

Cerebral blood flow changes in Parkinson's disease associated with dementia

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Abstract

Dementia is one of the main non-motor symptoms of Parkinson's disease (PD) and it is diagnosed in about 30% of cases. Its aetiology remains unclear and contributing factors are controversial. Dementia may be more common in old patients with severe motor symptoms and mild cognitive impairment. Clinico-pathological studies show the association between dementia in PD and the age-related group of dementias, such as AD and VaD.

A valuable aid in the assessment of dementia in PD is cerebral blood flow (CBF) brain SPECT scanning. It shows three different patterns of rCBF reduction, including frontal lobe hypoperfusion, "Alzheimer-like" type of hypoperfusion and multiple, vascular defects. The heterogeneity of rCBF reduction may reflect the multifactorial pathophysiology of dementia in PD. It may result from concomitant AD pathology, cerebrovascular disease, destruction of nigro-striato-frontal projection or may be a distinct disease of different aetiology.

Key words: cerebral blood flow, Parkinson's disease

Introduction

Dementia is an acquired and persistent deterioration of the intellect in an alert patient, with significant impairment in three or

more of the following areas: memory, language, visual-spatial skills, mood, personality, and cognition [1, 2]. Dementia can be divided into global dementia, when all intellectual functions are impaired, and lacunar dementia, with more selective functional impairment. The aetiology of dementia is complex. The large majority of dementias are a result of vascular dementia (VaD) and degenerative dementia, such as Alzheimer's disease (AD), fronto-temporal degeneration (FTD), dementia of Lewy bodies (DLB). More rare are reversible dementias caused by symptomatic factors like vitamin B-12 deficiency, chronic subdural haematoma, circulatory insufficiency and others.

Dementia of Alzheimer's type (DAT) and vascular dementia (VaD) are usually considered to be the two most frequent forms of dementia (3–6). Clinical and pathological studies show that approximately 50–60% of cases of dementia are due to DAT, 12–20% are due to VaD, and another 15–20% share neuropathological features of both DAT and VaD [7–9].

The prevalence of dementia in Parkinson's disease (PD) ranges from 10% to 95% [10–12]. This wide variation is related to differences in the diagnostic criteria used or the methods adopted by various investigators. Nevertheless, dementia in PD is seen quite often and its aetiology remains unknown. Old age, severe motor symptoms and mild cognitive impairment — particularly executive and visual-spatial dysfunction — are the risk factors of dementia in PD [13]. Some studies suggest that bradykinesia or masked face, but not tremor, predict the subsequent development of dementia [14, 15].

Presumably in elderly people dementias such as AD and VaD may be associated with PD [16–21]. This may suggest a remarkable overlap in clinical manifestation of dementia in PD, AD and VaD. For example, dementia with Lewy bodies (DLB) comprises features of PD and AD and is considered to be a variant of AD or a more extended form of PD [22, 23].

Dementia has severe consequences for patients with PD, including increased mortality and risk for nursing home placement, as compared with non-demented patients with PD. Moreover, dementia makes the therapeutic process more complicated, with increased incidence of behavioural dysfunction (hallucinations or delusions) in the course of PD [13].

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Early and accurate diagnosis of dementia in PD is essential for: planning of appropriate medical and psychological treatment, the identification of potentially reversible risk factors, and appropriate care-giver advice and intervention.

Recent attempts at treatment of cognitive symptoms in dementia have largely been aimed at AD and, to some extent, VaD. Acetylcholinesterase inhibitors (tacrine, donepezil, rivastigmine) have emerged as the only treatment approach with demonstrable efficacy in large-scale trials [24]. There is some evidence to suggest that patients with PD and dementia may benefit from treatment with cholinesterase inhibitors as well [25].

It is not clear if VaD also contribute to cognitive deterioration in PD. Therefore, in addition to symptomatic treatment strategies, it is essential to investigate an effective therapy of reversible causes of dementia such as cerebrovascular risk factors (hypertension, heart diseases, diabetes mellitus, hyperlipidaemia).

An important diagnostic tool in the investigation of dementia in PD seems to be cerebral blood flow brain (CBF) SPECT scanning. CBF SPECT scanning may detect specific patterns of rCBF deficits associated with dementia in PD and help the clinician to establish the diagnosis of dementia in the early stage of disease.

Most reports on CBF SPECT studies in patients with a clinical diagnosis of PD have concluded that PD is associated with a heterogeneous rCBF pattern. There may be distinguished three main subtypes of hypoperfusion in PD with dementia:

- predominantly frontal lobe type;
- posterior (“Alzheimer-like”) type;
- multiple small vascular defects [10, 11, 26].

Data on particular CBF changes in PD are summarised in the table below (Table 1).

Posterior type of hypoperfusion

The perfusion defects in the temporoparietal cortex were the most frequently found in demented patients with PD. Temporoparietal hypoperfusion is considered to be the most outstanding feature of CBF alterations in AD [28–33]. In demented patients with PD a hypoperfusion nadir of 45–65% was noted. On the other hand, in non-demented patients, the nadir value was 65% [28].

Regarding cognitive functions, the scores of the Mini Mental Score Examination show a high significant correlation with the blood flow in temporoparietal lobe, suggesting that dementia in PD might be caused by dysfunction of this lobe [34].

The rCBF pattern of AD found in the most demented patients with PD suggests that the underlying pathophysiology for dementia in PD may be similar to that seen in AD, or it may be due to a concomitant AD process.

The neuropathological studies indicate that up to 60% of clinically diagnosed PD patients had senile plaques and neurofibrillary tangles in the hippocampal area or neocortex [35–38]. Furthermore, the prevalence of dementia in “pure” PD is only 3.5%, while in PD with AD it is about 56.3% [39].

In AD, there is a degeneration of cortical cholinergic neurones originating in the subcortical basal nuclei of Meynert (nbM, *nucleus basalis Meynert*) — the main source of cholinergic neocortical innervation. Decreased rCBF may be secondary to cortical hypometabolism caused by damage of nbM. The same abnormalities are seen in PD with dementia [40].

These data suggest that dementia in PD may represent the onset of degeneration in a nondopaminergic neurotransmitter system. Additional evidence for this hypothesis is the lack of

Table 1. Brain Perfusion SPECT Patterns associated with dementia in PD

| | Frontal hypoperfusion | Temporoparietal hypoperfusion | Multiple focal defects (patchy pattern) |
|----------------------------|---|---|--|
| Pathogenesis | the frontal lobe deafferentiation hypothesis | cortical cholinergic system degeneration | vascular pathology (multiple cortical infarcts, single cortical infarcts in strategic location, small vessel diseases) |
| Neurotransmitters involved | nigrostriatal dopaminergic system | subcortico-cortical dopaminergic, noradrenergic, serotonergic, and cholinergic system | no involvement or cortical cholinergic system in concern |
| Mental status | impairment of verbal fluency, visual-spatial dysfunction, executive dysfunction (problem solving, planning abilities, generation of new concepts and mental sets) | global intellectual dysfunction assessed by total score on the MMSE, memory impairment, language and calculating disability | memory problems, deficits in more than two cognitive domains indicative of cortical or subcortical dysfunction |
| Frequency* | 22% | 64% | 14% |

* Reference no. 27

rCBF increase and mental deficit improvement, after treatment with levo-dopa [41]. On the other hand, there was found to be an improvement of selective cognitive impairment after levo-dopa administration in globally non-demented patients with PD [42–44]. Presumably, different pathological mechanisms underlie neuropsychiatric symptoms in demented and non-demented patients with PD.

Frontal lobe type of hypoperfusion

Reduction of rCBF in the frontal lobe is considered to be the second most common type of hypoperfusion seen in demented PD patients [27]. Slight hypoperfusion in the frontal area was also found in non-demented patients with PD [45–47]. In contrast, the marked frontal hypoperfusion seen in the demented group suggested that alterations had occurred in the cortex or in the subcortical nuclei projecting to the frontal lobes. This process could lead to frontal hypoperfusion (the frontal lobe deafferentiation hypothesis) [48]. The subcortico-frontal projections may include two different nigro-striato-cortical loops: a “motor loop” and a “complex loop”. Neurones in the rostromedial compacta of the substantia nigra project to the caudate, then connect to the frontal association area (the “complex loop”); neurones in the caudolateral compacta project to the putamen and then connect to the pre-motor areas (the “motor loop”). The “complex loop” is related to psychomotor function and motivation, while the “motor loop” is related to motor function. The predominance of blood flow changes in the frontal association cortex may reflect alterations in the “complex loop” due to neuronal loss in the medial substantia nigra.

It has been established that frontal CBF deficit is a marker for depression, and the severity of depression has been associated with the severity of cognitive impairment in PD [49–51]. The neuropathological studies indicate that the additional dysfunction of the serotoninergeric system may explain the development of both entities [52].

Multiple small vascular defects

In some PD patients, SPECT scanning reveals asymmetrically distributed multifocal CBF deficits, also so-called ‘patchy’ changes, in about 13% of demented patients with PD [27]. These CBF changes are considered to be the typical SPECT scanning feature of vascular dementia (VaD) [53, 54].

VaD is a complex disorder characterised by cognitive impairment resulting from ischaemic or haemorrhagic stroke or from ischaemic-hypoxic brain lesions. Focal neurological signs suggestive of cerebrovascular disease, such as hemiparesis, lower facial weakness, hemianopia, sensory deficits, dysarthria or Babinski sign, may accompany mental deficits. There are various types of underlying damage to tissue and vessels in VaD, including single or multiple infarcts that involve association and limbic cortices, small subcortical infarcts disrupting cortico-subcortical circuits and white matter lesions [55]. However, the most frequent types of lesions are multiple lacunar infarctions of the brain (43%) [7].

The diagnosis of VaD cannot be made without neuroimaging evidence of cerebrovascular disease (CVD). The most highly recommended forms of brain imaging in the diagnosis of VaD are CT and MRI. CT is highly sensitive, up to 95% in severe brain ischaemia [56]. However, rCBF brain seems to be superior to CT in the as-

essment of perfusion in moderate ischaemia [57]. The crucial point in the diagnosis of multi-vascular lesion using SPECT scanning is the possibility of showing cortical infarctions and concomitant neurodegenerative diseases, especially in older patients. Presumably, neuronal damage and loss of metabolic demand are responsible for decrease in CBF SPECT [58].

Data on the relationship between PD and CVD are conflicting. There are data both on prevalence of CVD increased to 27% in PD patients and on low prevalence [59]. The associated risk factors for stroke, such as hypertension, heart disease, cigarette smoking, diabetes mellitus, hyperlipidaemia and moderate alcohol consumption are found to be present in 32% of patients with PD [60, 61].

Pathological studies have shown that vascular lesions alone are probably unable to provoke a clear clinical syndrome of dementia, but can modify the presentation or severity of any dementia [62, 63]. For example, recent evidence found that the selective loss of nbM neurones as part of early AD could perhaps be exacerbated by the further destruction of cholinergic neurones caused by stroke. Possibly the destruction of cholinergic neurones can contribute to the symptomatology of VaD.

This hypothesis may explain the beneficial effects of ChE inhibitors found in patients with VaD [24].

Conclusions

There are different patterns of rCBF changes revealed by SPECT studies in demented patients with PD. This heterogeneity may reflect the multifactorial pathophysiology of the disease:

- the hypoperfusion in the temporoparietal cortex may be due to concomitant AD pathology or may be induced by changes in the cholinergic system similar to AD;
- frontal lobe hypoperfusion may be related to dopaminergic deficiency, which is responsible for the destruction of nigro-striato-frontal projections;
- multifocal CBF deficits may suggest that CVD contribute to dementia in PD.

Presumably, dementia in PD patients results from the overlapping of the above-mentioned syndromes or is a completely distinct disease of different aetiology.

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