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Marinesco Bodies and Substantia Nigra Neuron Density in Parkinson's Disease

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Abstract

Aim—Marinesco bodies (MB) are intranuclear inclusions in pigmented neurons of the substantia nigra (SN). While rare in children, frequency increases with normal aging and is high in Alzheimer's disease, dementia with Lewy bodies, and other neurodegenerative disorders. Coinciding with the age-related rise in MB frequency is initiation of cell death among SN neurons. Whether MB have a role in this process is unknown. Our aim is to examine the association of MB with SN neuron density in Parkinson's disease (PD) in the Honolulu-Asia Aging Study.

Methods—Data on MB and neuron density were measured in SN transverse sections in 131 autopsied men aged 73–99 years at the time of death from 1992–2007.

Results—MB frequency was low in the presence versus absence of PD (2.3 versus 6.6%, $p<0.001$). After PD onset, MB frequency declined as duration of PD increased ($p=0.006$). Similar patterns were observed for SN neuron density. When MB frequency was low, neuron density was noticeably reduced in the SN ventrolateral quadrant, the region most vulnerable to PD

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Author contributions

RDA, JSN, GWR, and HP participated in study conception, interpretation of findings, and drafting the report; JSN and ***JHU*** conducted the neuropathologic examinations; RDA conducted all statistical analyses; ***JHU***, CMT, KHM, LJL, and LRW provided critical input and helped draft the report.

Ethical approval

Procedures were in accordance with institutional guidelines and approved by the Institutional Review Board of Kuakini Medical Center. Written informed consent was obtained from study participants. Autopsy consent was obtained from a legal authorized representative according to Hawaii State law.

Conflict of interest

The authors declare that they have no conflict of interest.

neurodegeneration. Low MB frequency was unique to PD as its high frequency in non-PD cases was unrelated to parkinsonian signs and incidental Lewy bodies. Frequency was high in the presence of Alzheimer's disease and apolipoprotein ε4 alleles.

Conclusions—While findings confirm that MB frequency is low in PD, declines in MB frequency continue with PD duration. The extent to which MB have a distinct relationship with PD warrants clarification. Further studies of MB could be important in understanding PD processes.

Keywords

Parkinson's disease; aging; Marinesco bodies; neurodegeneration; substantia nigra

Introduction

Marinesco bodies (MB) were first described in 1902 as intranuclear inclusions in the pigmented neurons of the substantia nigra (SN) [1,2]. While rare in childhood, MB frequency can increase 4-fold from the third to the seventh decades of life [1,3–6]. In contrast, in the presence of Parkinson's disease (PD), MB frequency is reduced, reaching levels similar to that found in early adulthood [3]. Low MB frequency in PD is distinct from higher frequencies often found in other movement disorders and neurodegenerative diseases, including Alzheimer's disease and dementia with Lewy bodies [3,6].

Coinciding with initiation of MB formation in early adulthood, cell death among the pigmented SN neurons begins to occur. Between the ages of 20 and 90 years, more than a third of SN neurons are lost [7,8]. Although cell death continues in the presence of PD, low MB frequency in PD corresponds with a time when neuron density has reached a critical threshold. Some suggest a threshold of near 50% in SN neuron loss is needed before the classic motor signs of PD begin to appear [8,9].

While cell death in the SN is considered part of PD progression [7,8], changes in MB frequency at PD onset could be a feature that distinguishes PD from other neurodegenerative disorders. If this is the case, then studies of MB could be important in understanding mechanisms unique to PD. Our objective is to examine the association of MB with SN neuron density in PD in the Honolulu-Asia Aging Study (HAAS).

Materials and Methods

Background and Study Sample

From 1965 to 1968, the Honolulu Heart Program enrolled 8,006 men of Japanese ancestry residing on the island of Oahu, Hawaii in a long-term follow-up study of cardiovascular disease [10]. Participants were aged 45 to 68 years. From 1991 to 1993, the HAAS was created as a continuation of the Honolulu Heart Program with a focus on neurodegenerative disease and cognitive function [11]. Subjects included 3,741 men aged 71 to 93 years (approximately 80% of the surviving members of the original Honolulu Heart Program cohort). Procedures were in accordance with institutional guidelines and approved by the Institutional Review Board of Kuakini Medical Center. Written informed consent was obtained from the study participants.

At initiation of the HAAS, an autopsy study was launched with postmortem examinations following a rigorous protocol for brain dissection [9]. Autopsy consent was obtained from a legal authorized representative according to Hawaii State law. Microscopic surveys for MB were based on selection of 131 decedent brains without dementia with Lewy bodies [12] from 5 sampling strata. Two strata included brains from all decedents with incidental Lewy bodies (N=41) and a diagnosis of PD (N=20). The other strata included randomly selected decedents with 0 (N=23), 2 (N=22), and ≥4 (N=25) parkinsonian signs that were present at initiation of the HAAS based on performance on the Unified Parkinson's Disease Rating Scale (UPDRS) [13,14]. Parkinsonian signs included UPDRS codes >0 for speech, facial expression, left foot agility, right foot agility, arising from chair, posture, gait, postural stability, and body bradykinesia. Deaths occurred from 1992 to 2007.

Autopsy and Diagnostic Methods

Since 1991, clinical diagnosis of PD considered data from repeat physical and neurologic examinations that were given until the time of death in the sampled decedents. Participants with parkinsonian signs, those receiving PD medications, and those with a history of PD were referred to a study neurologist for further evaluation. Clinical diagnosis was based on consensus from at least two study neurologists trained in movement disorders using published criteria [15,16]. All PD diagnoses were pathologically confirmed by the presence of Lewy bodies in the SN or locus ceruleus based on findings from H&E stained sections from the midbrain and pons [12].

Pigmented neurons in the SN containing the whole nucleus were counted in a 30X, scaled, microprojector tracing of a single transverse H&E stained 10 μm thick section at the level of the roots of the oculomotor nerve. Details are provided in an earlier report from the HAAS [9]. Here, midbrain tegmentum and the crus cerebri formed dorsal and ventral borders of the nucleus. The lateral mesencephalic sulcus and the margin of the cerebral peduncle next to the oculomotor nerve roots marked the medial and lateral extent of the nucleus. The nucleus was divided into medial and lateral halves by a line drawn perpendicular to the midpoint of the transverse dimension. The tracing further divided the nucleus into dorsal and ventral halves forming the dorsolateral, ventrolateral, dorsomedial, and ventromedial quadrants. Neurons were counted in each quadrant. The area of each quadrant was determined from planimetric measurement of the traced quadrant. *As illustrated in the selected scaled SN images in* figure 1 [9], *neuron density was calculated as count/mm^2. While this approach could have overestimated neuron loss in the entire SN, others suggests that counts from single SN sections can reasonably approximate measurements from more labor intensive methods* [17]. *Further discussion on this issue and our decision to utilize single sections to estimate neuron density is provided elsewhere* [9].

For MB, neurons were counted in a histologic cross section of the SN in a 10 μm thick H&E stained section at a magnification increased to 400X. Counts included the entire nucleus contralateral to the SN nucleus used in deriving neuron density. Division of the nucleus into quadrants was not performed. Frequency of MB was recorded as the percent of counted neurons with the inclusion. Figure 2 *provides examples of SN images and MB counting in*

selected decedents where MB are frequent and sparse. For both neuron density and MB frequency, measurements were made by a senior neuropathologist.

Subject Features Measured During Life

Subject features measured during life included those with known relationships with PD incidence and SN neurodegeneration. Mid-life characteristics included pack-years of cigarette smoking and coffee intake. Pack-years of smoking and coffee intake were measured at the baseline examination of the Honolulu Heart Program (1965–1968) as markers of typical lifetime exposure to these factors [18]. Data on late-life coffee intake was not collected at initiation of the HAAS (1991–1993) and late-life cigarette smoking was too uncommon to be a reliable measure of lifetime exposure. Information on coffee consumption was obtained by a dietitian based on 24-hour recall methods and validated against a 7-day dietary record in a subset of the original cohort [19].

Characteristics measured in later life (1991–1993) included constipation (<1 bowel movement/d) and excessive daytime sleepiness [20,21]. Decedents were also classified by the presence of a clinical diagnosis of Alzheimer's disease [11]. Presence of apolipoprotein ε4 alleles was identified through genotyping performed at Duke University, Durham, NC, following conventional methods [22]. For those with PD, years of PD duration from the time of diagnosis to the time of death were recorded.

Statistical Methods

As primary dependent variables, MB frequency was modeled using logit regression methods while SN neuron density (count/mm^2) was modeled as an over dispersed integer response following a negative binomial distribution [23]. In both instances, generalized linear models were used with continuous and categorical independent variables. Modeling continuous independent variables allowed for the assessment of effects on the dependent response while modeling categorical independent variables allowed for a comparison of responses between sampling strata. Generalized linear models were also used to compare SN neuron density and subject features during life between strata of MB frequency. For study features that were dichotomous, logistic regression was used. In the instance when the number of dichotomous features was small, exact testing methods were implemented [24]. All reported p-values were based on two-sided tests of significance.

Results

Among the 131 decedents, the average age at death was 85.9 years (range: 73–99 years). Overall, average MB frequency was 5.9% (range: 0–22.4). Average neuron density across all SN quadrants was 15.9/mm^2 (range: 3–32). In the ventrolateral quadrant, the region of the SN most vulnerable to neuron loss in PD [8,9,25], average neuron density was 17.0/mm^2 (range: 0–39).

Frequency of MB is further described in figure 3 (left panel) for each of the 5 strata from which samples were drawn (0, 2, and ≥4 parkinsonian signs and for decedents with incidental Lewy bodies and PD). For the first 4 strata, MB frequency was similar (the overall average was 6.6%, 95% confidence interval: 5.8–7.4). In comparison, MB frequency was

more than halved in those with PD ($p<0.001$) where the average was reduced to 2.3% (95% confidence interval: 1.4–3.7). Unlike decedents with PD, MB frequency was high in cases of incidental Lewy bodies ($p<0.001$ when compared to PD cases). Frequency of MB in the presence of incidental Lewy bodies was modestly higher than in the remaining decedents without PD.

The average neuron density in the SN ventrolateral quadrant for each of the 5 sampling strata is also shown in figure 3 (right panel). For the first 4 strata, there were no significant differences, although neuron density was highest in the strata with 0 parkinsonian signs. The lower neuron density in decedents with incidental Lewy bodies versus those with 0 parkinsonian signs coincides with earlier findings [9]. As with MB, the presence of PD was clearly associated with low neuron density. In the absence of PD, average neuron density was 19.3/mm^2 (95% confidence interval: 17.8–20.8/mm^2). It was reduced to an average of 5.0/mm^2 (95% confidence interval: 3.1–8.0/mm^2) when PD was present ($p<0.001$).

Subject features during life by strata of MB frequency at death are summarized in table 1. Given the marked difference in MB frequency in the presence versus absence of PD, MB frequency was dichotomized as ≤3.5 and >3.5%. Selection of the 3.5% cut-point was based on jointly maximizing the sensitivity and specificity associated with PD. For decedents with PD, 75% (sensitivity) had an MB frequency ≤3.5%. For those without PD, 73.9% (specificity) had an MB frequency >3.5%.

Corresponding to the 3.5% cut-point, prevalence of PD in decedents with low MB frequency (≤3.5%) was nearly 6-times greater when compared to MB frequency that was higher (34.1 versus 5.7%, $p<0.001$). Although most of the other differences in table 1 failed to reach statistical significance, there are patterns of association worth noting that correspond with relationships with PD [20,21,26]. For MB frequency ≤3.5% (where most PD cases fall), presence of late-life constipation was more than doubled when compared to frequencies that were higher (23.7 versus 9.1%, $p=0.041$). Low MB frequency (≤3.5%) was also associated with fewer pack-years of smoking (23.0 versus 31.0, $p=0.136$) and a 50% greater frequency of excessive daytime sleepiness (35.9 versus 23.9%, $p=0.183$). Consistent with earlier findings of frequent MB in cases of Alzheimer's disease [3], the percent of decedents with Alzheimer's disease was nearly doubled when MB frequency exceeded 3.5% (21.8 versus 11.4%, $p=0.143$). Apolipoprotein ε4 alleles were also more common when MB frequency exceeded 3.5% (18.0 versus 9.8%, $p=0.236$). After removing cases of PD, MB associations with study features weakened, although a high percent of decedents with apolipoprotein ε4 alleles persisted for those with MB frequency >3.5% versus when it was lower (18.7 versus 3.7%, $p=0.109$).

The relationship between MB frequency and SN neuron density is described in table 2. Here, the strongest associations occur in the SN ventral tier. For the ventrolateral quadrant, neuron density was more than 40% lower when MB frequency was ≤3.5% versus frequencies that were higher (11.4 versus 20.0%, $p<0.001$). In the ventromedial quadrant, neuron density was 30% lower when MB frequency was ≤3.5% (13.0 versus 18.4%, $p<0.001$). Associations in the dorsal tier were weaker but present in the dorsomedial quadrant ($p=0.017$). After removing cases of PD, those with MB frequency ≤3.5% continued to have significantly

lower neuron density in the SN ventrolateral quadrant (p=0.001). Associations were noticeably absent in the SN dorsal tier.

After PD onset, figure 4 further shows that MB frequency continues to decline as duration of PD increases (p=0.006). In the SN quadrant most strongly related to MB, ventrolateral neuron density was also associated with PD duration (p<0.001).

Discussion

Findings confirm that frequency of MB in elderly men with PD is lower than would be expected in normal aging [3]. Findings further demonstrate that while MB frequency is low in PD, there are continued declines in their frequency as PD duration increases. Low MB frequency is also related to lower nigral neuron density (largely in the SN ventrolateral quadrant). This relationship remains significant even in subjects without PD.

In contrast to elderly samples, MB are either absent or rare in children, suggesting that a low MB frequency is natural at birth and in the early years of life [1,3]. In decedents with PD, the meaning of a low MB frequency is clearly different. Whether the appearance of MB in infancy and childhood has adverse consequences is unknown, although elevated MB frequency has been reported to exist in genetic disorders, including myotonic dystrophy and other trinucleotide repeat expansion disorders [3,4,6,27]. High MB frequency is also common in chronic hypoxic encephalopathy and in metabolic disorders that include hepatic encephalopathy [4,5]. MB are also common in Alzheimer's disease [3] and seem unrelated to neurofibrillary tangles and neuritic plaques [6]. Our data are in agreement, where Alzheimer's disease and apolipoprotein ε4 alleles were more common when MB frequency was high. Additional evidence for a high MB frequency in asphyxia and drowning further suggests that MB can appear as a sudden response to cellular stress [2,4–6]. This abrupt response is seldom associated with neurodegeneration.

In contrast to normal aging and other conditions associated with elevated MB frequency, the inverse association between PD and MB is noteworthy. Whether low MB frequency is a marker of a form of neurodegeneration that is unique to PD warrants consideration. While there are no cases of dementia with Lewy bodies among our decedents, others have shown that MB frequency is significantly higher in their presence [3]. They are also more common in neurons containing Lewy bodies [3]. *Whether Lewy pathology provides further inducement to cell death in neurons containing MB is unknown. Although MB frequency is high in the presence of incidental Lewy bodies, the combination of MB and Lewy pathology could synergistically presage the marked cell death that is unique to decedents with PD*. Additionally, MB and Lewy bodies are thought to be morphologically and antigenically distinct [5]. Data in the current report are consistent with the latter finding as MB frequency is at least as high in cases of incidental Lewy bodies as compared to other decedents where PD is absent (figure 3). Incidental Lewy bodies are often thought to be a hallmark of presymptomatic PD [8,28–30]. The corresponding implication is that among PD cases, MB frequency could have been high prior to PD onset, even during the preclinical phase of Lewy body formation. Whether the drop in MB frequency in the presence of PD is sudden or protracted is unknown.

Unfortunately, a link between MB and PD pathogenesis remains uncertain, although evidence suggests that there may be a role [3,4]. MB are known to contain ubiquitin which is important in cell repair through removal of damaged proteins [4–6]. Whether ubiquitination and other proteins (e.g., expression of synphilin-1) contribute to MB persistence or degradation is unknown [5,6]. In the presence of PD, MB are often found to be immunoreactive to glyceraldehyde 3-phosphate dehydrogenase, suggesting a partial role in apoptosis [27]. Other structures may also be involved, including neuronal intranuclear rodlets [31] and polymyelocytic leukemia protein [4]. Ataxin-3, recruited into intranuclear inclusions before ubiquitin, may additionally be part of a cellular reaction to stress [4]. *The role of valosin-containing proteins (VCP) and factor-induced-gene 4* (FIG 4) *are also considered important in multiple cellular processes, including neural development and degradation of several pathologic lesions in neurodegenerative disease* [32,33]. *Lewy bodies and MB have both been found to be immunoreactive for VCP and* FIG 4 [32,33].

The low frequency of MB in neurodegeneration is also not uniform. Distinct from other neurons in the SN, those that are exclusively dopaminergic (and most vulnerable to PD processes) may selectively accumulate MB. In a study of SN neuron morphology in the brains of rhesus monkeys [34], the appearance of MB were limited to large dopaminergic multipolar neurons. MB were absent in GABA-ergic bipolar and smaller neurons. Additionally, neurons containing MB may be more vulnerable to cell death than neurons without MB [3]. This would explain the low frequency of neurons containing MB in cases of PD. Melanin content in SN neurons is also less when MB are present versus their absence [5]. Others have also noted that relationships between MB frequency and neuron density are most apparent in the SN ventral tier, with the dorsal tier being less affected [8,9,25]. Our data confirm this finding (table 2). After removing PD cases, an association persists for the ventrolateral quadrant and is noticeably absent in the dorsal tier. The opposite occurs for neuron loss in the absence of PD where loss in normal aging is greatest in the dorsal tier, with the ventral tier being relatively unaffected [8,9,25]. Whether the ventrolateral quadrant is more vulnerable to neuron loss because of the presence of MB and a role in cell death is unknown [25]. Significant accumulation of MB in the ventrolateral quadrant could be an essential factor that predates or initiates the decline in neuron density in this strategic area of the SN.

Although the contribution of MB to neuron loss is poorly understood, a substantial decline in SN neuron density is largely thought to predate the clinical diagnosis of PD [7–9,35]. A 50% loss of SN neurons may be needed before parkinsonian symptoms and the motor signs of PD begin to appear [8,9]. Whether the timing of this conversion to clinical PD coincides with a similar threshold for MB degradation warrants consideration. The possibility that such a threshold exists is consistent with the high frequency of MB in decedents with 0, 2, and ≥4 parkinsonian signs and in those with incidental Lewy bodies (figure 3).

Regardless of the existence of a threshold, the difference in MB frequency between decedents with incidental Lewy bodies and PD is large enough to justify closer study of their formation and degradation as they affect PD progression. Whether neurodegeneration in PD is altered by modifications in MB function is unknown. The extent to which MB have a distinct relationship with PD versus opposite associations that occur in other

neurodegenerative disorders warrants clarification. A loss of MB in elderly individuals where MB frequency is expected to be high could be an important part of a neurodegenerative process that is unique to PD.

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Abbreviations

MB	Marinesco bodies
SN	Substantia Nigra
PD	Parkinson’s disease
ILB	Incidental Lewy bodies
HAAS	Honolulu-Asia Aging Study
UPDRS	Unified Parkinson’s Disease Rating Scale
VCP	Valosin-containing protein
FIG4	Factor-induced-gene 4

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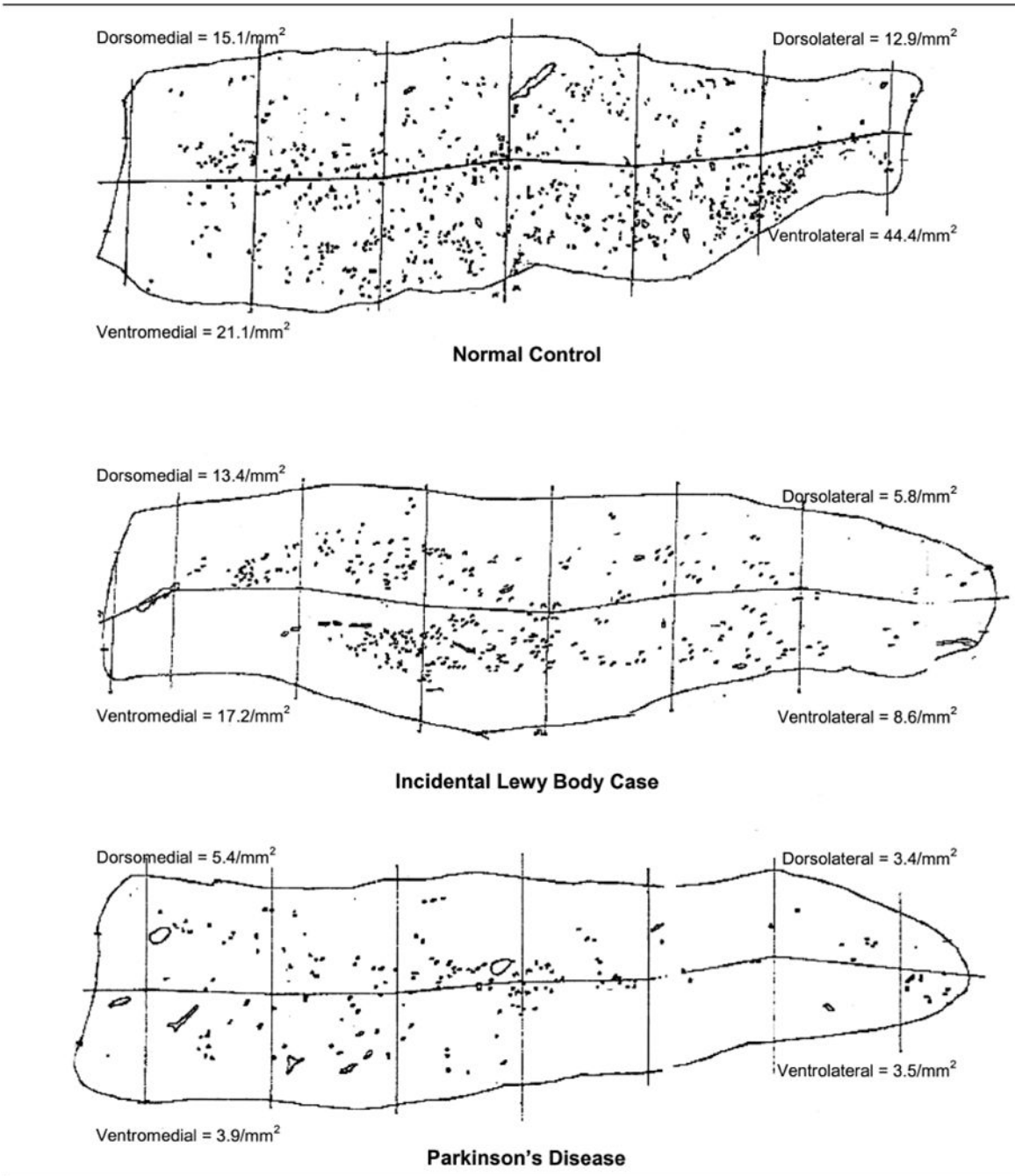

Figure 1.

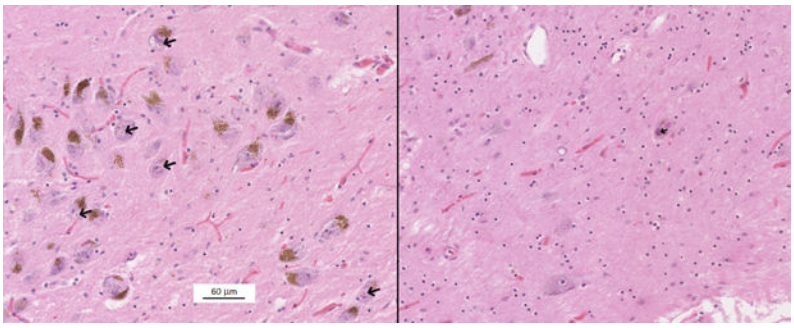

Figure 2.

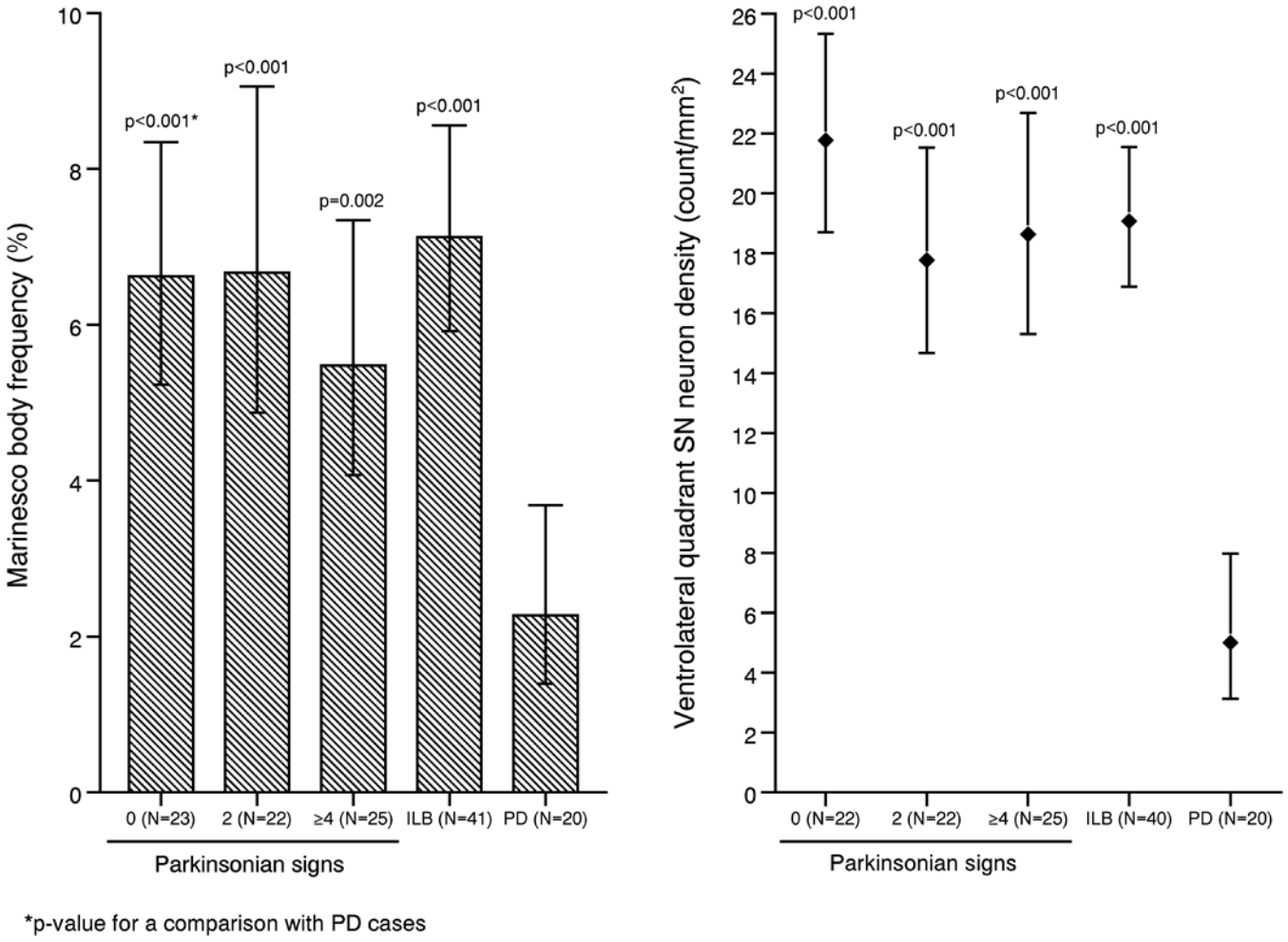

Figure 3.

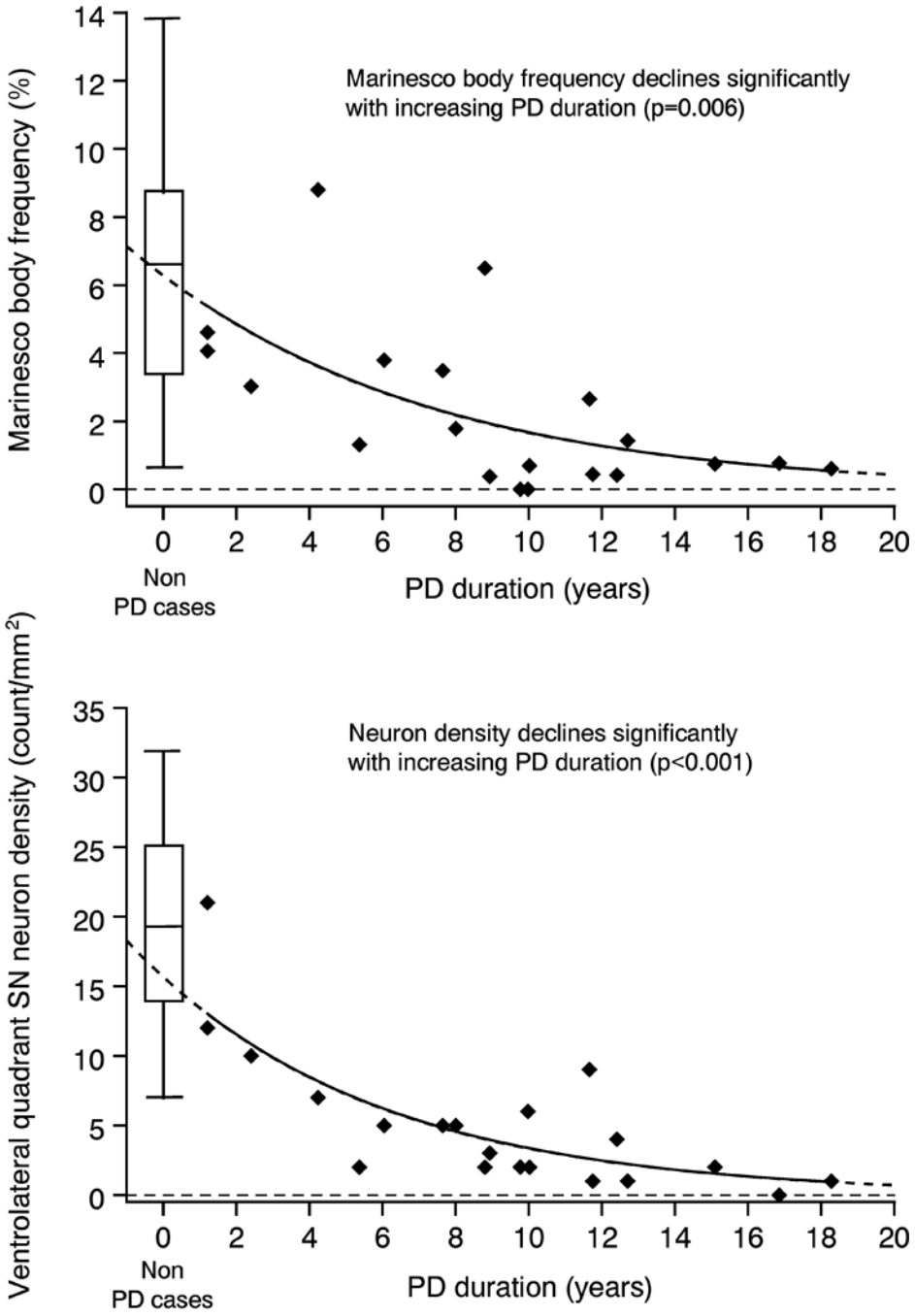

Figure 4.

Table 1

Average age at death and study features during life by frequency of Marinesco bodies

	Frequency of Marinesco bodies (%)		
Age at death and study features	**0 to ≤3.5**	**>3.5 to 22.4**	**p-value**
All decedents	44 *	87	
Parkinson's disease (%)	34.1 (15/44) †	5.7 (5/87)	<0.001
Age at death (y)	85.7 ± 5.0 ‡	86.1 ± 5.0	0.687
Mid-life pack-years of smoking	23.0 ± 23.0	31.0 ± 31.2	0.136
Mid-life coffee intake (oz/d)	13.1 ± 11.5	14.3 ± 13.9	0.608
Late-life constipation (%)	23.7 (9/38)	9.1 (6/66)	0.041
Late-life excessive daytime sleepiness (%)	35.9 (14/39)	23.9 (17/71)	0.183
Presence of apolipoprotein ε4 alleles (%)	9.8 (4/41)	18.0 (14/78)	0.236
Alzheimer's disease (%)	11.4 (5/44)	21.8 (19/87)	0.143
Without Parkinson's disease	29	82	
Age at death (y)	86.0 ± 5.6	86.2 ± 5.1	0.852
Mid-life pack-years of smoking	24.7 ± 21.0	31.1 ± 31.8	0.314
Mid-life coffee intake (oz/d)	14.8 ± 12.8	14.9 ± 14.0	0.968
Late-life constipation (%)	11.5 (3/26)	9.5 (6/63)	0.717
Late-life excessive daytime sleepiness (%)	26.9 (7/26)	22.1 (15/68)	0.618
Presence of apolipoprotein ε4 alleles (%)	3.7 (1/27)	18.7 (14/75)	0.109
Alzheimer's disease (%)	17.2 (5/29)	22.0 (18/82)	0.591

*Sample size

†Subjects with the feature/available sample

‡Average ± standard deviation

Table 2

Substantia nigra (SN) neuron density by frequency of Marinesco bodies

	Frequency of Marinesco bodies (%)		
SN quadrant	**0 to ≤3.5**	**>3.5 to 22.4**	**p-value**
All decedents	44*	85†	
Ventrolateral	11.4 ± 8.6‡	20.0 ± 7.9	<0.001
Ventromedial	13.0 ± 9.3	18.4 ± 7.9	<0.001
Dorsolateral	9.9 ± 7.3	11.8 ± 5.6	0.067
Dorsomedial	15.7 ± 9.4	19.2 ± 7.4	0.017
Total	12.8 ± 7.1	17.6 ± 5.2	<0.001
Without Parkinson's disease	29	80†	
Ventrolateral	15.5 ± 7.6	20.6 ± 7.5	0.001
Ventromedial	15.8 ± 9.2	18.9 ± 7.7	0.078
Dorsolateral	12.1 ± 8.0	12.1 ± 5.5	0.996
Dorsomedial	19.1 ± 8.7	19.4 ± 7.4	0.873
Total	16.0 ± 5.9	18.0 ± 5.0	0.078

*Sample size

†Neuron density is missing for 2 decedents

‡Average ± standard deviation