Acta neuropath. (Berl.) 19, 347—352 (1971)

Progressive Supranuclear Palsy

(Subcortical Argyrophilic Dystrophy)

K. JELLINGER

Neurological Institute of University of Vienna

Received July 5, 1971

Summary. Two female cases of progressive supranuclear palsy ("heterogeneous system degeneration") with histological findings are reported. Clinically, vertical gaze palsy, dystonia, akinesia, pseudobulbar palsy and mental impairment were prominent. Pathologically, widespread appearance of neurofibrillary tangles of the subcortical type in the brain stem and basal ganglia was associated with neuronal loss and gliosis in the substantia nigra, subthalamic nuclei and pallidum. There was less severe affection of the dentate nuclei and minimal cortical involvement. The distribution of changes in "subcortical argyrophilic dystrophy" is critically compared with and separated from brain stem affection in (pre)senile Alzheimer's disease.

Key words: Progressive Supranuclear Palsy — Heterogenous System Degeneration — Subcortical Argyrophilic Dystrophy — Neurofibrillary Tangles — Brain Stem.

Progressive supranuclear palsy [14] is a peculiar heterogeneous system degeneration of the CNS characterized clinically by vertical gaze palsy, paroxysmal dysequilibrium, dystonic rigidity of the neck and upper trunk, pseudobulbar palsy, personality changes and variable corticospinal and cerebellar symptoms. The pathological changes include a widespread presence of neurofibrillary tangles and granulovacuolar degeneration mainly in the brain stem, cerebellum and basal ganglia associated with neuronal loss, demyelination and gliosis of the affected systems, but there is surprising lack of cortical involvement. From the distinctive subcortical pattern of the neurofibrillary degeneration, Seitelberger [12] considered the locally accentuated argyrophilic dystrophy as the basic lesion and atrophy as a secondary phenomenon. He suggested that this condition should be called "subcortical argyrophilic dystrophy". Up to date, there are almost 60 published cases, of which 27 were submitted to neuropathological studies [cf. 1—6]. The purpose of this report is the presentation of the clinicopathological findings in a further two cases.

Case Reports

Case 1 (NI 132-67) — K., Therese, 73-year-old woman.

The patient first attended hospital in 1962, at the age of 68, with a 6-month history of unsteady gait, falling episodes, decreased movements, speech difficulties and impairment of vision. Her past history had been uneventful and there was no family history of neurological disease. The patient deteriorated over the next few months with worsening of gait and speech and intellectual impairment. At age 69 she was readmitted to hospital. On examination the patient had a mask-like face, blinkless gaze, loss of convergence and markedly decreased vertical movements of both eyes, rigidity of the neck and limb muscles, increased jaw-jerk

and reflexes, and mild tremor of the hands. There was considerable impairment of memory. Laboratory data were unremarkable except for abnormal EEG records with frequent slow theta activity in the frontal and temporal regions. I.V. application of L-Dopa had no favourable effect. Deterioration continued steadily and the patient became completely immobile, rigid in all limbs and anarthric, and her swallowing difficulties and mental impairment increased. 9 months prior to death vertical gaze palsy became complete. There was complete immobility of the limbs suggesting catatonia and lack of mental response. She died of pneumonia in May 1967.

Clinical diagnosis suggested presenile dementia and parkinsonism. At *autopsy*, bilateral bronchopneumonia was found.

The *brain* showed mild diffuse cortical atrophy, bilateral atrophy of the pallidum and subthalamic nucleus, and reduced pigmentation bilaterally in the substantia nigra.

Case 2 (NI 368-70) — F., Ida, 58-year-old woman.

The patient was admitted to a psychiatric hospital in 1949 at the age of 37 because of mental subnormality. Her past history had been uneventful and there was no family history of similar disease. No abnormality was found on neurological examination. Some years prior to death peculiar attacks occurred: the patient was aggressive, disorientated, her speech was slurred, she had swallowing dificulties, bilateral lid retraction, frequent falls and generalized tremor-like involuntary movements lasting for several days. Laboratory tests including skull X-rays, CSF and EEG records were unremarkable. About 5 months prior to death the condition deteriorated. The patient became immobile, rigid in all limbs and anarthric, and her swallowing difficulties increased. There was almost complete vertical gaze palsy and lack of convergence of both eyes. The jaw-jerks and tendon reflexes were exaggerated. I.V. L-Dopa treatment induced slight and transient reduction of rigidity and akinesia but had no effect on the optomotor disorders. It had to be discontinued because of severe "dyskinesia" and catatonia-like bizarre abnormal postures. The patient died of gastric haemorrhage in August 1970.

Clinical diagnosis was "mental retardation and parkinsonism". *Necropsy* showed haemorrhagic gastroenteritis and pneumonia. The *brain* showed mild diffuse cortical atrophy and bilateral depigmentation of the substantia nigra.

Histological Findings

The CNS changes in both cases were very similar. In each case the cerebral cortex and white matter were within normal limits. There were a few senile plaques and sparse neurofibrillary tangles in the hippocampus and amygdaloid nucleus. In the putamen and caudate nucleus of case 2 and in the ventrolateral thalamus of case 1 very few neurofibrillary changes were seen. The inner segment of the *globus pallidus* was shrunken, with severe loss of nerve cells and myelin, astrocytosis and many neurofibrillary tangles (Fig. 1 H). These lesions were more pronounced in case 1 where they were accompanied by pallor of the ansa lenticularis. The *subthalamic nucleus* showed severe neuronal loss and gliosis, chiefly in case 1 (Fig. 1 A), and many neurofibrillary tangles (Fig. 1 B). Similar but less severe changes were seen in the *zona incerta*. Neurofibrillary tangles were present in the nucleus basalis, zona perforata anterior, nucl. tubero-mamillaris, dorsolateral hypothalamus, and in the lateral and posterior walls of the 3rd ventricle. There were no changes in the dorsal thalamus, mamillary bodies, supraoptic and paraventricular nuclei, claustra, medial and lateral geniculate nuclei, optic nerves, chiasm and tracts. In the *substantia nigra* pars compacta there was heavy neuronal loss, most severe in the oral parts and in the ventral and medial nuclei of the caudal part, free-lying pigment and considerable astrocytosis. Some of the remaining nerve cells contained neurofibrillary tangles (Fig. 1 D). No Lewy bodies were seen. The reticulata nigrae presented moderate neuroaxonal dystrophy with spheroids. In the red nucleus only occasional neurons contained neurofibrillary changes. The *mesencephalic tegmentum* and tectum disclosed slight myelin pallor and gliosis. Many neurofibrillary tangles were present in the periaqueductal grey matter, in the reticular nuclei and in various parts of the nuclei of the oculomotor nerve (Fig. 1 I), and occasionally in the inferior colliculi. Severe changes affected the supratrochlear and trochlear nerve nuclei. The *pontine tegmentum* showed moderate diffuse gliosis. There were neurofibrillary changes in the neurons of the locus coeruleus, central pontine and reticular

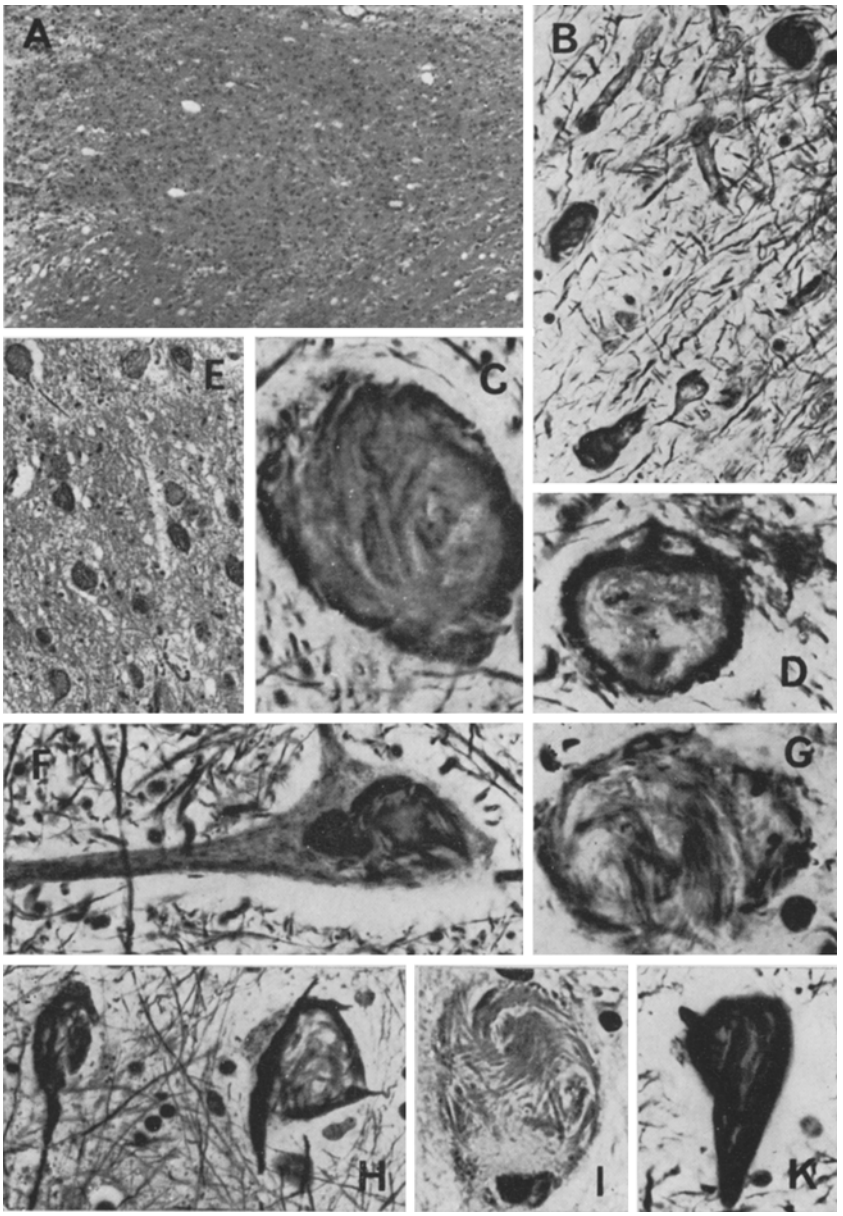

Fig. 1 A—D. Case 1. A Nerve cell loss and gliosis in subthalamic nucleus. H.-E. ×60. B. Neurofibrillary tangles in subthalamic nucleus. Bodian stain ×500. C. Whorled fibrils in neuron from nucl. paragigantocellularis lat. Bodian stain ×1200. D. Nerve cell with fine argyrophilic fibrils from substantia nigra. Bodian stain ×800

Fig. 1 E. Senile dementia (77 yr. male). Multiple neurofibrillary tangles in nucl. centralis pontis sup., subnucl. oralis. Bodian stain ×150

Fig. 1 F—K. Case 2. F. Tangle in neuron from nucleus of hypoglossal nerve. Bodian stain ×800. G Whorled fibrils in neuron from lateral hypothalamus. Bodian stain ×1250. H Neurofibrillary tangles in inner pallidum. Bodian ×600. I Whorled cytoplasmic fibrils in neuron from medial nucleus of oculomotor nerve. K. V. ×800. K Flame-shaped tangle in magnocellular reticular nucleus of medulla. Bodian stain ×800

nuclei, while in the basal pontine nuclei only occasional nerve cell swelling and neurofibrillary changes were present. The *dentate nucleus* showed only mild neuronal loss and gliosis, particularly in the dorsal parts. Here and in the globose nucleus occasional tangles were seen. The cerebellar cortex and white matter were not abnormal. In the *medulla*, a considerable number of neurofibrillary changes were present in the raphé nuclei, magnocellular reticular nuclei (Fig. 1 C,K), the dorsal motor nucleus of the vagus, nucleus ambiguus, solitary nucleus and, less often, in the nucleus of the hypoglossal nerve (Fig. 1 F). Occasional granulovacuolar degeneration was seen in the spinal trigeminal nucleus. The inferior olives looked normal.

Some of the neurofibrillary tangles were like those seen in the cerebral cortex, while most of them were less strongly argyrophilic, not congophilic and showed inconstant birefringence. They were either large spherical skeins consisting of fine filaments—globose type (Fig. 1 C, G, I) or, less often, strands of slightly basophilic and argyrophilic fibrils—flame-shaped or golf-ball type (Fig. 1 K). In some instances they occupied only a part of the nerve cell (Fig. 1 F). Often, the tangles appeared to have replaced the whole cell and to have changed into coarse lumps (Figs. 1 C, D, G, I). The appearance of the tangles was similar in both cases and in all subcortical sites. Occasional neuronophagia was seen in the most severely affected nuclei. No inflammatory vascular lesions or glial nodules were noticed. The cerebral vessels were normal for age. The spinal cord and roots and peripheral nerves were not examined.

Comments

The clinical and pathological findings in both cases conform to the criteria set up by Steele *et al.* [14] and are similar to the majority of the reported cases of "progressive supranuclear palsy" (PSP). Some clinical features were reminiscent of akinetic forms of Parkinsonism [13]. A favourable effect of L-Dopa treatment, occasionally reported [5,10a], was not observed in these patients. The histological hallmarks are the presence of neurofibrillary tangles of the subcortical type [8,12] in many regions of the brain stem and diencephalon accompanied by systemic neuronal loss and gliosis chiefly in the substantia nigra, globus pallidus and subthalamic nucleus, while the affection of the dentate nucleus was much less severe than in most published cases. Fig. 2 shows the distribution of the lesions in each patient.

The widespread appearance of neurofibrillary changes in subcortical areas, with little or even lacking cortical involvement, is known to occur in various conditions. In some of them, e. g. in postencephalitic Parkinsonism and in the Parkinson-Dementia complex on Guam [7], it is accompanied by systemic neuronal atrophies reminiscent of PSP. This combination is not seen in Alzheimer's disease and senile dementia where neurofibrillary tangles inconstantly occur in various brain stem nuclei [8—11]. In addition to an inverse relationship between the frequency of neurofibrillary changes in the cerebral cortex and brain stem, Alzheimer's disease shows a different distribution of the tangles in the brain stem. Examining 50 subsequent cases aged from 52 to 92 years (average 75 years) we found the following pattern in descending order of frequency: nucl. supratrochlearis, nucl. centralis pontis oralis (Fig. 1 E), nucl. dorsalis raphé—locus coeruleus, nucl. magnocellularis reticularis, nucl. interpeduncularis, substantia innominata, lateral and posterior hypothalamus—zona incerta and zona compacta nigrae, while the pallidum, subthalamic nucleus, the nuclei of the oculomotor nerve and dentate nucleus were constantly preserved. This conforms to the findings of other authors [8,9,11]. Occasional senile plaques in the inferior colliculi in (pre-) senile dementia were never reported in PSP. Although there is a considerable variability in the distribution of subcortical argyrophilic dystrophy within one and the same

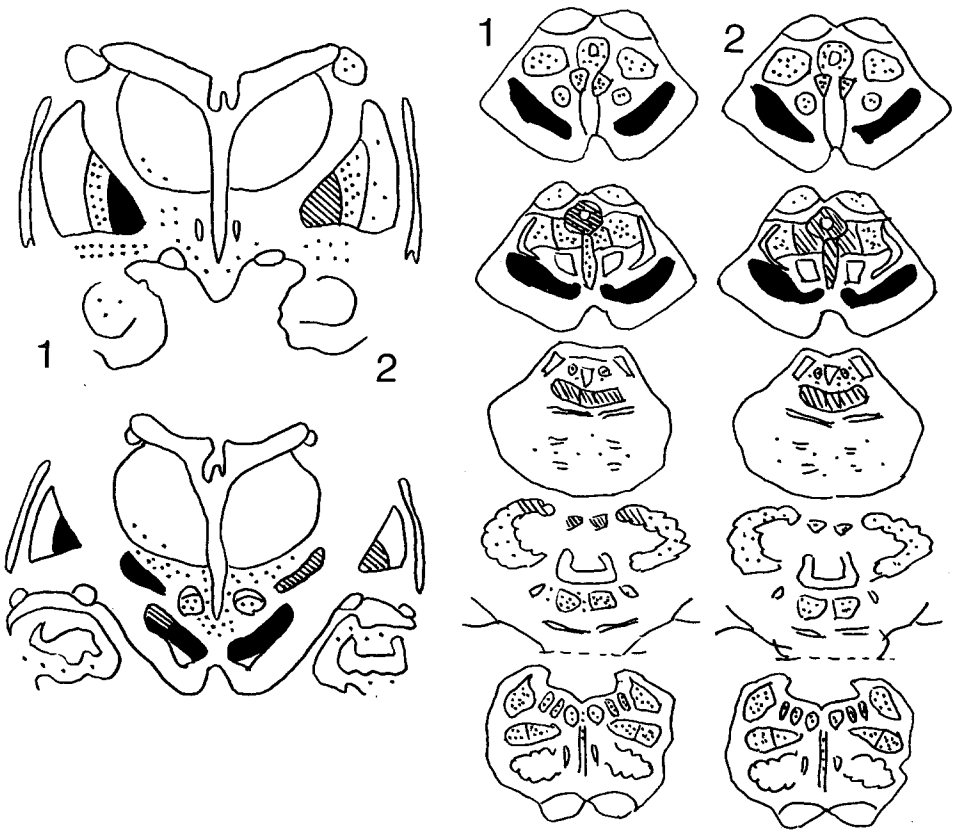

Fig. 2. Schematic distribution of the lesions in Case 1 and 2. Black: severe changes with considerable neuronal loss and gliosis; striped: moderate argyrophilic changes with slight neuronal loss; pointed: moderate to mild argyrophilic dystrophy without considerable neuronal loss

morbid entity, from the above topographical differences between Alzheimer's disease of the "cortical type" and "heterogeneous system degeneration" or PSP and other conditions with associated system-bound neuronal atrophies it is concluded that these particular disorders represent distinct nosological entities which could be designated as "subcortical type of Alzheimer's syndrome". Local accentuation of the argyrophilic dystrophy in the limbic structures etc. may be associated with circumscribed cerebral atrophy in Alzheimer's disease [15] or senile dementia [8, 10] due to severe neuronal loss. Similar pathogenic mechanisms might be responsible for localized or system-bound neuronal depletion and gliosis in the brain stem and basal ganglia associated with severs degrees of subcortical argyrophilic dystrophy. It seems impossible, however, to decide whether the disease referred to as PSP should be classified as a primary degeneration of the CNS related to ageing processes or whether it may be caused by another agent, e. g. chronic viral infection. Although the combination of clinical and pathological features does allow ready recognition of this entity, the aetiology and the mechanisms of the disturbed function are still poorly understood.

References

1. Anzil, A. P.: Progressive supranuclear palsy. Case report with pathological findings. Acta neuropath. (Berl.) **14**, 72—76 (1969).
2. Behrman, S., Carroll, J. D., Janota, I., Matthews, W. B.: Progressive supranuclear palsy. Clinico-pathological study of four cases. Brain **92**, 663—678 (1969).
3. Cambier, J., Escourolle, R., Masson, M., Lechevalier, B.: La paralysie supra-nucléaire progressive. A propos d'une observation anatomo-clinique. Rev. neurol. **121**, 139—154 (1969).

3a. Colmant, H. J.: Progressive supranuclear palsy. Arch. Psychiat. Nervenkr. **214**, 324—330 (1971).

4. Constantinidis, J., Tissot, R., de Ajuriaguerra, J.: Dystonie oculofacio-cervicale ou paralysie progressive supranucléaire de Steele-Richardson-Olszewski. Rev. neurol. **122**, 249—262 (1970).
5. Dehaene, I., Bogaerts, M.: La paralysie supranucléaire progressive. Acta neurol. belg. **71**, 141—151 (1971).
6. Dix, H. R., Harrison, M. J. G., Lewis, P. D.: Progressive supranuclear palsy (The Steele-Richardson-Olszewski syndrome). A report of 9 cases with particular reference to the mechanisms of the oculomotor disorders. J. neurol. Sci. **13**, 237—256 (1971).
7. Hirano, A., Malamud, N., Elizan, T. S., Kurland, L. T.: Amyotrophic lateral sclerosis and Parkinson-dementia complex on Guam. Arch. Neurol. (Chic.) **15**, 35—51 (1966).
8. — Zimmerman, H. M.: Alzheimer's neurofibrillary changes. A topographic study. Arch. Neurol. (Chic.) **7**, 227—242 (1962).
9. Ishii, T.: Distribution of Alzheimer's neurofibrillary changes in the brain stem and hypothalamus of senile dementia. Acta neuropath. (Berl.) **6**, 181—187 (1966).
10. Jellinger, K.: Morphologische Gesichtspunkte zur Differenzierung sog. hirnatrophischer Prozesse. 1. Symposium A. G. für Gerontopsychiatrie. Krefeld, 8.—9. 5. 1971.

10a. Klawans, H. L., Jr., Ringel, S. P.: Observations on the efficacy of L-Dopa in progressive supranuclear palsy. Europ. Neurol. **5**, 115—129 (1971).

11. Mehraein, P.: Argyrophilic dystrophies. Proc. IInd Int. Congr. Ass. Sci. Study Ment. Retard., Warszaw 1970.
12. Seitelberger, F.: Heterogenous system degeneration. Subcortical argyrophilic dystrophy. Acta neurol. (Bari) **24**, 276—284 (1969).
13. Stadlan, E. M., Duvoisin, R., Yahr, M.: The pathology of parkinsonism. Proc. VIth. Int. Congr. Neuropath., Exc. med., I. C. S. Nr. 100, pp. 569—571. Amsterdam-New York: Excerpta medica 1966.
14. Steele, J. C., Richardson, J. C., Olszewski, J.: Progressive supranuclear palsy. Arch. Neurol. (Chic.) **10**, 333—359 (1964).
15. Tariska, St.: Circumscribed cerebral atrophy in Alzheimer's disease. A pathological study. In: Alzheimer's disease and Related Conditions. G. E. W. Wolstenholme and M. O'Connor (ed.), pp. 51—73. London: Churchill 1970.

Prof. Dr. K. Jellinger
Neurologisches Institut der Universität
Schwarzspanierstraße 17
A 1090 Wien, Austria