Published in final edited form as:

Parkinsonism Relat Disord. 2009 February ; 15(2): 144–148. doi:10.1016/j.parkreldis.2008.04.038.

The neuropathological basis for depression in Parkinson's disease

Pasquale G. Frisina^{a,c,*}, Vahram Haroutunian^{b,d}, and Leslie S. Libow^{a,c}

^aThe Jewish Home and Hospital Lifecare System, 120 West 106th Street, New York, NY 10025, USA

^bDepartment of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA

^cDepartment of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, NY, USA

^dBronx Veteran Administration Hospital, New York, USA

Abstract

Depression is found in 30–40% of all patients with Parkinson's disease (PD), but its etiology is unclear. Using neuropathology as a signpost for neurotransmitter function, we investigated the prevalence of pathological features found at postmortem and sought to uncover differences between depressed ($n = 11$) and non-depressed ($n = 9$) elderly PD patients. The results indicate a higher prevalence of pathological features in depressed compared to non-depressed PD patients, particularly in catecholamine areas of the brain; the locus coeruleus (neuronal loss: odds ratio = 7.2, $p = .08$; gliosis: odds ratio = 18.0, $p = .008$); dorsal vagus nerve (gliosis: odds ratio = 7.63, $p < .05$), and substantia nigra pars compacta (gliosis: odds ratio 2.85, ns). However, neuropathological differences were absent in the dorsal raphe nuclei, amygdala, and cortical regions. Our evidence suggests that depression in PD is related more to catecholaminergic than serotonergic system dysfunction.

Keywords

Depression; Parkinson's disease; Clinical-neuropathological

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of dopaminergic neurons in the midbrain, which results in dysfunction of the nigrostriatal system producing alterations in movement such as tremor, bradykinesia, rigidity, and postural abnormalities. PD had generally been characterized as a movement disorder, but non-motor abnormalities, including depression and dementia [1], are now more recognized and are widespread in PD. Depression occurs frequently in this population with a prevalence estimated at 30–40% [2]. Unfortunately, however, only 20% of all depressed PD patients receive treatment for their depression [3]. If depression is left untreated, there is an increased risk for greater disability

© 2008 Elsevier Ltd. All rights reserved.

*Corresponding author. The Jewish Home & Hospital Life Care System, 120 West 106th Street, New York, NY 10025, USA. Tel.: +1 212 870 5957. pfrisina@jhha.org (P.G. Frisina)..

This work was presented at the XVII WFN World Congress on Parkinson's Disease and Related Disorders, Amsterdam, Netherlands, December 2007.

and reduced quality of life for this PD population [4]. A better understanding of the etiology of depression in PD may lead to the selection of more effective treatments. This in turn could lead to an improved quality of life for PD patients who suffer from depression [5].

The etiology of depression in PD is complicated and may result from changed serotonin (5-HT) brain chemistry that is separate from the central dopaminergic deficiency associated with PD motor symptoms [6]. This premise is based on the observation that depressed PD patients evidence greater neuronal loss in the dorsal raphe (DRN) nuclei (5-HT secreting neurons) relative to non-depressed PD patients [7]. Moreover, cerebrospinal fluid (CSF) 5-HIAA levels, a metabolite of serotonin (5-HT), are reduced in depressed PD patients [3,6]. However, it has been reported that even non-depressed PD patients show serotonin metabolite reductions in their CSF [5,8], suggesting that indolamines may not be uniquely related to depression in PD. On this note, several PET/SPECT studies have not observed a relationship between depressive symptoms and serotonin dysfunction in PD patients [9-11], bolstering the notion that serotonin may not play a direct role in PD depression [12]. The 5-HT hypothesis is also controversial because SSRIs have produced mixed results in several placebo-controlled trials on depressed PD patients [13,14]. For these reasons, it has been proposed that other non-serotonin linked brain areas and neurotransmitter systems are involved with the etiology of PD-related depression [5,12].

Neuroanatomical and neuropharmacological research suggests that catecholamine (norepinephrine and/or dopamine) dysfunction is related to depression in PD. For instance, TCAs (i.e., imipramine, desipramine, nortriptyline, and amitriptyline) which block the reuptake of norepinephrine (NE) have reliably reduced depression in PD [15,16]. Furthermore, dopamine (DA) agonists (e.g., pramipexole and pergolide) have recently proven useful in treating depression in PD patients [17]. An older postmortem study observed that the presence of depression in PD was accompanied by a significant loss of locus coeruleus (LC) neurons [18]. Finally, a recent PET study has observed reduced NE and DA outflow from brain stem regions (e.g., LC) to the limbic system (e.g., amygdala) in depressed patients in comparison to non-depressed PD subjects [19]. Thus, it is likely that though 5-HT changes may be important in PD depression, deficits in catecholamines (i.e., NE and DA) do contribute to major depression in PD.

Taken together, the neuropathological basis for depression in PD has not been established. Neuropathology studies may allow a clear differentiation between sites of abnormality in PD depression compared to PD patients without depression. Therefore, the purpose of this exploratory/pilot study is to reevaluate the neuropathology of depression in elderly PD patients by examining the prevalence of neuronal loss and gliosis in both cortical and subcortical brain regions.

2. Methods

2.1. Subjects

Twenty brain tissue specimens were used in this study and derived from very elderly subjects that were clinically diagnosed with PD by movement disorder specialists, neurologists, and/or geriatricians. The majority of subjects had been residents of the Jewish Home and Hospital (90%). All autopsies were performed by the Mount Sinai School of Medicine Department of Pathology on subjects after receiving consent for autopsy from each subject's legal next-of-kin. The neuropathological study of these specimens was approved by both the Mount Sinai School of Medicine and Jewish Home and Hospital Institutional Review Boards for the protection of human subjects of research protocols. The demographic/clinic characteristics of subjects within this study can be seen in Table 1.

2.2. Materials and procedure

2.2.1. Assessment of depression—The patient's clinical depression was evaluated by examining the patient's psychiatric evaluation notes. Patients were included in the PD-depressed group if they had received a clinical diagnosis of depression by consulting psychiatrists no more than 6 months prior to death. It is important to note that all depressed PD patients carried this psychiatric diagnosis until death. For patients that were "not" clinically diagnosed with depression ($n = 9$) by a consulting psychiatrist, we verified the presence or absence of depression by examining their clinical/medical records, nursing protocols, use of antidepressant medications, and social work progress notes. In line with previous reports on the prevalence of depression in PD [2], we observed that approximately half (55%) of our patients suffered with clinical depression ($n = 11$), ranging from moderate to severe.

2.2.2. Neuropathological assessment—The neuropathological procedures have been described previously [20]. Representative blocks of the following were examined selectively: (1) the neuronal population of the substantia nigra pars compacta (SNpc); (2) the LC, the well-demarcated nucleus composed of neurons enriched with norepinephrine; (3) the DRN, containing 5-HT neurons; (4) the dorsal vagus nerve (DVN); and (5) the amygdala. The frontal, temporal, occipital, and parietal cortices were also investigated. Histological sections from paraffin-embedded blocks of formalin-fixed specimens were stained using hematoxylin–eosin, modified Bielschowsky, modified thioflavin S, anti- β amyloid, anti- τ , and anti-ubiquitin. If brain specimens did not stain positive for Lewy bodies (LB) with ubiquitin then alpha-synuclein staining was utilized by the neuropathologists. Multiple high-power fields (5 fields, $\times 20$) were examined blindly, and the density of LBs, neuronal loss, and gliosis was rated within each brain region described above. The tissue sampling and microscopic rating protocols were those recommended by CERAD [21] and used in previous research [20].

The immunohistochemical method used was an avidinbiotin staining procedure with diaminobenzidine detection. The following histopathological criteria for PD diagnosis were applied [22]: (1) substantial depletion of pigmented neurons from the substantia nigra; (2) at least one LB in the substantia nigra; and (3) no pathological evidence for other diseases such as Alzheimer's disease, supranuclear palsy, corticobasal degeneration, and multiple system atrophy were responsible for Parkinsonism. It is important to note that all patients stained positive for LBs in the substantia nigra with ubiquitin. Because we only used the LB to diagnose PD neuropathologically, we did not consider its use for the neuropathological staging of PD [23].

Because the PD subjects were very old (i.e., mean age 83 years), any group differences for depression could be attributed to age-related factors (e.g., vascular disease) other than PD. In order to rule out this potential confound, we tested for group differences in Alzheimerization and microangiopathic load in all PD brains using published criteria for AD [21] and vascular disease [24] as a framework.

2.2.3. Data analysis and statistics—All analyses were performed with SPSS 14.0 (SPSS Inc, Chicago, IL, USA) and MedCalc Software, run on an IBM compatible computer. For between group comparisons, we used the odds ratio statistic because all data was expressed in terms of frequencies based on the presence or absence of neuronal loss and gliosis. The presence of neuropathology was operationally defined as a rating of at least "sparse pathology" within the brain regions of interest. The semi-quantitative nature of the pathological ratings (i.e., none, sparse, moderate, and frequent) and the limited sample size

of this study precluded statistical analyses on the severity and/or relationship of pathology between groups.

3. Results

Looking at Table 1, the majority of depressed PD subjects were treated with antidepressant medications (82%), and significant differences were present with respect to antidepressant class (SSRIs = 64%, TCAs = 9%, atypical = 9%, $\chi^2 = 7.99$, $p = 0.02$). The proportion of men and women in the depressed and non-depressed PD groups did not differ significantly, ($\chi^2 = 0.03$, $p = 0.86$). Additionally, the results from our chi-squared analyses did not produce significant differences between the depressed and non-depressed PD subjects with respect to the proportion of patients containing AD ($\chi^2 = 1.45$, $p = 0.23$) and/or vascular ($\chi^2 = 0.02$, $p = 0.89$) pathology. Independent samples t-test showed that the groups also did not significantly differ with respect to age ($p = 0.45$), dementia severity ($p = 0.40$), PD duration ($p = 0.52$), or severity of PD symptoms ($p = 0.21$).

As expected, both the depressed and non-depressed PD patient groups exhibited a high prevalence (100%) of neuronal loss and LBs in the SNpc, as this was one of the key criteria for classification of neuropathological PD. Although the difference in the prevalence of gliosis in the SNpc was not statistically significant, this pathological feature was almost three times greater in the depressed relative to the non-depressed group (OR 2.85).

Another salient finding from this study is the higher prevalence of LC pathological features in the depressed relative to non-depressed elderly PD subjects (see Table 2). Specifically, difference in the prevalence of neuronal loss in the LC was more than seven times greater and trending toward significance in the depressed relative to the non-depressed PD group (OR = 7.2, $p = 0.08$). Moreover, the difference in the prevalence of gliosis between depressed and non-depressed PD subjects was robust and reached statistically significant levels (OR = 18.0, $p = 0.008$). Interestingly, we did not observe any neuropathology within the DRN (nor in the amygdala and cerebral cortices) of depressed and non-depressed PD patients. Taken together, the results from these data suggest an important role for catecholaminergic (DA and NE) and a lesser role for serotonergic system etiology in the depression of PD.

Finally, we observed a higher prevalence of neuropathology in the DVN of depressed than in non-depressed PD subjects (see Table 2). Specifically, the prevalence of gliosis was almost eight times greater and statistically significant in the depressed relative to the non-depressed PD group (OR = 7.63, $p < 0.05$).

4. Discussion

The results of this neuropathology—clinical correlative study indicate that depression in PD was related to brainstem neuropathology within areas known to be sites where catecholamine (NE and DA) and not indolamine (5-HT) neurotransmitter systems are concentrated. Our findings support the “catecholamine”-dopaminergic and noradrenergic hypothesis for depression in PD [5]. The notion of a DA etiology for depression in PD is not surprising, and is somewhat supported by clinical research showing a high association between mood changes and lesions to the basal ganglia [25]. The basal ganglia receive DA input from the SNpc, which of course, is known to be impaired in PD patients. Thus, our observation of pathological features in the SNpc of depressed PD patients, though only trending toward significance appears relevant and bolsters the notion that the nigrostriatal circuit is implicated in the depression of PD [26].

Our other findings also suggest a linkage of noradrenergic mechanisms to depression of PD. We observed a higher prevalence of cell loss and gliosis in the LC of depressed compared to non-depressed PD patients. Whereas previous research has independently observed NE/LC pathology [18,19] and the absence of serotonin dysfunction [9-11] in depressed PD patients, our study's findings are the first to directly emphasize that NE (and to a lesser extent DA) may play a more critical role than 5-HT in modulating affective disturbances in PD. Indeed, pathological abnormalities within the DRN, a serotonergic center, were absent in both our depressed and nondepressed PD patients. It is hoped that this research will lead to an expanded and renewed interest in the role(s) of catecholaminergic systems in PD-associated depression.

The alpha-synuclein abnormalities typically found in PD may help explain our findings which link apparent catecholamine-deficits with depression in PD. Specifically, it has been observed in animal studies that the overexpression of alpha-synuclein reduces catecholamine release from presynaptic nerve terminals [27]. Furthermore, human studies of the familial early onset forms of PD [28] link mutant forms of alpha-synuclein protein to decreased storage of dopamine, and thus to the likely involvement of the motor aspects of familial PD. However, PD patients also exhibit behavioral (e.g., depression) and cognitive (e.g., dementia) abnormalities which may be related to catecholamine deficits. The widespread presence of increased alpha-synuclein in the brains of PD patients may reflect the above noted defect in vesicle storage, producing diffuse brain alpha-synuclein abnormalities beyond the nigral-striatal motor system, and providing a basis for a synuclein—catecholamine mechanism for the PD-related manifestations of depression. Our neuropathology findings certainly suggest this link between catecholamine deficiencies and depression of PD. Future research should be directed at examining differences in alpha-synuclein expression (i.e., LBs) between depressed and non-depressed PD patients, particularly in brain regions that are rich in catecholamines and possibly related to depression.

We have also noted that our depressed PD sample had a higher prevalence of gliosis in the DVN in comparison to non-depressed PD subjects. To our knowledge there have been no other reports directly relating DVN abnormalities to depression in PD, even though previous research suggests a physiological relationship between the DVN and LC [29]. Specifically, it has been observed that stimulation of the DVN increases the firing rate of NE in the LC within the rat brain [29]. Thus, our unique pathological findings of DVN abnormalities in depressed PD subjects merits further investigation.

Finally, the present study did not observe amygdala or cortical pathology in either our depressed or non-depressed elderly PD patients. These findings are discrepant from previous research that observed amygdala pathology in PD patients irrespective of affective state [30]. One possibility, though doubtful in such an elderly population, is that our sample of PD subjects were in the earlier-intermediate Braak neuropathological stages (i.e., stages 3–4) of PD, and limbic-cortical pathology occur at the more intermediate-later neuropathological stages (i.e., 4–6) of PD [31]. The design of the current study and its limited sample size precluded analysis of the results relative to Braak neuropathological staging. For this reason, future clinicopathological studies should continue to examine amygdala and cortical pathology in depressed and non-depressed subjects, particularly in the more advanced neuropathological stages of PD [31].

One possible confound in this study is that because the PD subjects were very old (i.e., mean age = 83 years), their depression could have been caused by other age-related factors instead of PD. For instance, it has been observed that late-onset depression is associated with Alzheimer's disease (AD) pathology [32] and cerebrovascular disease [33]. Therefore, we

analyzed all brain specimens for the classic neuropathological lesions that are associated with AD and vascular disease pathology (e.g., plaques, tangles, and multiinfarcts), and the results from our chi-squared analyses did not produce significant differences between the depressed and non-depressed PD subjects. Thus, our study is in agreement with other work where depression in our elderly sample appears to be an integral part of the PD syndrome [34].

In conclusion, our study reveals different neuropathological findings in depressed PD patients compared to non-depressed PD patients. These findings highlight neuronal loss and gliosis in brain areas known to be rich in catecholamines. Although the present work is exploratory/pilot in nature, it does emphasize the apparent important role of catecholamine deficiency in the depression of PD. Future research will be directed at examining other important catecholamine regions (e.g., ventral tegmental area and nucleus accumbens) that may be related to the pathogenesis of depression in PD. Nonetheless, our initial pilot findings may have direct implications for current treatment and for treatment trials with catecholamine enhancing medications for the depression of PD, especially elderly PD patients.

Acknowledgments

The authors thank Drs Daniel P. Perl and Dushyant P. Purohit of the Mount Sinai School of Medicine, Department of Neuropathology, for their neuropathological assessments of all patients in this study. This work was supported, in part, by a grant award from The Leir-Ridgefield Charitable Foundations to The Jewish Home and Hospital for Parkinson's disease research and by NIH-AG02219.

References

- [1]. Sinanovic O, Hudic J, Ibrahimagic O. Dementia and depression in Parkinson's disease. *Parkinsonism Relat Disord.* 2007; 13:S53.
- [2]. Slaughter JR, Slaughter KA, Nichols D, Holmes SE, Martens MP. Prevalence, clinical manifestations, etiology, and treatment of depression in Parkinson's disease. *J Neuropsychiatry Clin Neurosci.* 2001; 13:187–96. [PubMed: 11449025]
- [3]. Mayeux R, Stern Y, Williams JBW, Cote L, Frantz A, Dyrenfurth I. Clinical and biochemical features of depression in Parkinson's disease. *Am J Psychiatry.* 1986; 43:756–9. [PubMed: 2424323]
- [4]. Edwards E, Kitt C, Oliver E, Finkelstein J, Wagster M, McDonald WM. Depression and Parkinson's disease: a new look at an old problem. *Depress Anxiety.* 2002; 16:39–48. [PubMed: 12203670]
- [5]. Yamamoto M. Depression in Parkinson's disease: its prevalence, diagnosis, and neurochemical background. *J Neurol.* 2001; 248(Suppl 3):III/5–11.
- [6]. Mayeux R, Stern Y, Cote L, Williams JB. Altered serotonin metabolism in depressed patients with Parkinson's disease. *Neurology.* 1984; 34:642–6. [PubMed: 6200801]
- [7]. Paulus W, Jellinger K. The neuropathological basis of different clinical subgroups of Parkinson's disease. *J Neuropathol Exp Neurol.* 1991; 50:743–55. [PubMed: 1748881]
- [8]. Kostic VS, Djuricic BM, Covickovic-Sternic N, Bumbasirević L, Nikolić M, Mrsulja BB. Depression and Parkinson's disease: possible role of serotonergic mechanisms. *J Neurol.* 1987; 234:94–6. [PubMed: 2435855]
- [9]. Doder M, Rabiner EA, Turjanski N, Lees AJ, Brooks DJ. Tremor in Parkinson's disease and serotonergic dysfunction: an (11)C-WAY 100635 PET study. *Neurology.* 2003; 60:601–5. [PubMed: 12601099]
- [10]. Kim SE, Choi JY, Choe YS, Choi Y, Lee WY. Serotonin transporters in the midbrain of Parkinson's disease patients: a study with ¹²³I-beta-CIT SPECT. *N Nucl Med.* 2003; 44:870–6.
- [11]. Guttman M, Torti M, Warsh J, Houle S, Cyr J, Bamsey T, et al. Are brain serotonin transporter levels decreased in depressed patients with Parkinson's disease? *J Neurol Sci.* 2006; 248:299.

- [12]. Brooks DJ. Assessment of Parkinson's disease with imaging. *Parkinsonism Relat Disord.* 2007; 13:S268–75. [PubMed: 18267249]
- [13]. Leentjens AFG, Vreeling FW, Luijckx GJ, Verhey FR. SSRIs in the treatment of depression in Parkinson's disease. *Int J Geriatr Psychiatry.* 2003; 18:552–4. [PubMed: 12789682]
- [14]. Wermuth L, Sorensen PS, Timm S, Christensen B, Utzon NP, Boaset J, et al. Depression in idiopathic Parkinson's disease treated with citalopram. *Nord J Psychiatry.* 1998; 52:163–9.
- [15]. Anderson J, Aabro E, Gulmann N, Hjelmsted A, Pedersen HE. Antidepressive treatment in Parkinson's disease: a controlled trial of the effect of nortriptyline in patients with Parkinson's disease treated with L-dopa. *Acta Neurol Scand.* 1980; 62:210–9. [PubMed: 7010875]
- [16]. Laitinen L. Desipramine in treatment of Parkinson's disease. *Acta Neurol Scand.* 1969; 45:109–13. [PubMed: 4896078]
- [17]. Rektorova I, Rector I, Bares M, Dostál V, Ehler E, Fanfrdlová Z, et al. Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. *Eur J Neurol.* 2003; 10:399–406. [PubMed: 12823492]
- [18]. Chan-Palay V, Asan E. Alterations in catecholamine neurons of the locus coeruleus in senile dementia of the Alzheimer type and in Parkinson's disease with and without dementia and depression. *J Comp Neurol.* 1989; 287:373–92. [PubMed: 2570794]
- [19]. Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain.* 2005; 128:1314–22. [PubMed: 15716302]
- [20]. Haroutunian V, Serby M, Purohit DP, Perl DP, Marin D, Lantz M, et al. Contribution of Lewy body inclusions to dementia in patients with and without Alzheimer disease neuropathological conditions. *Arch Neurol.* 2000; 57:1145–50. [PubMed: 10927794]
- [21]. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology.* 1991; 41:479–86. [PubMed: 2011243]
- [22]. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry.* 1992; 55:181–4. [PubMed: 1564476]
- [23]. Braak H, Del Tredici K, Bratzke H, Hamm-Clement J, Sandmann-Keil D, Rub U. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). *J Neurol.* 2002; 249:III/1–5.
- [24]. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdev JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology.* 1993; 43:250–60. [PubMed: 8094895]
- [25]. Mayberg HS. Frontal lobe dysfunction in secondary depression. *J Neuropsychiatry Clin Neurosci.* 1994; 6:428–42. [PubMed: 7841814]
- [26]. Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res.* 1990; 85:119–46. [PubMed: 2094891]
- [27]. Yavich L, Oksman M, Tanila H, Kerokoski P, Hiltunen M, van Groen T, et al. Locomotor activity and evoked dopamine release are reduced in mice overexpressing A30P-mutated human alpha-synuclein. *Neurobiol Dis.* 2005; 20:303–13. [PubMed: 16242637]
- [28]. Cameron OG. Psychopharmacology. *Psychosom Med.* 1999; 61:585–90. [PubMed: 10511009]
- [29]. Dorr AE, Debonnel G. Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. *J Pharmacol Exp Ther.* 2006; 318:890–8. [PubMed: 16690723]
- [30]. Harding AJ, Stimson E, Henderson JM, Halliday GM. Clinical correlates of selective pathology in the amygdala of patients with Parkinson's disease. *Brain.* 2002; 125:2431–45. [PubMed: 12390970]
- [31]. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res.* 2004; 318:121–34. [PubMed: 15338272]

- [32]. Rapp MA, Beeri MS, Purohit D, Perl DP, Haroutunian V, Sano M. Increased neurofibrillary tangles in Alzheimer's disease patients with co-morbid depression. *Am J Geriatr Psychiatry*. 2008; 16:168–74. [PubMed: 18239198]
- [33]. Krishnan KR, Taylor WD, McQuoid DR, MacFall JR, Payne ME, Provenzale JM, et al. Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. *Biol Psychiatry*. 2004; 55:390–7. [PubMed: 14960292]
- [34]. Mayberg HS, Solomon DH. Depression in Parkinson's disease: a biochemical and organic viewpoint. *Adv Neurol*. 1995; 65:49–60. [PubMed: 7872152]

Table 1

Demographic and clinical characteristics of PD subjects

	NDPD	DPD
<i>n</i>	9	11
Male/female	5/4	4/7
Age, years, mean (SD)	85.00 (7.31)	82.18 (8.57)
Clinical Dementia Rating Scale, mean (SD)	3.33 (0.87)	2.78 (1.70)
% taking antiparkinsonian medication	89	91
% taking antidepressants	–	82
Hoehn and Yahr stage, mean (SD)	4.66 (0.58)	3.22 (1.79)
PD duration (years), mean (SD)	11.67 (2.89)	9.44 (5.36)

NDPD, non-depressed PD patients; DPD, depressed PD patients. Hoehn and Yahr staging derives from their last neurological assessment (no more than 6 months prior to death) and not necessarily at the time of death.

Prevalence of pathological features in subcortical brain stem regions in non-depressed and depressed Parkinson's patients

Table 2

Subcortical regions	SNpc		DRN		LC		DVN	
	NDPD	DPD	NDPD	DPD	NDPD	DPD	NDPD	DPD
Neuronal loss	100	100	0	0	56	90	33	36
Gliosis	89	100	0	0	33	90**	0	27*

NDPD, non-depressed PD patients; DPD, depressed PD patients; SNpc, sub-stantia nigra pars compacta; DRN, dorsal raphe nuclei; LC, locus coeruleus; DVN, dorsal vagus nerve.

* $p < 0.05$;

** $p < 0.01$.