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Neuronal Loss in the Basal Nucleus of Meynert in Progressive Supranuclear Palsy

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Summary. A morphometric study of the basal nucleus of Meynert (bnM) has been performed in a 70-year-old man with a 4-year history of pathologically confirmed progressive supranuclear palsy (PSP). An important neuronal loss (52%) was demonstrated in the bnM. This finding has not been previously documented with morphometric methods in PSP, but the involvement of the bnM is well known in other related conditions, i.e., Parkinson's disease, Alzheimer's disease, and Parkinson-dementia complex of Guam. Our findings yield support to the view that the involvement of the bnM, a nucleus with complex connections with various subcortical structures and diffuse cholinergic projections on the neocortex, could play an important role in the physiopathogeny of subcortical dementia.

Key words: Progressive supranuclear palsy (PSP) – Subcortical dementia – Basal nucleus of Meynert – Neuropathology

Introduction

The human basal nucleus of Meynert (bnM) is a well defined formation of large multipolar neurons, cholinergic in character [8], lying in the substantia innominata. In mammals the size and differentiation of this structure increase in parallel with the neocortical development [11, 12]; moreover, its neurons exhibit a generalized isodendritic pattern suggesting complex integrative functions [26]. Indeed, experimental studies using retrograde and anterograde axonal transport methods have shown that in primates the bnM receives multiple afferents from heterogeneous subcortical structures and projects widely on all neocortical areas [10, 17, 18, 21] representing a major source of ascending cholinergic inputs. Despite these anatomic data the functional role of the bnM is unknown.

Neuropathologic changes in the bnM with severe neuronal loss have been systematically observed in two degenerative conditions, i.e., Parkinson's disease [5, 7, 13, 19, 20, 32] and Alzheimer's disease [7, 22, 30, 33, 34], whereas in the normal aging the cell number is not significantly reduced [5, 31]. The functional significance of the involvement of the bnM in these disorders is unknown. Nevertheless, it has been suggested that the bnM neuronal loss may have a pathophysiologic correlation with the "bradyphrenia" commonly observed in parkinsonian patients [14], and that may be partly responsible for some of the cognitive or behavioral disturbances occurring in Alzheimer's disease [33]. Recently, a severe neuronal loss has been described in the bnM of two patients with Parkinson-dementia complex of Guam, a condition closely related to both Parkinson's disease and Alzheimer's disease [23].

In progressive supranuclear palsy (PSP), another degenerative disorder sharing several clinical and pathologic aspects with the above conditions, the bnM has been found to display neurofibrillary degeneration, but no significant cell loss has been described [15, 16, 28, 29]. In this paper we report the first morphometric study of the bnM in a case of PSP documenting a remarkable neuronal loss, and we discuss the possible pathophysiologic significance of this finding.

Case Report

The clinical history and the neuropathologic study of this patient have been previously reported in detail in view of the association of PSP with subclavian steal syndrome [6]. He began to complain of an unsteady gait and visual disturbances at the age of 66. The full clinical picture included palsy of the upward gaze with restricted ocular movements in the other directions, dysarthria, dysphagia, forced laughing, marked rigidity of the neck and trunk, clumsiness of gait. The disease was relentless progressive, and the patient died of bronchopneumonia at the age of 70. A neuropsychologic examination performed at the age of 68 showed a mild diffuse mental

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deterioration (11%); the full IQ was 105, with a verbal score of 114 and a performance score of 96.

The brain weighed 1,460 g. Gross examination revealed slight frontocortical atrophy, slight enlargement of the lateral ventricles, and pallor of the substantia nigra. Microscopic examination showed typical features of PSP, i.e., variable degree of neuronal loss with gliosis in the globus pallidus, subthalamic nucleus, red nucleus, substantia nigra, reticular formation of the brain stem, locus ceruleus, dentate and olivary nuclei. Several surviving cells in these structures, especially in the globus pallidus, subthalamic nucleus and reticular formation, exhibited neurofibrillary degeneration. Neither neurofibrillary tangles nor senile plaques were observed in the neo- and archicortex.

Table 1. Neuronal counts of the magnocellular population of the bnM in the PSP patient and in three controls

Subjects	Sex	Age at death (yr)	Mean number of neurons per section $\bar{x} \pm SE$	Loss of cells (%)
Controls	2 M 1 F	70 ± 4	619.4 ± 16.7	
PSP patient	M	70	295.7 ± 6.7	52.3

Material and Methods

A comparative morphometric study of the magnocellular population of the bnM in the patient and in three control cases (mean age 70 ± 4) was performed on coronal sections at the level of the infundibulum. For each brain a count was made of the whole population of large neurons with visible nucleoli in three 20 µm thick paraffin sections stained with thionin, using a square ocular grid. The sections were moved systematically inside the bnM by means of a superimposed squared graticule, whose single fields covered an area corresponding to that of the ocular grid (0.59 mm^2 at a magnification of × 115). For each section were also measured the nucleolar diameters of 40 neurons randomly distributed within the bnM using a micrometer at a magnification of × 1,152, and Abercrombie's formula [1] was applied to calculate the actual number of cells. The arithmetic mean of the neuronal population of the bnM cross-sections of the patient and the overall mean values of the controls were then compared statistically using Student's *t*-test. Finally, 10 µm thick paraffin sections stained with HE, van Gieson, Klüver-Barrera, Holzer, Bodian, von Braunmühl, and thioflavine S were examined with regard to morphological changes.

Results

The mean number of bnM neurons per section was significantly decreased in the patient ($P < 0.01$). Compared with the age-matched controls the reduction in number amounted to 52.3% (Table 1, Fig. 1a, b). The majority of the surviving cells exhibited an excess of lipofuscin as well as a reduction and a dispersion of the Nissl substance. Several neurons showed globose neurofibrillary degeneration (Fig. 1c); occasionally, the neurofibrillary tangles were well circumscribed in the central part of the cytoplasm resembling a Pick body (Fig. 1d, e). In Holzer-stained sections a moderate gliosis could be observed; the glial reaction was more severe at the boundary with the globus pallidus. Neither other degnerative nor ischemic cell changes were present in the bnM.

Discussion

The clinical and pathologic picture of the present case is consistent with PSP [29], as discussed in a previous report [6]. The neuropathologic study shows, beside the topographically and morphologically typical alterations, a remarkable neuronal loss in the bnM with globose neurofibrillary degeneration of surviving cells. This finding has not been previously documented with morphometric methods in PSP, although the bnM is known to exhibit neurofibrillary degeneration [15, 16, 28, 29].

Up to the present the involvement of the bnM has been observed, apart from PSP, in Parkinson's disease [5, 7, 13, 19, 20, 32], Alzheimer's disease, [7, 22, 30, 33, 34] and Parkinson-dementia complex of Guam [23]. Quantitative studies of the bnM of patients with Parkinson's disease have revealed an extensive neuronal loss [7], mostly marked in the cases with dementia [32]. Cell counts from bnM cross-sections of patients with Alzheimer's disease and Parkinson-dementia complex of Guam have demonstrated that the total number of large neurons may show a reduction of up to 90% [23, 33]. Similarly, the present analysis, performed with comparable assessment methods, has shown a 52% neuronal loss in the bnM of a PSP patient. Such a finding needs to be confirmed in a large series of cases to assess the degree of bnM involvement in relation to age of patients, duration of illness, and severity of disease; nevertheless, it implies some degree of overlap of PSP with Parkinson's disease, Alzheimer's disease, and Parkinson-dementia complex of Guam with respect to the bnM damage, which is consequently expected to underlie some symptoms shared by these conditions.

It has been suggested that the bnM neuronal loss may play a role in the pathogenesis of some of the cognitive deficits occurring in Parkinson's disease [14, 32] and in Alzheimer's disease [33, 34]. The disorder of mentation in PSP and Parkinson's disease shows quite peculiar features configuring the "subcortical dementia", mainly characterized by a general slowing down of intellectual activity in absence of an evident impairment of the higher mental functions [2]. Furthermore, symptoms of subcortical dementia are also present in Alzheimer's disease in addition to aphasia, apraxia, and agnosia [2]. The suggested pathophysiologic mechanism of subcortical dementia is represented by a disorder of timing and activation of mental processes

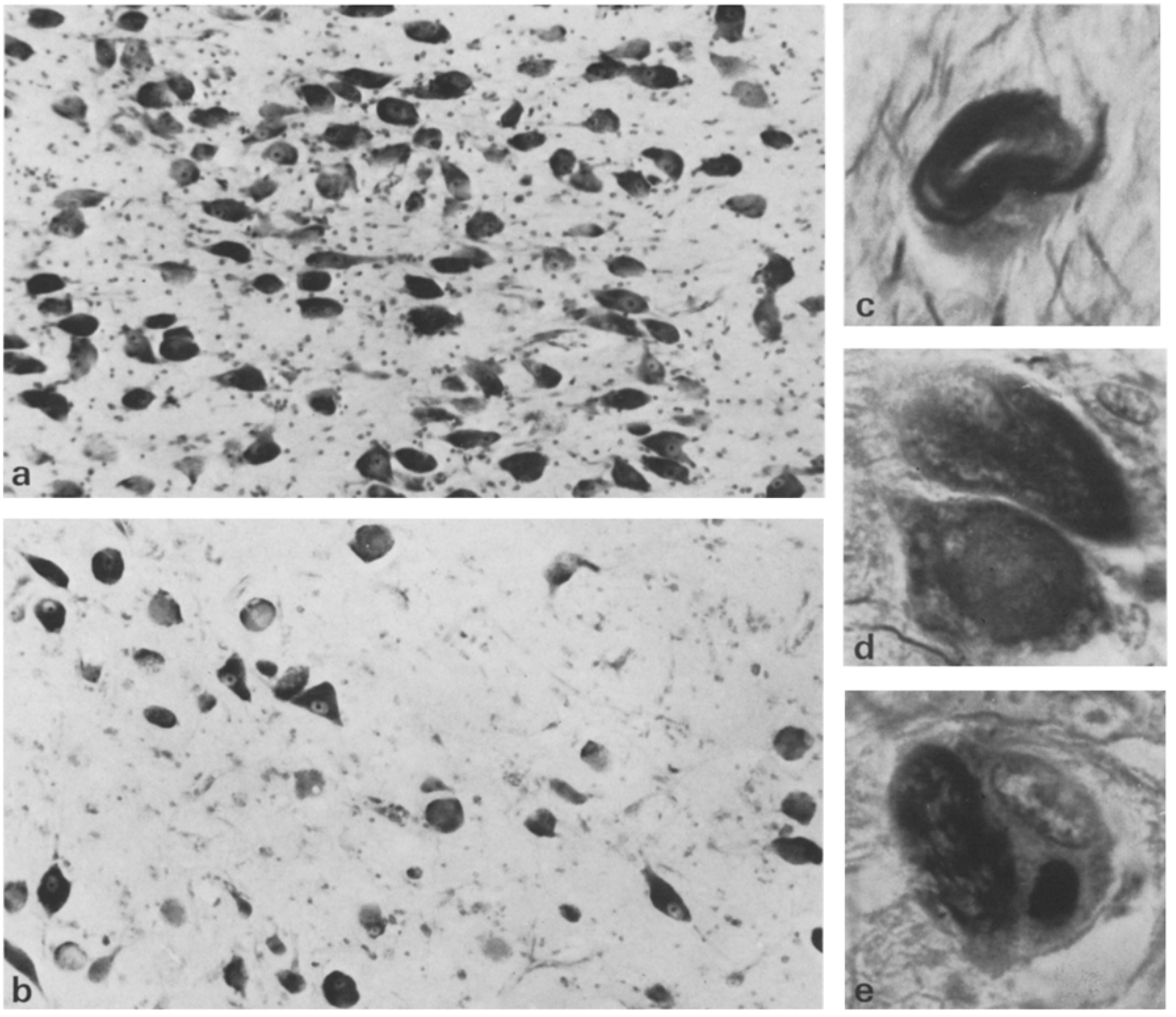

Fig. 1. Frontal sections through the bnM at the level of the infundibulum in a control (**a**) and in the PSP patient (**b**). Neurofibrillary degeneration in the bnM of the PSP patient (**c**, **d**, **e**). **a**, **b** Nissl, ×175. **c**, **d**, **e** von Braunmühl ×1,700

[3]. The involvement of the bnM can be thought to be responsible for the failure of such an activation, in view of the complex connections of the nucleus with various subcortical structures and its diffuse projections on the neocortex [10, 17, 18, 21].

A significant reduction of the activity of the enzyme choline acetyltransferase, a specific cholinergic marker, has been found in the neocortex of patients with Alzheimer's disease [4, 9, 24], positively correlating with the severity of dementia [25]. This cholinergic abnormality is considered as a consequence of the bnM neuronal loss [33]. Similar findings have been also reported in the neocortex of parkinsonian patients with dementia [27]. Biochemical studies of the cholinergic system and further neuropathologic investigations of the bnM in PSP, as well as in other types of subcortical dementia, may shed light on the function of the nucleus and contribute to a better understanding of dementia.

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