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Heterogeneous neuropathological findings in Parkinson's disease with mild cognitive impairment

Charles H. Adler,
Department of Neurology, Mayo Clinic Arizona, 13400 E. Shea Boulevard, Scottsdale, AZ 85259, USA

John N. Caviness,
Department of Neurology, Mayo Clinic Arizona, 13400 E. Shea Boulevard, Scottsdale, AZ 85259, USA

Marwan N. Sabbagh,
Cleo Roberts Center for Clinical Research, Banner Sun Health Research Institute, Sun City, AZ, USA

Holly A. Shill,
Cleo Roberts Center for Clinical Research, Banner Sun Health Research Institute, Sun City, AZ, USA

Donald J. Connor,
Cleo Roberts Center for Clinical Research, Banner Sun Health Research Institute, Sun City, AZ, USA

Lucia Sue,
Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, AZ, USA

Virgilio G. H. Evidente,
Department of Neurology, Mayo Clinic Arizona, 13400 E. Shea Boulevard, Scottsdale, AZ 85259, USA

Erika Driver-Dunckley, and
Department of Neurology, Mayo Clinic Arizona, 13400 E. Shea Boulevard, Scottsdale, AZ 85259, USA

Thomas G. Beach
Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, AZ, USA

Charles H. Adler: cadler@mayo.edu

Parkinson's disease (PD) patients often develop mild cognitive impairment (PD-MCI) and dementia (PDD) [5, 8]. The pathologic substrate for PDD appears to be heterogeneous and includes Lewy bodies, Alzheimer's disease (AD) pathology, and cerebrovascular disease [6, 7, 9, 10]. Neuropathological changes in PD-MCI have not been described.

We present eight PD-MCI cases clinically and neuropathologically characterized as previously described [2, 4, 5]. The cognitive battery assessed five domains (memory, frontal/executive, language, attention, and visuospatial) using previously described PD-MCI

Correspondence to: Charles H. Adler, cadler@mayo.edu.

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criteria [5]. Lewy bodies were staged using the Unified Lewy Body Staging System [3] while AD and cerebrovascular pathology were assessed using standardized procedures [4].

Of 356 subjects autopsied from 1987 to 2010, 80 had PD (21 PD-cognitively normal, 8 PD-MCI, 51 PDD). The 8 PD-MCI cases (2 females, 6 males) were Hoehn and Yahr stage 2–3, mean age 82.8 years (range 74–89), and mean PD duration 11.4 years (range 2–25 years) (Table 1). All were examined within 18 months of death and mean post-mortem interval was ~3 h. MCI subtypes were: amnestic MCI-memory only (n = 4), non-amnestic MCI with frontal executive dysfunction (n = 3), and non-amnestic MCI with frontal executive/visuospatial dysfunction (n = 1).

Using our Unified Lewy Body Staging scheme three cases were brainstem-predominant (stage 2a), three were brainstem-limbic predominant (stage 3), and two were neocortical Lewy body stage (stage IV) (Table 1). Three cases had no neuritic plaques, one had sparse plaques, and four had moderate neuritic plaques present (Table 1). Braak AD staging ranged from stages II to IV (Table 1) with two meeting NIA-Reagan clinicopathologic criteria for AD (intermediate or higher), both having amnestic MCI. Cerebrovascular findings are in Table 1. The sample size was too small to correlate pathologic and clinical findings.

This study revealed heterogeneous pathologic findings in eight PD-MCI patients. The Lewy body distribution varied [brainstem-predominant (IIa), brainstem-limbic (III), and neocortical (IV)], with five of the eight cases having at least limbic involvement. Therefore, whether Lewy body pathology is the cause of cognitive impairment remains unclear, although limbic involvement may be a key factor. In a much larger series we previously found that PDD was associated with increasing neocortical Lewy body staging, and more than 50% or our PDD cases met neuropathological criteria for AD [10]. Interestingly, the two PD-MCI cases that met neuropathological criteria for AD had amnestic MCI.

Literature review revealed four PD cases with cognitive impairment, but not clear dementia, three with neocortical Lewy body stage and one limbic stage [1]. This group also found that none of their 18 PDD cases met neuropathological criteria for AD [1]. While not reporting on PD-MCI cases, Jellinger reported that neuritic plaque pathology was greater in PDD cases compared with non-demented cases [9]. In our series the majority of PD-MCI cases were Braak AD stages III–IV (two amnestic MCI cases being stage IV), as we found with our PDD cases [10]. These findings are similar to those found in amnestic MCI cases without PD [11].

In summary, this study provides an initial evaluation of the neuropathologic findings in PD-MCI. These preliminary data indicate that the underlying neuropathology is heterogeneous, similar to MCI without PD [11]. It seems likely that the major contributors, however, are limbic and/or neocortical Lewy body and AD histopathology and possibly cerebrovascular pathology. Further detailed clinicopathological studies will help further illuminate this issue.

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Table 1

Demographics and neuropathologic findings

Age	Gender	PD duration	MCI type	Unified Lewy body stage [3]	Neuritic plaques	Braak AD stage	Infarct total cerebral volume (ml)	Cerebral white matter score [6]
74	Male	25	Nonamnestic MCI-frontal executive, visuospatial	Brainstem-Limbic	0	III	0	0
77	Male	14	Amnestic MCI-memory only	Brainstem	0	III	13.5	0
79	Female	17	Amnestic MCI-memory only	Neocortical	Moderate	IV	0	1
81	Male	11	Amnestic MCI-memory only	Brainstem	0	II	0	0
85	Male	13	Amnestic MCI- memory only	Brainstem-Limbic	Moderate	IV	0	0
88	Female	2	Nonamnestic-frontal executive	Neocortical	Sparse	II	24.5	6
89	Male	7	Nonamnestic-frontal executive	Brainstem-Limbic	Moderate	III	1.7	5
89	Male	2	Nonamestic-frontal executive	Brainstem	Moderate	III	0	0