PICTORIAL ESSAY

Neuroscintigraphy of Non-Alzheimer’s Disease Dementias

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ABSTRACT
Neuroscintigraphy for dementia includes brain perfusion single-photon emission computed tomography (SPECT) [hexamethylpropyleneamine oxime or ethyl cysteinate dimer] and fluorodeoxyglucose positron emission tomography (PET), which are the two most common functional imaging procedures for the brain. The two procedures detect the physiological blood flow and metabolic glucose uptake in the brain, respectively. These functional scans are invaluable in early diagnosis, as well as for confirmation in difficult clinical cases of dementia. Various types of dementia show specific scintigraphic patterns and, together with clinical correlation and anatomical imaging correlation, accurate clinicoradiological diagnosis can often be achieved. Advanced software such as Talairach analysis further improves the sensitivity of brain SPECT by showing a 3-dimensional surface display of the perfusion pattern. Additional brain scintigraphy — including cerebral amyloid PET, cerebral dopaminergic PET, and indium-111 cisternogram — are sometimes indicated for special reasons such as atypical clinical presentation or equivocal imaging findings. Finally, frequent clinicoradiological conference helps mutual improvement in clinical utilisation as well as the specificity of neuroimaging.

Key Words: Alzheimer disease; Aphasia, primary progressive; Hydrocephalus, normal pressure; Lewy body disease; Supranuclear palsy, progressive; Tomography, emission-computed, single-photon

中文摘要
非阿爾茨海默型癡呆症的腦神經顯像
王琪、戴毓玲、張智欣、戴樂群
老年癡呆症的神經顯像技術包括腦灌注單光子發射腦部斷層顯像（SPECT）〔hexamethylpropyleneamine oxime或ethyl cysteinate dimer〕和氟正電子發射斷層顯像（PET），這是兩種最常見的腦部功能成像方法。腦SPECT顯像分析血流灌注的生理狀況，PET則檢查腦部攝取葡萄糖代謝狀況，這些腦功能成像檢查對於早期診斷相當重要，而且對於臨床上難以以其他疾病鑑別的癡呆症病例更加有用。不同類型的癡呆症有其獨特的影像學表現，通過結合臨床表現及解剖結構的特點，便能做出明確診斷。先進軟件的分析（如Talairach analysis）能顯示腦灌注成像的三維模型，進一步提高腦SPECT的靈敏度。有時基於特別的原因（如出現非典型臨床表現或一些模棱兩可的影像表現）須進行額外的大腦顯像分析，如腦內澱粉樣蛋白PET、腦多巴胺PET和銦111腦池顯像。經常舉行臨床影像研討會有助提高對腦神經影像學檢查在臨床中的應用，並且能發揮其特有的檢查優勢。

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INTRODUCTION
Non-Alzheimer’s disease (non-AD) dementia consists of a variety of dementia syndromes, which typically do not present as memory decline in the early stages. As a result, differential diagnoses such as depression or psychiatric illness with pseudodementia can be confused with frontotemporal dementia (FTD), and atypical parkinsonism can be confused with corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), multisystem atrophy, and Lewy body dementia (LBD). Anatomical imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) could provide specific cerebral atrophy patterns to suggest the correct diagnosis. However, overlapping features of cerebral atrophy of non-AD dementias sometimes cause diagnostic uncertainty for early presentation. In addition, the anatomical manifestations of cerebral atrophy can lag behind the underlying neurophysiological and neurobiochemical abnormalities. In this respect, functional neuroimaging such as neurophysiological brain perfusion single-photon emission computed tomography (SPECT) and neurobiochemical fluorodeoxyglucose positron emission tomography (FDG PET) could reveal earlier changes in the functional deficit of non-AD dementias when there are both clinical and radiological uncertainties.

CEREBRAL PERFUSION SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY
Cerebral perfusion SPECT using 20 mCi injection of technetium-99m ethyl cysteinate dimer (ECD) or technetium-99m hexamethylpropyleneamine oxime (HMPAO) are commonly selected as brain perfusion agents. Study has shown that HMPAO and ECD perfusion SPECT have different age and gender effects on perfusion in the cortical and subcortical areas, whereas there are no morphometric differences in the grey matter. In the authors’ experience of more than 200 ECD scans and more than 150 HMPAO scans performed in the past 10 years, there is no significant diagnostic limitation in the interpretation of regional brain abnormality using these two tracers. At the Prince of Wales Hospital, Hong Kong, cerebral perfusion SPECT is performed by a dual-headed gamma camera (Infinia Hawkeye; General Electric, Milwaukee [WI], USA) equipped with a fan-beam collimator. Images are acquired in 120 projections over a 360° arc using the step-and-shoot mode with an acquisition time of 20 seconds per projection. Transverse slices are created by ordered subset expectation maximisation using a Butterworth filter with a critical frequency of 0.44 and power order of 10. The transverse slices are

Figure 1. (a) Axial computed tomography of the brain shows asymmetrical left frontotemporal atrophy in a patient with frontotemporal dementia. (b and c) Corresponding axial and coronal technetium-99m hexamethylpropyl-eneamine oxime single-photon emission computed tomography shows conspicuous hypoperfusion in the bilateral frontotemporal regions, which is more severe on the left side (arrows). There is unremarkable perfusion of the basal ganglia, which distinguishes frontotemporal dementia from corticobasal degeneration with unilateral hypoperfusion of the basal ganglion, and primary progressive aphasia with unilateral frontoparietal hypoperfusion.
corrected for attenuation by change order of threshold 20. Talairach analysis (NeuroGam, Segami, Columbia [MD], USA) yields a stereotactic atlas compared with the normal database installed.

FRONTOTEMPORAL DEMENTIA
FTD is a complex dementia syndrome that results in progressive damage to the anterior temporal and/or frontal lobes of the brain. Antisocial behaviour in FTD patients is associated with significant hypoperfusion in the frontal lobes, especially in the orbitofrontal cortex, whereas temporal lobe involvement is associated with hypomania-like behaviour. FTD patients with change in personality rather than memory decline as the initial presentation can be misdiagnosed with psychiatric illness and wrongly stigmatised, resulting in unpredictable stress in personal, interpersonal, and social relationships. Clinical diagnosis of FTD requires experienced clinicians, and anatomical imaging such as CT or MRI usually provides supportive evidence of the cerebral atrophy pattern in established cases (Figure 1). However, since FTD is more commonly seen in younger patients aged from 50 to 60 years, the degree of cerebral atrophy in anatomical imaging may not always be classical for a prompt diagnosis. Functional neuroimaging such as brain perfusion SPECT or FDG PET can provide invaluable information for the diagnosis of FTD in its early stage (Figure 2). Overlapping clinical features of FTD, primary progressive aphasia (PPA) and CBD due to common tauopathy in ‘three-in-one’ syndrome can be differentiated by specific perfusion SPECT abnormality,
providing much higher diagnostic accuracy than conventional imaging.

**PRIMARY PROGRESSIVE APHASIA**

There are three types of PPA, which are due to neurodegenerative atrophy in the areas of the brain responsible for the speech production and conduction pathway. PPA is a complex language disorder that involves changes in the ability to speak, read, write, and understand what others are saying (Table).

Since the left cerebral hemisphere is usually the dominant hemisphere for speech production, PPA almost always involves pathological changes in the left cerebral hemisphere. We have found three patterns of SPECT for PPA. In classical non-fluent PPA, the arcuate fasciculus that connects Broca’s area to Wernicke’s area in the left cerebrum is atrophic with hypoperfusion defects in these two areas (Figure 3). The arcuate fasciculus, which is part of the superior longitudinal fasciculus bidirectionally, connects the caudal temporal cortex to inferior parietal cortex. In semantic PPA, hypoperfusion areas mainly lie over the orbitofrontal, anterior temporal, and temporo-occipital regions, where the uncinate fibres and the inferior longitudinal fasciculus form the major pathways for semantic PPA outlined by tractography (Figure 4). In logopenic PPA, areas of hypoperfusion mainly lie over the frontoparietal region towards the temporal region, corresponding to the tractography shown for logopenic PPA (Figure 4). Diffusion tensor tractography and cerebral perfusion SPECT are useful in demonstrating the distinct pathoanatomy and pathophysiology, respectively, in various subtypes of PPA (Figure 4).

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**Table.** Features of primary progressive aphasia.

<table>
<thead>
<tr>
<th>Non-fluent / agrammatic</th>
<th>Semantic variant</th>
<th>Logopenic variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow and interrupted speech</td>
<td>Fluent speech</td>
<td>Slow speech with frequent mutism</td>
</tr>
<tr>
<td>Uncoordinated and imprecise speech but able to comprehend</td>
<td>Deterioration of understanding words especially nouns, cannot name familiar objects</td>
<td>Difficulty finding the correct words for speech, but retaining the underlying meanings of words</td>
</tr>
<tr>
<td>Left perisylvian atrophy</td>
<td>Left perisylvian atrophy</td>
<td>Left temporoparietal atrophy</td>
</tr>
<tr>
<td>Tau protein &gt; TDP-43</td>
<td>TDP-43 &gt; Tau protein</td>
<td>Apolipoprotein-E4, amyloid</td>
</tr>
</tbody>
</table>

Abbreviation: TDP-43 = transactive response DNA binding protein 43 kDa.

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**Figure 3.** (a) Computed tomography of the brain of a non-fluent primary progressive aphasia patient shows left perisylvian fissure atrophy. (b) Corresponding left lateral view of brain perfusion scan (Talairach analysis) shows the diagrammatic arcuate fasciculus overlying Broca’s and Wernicke’s areas. Defects in this main speech conduction pathway will result in non-fluent speech similar to aphasia in patients with massive left middle cerebral artery territory infarction.
SPECT is more widely used than diffusion tensor imaging tractography due to the complex processing in tractography. In particular, Talairach analysis in cerebral perfusion SPECT can display the perfusion deficits on the surface of a 3-dimensional brain map, which is better appreciated.

CORTICOBASAL DEGENERATION

CBD is a rare neurodegenerative disease involving the cerebral cortices and extrapyramidal structures. Cortical signs usually consist of apraxia, cortical sensory loss, and involuntary movements, which have been referred to as alien hand (feeling that one limb is foreign with observable involuntary motor activity).

In structural imaging studies (CT or MRI), asymmetric cerebral atrophy is a characteristic finding in CBD, which is predominantly seen at the paracentral sulcus region (Rolandic region) and most often contralateral to the clinically first or most severely affected side. Atrophy at the mid-portion of the corpus callosum, cerebral peduncle, and midbrain tegmentum are also reported. This middle predominance may reflect both the severity and location of neuronal loss.

In brain perfusion study (either ECD or HMPAO-SPECT), asymmetrical hypoperfusion is seen in the frontoparietal lobe (paracentral sulcus region), basal ganglia, particularly the putamen, and thalamus. The side of hypoperfusion is again contralateral to the side more severely affected clinically (Figure 5).

The cortical sensory deficits are most likely related to severe neuronal loss in the post-central gyrus and superior parietal lobule (sensory cortex). Myoclonus is also likely to be related to the involvement of the precentral gyrus (motor cortex). Involvement of the inferior parietal lobule of the dominant hemisphere probably accounts for the apraxia. The corpus callosum also plays a significant role in cognitive function. The specific atrophic pattern (reflecting neuronal loss) in structural imaging and cerebral hypoperfusion in functional imaging (reflecting decrease in neuronal activity) can be correlated with the clinical neurological deficits.
Figure 5. Cerebral perfusion single-photon emission computed tomography of a patient with corticobasal degeneration. (a and b) Talairach analysis shows moderate-to-severe hypoperfusion in the frontoparietal region of the right cerebral hemisphere (Rolandic region) with clinical left dystonia. The right frontal lobe also shows mild-to-moderate hypoperfusion. (c) Axial and (d) coronal images show right frontal lobe hypoperfusion (broad arrows) and right temporal hypoperfusion (dotted arrow) with right basal ganglion hypoperfusion (narrow arrows) when compared with relatively normal left cerebrum.

Figure 6. Magnetic resonance images of a patient with early-stage progressive supranuclear palsy. (a) A coronal T1-weighted image shows asymmetrical left mild cerebral atrophy around the sylvian fissure, and (b) sagittal T2-weighted image shows early midbrain and pontine atrophy. The findings are not specific for progressive supranuclear palsy in the early stage (equivocal Hummingbird sign), and the differential diagnoses include frontotemporal dementia and primary progressive aphasia.
PROGRESSIVE SUPRANUCLEAR PALSY
PSP is a neurotauopathic degenerative disorder typically presenting with upward gaze palsy, parkinsonism features, and postural instability. The classical MRI sign of Hummingbird appearance of the brainstem occurs at the advanced stage of the disease, while a Hummingbird sign may be equivocal at the early stage (Figure 6), rendering early diagnosis for clinical management difficult. Functional scintigraphy such as cerebral FDG PET or perfusion SPECT may be more sensitive for early diagnosis of PSP. Brainstem hypometabolism or perfusion in brain scintigraphy is the predominant feature in PSP, associated with a lesser degree of asymmetrical cerebral hypofunctioning (Figure 7). Additional scintigraphic findings include hypometabolism in the medial frontal regions, superior frontal and insular regions, and the caudate nucleus. Differential diagnoses include FTD, PPA, and CBD, which are also tauopathies and are typically associated with predominant asymmetrical cerebral atrophy and hypofunctioning, but a lesser degree of brainstem abnormality.

LEWY BODY DEMENTIA
LBD is considered to be the second most common cause of dementia in elderly people after AD. Intraneuronal cytoplasmic inclusion Lewy bodies are characteristically found in the midbrain and cerebral cortex in LBD patients. The diagnostic criteria for LBD include progressive dementia as a central feature. Fluctuating cognition with pronounced variations in attention and alertness, recurrent complex visual hallucinations, and spontaneous parkinsonism are regarded as core features. Rapid-eye-movement sleep behaviour disorder, particularly vivid dreams with
violent behaviour, repeated falls and syncope, severe neuroleptic sensitivity, severe autonomic dysfunction, and depression are considered to be supportive features. Both LBD and Parkinson’s disease (PD) are associated with abnormal deposition of α-synuclein (synucleiopathy); development of dementia within 12 months of the onset of parkinsonism features suggests LBD, while late development of dementia after extrapyramidal signs suggest that PD with dementia is more likely. Both LBD and PD are associated with decreased striatal dopamine synthesis and storage in presynaptic dopaminergic imaging such as 18F-fluorodopa PET and variable response in postsynaptic dopaminergic imaging such as 11C-raclopride PET.

LBD is easily confused with AD, which may be due to amyloid deposition. Patients with LBD more frequently show signs of frontal lobe dysfunction, more visual and auditory hallucinations, and more severe dopamine and acetylcholine loss than patients with AD. Predominant occipital lobe hypoperfusion and hypometabolism in perfusion SPECT by HMPAO and FDG PET, respectively, are considered to be highly specific for differentiating LBD from other dementias (Figure 8). The authors’ experience is that LBD is usually associated with posterior parietal lobe and occipital lobe hypoperfusion on perfusion SPECT and often mild frontal lobe abnormality (Figure 9). However, AD shows predominant bilateral symmetrical hypoperfusion in the temporal and parietal regions (Figure 10). Combining MRI with SPECT can increase the diagnostic differentiation of mild LBD from AD by lower grey matter volume in the striatum in LBD than in AD, and much higher cerebral blood flow reduction in the occipital lobe in LBD than in AD. However, volumetric analysis and regional cerebral blood flow analysis are not feasible in daily practice. The authors’ experience shows that relatively greater loss in hippocampal volume is more suggestive of AD than LBD but, very often, occipital lobe atrophy may not be the most prominent feature in LBD on MRI. Functional scintigraphy may be more diagnostic than MRI if there is a clinical suspicion of LBD.

NORMAL-PRESSURE HYDROCEPHALUS

Normal-pressure hydrocephalus (NPH) is relatively uncommon when compared with other dementias, but it is clinically important because its diagnosis relies on neuroimaging and it is potentially treatable by a ventricular shunting procedure in suitable patients. Although the classical triad of gait disturbance, urine incontinence, and dementia are well known, a definite clinical diagnosis is often difficult without compatible neuroimaging findings. About half of the patients have idiopathic NPH, which usually manifests in elderly people, who seem to be less responsive to the ventricular shunting procedure. The other 50% of NPH patients have chronic communicating hydrocephalus from prior subarachnoid haemorrhage, meningitis, neurosurgery, or head trauma, and tend to present at an earlier age and have a better response to ventricular shunting than patients with idiopathic NPH. The exact

**Figure 8.** (a) Magnetic resonance imaging of a patient with a clinical diagnosis of Lewy body dementia: a sagittal T2-weighted image shows prominent occipital sulcal dilatation over the rest of brain (red circle), and (b) corresponding technetium-99m hexamethylpropyleneamine oxime brain scan (Talairach analysis) shows a large area of hypoperfusion over the occipital lobe.
pathological mechanism of NPH is still unclear, but imaging findings suggest the following mechanisms: increased resistance to cerebrospinal fluid (CSF) flow with preserved autoregulation of carbon dioxide reactivity in transcranial Doppler ultrasonography; increased CSF flow rate (>18 ml/min) and higher CSF stroke volume (>42 μl) on cardiac-gated phase-contrast MRI; reduced periventricular tensile strength by deep white matter infarcts; and decreased vascular compliance of the superior sagittal sinus and straight sinus on MRI. The alarming radiological features of NPH are usually disproportionate enlargement of the lateral ventricles together with temporal horns to the sulcal prominence (Figure 11), with an Evans ratio of...
0.32 or greater (Evans ratio is defined as the measured distance of the frontal horns divided by the inner table width of the calvarium at the same level). However, there is some overlap in Evans ratio between NPH and cerebral atrophy, and this parameter may not always differentiate NPH from obstructive hydrocephalus. While MRI focusing on CSF dynamics, distinguishing intraventricular lactate peak on proton chemical shift imaging or MR spectroscopy and elevated apparent diffusion coefficient on diffusion-weighted imaging are commonly used to diagnose and triage NPH patients for neurosurgery; many neurosurgeons still prefer CSF infusion test and radionuclide cisternography (Figure 12), which are more familiar. The main cisternal scintigraphic features for NPH are early ventricular reflux, particularly in the 4-hour period post-injection, persistent or even progressive increase in ventricular activity, and significantly decreased subarachnoid (cerebral convexity) activity in the 24- to 48-hour delay period. Contrarily, in a normal cisternogram, no ventricular reflux activity is appreciated and there is rapid appearance of subarachnoid activity within 24 hours. In compensatory hydrocephalus for cerebral atrophy, there may be mild ventricular reflux, but this should not be persistent, and slightly delayed appearance of subarachnoid activity in 24 to 48 hours.

**DISCUSSION**

Diagnosing dementia by neuroscintigraphy is a great challenge, but it can be more specific if we could incorporate the neuroradiology findings and clinician’s perspectives. For example, FTD, PPA, PSP, and CBD (4 in 1 syndrome) all show asymmetrical cerebral atrophic change, which can be very subtle at the early stage, while a more specific scintigraphic perfusion or metabolism pattern may show up on functional scintigraphy to enable better differentiation. On the other hand, vascular dementia usually has specific neuroradiological features on CT and MRI, but can sometimes be confused with NPH, which can be differentiated by CSF flow dynamics MRI study or cisternography. Most importantly, clinicians’ input is invaluable, especially for AD and LBD, both of which may have overlapping neuroradiological and neuroscintigraphic features. Finally, the authors benefit most from the clinical radiological meeting, for mutual understanding and education.

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Figure 12. Indium-111 diethylene triamine pentaacetic acid cisternogram of the patient in Figure 11 shows (a) abnormal reflux of radioactivity into the lateral ventricles and sylvian fissure at 4 hours post-injection period with (c) persistent ventricular activity in the 24-hour delay period and (e) reduced subarachnoid activity in the 48-hour delay period. (b, d, and f) single-photon emission computed tomography at 48 hours shows marked retention of radioactivity in the lateral ventricles and sylvian fissure with reduced subarachnoid activity.
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