PARKINSON’S DISEASE DEMENTIA: Clinical correlates of brain SPECT perfusion and treatment


1Department of Neurology, University Medical Centre Ljubljana, Slovenia  
2Faculty of Arts, Department of Psychology, Ljubljana, Slovenia  
3Department of Nuclear medicine, University Medical Centre Ljubljana, Slovenia  
4Institute of Radiology, University Medical Centre Ljubljana, Slovenia  
5Psychiatry Clinic Ljubljana, Ljubljana, Slovenia

SUMMARY

Background: The main clinical feature of dementia in Parkinson's disease is a dysexecutive syndrome. The neuropathology of PD dementia (PDD) is likely multifactorial and affects several neuronal populations. There is evidence that Parkinson’s disease dementia is associated with a cholinergic deficit, supporting the therapeutic role of cholinesterase inhibitors, which are already first-line agents in the treatment of Alzheimer's disease.

The paper includes short report on a pilot study with description of cognitive and imaging profiles in patients with mild to moderate stage of Parkinson disease dementia (PDD).

Subjects and methods: A random sample of 16 patients with clinical diagnostic criteria for probable PDD was included in the study. Patients were characterized with mild to moderate cognitive decline slightly depressive mood and moderate motor performance. Brain perfusion [99mTc]ECD / SPECT and structural MRI with emphasis on evaluation of the degree of cortical atrophy and the medial temporal atrophy index was performed. All patients had detailed neuropsychological evaluation using a “cognitive process approach”. Neuropsychological data were correlated voxel-wise with normalized brain perfusion images, creating whole-brain correlation maps.

Conclusions: Previously reported generalized cognitive impairment in PDD with predominant executive, visuospatial and attentional deficits was confirmed. Performance on specific cognitive measures was correlated with perfusion brain SPECT findings. It could be speculated that different pathological mechanisms underlie widespread significant brain perfusion decrements in temporal, parietal and frontal regions.

Key words: Parkinson’s disease dementia - perfusion brain SPECT - cognitive and imaging profile - treatment

OVERVIEW

Parkinson’s disease (PD) is the second most common neurodegenerative disease after Alzheimer’s disease (AD), affecting up to 1% of the elderly population. Dementia with Lewy bodies (DLB), which may be indistinguishable from PD neuropathologically and has similar clinical features (e.g., dementia, spontaneous parkinsonism, and attention impairment), is thought by many to be the second most common dementia after Alzheimer’s disease in Western countries. Dementia also occurs commonly in PD, affecting up to 75% of PD patients over the long term. The distinguishing clinical characteristic between PD with dementia and DLB is the timing of dementia onset: dementia that occurs with, at the time of, or within 1 year of the onset of parkinsonism is diagnosed as DLB, whereas a dementia onset more than 1 year after the onset of parkinsonism is diagnosed as PD with dementia.

It is being increasingly recognized that non-motor symptoms of PD such as cognitive impairment, dementia, psychosis, depression, autonomic dysfunction and sleep disturbances are as integral to the disease spectrum, as are motor symptoms.

The two most common age-related neurodegenerative disorders, AD and PD have been traditionally considered as separate clinical entities. But the recognition of extrapyramidal features in up to 30 to 70% of clinically diagnosed AD patients (Aarsland et al. 2003) and the increasing number of studies demonstrating the presence of dementia in patients with PD (McKeith et al. 2005) have changed this strict dichotomy.

Also DLB, which is characterized by a progressive and fluctuating cognitive impairment associated with psychosis and extrapyramidal features, has emerged as one of the most common types of degenerative dementia. (McKeith et al. 1996, McKeith et al. 1999)

Many studies have demonstrated different neuropsychological presentations in AD compared to PD dementia (PDD) (Stern et al.1993, Stern et al. 1998). Dementia in AD is characterized by an early and progressive memory impairment accompanied by an increasing disorder of perception, language, praxis, and calculation. On the other hand, a prominent impairment of executive functions associated with a slowing of thought processes and a relative sparing of memory and other cortical functions has been described in PDD.
Characterization of DLB, which shows a mixed cortico-subcortical neuropsychological pattern, has linked these extremes but at the same time has opened a debate about whether or not DLB it is a distinct entity of PD, a variant form of AD, or a separate individual condition. This nosological puzzle is highlighted by additionally recognized overlapping neuropathological findings (McKeith et al. 1999). Because there are no known clinical markers for these neurodegenerative diseases, diagnosis is based on detailed clinical history, careful physical examination, and neuropsychological evaluation.

Parkinson's disease affects millions of people worldwide and the prevalence of the disease is expected to increase substantially. Correct diagnosis of the condition is crucial for planning the appropriate therapeutic approach, prognosis, and calculation of the future epidemiological and economic characteristics important for society. The mainstay of treatment of PD is dopamine replacement therapy with carbidopa, levodopa, dopamine agonists, monoamine oxidase type B inhibitors, catechol-O-methyltransferase inhibitors and amantadine. Non-motor features, such as cognitive impairment, mood disorders, autonomic dysfunction, gastrointestinal and genitourinary dysfunction, have a substantial impact on Parkinson's disease patients and their quality of life.

CORRELATES IN NEUROIMAGING

Structural and functional imaging studies with different methods and tracers have been conducted in demented patients with PD. Whereas Huber and co-workers (Huber et al. 1989) reported that dementia in patients with PD was not associated with any specific pattern of structural MRI abnormalities, in contrast the hippocampal atrophy described on MRI in demented patients with PD was even more severe than in patients with AD (Laakso et al. 1996). It has been shown that atrophy of the medial temporal lobe structures such as the hippocampus and the entorhinal cortex shown on MRI may distinguish patients with Alzheimer’s disease from healthy controls. However, the diagnostic value of visual inspection and volumetry of medial temporal lobe atrophy (MTA) on MRI in a clinical setting is insufficiently known. Medial temporal lobe atrophy scale (MTA) is a rating scale based on a visual estimation of both the volume of the medial temporal lobe, including the hippocampus proper, dentate gyrus, subiculum, and parahippocampal gyrus and the volume of the surrounding cerebrospinal fluid (CSF) spaces, in particular the temporal horn of the lateral ventricle and the choroid fissure on both sides, left and right side separately (Scheltens et al. 1992). Studies show that hippocampal atrophy may not be specific to Alzheimer’s disease but also occurs in vascular dementia (VaD) (Barber et al. 2000) and Parkinson’s disease with and without dementia (Laakso et al. 1996). Frontal lobe atrophy has also been described as a feature of both late-onset Parkinson’s disease and DLB, while frontal lobe atrophy correlated with duration of motor symptoms (Double et al. 1996). Frontal lobe changes could be consistent with the prominent executive impairment characteristic of Parkinson’s disease with early cognitive impairment and PDD (Owen & Doyon 1999).

In PDD relative to DLB, there was no significant difference in the pattern of cerebral atrophy in either group described. This strengthens the hypothesis that PDD is similar to DLB and might be part of the same disease spectrum. This is also consistent with studies showing similarities in extrapyramidal motor features (Aarsland et al. 2001) and fluctuating attention (Ballard et al. 2002) in PDD and DLB.

A valuable aid in the assessment of dementia in PD is cerebral blood flow (CBF) brain SPECT scanning. Studies of cerebral perfusion in cognitively intact subjects with Parkinson’s disease have found either no difference from controls (Spampinato et al. 1991, Sawada et al. 1992) or hypoperfusion in the parietal (Markus et al. 1994, Tachibana et al. 1995), frontal (Markus et al. 1994, Antonini et al. 2001) and temporal areas (Antonini et al. 2001). Those with more advanced disease have more severe hypoperfusion, particularly in the frontal area (Tachibana et al. 1995). In a review of single-photon-emission CT studies, Bissessur and colleagues (Bissessur et al. 1997) concluded that in demented patients with PD, regional cerebral blood flow assessments commonly show frontal hypoperfusion or bilateral temporoparietal deficits.

The heterogeneity of regional CBF 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.

TREATMENT

Despite optimistic reports in the early years of levodopa therapy, it became apparent in subsequent studies that levodopa has a limited effect on cognitive impairment in PD. The positive effects are probably due to non-specific actions on alertness, mood, and arousal although some more specific effects on dopaminergic transmission may exist for some components of information processing, working memory, or internal control of attention (Pillon et al. 2001).

These beneficial effects, however, may be complicated by serious side-effects such as confusion and psychosis, mainly in demented patients (Sacks et al. 1972, Hietanen & Teravainen 1988).

Parkinson's disease patients do not generally tolerate classical antipsychotic drugs, and there is much interest in data on newer atypical substances. As is the case in DLB, Parkinson's disease patients, and in particular those with dementia, may experience marked sensitivity
We performed a pilot study with the objective to describe cognitive and imaging profiles in patients with mild to moderate stage of Parkinson disease dementia (PDD).

**Methods:** 16 patients (12 males, average 71.9±4.28 yrs,) with fulfilled clinical diagnostic criteria for probable PDD(34) were included and underwent detailed physical and neurological evaluation, which included clinical history, mental state and physical examination, a standard blood screen with thyroid function tests, B12, folate and syphilis serology. Patients were characterized with MMSE-Mini Mental State Examination (Folstein et al. 1975) 23.1±0.57, (Clinical Dementia Rating scale (35) 1.6±0.41), resulting in mild to moderate level of cognitive decline, slightly depressive mood according to (Beck Depression Inventory 8.6±0.44) and moderate motor performance (“on” UPDRS, III - the Unified Parkinson’s Disease Rating Scale (Fahn et al. 1987) 36.1±2.74). We performed also brain perfusion [99mTc] ECD / SPECT imaging, and structural MRI – magnetic resonance imaging, with evaluation of the medial temporal atrophy index (MTA) (Scheltens et al. 1992).

Patients underwent also a detailed neuropsychological evaluation, using a “cognitive process approach”, the following tests were used: Conners’ Continuous Performance Test, II, D-KEFS (Delis-Kaplan Executive Function System) Trail Making Test, CVLT-II California Verbal Learning Test, verbal fluency tests, Boston Naming Test and Osterrieth complex figure test- The Boston Qualitative Scoring System. Data were correlated voxel-wise with normalized brain perfusion images MRI scan.

**Results** of the study showed that the quality of executive planning and problem solving positively correlated with perfusion in bilateral frontal cortex. Speed of cognitive processing and habitual response inhibition positively correlated with perfusion in fronto-parietal regions - correlations were bilateral but stronger in the left hemisphere. Measures of verbal and semantic fluency showed negative correlations with bilateral frontotemporal perfusion. Visuospatial abilities, attentional span and manipulation in working memory negatively correlated with bilateral, predominately right parietal perfusion. Qualitative MRI assessment showed average MTA index 2.2 (range 0-4).

**Conclusion:** we confirmed previously reported generalized cognitive impairment in PDD with predominant executive, visuospatial and attentional deficits. Performance on specific cognitive measures was correlated with perfusion brain SPECT findings. It could be speculated that different pathological mechanisms underlie widespread significant brain perfusion decrements in temporal, parietal and frontal regions.

**REFERENCES**


Correspondence:
Milica Gregorič Kramberger
Department of Neurology, University Medical Centre Ljubljana
Zaloška cesta 2, 1000 Ljubljana, Slovenia
E-mail: milica.kramberger@gmail.com