

## **Neuropathology of the locus ceruleus: a semi-quantitative study**

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**Summary.** The locus ceruleus was studied in 86 brains of the elderly, with or without degenerative disease. Parkinson's disease, multiple system atrophy, progressive supranuclear palsy and senile dementia were among the diseases studied. Nerve cell loss, the appearance of neurofibrillary changes and Lewy bodies were examined semi-quantitatively. The number of nerve cells diminished in old age, especially over 90 years. The decrease of nerve cells was greater in cases with Lewy bodies. A marked loss of nerve cell was observed in multiple system atrophies, including Shy-Drager syndrome, olivopontocerebellar atrophy and striatonigral degeneration, and in some cases of Parkinson's disease and senile dementia. The number of nerve cells did not decrease in cases of progressive supranuclear palsy. Lewy bodies and neurofibrillary tangles appeared increasingly in old age. However, the incidence of both changes in the same neuron was rare, and in such cases their structures appeared not to be related.

**Key words:** Locus ceruleus – Aging – Lewy body – Neurofibrillary tangle – Nerve cell count

**Zusammenfassung.** Es wurden 24 Hirne von Individuen von über 60 Jahren untersucht sowie 22 Gehirne von Patienten mit Parkinsonscher Krankheit, multipler Systematrophie, seniler Demenz, progressiver supranukleärer Lähmung etc. Es wurden semiquantitative Untersuchungen über die Anzahl der Nervenzellen und das Auftreten der Neurofibrillenveränderungen und Lewyschen Körperchen im Locus ceruleus angestellt.

1. Die Durchschnittszahl der Nervenzellen im Locus ceruleus bei 60 Individuen von über 60 Jahren war geringer als jene bei 12 jüngeren Fällen. Besonders deutlich waren die zahlenmäßige Abnahme in den Fällen von über 90 Jahren. Das Volumen der Nervenzellen an Serienschnitten zeigte in den Fällen von über 80 Jahren einen Verlust von ca. 40%.

2. Der Verlust an Nervenzellen war besonders ausgeprägt bei jenen Fällen, die auch Lewy-Körperchen zeigten.

3. Ein besonders hochgradiger Verlust an Nervenzellen wurde in den Fällen mit multiplen Systematrophien, zum Beispiel Shy-Drager-Syndrom, olivo-ponto-cerebelläre Atrophie und striato-nigraler Degeneration sowie in einigen Fällen der Parkinsonschen Krankheit und senilen Demenz festgestellt. Andererseits war die Zahl der Nervenzellen in drei Fällen von progressiver supranukleärer Lähmung nicht vermindert.

4. Im hohen Alter waren die Lewyschen Körperchen und die Veränderungen der Neurofibrillen besonders ausgeprägt. Hingegen war das gleichzeitige Vorhandensein beider Veränderungen in ein und derselben Nervenzelle sehr selten und wenn dies einmal zusammen vorhanden war, war keine strukturelle Beziehung zwischen den zwei Veränderungen vorhanden.

## Introduction

The locus ceruleus is a nucleus in the tegmentum of the upper pons and consists mainly of pigmented nerve cells. Its significance has long remained unknown. Recently, it has been confirmed that the nerve cells of the locus ceruleus contain catecholamines, mainly norepinephrine, and that the noradrenergic pathways originating from the locus ceruleus influence neural activity in many cortical regions of the brain. They are thought to be distributed also to subcortical structures, including the hypothalamus and also to the cerebellar cortex [2].

Neurons of the locus ceruleus are known to be affected in various conditions. Brody and his group [4, 18] reported that the number of nerve cells in the locus ceruleus decreased markedly in old age, compared with other brain-stem nuclei, with the exception of the substantia nigra, which also contains pigmented nerve cells. In various degenerative diseases, such as Parkinson's disease, multiple system atrophy, Alzheimer's disease and progressive supranuclear palsy, the locus ceruleus is also affected.

This paper reports the morphological changes of the locus ceruleus in the brains of the elderly and in some pathological conditions, by semi-quantitative examination.

## Material and methods

Material came from 64 autopsy brains of the elderly, over age 60, all of whom had no degenerative neurological disease, and as a control, 12 brains of younger subjects were examined. Twenty-two autopsy brains showing degenerative diseases, including Parkinson's disease, multiple system atrophy, progressive supranuclear palsy (PSP) and senile dementia etc. were also examined (Table 1). Paraffin-embedded material containing the locus ceruleus was cut in 9  $\mu$ m thickness and stained by haematoxylin and eosin.

Counting of nerve cells of the locus ceruleus was made on the cross-section of the middle part of the upper pons, which corresponds to the mid-part of the nucleus. All nerve cells with melanin pigment were counted. For some cases, whole nerve cells of the locus ceruleus were counted on serial sections. In these, counting was of the nerve cells with melanin pigment and distinct nuclei. Besides the nerve cell number, the incidence of Lewy bodies and neurofibrillary tangles was noted. Further, an electron microscopic study was made of the case which showed both Lewy bodies and neurofibrillary tangles in the locus ceruleus.

**Table 1.** Examined material

Younger cases (under 59 years)	12
Aged cases (over 60 years)	64
60-	11
70-	29
80-	14
90-	10
Degenerative disease	22
Parkinson's disease	7
OPCA	2
SND	1
Shy-Drager syndrome	1
LCCA	2
PSP	3
Senile dementia	6

OPCA: Olivopontocerebellar atrophy

SND: Striatonigral degeneration

LCCA: Late cortical cerebellar atrophy

PSP: Progressive supranuclear palsy

**Table 2.** Nerve cell number of locus ceruleus in right and left sides

	Right	Left	Total
65 years, M	51.3%	48.7%	17,630
84 years, M	49.4%	50.6%	11,354
96 years, F	51.4%	48.6%	11,515
74 years, M*	43.1%	56.9%	1,191

Percentage of total number on serial section

\* Parkinson's disease

## Results

### *Nerve cell count*

Table 2 shows the percentage of the total number of nerve cells in the left and right sides counted on the serial sections. There was no significant difference in cell numbers between the two sides. Then, the mean number of nerve cells on both sides of the cross-section was calculated. In cases without degenerative diseases or gross macroscopical changes, such as cerebral infarctions, the mean number of nerve cells was 52 in the cases under age 60 years, 48 in the 7th decade, 41 in the 8th decade, 35 in the 9th decade and 29 in those aged over 90 years. This decrease in the number of nerve cells is significant when comparing the cases over 90 years of age with those under age 59.

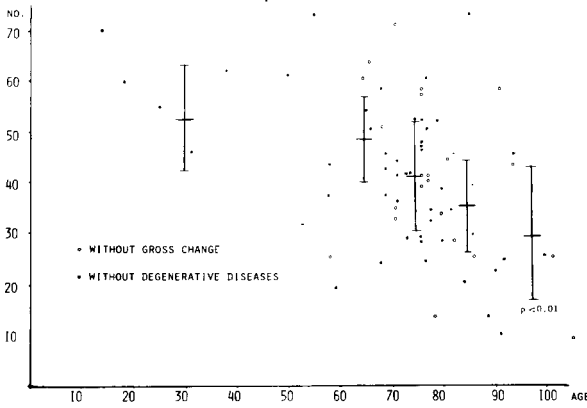


Fig. 1. Nerve cell number of the locus ceruleus at various ages

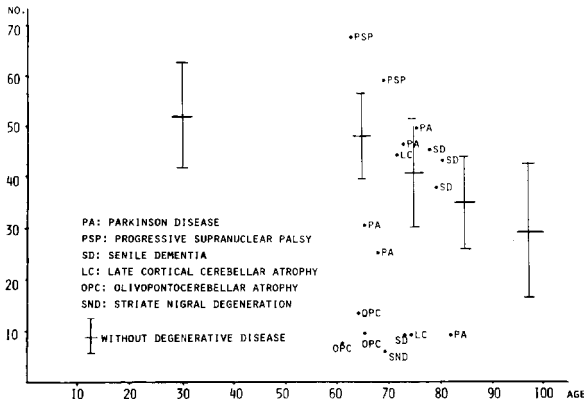


Fig. 2. Nerve cell number of the locus ceruleus in degenerative disease

However, there were large differences in cell numbers among individual cases (Fig. 1). Figure 2 shows the number of nerve cells in the locus ceruleus counted in the same fashion in cases with degenerative neurological diseases, i.e. Parkinson's disease, PSP, senile dementia, cerebellar degeneration, striatonigral degeneration etc. In Parkinson's disease, the number of nerve cells decreased in three of five cases examined. For the olivopontocerebellar atrophy and striatonigral degeneration, which belong to the so-called multiple system atrophy group, all cases showed a marked decrease in the number of nerve cells. In senile dementia, one case showed a marked decrease and three cases showed normal numbers of nerve cells for their age. On the other hand, there was no decrease in the number of nerve cells in two cases of PSP, which showed the usual abundant neurofibrillary tangles in the locus ceruleus.

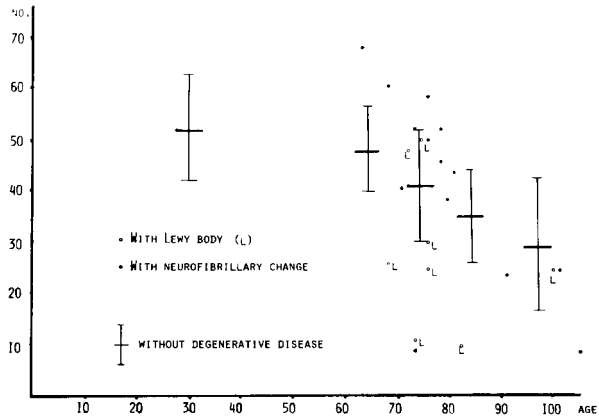
*Lewy bodies and neurofibrillary tangles*

In the nerve cells of the locus ceruleus of the aged brain we found occasional Lewy bodies and neurofibrillary tangles in cases without any neurological or

**Table 3.** The incidence of cases with neurofibrillary tangles and Lewy bodies in the locus ceruleus

Age		Neurofibrillary tangle		Lewy body	
			%		%
-59	(12)	0	0	0	0
60-	(39)	4	11	1	3
70-	(82)	9	11	8	10
80-	(65)	9	14	10	15
90-	(15)	3	20	5	33
100-	(3)	3	100	1	33

( ) No. of cases without degenerative diseases



**Fig. 3.** The number of nerve cells with neurofibrillary tangle or Lewy body in locus ceruleus

psychiatric symptoms. The percentage of the cases with these pathological changes is shown in Table 3. The incidence of the cases with neurofibrillary tangles increased with age and all three cases aged over 100 years showed this change. On the other hand, Lewy bodies were also observed more frequently in older subjects, but did not exceed 33%. Therefore, the neurofibrillary tangle seemed to be a more age-related change in the locus ceruleus.

The nerve cell numbers in the cases with these pathological changes are shown in Fig. 3. For the neurofibrillary tangles, almost all cases with this change, except one case aged over 100, showed a normal number of nerve cells for the age, while cases with Lewy bodies showed a decrease in five of eight cases examined.

*Total cell count*

The total number of nerve cells in the locus ceruleus was counted by serial section on three of the aged controls, one case of Parkinson's disease, one case of PSP, and two cases of senile dementia (Table 4). A 65-year-old man, who died

	Total number
65 years, M Gastric cancer	17,630
84 years, M Pneumonia	11,354
96 years, F Ischaemic colitis Old TBC	11,515
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74 years, M Parkinson's disease	1,191
78 years, M PSP	16,440
79 years, M Senile dementia	10,696
67 years, M Senile dementia	3,750

TBC: Tuberculosis

PSP: Progressive supranuclear palsy

	Lewy body	Neurofibrillary tangle	
65 years, M	2 (0.01%)	82 (0.47%)	(-)
84 years, M	0	13 (0.11%)	(+)
96 years, F	9 (0.07%)	85 (6.6%)	(+)
74 years, M Parkinson's disease	387 (32.1%)	9 (0.8%)	(+)

Total number of nerve cells = 100%

( ) Neurofibrillary tangles in cerebral cortex

**Table 4.** Total nerve cell number of the locus ceruleus in cases of various ages and diseases by serial horizontal section, H. and E. stain

**Table 5.** Incidence of nerve cells with Lewy body and neurofibrillary tangle in the locus ceruleus in cases of various ages and Parkinson's disease

from gastric cancer, showed 17,630 nerve cells; an 84-year-old man, who died from pneumonia, showed 11,354 nerve cells; and a 96-year-old woman showed 11,515. On the other hand, a 74-year-old case with Parkinson's disease showed 1,191. This case had had marked orthostatic hypotension since 60 years of age, in addition to parkinsonism.

The incidence of Lewy bodies and neurofibrillary tangles was examined on the serial sections. Lewy bodies appeared in up to 0.07% of nerve cells in the control cases. On the other hand, a case of Parkinson's disease showed Lewy

**Table 6.** The incidence of nerve cells with Lewy body and neurofibrillary tangle in the locus ceruleus of a 96-year-old female

Total nerve cells	11,515
Nerve cell with Lewy body	9 (0.07%)
Nerve cell with neurofibrillary tangle	85 (6.6%)
Nerve cell with Lewy and neurofibrillary tangle	1 (0.008%)

bodies in 32.1% of nerve cells. The neurofibrillary tangle was observed in a higher incidence than the Lewy body, particularly in older subjects (for example, 6.6% in a 96-year-old case). In Parkinson's disease, the incidence of neurofibrillary tangles was almost the same as in the controls and this case also showed neurofibrillary tangles in the hippocampus (Table 5).

The total nerve cells were also counted for the PSP cases and those of senile dementia. These cases showed abundant neurofibrillary tangles in the neurons of the locus ceruleus. The number of nerve cells in a 78-year-old case of PSP was 16,440, a slight decrease compared to the control. This finding was similar in two other cases of PSP. Two cases of senile dementia showed a moderate or marked decrease in the number of nerve cells: a 79-year-old case showed 10,696 and a 67-year-old case 3,750. The cerebral cortex was also affected more severely in the latter case than the former.

#### *Coexistence of Lewy body and neurofibrillary tangle*

The relationship between the Lewy body and the neurofibrillary tangle is not clear, although both changes appeared occasionally in the locus ceruleus of the same case. It is very rare, however, for both changes to be observed in the same neuron. By serial section of the locus ceruleus of a 96-year-old female, showing both Lewy bodies and neurofibrillary tangles, one neuron with both changes was observed among a total of 11,515 nerve cells (Table 6).

On electron microscopic examination, we found one such rare neuron. The Lewy body showed the vesicular structure of the core and filamentous radiations from the core, which is a characteristic feature of the Lewy body. In the outer margin of the Lewy body, twisted tubules were observed, which are a typical ultrastructure of the neurofibrillary tangle. However, no structural relationship between both changes could be found.

## **Discussion**

The physiological significance of the locus ceruleus has recently become clearer, especially its role in sleep-awakeness regulation, emotion, memory and several autonomic nerve functions. It is known that frequent sleep disturbance is observed in cases of mental retardation, olivopontocerebellar atrophy, PSP and

Parkinson's disease [3, 7, 11] as well as in aged persons [6]. Marked autonomic disorders, including orthostatic hypotension, are also frequent in Shy-Drager syndrome and Parkinson's disease. Some cases of Parkinson's disease also show a decrease in intelligence.

The number of nerve cells in the locus ceruleus decreased markedly in elderly persons. Counting the total nerve cells on the serial section for three elderly cases revealed about 40% loss in cases aged over 80 years. Marked loss of nerve cells was observed in the cases of Parkinson's disease, multiple system atrophy and senile dementia. Counting the total nerve cells in a case of Parkinson's disease revealed about 90% loss. Neurofibrillary tangles were found in 0.8% and Lewy bodies in 32.1%. These results may be closely related to the disturbance of the above-mentioned physiological functions.

The decrease in nerve cell number was more prominent in the elderly cases showing Lewy bodies than in the cases showing neurofibrillary tangles, which may mean that the appearance of Lewy body plays a more important role in nerve cell loss. On the other hand, the increase in neurofibrillary changes was more closely related to age in the aged control, and may be less important for nerve cell loss than the Lewy body.

A decrease in the total number of nerve cells was also observed in senile dementia, in which the subcortical involvement as well as cortical changes have been reported. On the other hand, two cases of PSP showed no decrease in the number of nerve cells, in spite of the appearance of abundant neurofibrillary tangles. Counting the total nerve cells in a case of PSP also revealed no decrease. It is not clear why there was no decrease in nerve cell number in PSP. However, the neurofibrillary tangle of PSP consisted mainly of straight tubules ultra-structurally, in contrast to the twisted tubules in senile dementia.

Tomlinson et al. [15] counted the nerve cell numbers in the locus ceruleus of 15 cases of senile dementia; 7 counts were within the lower range for the controls, but 8 had fewer neurons than any control. The more severe cases of senile dementia in terms of neocortical plaque formation lost the most locus ceruleus neurons. In our cases of senile dementia, the lower count case showed the abundant neurofibrillary tangles in the locus ceruleus and more severe changes in the neocortex. These results mean that the noradrenergic system is also involved in the senile dementia, in addition to the cholinergic pathology, as suggested by Perry et al. [14] and Mann et al. [12, 13].

Both Lewy bodies and neurofibrillary tangles are not infrequent changes in the brain of the aged, but the relationship between them is not clear. In Parkinson's disease, which usually shows abundant Lewy bodies, the appearance of the neurofibrillary tangle has been reported to be more frequent than in age-matched controls. This suggests a more frequent incidence of senile dementia in Parkinson's disease [1] and particularly in so-called "diffuse Lewy body disease" [19]. On the other hand, another study did not find frequent brain atrophy and higher occurrence of Alzheimer's disease in parkinsonism [10]. We have obtained the same finding by the study of total nerve cell counting in the locus ceruleus. A 74-year-old case of Parkinson's disease showed neurofibrillary tangles in 0.8% of nerve cells, which is more frequent than the incidence of 0.47% in a 65-year-old man and 0.11% in an 84-year-old man, but less than that of 6.6% in a 96-year-old



woman. Further, the study of serial sections suggests that the coexistence of the Lewy body and neurofibrillary tangle in the same neuron is extremely rare and, therefore, the formation of Lewy bodies and neurofibrillary tangles has different mechanisms which probably exclude each other in the nerve cell cytoplasm [16]. The reason is not known. A similar neuron was described by Hirano [9] in a case of Guamanian Parkinson-dementia complex.

The Lewy body in Parkinson's disease also appears in other neurons than those of the locus ceruleus and the frequency of this appearance in the locus ceruleus is thought to be parallel to the incidence of the Lewy body in the sympathetic ganglia [8] and also to the incidence of the adrenal body in the adrenal medulla [5]. The adrenal body has also been observed in the Shy-Drager syndrome [17]. These facts suggest that the changes in the locus ceruleus may be related to the disturbance of general adrenergic mechanism in these diseases and also in old age.

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