putamen, followed by the anterior putamen and the caudate nucleus44</td>
</tr>
<tr>
<td>VP</td>
<td>Parkinsonism</td>
<td>MRI: asymmetrical cortical atrophy especially in frontotemporal areas31</td>
</tr>
<tr>
<td>CBD</td>
<td>Signs of pyramidal dysfunctions plus mielokinetic apraxia and mild cognitive impairment22</td>
<td>MRI: mid-sagittal T1-weighted images showed midbrain atrophy without pontine atrophy, forming the silhouette of the “penguin” sign, with the shapes of midbrain tegmentum31</td>
</tr>
<tr>
<td>PSP</td>
<td>Parkinonism plus early history of falls and vertical supranuclear palsy21</td>
<td>MRI: axial T2-weighted MR images: 1. putaminal atrophy (hypointensity or hyperintensity); 2. “hot-cross bun” sign in the basis pontis31</td>
</tr>
<tr>
<td>MSA</td>
<td>Parkinsonism plus evident orthostatic hypotension, cerebellar signs, autonomic dysfunctions24</td>
<td>MRI: axial T2-weighted MR images: 1. putaminal atrophy (hypointensity or hyperintensity); 2. “hot-cross bun” sign in the basis pontis31</td>
</tr>
<tr>
<td>Iatrogenic parkinsonism</td>
<td>Parkinsonism</td>
<td>Negative features on MRI or CT scan and normal SPECT tracer uptake</td>
</tr>
</tbody>
</table>
Two features of DLB are diagnostic: marked day-to-day fluctuations in cognitive function and the presence of well-formed visual hallucinations (typically animals, inanimate objects, or people). Patients affected by DLB are extremely sensitive to the adverse effects of antipsychotic drugs. Neuropsychological findings in DLB include extensive amyloid-beta plaques (as seen in AD), but relatively few tangles. Lewy bodies are characteristic and are found extensively throughout the brain. Markers of cholinergic activity are reduced to a magnitude even greater than that observed in AD. In PDD, patients with Parkinson’s disease typically develop dementia later in the course of their illness. Executive cognitive impairment is most common, but progression of the dementia will include other aspects of cognitive function. Although the clinical presentation of DLB and PDD are quite different, there are similar underlying neuropathological abnormalities. Current consensus is that these two disorders exist as part of a spectrum, rather than discrete entities.4-6

In contrast to AD, DLB, and PDD, Frontotemporal Dementia (FTD) comprises a group of clinical syndromes that share a common pattern of relatively focal degeneration of the frontal and temporal lobes of the brain.7 In addition to meeting criteria for dementia, the core feature of FTD is an early and prominent decline of social interpersonal conduct, with impairment in regulation of personal conduct, emotional blunting, and loss of insight. The typical neuropathological finding is frontal and antero-temporal atrophy. In some cases, Pick’s bodies are found. Although these appear to be reactive to neurofibriillary tau-protein, they are distinct from the amyloid-beta plaques and neurofibrillary tau-protein tangles characteristics of AD. Abnormalities in frontotemporal lobes are seen clinically by MRI and/or PET scanning.7

Because some types of dementia are at least partially treatable, it is not recommended to consider untreatable any patient showing symptoms of dementia. Partially treatable dementia include: i) chronic drug abuse; ii) tumours that can be removed; iii) subdural haematoma; iv) normal pressure hydrocephalus; v) metabolic disorders, such as a vitamin B12 deficiency; vi) hypothyroidism; vii) hypoglycaemia.

When extrapyramidal symptoms predominate at the time of the diagnosis, PD should be differentiated from VP and DLB (Table 1).

Parkinson disease (PD) is an age-related neurodegenerative disorder affecting as many as 1-2% of persons aged 60 years and older and is expected to increase with ageing of the population in the forthcoming decades.8,9 Pathologically, PD is characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) coupled with intracytoplasmic proteinaceous inclusions known as Lewy bodies. Parkinson’s disease is clinically diagnosed on the basis of the classical motor features (ie, bradykinesia, rigidity, rest tremor). However, according to the United Kingdom Brain Bank’s criteria,10 bradykinesia is the cardinal symptom plus at least two between rigidity, rest tremor and postural instability and without the presence of supportive features (asymmetric onset of bradykinesia symptoms, tremor-dominant disease, marked and prolonged L-DOPA benefit). Absence of exclusion criteria is an exception.10

Falls at presentation or early in the disease course, poor response to levodopa, symmetry of motor signs, rapid progression (to Hoehn and Yahr stage 3 in 3 years), lack of tremor, and early dysautonomy (urinary urge incontinence, fecal incontinence, urinary retention requiring catheterization, persistent erectile failure, and symptomatic orthostatic hypotension) are signs that are probably useful in identifying patients with forms of parkinsonism other than PD. The simultaneous presence of these signs are particularly useful when coexist.12

In most of the cases the treatment is straightforward, and no ancillary tests are required, while in the elderly, the diagnosis is more complex given that complaints of aching stiffness with subtle changes in body posture and speed of movement are frequently and incorrectly dismissed as normal aging, leading to inappropriate referrals, for example, to rheumatologists or orthopedics.13

Two clinic-pathological studies published in the early 1990s both found an accuracy of clinical diagnosis of PD of 76%.14 A more recent study in a tertiary referral centre in the UK, using ascertainment and methodology comparable with one of the earlier studies, has shown an improvement in this diagnostic accuracy, with a positive predictive value for those fulfilling pre-established diagnostic criteria of 90%.15

Recently, non-motor symptoms have been described and a new approach on the treatment of this disease is needed, confirming the heterogeneity of the phenotype of the PD.16,17 Cognitive dysfunction, for example, is common in Parkinson disease (PD), with executive dysfunction typically present in almost all patients. However, in the idiopathic disease a frank dementia appears at least one year after motor symptoms.18 When severe, the dementia in Parkinson’s disease (PD-D) is considered the major cause of disability and mortality irrespective of motor symptoms.19 In recent years, a number of ancillary tests have been developed to improve diagnostic accuracy of parkinsonism with focus on early stages, such as autonomic function tests based on magnetic resonance (MRI) or positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging techniques.20

The diagnosis of Vascular Parkinsonism (VP) often raises problems in the daily clinical practice not only for general neurologists but also for movement disorders specialists and has remained a controversial clinical concept.21 The classical sudden-onset lower-body parkinsonism is present only in the minority of cases and often appears slowly progressive as seen in neurodegenerative causes of parkinsonism. The criteria for VP include: i) bradykinesia; ii) cerebrovascular disease confirmed by CT or MRI; iii) a temporal relationship between the location of vascular lesions and the appearance of parkinsonism symptoms or the presence of extensive sub-cortical white-matter lesions and bilateral symptoms at onset. Strategic infarcts responsible for parkinsonism involve the substantia nigra, the ventrolateral nucleus of the thalamus (VL), the globus pallidum (GPe) or a large frontal lesion. The proposed criteria also suggest the exclusion of other causes of parkinsonism such as space-occupying lesions, drugs and toxins, head trauma or encephalitis.22

Finally, when marked parkinsonian signs plus other motor symptoms, are present as cerebellar or pyramidal dysfunction, with falls and autonomic dysfunction, with or without cognitive deficits, diagnosis of atypical parkinsonism should be made, focusing on Cortical-basal degeneration (CBD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP) (Table 1).

The Cortical-basal degeneration (CBD) was originally defined as an asymmetric extrapyramidal syndrome with prominent apraxia and unilateral rigidity with distinctive tau-positive pathology.23 Though the initial emphasis was on the movement disorder early cases also reveal evidence of dysphasia and dementia. Awareness of cognitive deficits in CBD has grown leading to the suggestion that both CBD and primary progressive aphasia should be taken into consideration.

A different atypical parkinsonism is the multiple system atrophy (MSA). Clinical features of the MSA are: prominent cerebellar symptomatology or unexplained early and prominent incontinence, impotence, or marked postural hypotension. In details, diagnosis is possible when parkinsonism (bradykinesia with rigidity, tremor, or postural instability) and a cerebellar syndrome (gait ataxia with cerebellar dystarthritis, limb ataxia, or cerebellar oculomotor dysfunction) and at least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline) are present.24

Finally, although uncommon, the progres-
sive supranuclear palsy (PSP) should be suspected when bradykinesia, gait disorder, falls, rigidity, neck dystonia, no levodopa benefit, no tremor, vertical eye movement palsy, dysarthria, bulbar palsy with dysphagia occur.

The normal pressure hydrocephalus (NPH) is referred to a condition of pathologically enlarged ventricular size with normal opening pressures on lumbar puncture. NPH is distinguished from obstructive or non-communicating hydrocephalus, in which there is a structural blockage of the cerebrospinal fluid (CSF) circulation within the ventricular system (eg, stenosis of aqueduct of Sylvius). NPH is associated with a classic triad of dementia, gait disturbance and urinary incontinence. Because this clinical syndrome is potentially reversible by the placement of a ventriculo-peritoneal shunt, its early diagnosis is crucial. However, there is still little consensus regarding the diagnosis of NPH and the selection of patients for shunt placement.

Clinical use of structural MRI in neurodegenerative disorders

Cross-sectional and longitudinal studies conducted in patients with AD show that the topography of brain tissue loss well correlates with cognitive deficits. Structural brain changes map accurately upstream to Braak’s stages of neurofibrillary tangle deposition and downstream to neuropsychological deficits.27 The earliest sites of tau deposition and MRI-based changes typically lie along the perforant (polysynaptic) hippocampal pathway (entorhinal cortex, hippocampus and posterior cingulate cortex), consistent with early memory deficits. Later, atrophy in temporal, parietal and frontal neocortices is associated with neuronal loss, as well as language, praxic, visuospatial and behavioral impairments. The key role of imaging in AD diagnosis is highlighted by the inclusion of imaging markers in proposed new criteria for earlier diagnosis of AD. These criteria required at least one of the following three markers: i) medial temporal atrophy; ii) temporoparietal hypometabolism; iii) abnormal neuronal CsF markers (tau and/or α4), as already reported.

Consensus criteria for Fronto-Temporal Dementia (FTD) include frontal and/or temporal atrophy (especially focal atrophy) as supportive features, and relatively good correlations have been observed between the FTD subtype and the pattern of atrophy.28 Semantic dementia is associated with anterior (often asymmetrical) temporal lobe atrophy, while progressive non-fluent aphasia is associated with left perisylvian loss, and behavioral variant frontotemporal dementia is associated with frontal atrophy. Focal or asymmetrical frontal or temporal atrophy reduce the likelihood of a diagnosis of AD.27

Consensus criteria for the clinical diagnosis of dementia with Lewy bodies (DLB) include relative preservation of medial temporal lobe structures on computed tomography or MRI, although substantial overlap between DLB and AD with regard to atrophy in this region, detracts from the usefulness of this marker in individual cases.4 This overlap contributes to a blurring of the boundary between DLB and AD, but molecular imaging of the dopaminergic system can help to differentiate these two conditions (abnormal in DLB and normal in AD).27

Subcortical or cortical absence of vascular changes on MRI essentially excludes a diagnosis of vascular dementia according to internationally accepted criteria. However, a large proportion of patients with progressive cognitive deterioration show varying degrees of small vessel disease, identifiable in T2-weighted MRI as white matter changes with or without lacunes. Most individuals with progressive cognitive deterioration probably have a mixed etiology of AD and cerebrovascular changes.28

An important role of conventional magnetic resonance imaging (MRI) in first of all the differential diagnosis of parkinsonism is the differentiation between neurodegenerative and symptomatic parkinsonism secondary to multiple sclerosis, brain tumors, normal pressure hydrocephalus, vascular etiology, or other causes.29

Furthermore, MRI is usually normal in patients with PD, while it frequently shows characteristic abnormalities in patients with atypical parkinsonism (APD). This technique offers the potential for objective criteria in the differential diagnosis among the different forms of neurodegenerative parkinsonism. Overall, specificity of atrophy and signal changes in the putamen as well as in infratentorial structures on MRI in patients with MSA is considered quite high,30 while sensitivity seems to be suboptimal especially in the early disease stages. A number of findings suggestive of PSP have been described, such as midbrain atrophy with enlargement of the third ventricle, reduced anteroposterior midbrain diameter and tegmental atrophy, signal increase in midbrain and inferior olives, as well as frontal and temporal lobe atrophy.31 New measures have been recently developed to prospectively assess sensitivity and specificity of magnetic resonance imaging (MRI). They include measurements of midbrain, pons, middle cerebellar peduncles (MCPs), and superior cerebellar peduncles (SCP) and can be useful to differentiate progressive supranuclear palsy (PSP) from Parkinson disease (PD) and Parkinson variant of multiple system atrophy (MSA). Midbrain area and SCP width in patients with PSP are significantly smaller than in patients with PD, MSA, and controls. MR Parkinsonism index value is significantly larger in patients with PSP than in patients with PD, MSA, and controls, without overlap of values among groups. No patient with PSP receives a misdiagnosis when the index is used.27

Only few studies have investigated the role of MRI in patients with corticobasal degeneration (CBD), showing cortical atrophy especially in frontoparietal areas, which usually seems to be asymmetric, putaminal hypointensity, and hyperintense signal changes in the motor cortex or subcortical white matter on T2-weighted images.32

Clinical utility of nuclear medicine techniques in neurodegenerative disorders

In recent years, a number of ancillary tests have been developed to improve diagnostic accuracy of parkinsonism with focus on early stages. These tests include testing for dopaminergic responsiveness using levodopa or apomorphine, autonomic function tests based on magnetic resonance imaging (MRI) or positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging techniques. For SPECT studies, dopamine transporter (DAT) ligands ([123I]FP-CIT, [123I]b-CIT, [99mTc]–TRO-DAT-1) have become very popular.

SPECT study

In the early 1990s, the cocaine analogue b-CIT has been developed showing a high affinity to DAT and serotonin transporter (SERT). Pharmacological characterization of tracer uptake in primate brains has shown that striatal activity is associated mainly with DAT, whereas midbrain activity is mainly associated with SERT. One of the main problems associated with the use of [123I]b-CIT is that the uptake in human striatum is characterized by slow kinetics, with an increase in striatal activity for 15-20 h after injection, which requires a delay between injection and scan of 24 h. The fluoropropyll derivative of b-CIT, FP-CIT has been shown selective and reliable technique to measure human brain striatal DAT with SPECT camaras. ([123I]FP-CIT SPECT (DaTSCAN) has the main advantage of faster striatal kinetics, which allow imaging 3–6 h after injection.20

Abnormal DAT with SPECT has been found in idiopathic Parkinson’s Disease.20 Using statistical parametric mapping (SPM), it is now possible to realize a semi-quantitative
evaluation of the presynaptic dopaminergic uptake, resulting in an high sensibility and specificity for the diagnosis of presynaptic dopaminergic dysfunction, almost of 100%. Moreover, there are strong experimental and clinical data suggesting that DAT availability measured with SPECT mirrors the decline in levels of striatal dopamine. DAT-SPECT can provide valuable additional information in patients with clinically inconclusive parkinsonism or tremor, particularly in the early stages of the disease. Abnormal DAT-SPECT imaging supports nigro-striatal degeneration in patients presenting parkinsonism or supports an alternative diagnosis like atypical parkinsonism, psychogenic- or drug-induced parkinsonism, vascular parkinsonism, dystonic tremor, essential tremor or dopamine-responsive dystonia when DAT-SPECT is normal. Early and accurate diagnosis has implications not only for the choice of treatment but also for the cost efficiency for national health-care systems.

Recent clinical trials using [123I]-CIT SPECT and [18F]-DOPA PET as surrogate markers for disease progression have found that a proportion diagnosed as early PD have normal scans. In those cases, alternative diagnoses need to be considered.

Although marked asymmetry in reductions of putamenal DAT finding is more typical for PD when compared to other degenerative Parkinsonism disorders, SPECT imaging using DAT ligands do not help to differentiate between the neurodegenerative parkinsonian disorders. Only combining [123I]FP-CIT with postsynaptic imaging using [123I]iodobenzamide (IBZM) SPECT could identify progressive supranuclear palsy (PSP) although normal finding does not exclude it.

A normal striatal DAT signal can be helpful in discriminating psychogenic parkinsonism (PspP) from neurodegenerative forms of Parkinsonism.

Distinguishing VP from PD can be difficult since vascular lesions and white matter basal ganglia ischemia are frequent in the elderly people. Presynaptic dopaminergic circuitry is generally preserved in VP although a slight reduction in lateral substantia nigra is probably due to transneuronal degeneration and moderate cell nerve loss in substantia nigra due to massive unilateral basal ganglia infarction has been reported.

Antidopaminergic drugs (antipsychotics and centrally acting antiemetics) can cause subacute Parkinsonism, which is usually reversible. Postsynaptic imaging shows D2 receptor blockade. DAT imaging helps to confirm or reject underlying dopamine deficits in cases of unexpected severe or prolonged Parkinsonism and guides appropriate therapeutical management.

PET study

Using PET studies testing brain metabolic differences, it has been shown that normal aging of the brain is characterized by a regional decline in the cerebral glucose metabolism of the prefrontal cortex. The hypometabolism associated with AD and its progression probably reflects the vulnerability within the limbic-cortical network. Fluorodeoxyglucose (FDG) PET demonstrates reductions in the cerebral glucometabolism that may occur a few years before the overt clinical manifestation of disease. A classic pattern is bilateral parietotemporal and postero cingulate cortices hypometabolism, which may be asymmetric and be associated with hippocampal atrophy. There may also be crossed cerebellar and uncrossed basal ganglia and thalamic diaschisis.

Occipital hypoperfusion may occur in DBL but does not help in single case assessment, while hypoperfusion is common to both AD and DBL.

In PD patients, the regional glucose metabolism is 25% below control values for all brain regions with the greatest differences seen in the posterior brain areas (visual association cortex, primary visual cortex, and parietal cortex) and thalamus. This study suggested that in PD patients without dementia the cortical hypometabolism primarily affects the posterior brain areas. A recent study showed a moderate cholinergic dysfunction in non-demented patients with PD and demented PD patients presenting severe cholinergic deficit in various cortical regions.

FDG PET may be valuable in the clinical recognition of frontotemporal dementia (FTD). Patients with FTD showed significant symmetrical hypometabolism of the frontal lobes sparing the motor cortex, caudate, insula, and the thalamus. In early stages of FTD, the hypometabolism is limited to the frontal and anterior temporal lobes but during progression of disease, the pathological changes spread into the parietal and temporal cortices.

The recently revised consensus criteria for clinical diagnosis of DBL have suggested adding new features to improve DBL diagnosis. Both DBL and PD are characterized by nigro-striatal dopamine loss making DAT imaging helpful. Although DBL, PD with dementia and PD may share a common etiology, nigral neuron degeneration might be more widespread in DBL and also involve projections to the caudate nucleus. Striatal dopamine D2 receptor binding of [123I]-IBZM SPECT may also be reduced in DBL but overlap with AD is considerable.

Conclusions

In conclusion, clinicians actually have many neuroimaging techniques for improving accuracy on the diagnosis of neurodegenerative disease in the elderly. Conventional brain CT should be realized in all patients with suspected neurodegenerative disease. MRI appear to be one of the first choice for a fine differential diagnosis and as second line nuclear medicine techniques should actually be used especially when dementia should be characterized with a right cost-effectiveness.

References


