Dysfunction of the locus coeruleus—norepinephrine system and related circuitry in Parkinson’s disease-related dementia

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ABSTRACT
Although resting tremor, cogwheel rigidity, hypokinesia/bradykinesia and postural instability usually dominate the clinical picture of sporadic Parkinson’s disease (PD), both clinical and epidemiological data reveal that a wide variety of additional symptoms impair patients’ quality of life considerably, parallel to the chronic progressive neurodegenerative movement disorder. Autopsy based retrospective studies have shown that α-synuclein immunoreactive Lewy pathology (LP) develops in the locus coeruleus (LC) of patients with neuropathologically confirmed sporadic PD, as well as in individuals with incidental (prodromal or premotor) Lewy body disease but not in age and gender matched controls. Using five case studies, this review discusses the possible role of LP (axonopathy, cellular dysfunction and nerve cell loss) in the LC, catecholaminergic tract and related circuitry in the development of PD-related dementia. The contribution of noradrenergic deficit to cognitive dysfunction in PD has been underappreciated. Noradrenergic therapeutic interventions might not only alleviate depressive symptoms and anxiety but also delay the onset of cognitive decline.

INTRODUCTION
In sporadic Parkinson’s disease (PD), Lewy pathology (LP) is not only present in the brain but throughout the entire human nervous system.1–4 Morphologically, LP consists of insoluble intraneuronal inclusions that contain the misfolded protein α-synuclein in aggregated form5–13; immunoreactive pale neurites, thread-like or spindle-shaped Lewy neurites (LNs) in axons and dendrites14 15 (figure 1A) as well as particulate (or punctate) aggregates,16 pale bodies17 and Lewy bodies (LBs) within neuronal cell somata18 19 (figure 1B, C).

LP accompanied by nerve cell loss occurs in the locus coeruleus (LC) of the pontine tegmentum during PD,20–27 and there is firm evidence that involvement of this nucleus and other regions in incidental Lewy body disease (ILBD) precedes the appearance of α-synuclein aggregates and neuronal loss in the nigral pars compacta.28–33 Less attention, however, has been paid to the possible association of LP with noradrenergic axonal or cellular dysfunction there and its potential consequences. Until recently, for instance, diminution of tyrosine hydroxylase (TH) immunoreactivity in PD and ILBD had only been detected in cardiac sympathetic nerves,34 35 but several groups have shown that this phenomenon is not restricted to the peripheral nervous system: in an autopsy-based study, ILBD cases were seen to have reduced striatal TH,36 and subsequent reports have described abnormalities in TH immunoreactivity within the LC in cases with PD.37 For example, Dugger and Dickson recently found that compared with controls, coeruleus projection neurones of PD patients displayed reduced or depleted cytoplasmic immunoreactivity for TH (figure 1D) and that the melanised nerve cells there also sequestered TH within abnormal α-synuclein aggregates,37 thereby making it unavailable for essential brain functions.38 (figure 1D–F).

The LC is the largest source of noradrenergic innervation in the human brain with ascending projections to all regions of the cerebral cortex (hippocampal formation, entorhinal cortex with adjacent mediotemporal cortex, cingulate gyrus and neocortex).39–41 One of the major functions of the LC–norepinephrine system is to maximise task-oriented performance and behaviour, particularly under challenging (novel, stressful) circumstances.42–44 In addition, together with the gigantocellular nucleus of the pontine reticular formation and the nuclei of the lower raphé group, the LC receives supramedullary limbic (central subnucleus of the the amygdala) and somatomotor input (pedunculopontine tegmental nucleus (PPTN)). Together with the projections from the lower raphé group, projections from the LC have an inhibitory effect on responses to pain in decive situations and a facilitatory effect on the activity levels of spinal cord premotor and motoneurons that receive data from the neocortex, striatal and cerebellar circuits (figure 2). Finally, the LC participates in the sympathetic innervation and modulation of the brain microcirculation.44 45–58 Thus, loss or chronic reduction of the rate limiting enzyme TH for norepinephrine metabolism within the LC and/or the ascending catecholaminergic tract (equivalent to the rat dorsal noradrenergic ascending bundle)59 may be anticipated to contribute not only to some of the motor difficulties experienced by PD patients in ‘unexpected’ situations (eg, no abrupt turns and hesitation at thresholds) but also to problems with wake–arousal states or redirecting attention, and to deficits in cognitive function and the cerebral microcirculation.58 59

During PD neuropathological stage 2, the level setting nuclei (ie, LC, gigantocellular reticular nucleus and lower raphé nuclei) as a unit become involved and, during the following stage, a bifurcation, as it were, of the pathological process in the
brain occurs: LP develops in high order relay centres of the central autonomic network (central subnucleus of the amygdala, hypothalamus and limbic circuit components) and, at the same time, it progresses into superordinate centres of the somatomotor system, including the PPN nucleus and striatal circuit (figure 2). The central autonomic network and PPN nucleus regulate the brainstem level setting nuclei and send projections to all diffusely projecting non-thalamic nuclei. In other words, by the time the PD associated pathological process makes headway into cortical sites during PD neuropathological stage 4, the LP and axonal and/or cellular dysfunction and neuronal loss in key brainstem serotonergic, noradrenergic and cholinergic neurones are fairly advanced (figures 2 and 6).

There is now a consensus that PD patients develop dysexecutive symptoms and, provided they live long enough, dementia. However, the differential diagnosis between PD associated dementia (PDD) and dementia with Lewy bodies (DLB) is still fraught with difficulties. For instance, use of the 1 year rule originally proposed by McKeith et al—that is, parkinsonism prior to cognitive impairment/fluctuating cognition—to differentiate DLB from PDD clinically is, in our view, unsatisfactory because it is arbitrary and because comorbid pathologies also can contribute to the development of dementia in PD. In fact, depending on the parameters applied as well as cohort composition and size, the neuropathological substrates of cognitive decline and dementia in PD have been attributed not only to cortical (limbic and neocortical) but also to lesions compatible with Alzheimer’s disease (AD) and, somewhat more infrequently, comorbid argyrophilic grain disease (AGD). Potential mechanisms that might contribute to a synergistic effect between tau and α-synuclein or between α-synuclein and amyloid-β remain the object of ongoing research and discussion. In addition, intracerebral vascular disease, including amyloid angiopathies and subcortical arteriosclerotic encephalopathy (small vessel disease with white matter lesions) are recognised as contributory factors. Thus the entities cognitive dysfunction and dementia in PD are often associated with an admixture of pathologies—that is, PD plus AD or PD plus AD plus AGD—often accompanied by a vascular component.

Finally, dopamine replacement therapy can have undesirable effects not only on behaviour but also on cognitive function.

**CASE HISTORIES AND POST MORTEM DIAGNOSES IN FIVE PATIENTS WITH PD AND DEMENTIA**

Each of the autopsied PD cases below fulfilled the criteria for the clinical and neuropathological diagnoses of PD. One set of tissue blocks used for staging PD related synucleinopathy of the brain, as described earlier, was dissected from each case.

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**Figure 1** Lewy pathology in brains of demented patients with Parkinson’s disease. (A) Micrograph of a Lewy neurite showing immunoreactive material on the inner cellular membrane of a dendrite covered with short appendages. (B–F) Particulate α-synuclein aggregates in melanised projection neurones of the locus coeruleus (LC) (B) and substantia nigra (C, lower right). Lewy bodies are also seen (B, C), whereby in (D–F) (the LC), they clearly sequester tyrosine hydroxylase (TH, arrows) in their halos or centres. As such, the neurotransmitter presumably is not available for brain noradrenergic metabolism. (D) Compare the normal appearing melanised neurone at the left (dark blue, chromogen SK-4700) with that directly to the right: the cytoplasm of the latter nerve cell is pale, indicating reduced TH activity. Immunoreactions for α-synuclein (C) and for α-synuclein plus TH (A, B, D–F) in polyethylene glycol embedded 100 μm sections.
embedded in polyethylene glycol and sectioned at 100 μm. An additional set of three tissue blocks, including the hippocampus at the level of the uncus, the striate area and the LC, also underwent polyethylene glycol embedding and sectioning at 100 μm before staging for AD related neurofibrillary lesions and amyloid-β plaque deposition, as published previously. A diagnosis of AD was made when cognitive decline or dementia had been observed by the attending neurologists and when the degree of AD related neuropathology seen indicated the existence of a moderate likelihood for AD in accordance with the National Institute on Aging–Reagan criteria.

**Case No 1**

Case No 1 is a 71-year-old woman with a disease duration of 15 years, whose prodromal symptoms included left-sided shoulder pain, an aching left hand, nightly quivering of the left lower extremity in bed (possibly consistent with restless legs syndrome) and nocturnal insomnia. Five years after the initial PD diagnosis (she originally presented with unsteady turns, a left-sided resting tremor and bradykinesia of the left hand), her family noticed cognitive dysfunction in the form of increasing forgetfulness, confusion and spatial disorientation. She could not number the clock during testing. She experienced hallucinations, and her neurologist pondered the possibility of concomitant dementia. One year later, the same neurologist noted severe dyskinesia and sialorrhoea (choking while eating), further unwanted weight loss, agitation and frequent hallucinations. She was disoriented to time and could not solve complex problems.

At autopsy, this patient’s brain showed mild arteriosclerosis in the circle of Willis, PD stage 6 lesions, neurofibrillary tangle (NFT) stage V and stage 2 amyloid-β deposition (figure 3A, B). In the lower brainstem, the LC of this patient had been badly damaged not only by a late stage synucleinopathy (figure 3E) but also by a late stage tauopathy (AD) (figure 3F). In addition, a second dementing tauopathy was present, AGD: AT8 immunopositive oat shaped pathologically changed axons were present in the upper raphe nuclei, pigmented parabrachial nuclei, amygdala, hypothalamus (lateral tuberal nucleus) and especially in the entorhinal cortex (figure 3C, D) and hippocampal formation of the anteromedial temporal lobe. Thus the causes of her dementia were threefold: PD, AD and AGD.

As in the case of the previous individual, each of the following three patients who experienced cognitive decline and dementia subsequent to manifesting classical motor symptoms during the course of PD also suffered from one or more parkinsonias (eg, REM sleep behaviour disorder, nocturnal insomnia and intrusion of daytime sleep attacks). The literature regarding sleep disorders in PD is large and testifies to the fact that abnormalities within most arousal systems not only can precede but also can accompany motor as well as cognitive changes. The neuroanatomical substrates of cognition and sleep/arousal include the hypothalamus, PPN and LC.
Case No 2
Case No 2 is a 74-year-old man with a disease duration of nearly 7 years and a history of REM sleep behaviour disorder (RBD) beginning at age 66 years.126–131 Two years after developing RBD, his neurologist noted a clinical presentation compatible with PD: bent posture, hypophonia and hypomimia accompanied by a bilateral resting tremor, asymmetric mild cogwheel rigidity, apathy and bradyphrenia. Up to that point there were no hallucinations or measurable cognitive impairment (Mini-Mental State Examination (MMSE) score 27/30) and the patient’s independent activities of daily life (ADLs) were intact. Six years after developing RBD, the patient’s wife reported her husband was becoming increasingly forgetful and that his motor functions (gait, speech) as well as his cognitive skills were declining gradually but steadily. During the following period, he experienced difficulties eating, unwanted weight loss, urinary incontinence and periodic visual hallucinations. In the end, he could no longer bathe, dress, eat or drink independently. His MMSE score 4 months prior to death was 14/30.

At autopsy, the patient’s brain revealed mild vascular changes accompanied by lesions compatible with NFT stage III114 (figure 4B, D), stage 3 amyloid-β deposition85 115 and PD stage 622 (figure 4A, C). Thus, owing to the presence of the concomitant pathologies in the anteromedial temporal lobe, a limbic transitional portion of the cortex that is necessary for intact cognition, we made the diagnoses PD and AD.70 132 133 Moreover, the LC of this patient was also severely affected by the PD associated pathological process: figure 5 (A, B) shows not only the presence of LP but also sharply depleted TH immunoreactivity accompanied by heavy noradrenergic cell loss (compare age matched case shown in figure 5C).

Case No 3
Case No 3 is an 88-year-old man with a disease duration of 12 years whose prodromal symptoms included micrographia, stooped posture and arthritic-like pain. At the age of 76 years when PD was initially diagnosed, his ADLs were intact, but he reported occasional yelling and violent kicking in bed at night.
Figure 4  Hemisphere sections from a demented 74-year-old man (case No 2) with Parkinson’s disease (PD) (A, C) and Alzheimer’s disease (B, D). In an immunoreaction directed against α-synuclein, it is evident even without the aid of a light microscope that the amygdala (A) and all fields of the entire cerebral cortex (C) had become involved in the PD-related pathological process (stage 6). But this patient was also at neurofibrillary tangle stage III (B, D), as seen using AT8 immunohistochemistry. 100 μm sections.

(compatible with or indicative of RBD?), slowness of gait, a loss of left-handed strength, persistent micrographia and constipation. He presented with dysarthria, slight postural instability and mild rigidity of the right upper and lower extremities but no resting tremor. The neurologist noted mild depression and cognition well within the normal range. Later that same year and during the following 3 years, repeated complaints of falls (possibly in connection with orthostatic failure), extreme fatigue evenings, nightly sleep attended by quivering and jerking of the patient’s feet, and daytime sleep attacks (son: “father sometimes falls asleep while playing golf”).

Five years after receiving the diagnosis idiopathic PD, both the patient’s family and the attending neurologist noticed the beginning of cognitive dysfunction in the form of forgetfulness, disorientation and poor judgment. Frequent falls resulted in facial injuries (eg, six in a 2-month period), and the patient occasionally choked on food. He also began experiencing some hallucinations, reporting sensations of having ‘someone present’. The last 6 years of life were marked by increasing memory impairment, intermittent hallucinations and paranoid delusions, but above all by decreasing mobility owing to bradykinesia, an unsteady gait and poor balance. His wife reported 5–6 falls monthly owing to a loss of balance, freezing in doorways and when turning, but no motor fluctuations or tremor. Minimal assistance with ADLs was required (showering, toileting). The patient became increasingly disoriented with regard to dates, his own street address and name/word recall, and had difficulty with clock drawing (MMSE 20/30). The neurologists revised their earlier diagnosis to ‘dementia with diffuse Lewy bodies’. Following nursing home placement owing to frequent falls and severely impaired cognition, the patient experienced vivid dreams, hallucinations/delusions, depression and, increasingly, dyskinesias. He spent most of his time in a wheelchair and had not walked for 3 months when his wife saw him for the last time.

Post mortem examination revealed PD stage 5 brain pathology, NFT stage IV, stage 0 amyloid-β plaque deposition and severe atherosclerosis of the circle of Willis. As in the preceding case, the patient’s history was remarkable in that he had suffered from RBD prior to the onset of PD. Moreover, late in life, he had experienced two transient ischaemic attacks within a 3 year period. In other words, this patient had PD and AD accompanied by cerebrovascular disease.

By contrast, a smaller subset of patients display cognitive decline/dementia primarily or chiefly attributable to the distribution pattern and severity of PD related LP alone (ie, PDD). The following case represents such an individual.

Case No 4
Case No 4 is an 82-year-old man with a 10 year duration of disease. The clinical records dating from the time around the
PD diagnosis noted the presence of dysarthria, micrographia, difficulty arising from chairs, a shuffling gait and lack of balance on stairs, and nightly nocturia, but no cognitive problems. A right-handed resting tremor manifested itself the following year. In addition to motor and wearing off symptoms, the patient subsequently developed nocturnal insomnia and excessive daytime sleepiness attacks resulting in a minor car accident, and he eventually underwent arthroplastic surgery for persistent right-sided shoulder pain. Shortly thereafter he began complaining of unwanted weight loss with decreasing muscle mass (eventually 15 lbs over a 2 year period despite a hearty appetite). Seven years after the initial PD diagnosis, the patient reported troubling incidents of obsessive sexual thoughts and sexually inappropriate behaviour (repeatedly disrobing in public places). According to his spouse, his loss of inhibition generally occurred and even increased in the evenings. He was prescribed an anti-dementia medication and considered, but did not initiate, oestrogen therapy to reduce his sexually obsessive behaviour. Late in the disease course, he suffered frequent auditory hallucinations and paranoid delusions, vivid nightmares and moderate bradykinesia without dyskinesia. Shortly before transferring to a residential care facility where the patient died several months later, the attending neurologist noted “PD with Lewy body dementia manifested by cognitive slowing, psychosis and inappropriate sexual behaviour”.

At autopsy, the patient’s brain displayed lesions compatible with PD stage 4, NFT stage II and amyloid-β deposition stage 0. In view of this patient’s clinical course, low cortical NFT as well as amyloid-β deposition stages, and the notable absence of any cerebrovascular disease, we attributed his dementia to subcortical (ie, brainstem) and cortical (limbic) PD.

Case No 5
Case 5 is an 82-year-old woman with a disease duration of nearly 8 years, who initially presented with hypophonia and a mild right-handed resting tremor with right-handed bradykinesia and slight cogwheel rigidity. Late the following year, her parkinsonism was assessed as Hoehn and Yahr stage 3 and her ADLs were intact. Over the next 4 years, the patient was able to live independently but then began experiencing episodic visual
hallucinations, and her husband noticed cognitive dysfunction in the form of increasing forgetfulness. Her neurologists considered ‘PDD’ or ‘PD and dementia of the Alzheimer’s-type’ (MMSE 20/30). A single photon emission CT imaging examination 1 year later showed vascular changes in both temporal lobes as well as frontally (left hemisphere). During the later disease course, the patient hallucinated more frequently but also with paranoid content, and her cognition worsened. She became confused, apathetic and was mildly depressed. The patient transferred to a nursing home owing to her continuing decline in short term memory and disorientation to time as well as increasing need for assistance (bathing, toileting). She suffered from urinary incontinence, choking incidents when swallowing, motor fluctuations and frequent hallucinations. She became wheelchair bound (Hoehn and Yahr stage 5) and died of pneumonia less than a year after being admitted to resident nursing care.

At autopsy, the patient’s brain showed moderate vascular changes (arteriosclerosis of the circle of Willis, widespread amyloid angiopathy) accompanied by lesions compatible with NFT stage III,114 stage 3 amyloid-β deposition15 115 and PD neuropathological stage 6.22 In addition, LP was also present in the following central and peripheral nervous system sites: intermediolateral (IML) column, superior cervical ganglion (SCG), cervical sympathetic chain, submandibular gland, Auerbach plexus of the distal oesophagus and stomach, and peripheral vagal nerve.

Frontal sections through the LC and catecholaminergic tract double immunostained for aggregated α-synuclein, and TH showed not only severe neuronal and TH loss in the LC but also the presence of LNs in axons of the catecholaminergic tract and a severe TH deficiency we have not encountered in control individuals (figure 5D–F). This patient’s final neuropathological diagnoses included PD, AD and cerebrovascular disease. Although we cannot know for certain at this point, it seems reasonable to conclude that the lesions in the LC and catecholaminergic tract of this patient more than likely exacerbated (rather than attenuated) her risk for developing cognitive decline and dementia.

In the autonomic nervous system, preganglionic sympathetic (noradrenergic) nerve fibres from segments 1–4 in the IML nucleus of the thoracic spinal cord and within the paravertebral sympathetic chain synapse on three cervical ganglia, whereby the last of these, the inferior cervical ganglion, is often fused with the first thoracic ganglion to form the stellate ganglion. The SCG reaches indirectly (via the internal carotid plexus) or directly all cranial nerves except for the first, second and eighth; moreover, it innervates the first to fourth or fifth cervical spinal nerves.138–140

In addition to the pineal gland (LP has not been found there to date; authors’ unpublished data), the SCG innervates the orbital muscle, iris (dilator pupillae muscle), the nasal cavity, major salivary glands, oropharynx, larynx, thyroid gland and the heart.141–146 Thus the presence of α-synuclein immunolabelling with the IML, SCG, submandibular gland, larynx and cardiac nerves in early and late phase PD coupled with the existence of abnormalities in salivary production, swallowing, phonation and sympathetic heart rate variability148–160 make it reasonable to posit that compromised cellular and/or axonal integrity, wherever it occurs within the circuitry of the same anatomically functional system (eg, IML→SCG→target organ), likely contribute to neurodegeneration and autonomic dysfunction within that system.6 26 161

Notably, two of the SCG’s four postganglionic sympathetic efferent branches are responsible for vasoconstriction in the meningeal arteries of the posterior cranial fossa as well as for vasoconstriction in the anterior, middle and posterior cerebral arteries. Furthermore, if one recalls that the LC contributes to the modulation of local blood flow via the paracrine release of norepinephrine acting on astrocytes and non-neuronal cells near the cerebral microvasculature,44 58 162 163 then a chronic TH deficiency or noradrenergic inhibition within the LC–norepinephrine system as well as the LP related degeneration of the SCG might increase the development of cerebral hypoperfusion associated cognitive decline.164–167

CONCLUDING REMARKS

Recent research has furnished evidence of axonal and neuronal dysfunction in neuromelanised projection cells within the LC, not only in the form of diminished TH immunoreactivity within neuronal processes containing LNs (figure 5E, F) and within the neuronal cytoplasm (figure 1D) but also in the form of TH– neurotransmitter sequestered within immunolabelled LNs and somatic LBs (figure 1D–F, arrows). Loss of TH immunoreactivity in cellular somata and in neuronal processes and/or the presence of TH immunolabelling in LBs of the coeruleus noradrenergic nerve cells strongly indicate that, at least in

Figure 6 Tissue sections from an 82-year-old man (case No 4) with Parkinson’s disease (PD) dementia. (A) As shown by the extent of the Lewy pathology (LP) (involvement of the anteromedial and basal temporal cortex), this patient had reached PD stage 4. (B) Note also, however, that the entire locus coeruleus is filled with LP. Immunoreactions for α-synuclein in 100 μm sections.
this brainstem nucleus, the PD associated lesions are pathogenic rather than neuroprotective.

Despite the considerable role of the LC-norepinephrine system, the contribution of noradrenergic deficit (eg, TH metabolic deficits in the LC, the leading source of noradrenergic innervation in the brain) to cognitive dysfunction in PD, with some exceptions, is still underappreciated.\textsuperscript{42–44} but possibly also delay dementia onset.\textsuperscript{170}

Finally, studies devoted to the role not only of LP related dysfunction within the LC but also within related autonomic neurocircuity (IML, SCG) to concommitant neurodegenerative pathologies and their potential influence on the development of cerebrovascular disease during neurodegeneration are needed.

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REFERENCES


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