Virchows Archiv A Pathol Anat (1991) 418:99–103

Virchows Archiv A
Pathological Anatomy and Histopathology

Degeneration of the corticopontine tract in olivopontocerebellar atrophy

S. Yagishita [1], S. Yokoi [1], K. Iwabuchi [2], N. Amano [2], Y. Mashuda [3], K. Hasegawa [3], and H. Kohwa [3]

[1] Division of Pathology, [2] Division of Neuropsychiatry, Kanagawa Rehabilitation Center, Nanasawa 516, Atsugi-Shi, Kanagawa-ken, 243-01, Japan
[3] Department of Neurology, Kitazato Higashi Hospital, Kitazato University, School of Medicine, Kitazato, Sagamihara-shi, Kanagawa-ken, Japan

Received January 29, 1990 / Accepted October 4, 1990

Summary. Nine cases of sporadic olivopontocerebellar atrophy [Déjérine-Thomas type, multisystemic atrophy (MSA)] were examined histologically and electron microscopically with special reference to the corticopontine tract. Five of nine cases showed degeneration of the myelinated nerve fibres in this tract. More severe degeneration of the fibres at the level of the pons than the crus cerebri indicates that degeneration of the fibres may start axodistally. Electron microscopy revealed selective involvement of large fibres in olivopontocerebellar atrophy, in contrast to unselective axonal atrophy in dentatorubropallidoluysian atrophy. The problem whether the degeneration of the tract is primary or secondary due to the loss of the pontine neurons remains open. We believe the former to be most likely. Degeneration of the corticopontine fibres should be added to the list of neuropathological findings in sporadic olivopontocerebellar atrophy.

Key words: Corticopontine tract degeneration – Olivopontocerebellar atrophy – Electron microscopy – Morphometry

Introduction

The corticopontine tract consists of two main bundles. The frontopontine tract (bundle of Arnold) arises mainly from the lateral and superior convexity of furthest prefrontal cortex and passes through the anterior limb of the internal capsule; on reaching the midbrain, it forms the medial fifth of the crus cerebri and distributes to the medial pontine nuclei. Other corticopontine tracts arise from the parietal, temporal and occipital cortices, respectively. They are collectively known as the bundle of Türck and descend through the retrolenticular and sublenticular portions of the internal capsule. These fibres occupy the lateral fifth of the crus cerebri and distribute mainly to the lateral and dorsolateral cell groups of the pons (Truex and Carpenter 1969). Through these tracts the cerebral cortex is brought into an intimate association with the synergic regulating mechanism of the cerebellum. Thus, the corticopontine tract is one of the major systems afferent to the cerebellum.

However, little attention has been paid to changes in this tract in systemic degeneration of the cerebellum and related systems, including olivopontocerebellar atrophy (OPCA). As far as we know, only a few authors (Noica et al. 1936; Geary et al. 1956) have reported degeneration of the corticopontine tract in OPCA. The latter authors describe how in the "basis pedunculi – the region of the frontopontine and temporopontine tracts, seen in cross section, in the midbrain shows slight evidence of partial demyelination and astrocytosis", but do not illustrate and comment on degeneration of this tract. Eadie (1983) cited these papers and asserted that degeneration of the corticopontine tract is a sequela to retrograde transneuronal degeneration of the tract.

During the histopathological study of many cases of OPCA or multisystemic atrophy of Oppenheimer (1983), we found that degeneration of the corticopontine tract was frequently seen. The aim of this study was to present the pathology of the corticopontine tract in OPCA and to discuss the implication of the degeneration of this tract.

Materials and methods

Fourteen cases of sporadic OPCA were recorded in our autopsy files and nine cases were selected for this study. The other five cases were excluded, since they had incomplete clinical records or insufficient materials for thorough histopathological examination of the brain, including the spinal cord. These nine cases satisfy the criteria of OPCA or multisystemic atrophy (MSA) in their clinicopathology (Oppenheimer 1984). Representative sections of the brain and spinal cord in each case were embedded in paraffin wax and the sections were stained with haematoxylin and eosin, periodic acid-Schiff, Klüver-Barrera, and Bodian's silver impregna-

Offprint requests to: S. Yagishita

Table 1. Topography of degenerative lesions in CNS

Regions	Case no.								
	1	2	3[a]	4	5	6	7	8	9
Caudate nucleus	−	−	−	−	−	−	+	−	+
Putamen	+	+	±	+	+	++	±	+	++
Globus pallidus									
IS	+	+	−	±	±	+	+	±	+
OS	+	+	−	±	±	+	−	±	+
Nigra	±	++	+	+	+	+	++	++	++
Locus coeruleus	±	+	±	±	±	−	+	−	±
Cerebellar cortex	++	++	++	+	+	++	+	++	++
Cerebellar medulla	++	++	++	++	+	++	++	++	++
Dentate nucleus	−	−	+	−	−	−	−	−	−
Pontine nucleus	++	++	++	++	+	++	++	++	++
T-fibres in pons	++	++	++	++	+	++	++	++	++
Olivary nucleus	++	++	++	++	+	++	++	++	++
Dorsal nucleus of Vagus	−	+	±	+	+	−	−	−	+
Anterior horn	−	−	++	+	−	−	−	−	++
IMLN	−	−	+	+	−	−	+	+	+
Thoracic nucleus	−	−	+	+	−	−	−	−	+
Pyramidal tract	±	++	+−	−	−	−	−	−	++
Spinocerebellar tract	−	−	−	−	−	−	−	−	++

IS, Internal segment; OS, outer segment; T-fibres, transverse fibres; LMLN, intermediolateral nucleus;
[a] Case 3 is combined with amyotrophic lateral sclerosis

Table 2. Light microscopical findings of corticopontine tract

Case no.	At level of crus cerebri	At level of pons	Loss of neurons in pontine nuclei	Duration of illness (years)
1	+++	+++	+++	11
2	±	+	+++	7
3	±	++	++	10
4	−	−	++	4
5	−	−	+	3
6	−	−	++	8
7	++	++	++	12
8	−	−	++	5
9	+++	+++	+++	15

+++, Severe; ++, moderate; +, slight; ± minimal; −, spared

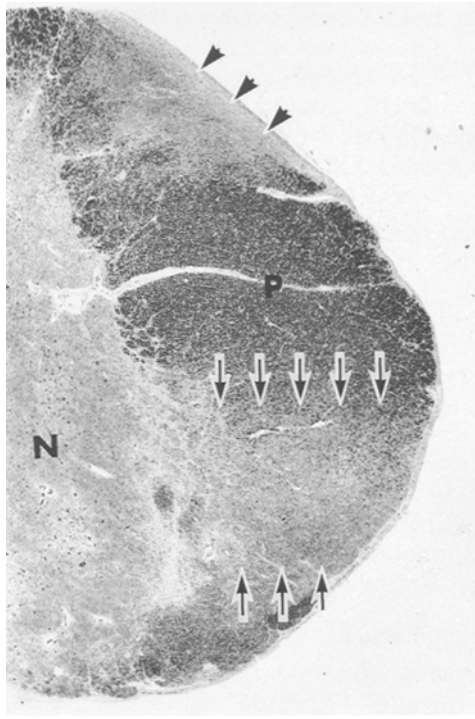

Fig. 1. Transverse section of midbrain. Pallor of myelin in the frontopontine (*arrows*) and parietotemporo-occipitopontine tracts (*arrowheads*). Case 1. *N*, Substantia nigra; *P*, pyramidal tract. 1% osmium tetroxide fixation. Sudan black B stain

tion, and Holzer stain for glial fibrils. In addition, transverse sections of the crus cerebri and pons in each case were re-fixed and stained in 1% osmium tetroxide and the frozen thin sections were stained with Sudan black B for myelin sheaths.

For electron microscopical examination, a part of the basis pontis and frontopontine tracts at the level of the crus cerebri in case 8 (Table 1) were directly fixed in 2.5% glutaraldehyde solution at the time of autopsy (4 h post mortem) and postfixed in 1% osmium tetroxide and embedded in Epon mixture. The semithin sections were stained with toluidine blue to select the frontopontine tracts at both levels. The large thin sections were stained with uranyl acetate and lead citrate and examined in a Hitachi H-7000 electron microscope. For morphometrical evaluations, photographs of most fields of each mesh were taken at 1000 magnification, and enlarged to about 3500 on printing papers. Each axonal area of 40000 myelinated fibres was measured by using a digital image analyser (Finetech corporation) and compared with those of control (48 year-old male without evidence of neurological disease, 8 h post mortem) and a case of dentatorubropallidoluysian atrophy (DRPLA) (24 year-old male, 4 h post mortem). The samples in both control and DRPLA were also treated in a similar manner.

Only sporadic cases of OPCA were used and hereditary cases (Menzel type OPCA) are excluded in this report, since Menzel-type OPCA is different from Déjérine-Thomas type OPCA in the strict sense.

Results

The mean age of onset was 49 (range 35–73 years); seven cases were male and two female. The mean duration of the illness was about 8 years, the longest being 15 years. The initial symptoms were cerebellar ataxia in four cases, parkinsonism in four cases, and orthostatic hypotension in one case. The clinical courses are summarized in Table 1. All but case 1 showed various combinations of cerebellar ataxia, parkinsonism and autonomic failure.

The topography of the degenerative lesions in each case is listed in Table 2. All cases showed considerable degeneration of the olivopontocerebellar system, combined with striatonigral degeneration of varying degree.

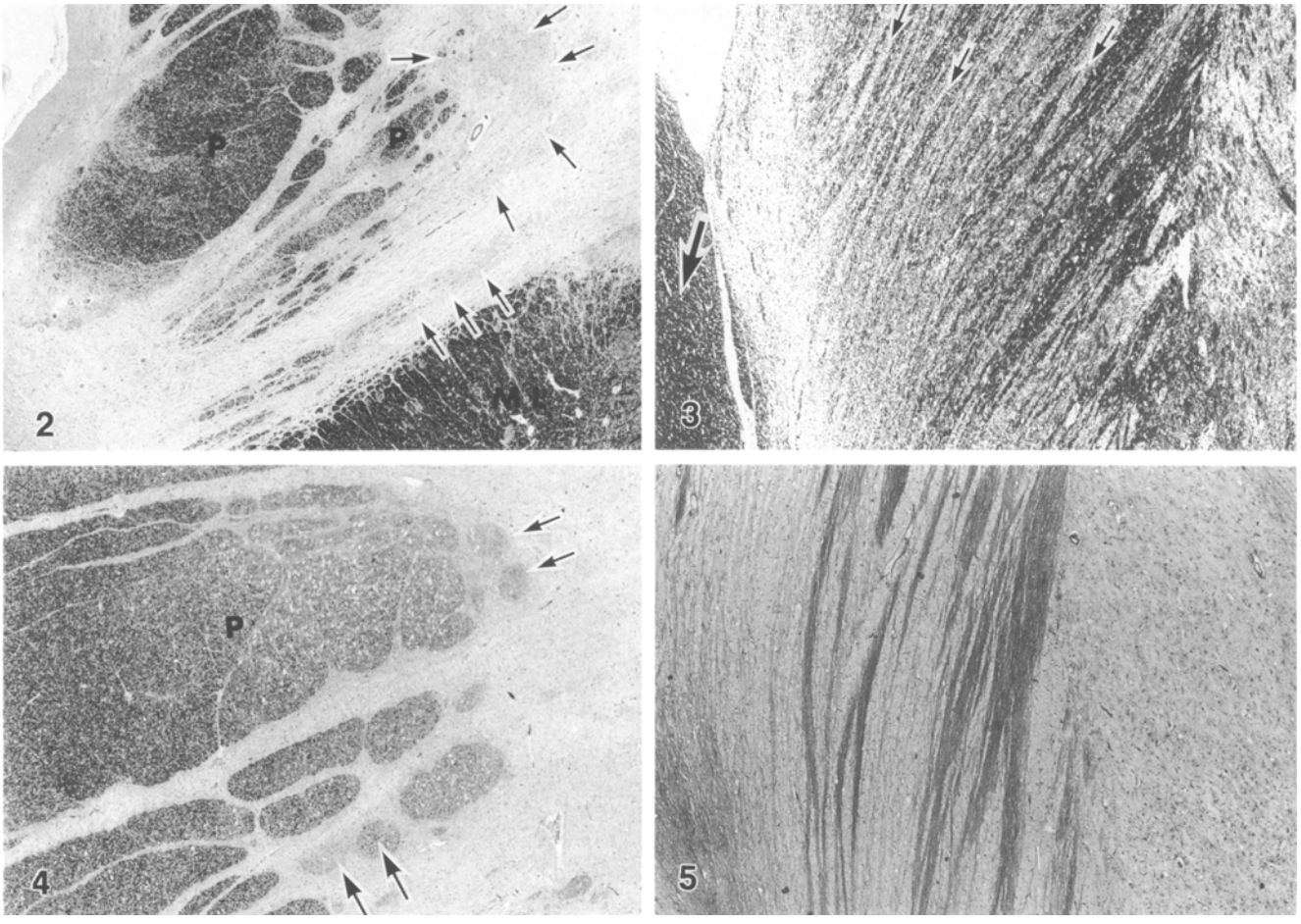

Fig. 2. Transverse section of the pontine basis. Pallor of myelin in some corticopontine bundles (*arrows*). The corticospinal bundles (*P*) and medial leminicus (*ML*) stand out clearly on the background. Case 1. 1% osmium tetroxide fixation. Sudan black B stain

Fig. 3. Transverse section of the pontine basis. Slight pallor of myelin in some corticopontine bundles (*arrows*) and corticospinal tracts (*P*) are spared. Case 3. 1% osmium tetroxide fixation. Sudan black B stain

Fig. 4. Selective loss of myelin in the corticopontine bundles (*arrows*) in a part of the lowermost internal capsule. Case 7. A *large arrow* shows the optic tract. Klüver-Barrera stain

Fig. 5. Isomorphic fibrous gliosis in the corticopontine bundles at the level of the lowermost internal capsule. Case 7. Holzer stain

Table 3. Chief complaints and clinical course

Case no.	Age at death (years)	Sex	Age of onset (years)	Clinical signs
1	53	M	42	Cerebellar · · · · → pyramidal
2	50	F	43	Cerebellar → parkinsonism, pyramidal
3	54	M	44	Cerebellar → orthostatic hypotension, pyramidal
4	50	M	46	Cerebellar → orthostatic hypotension
5	76	M	73	Parkinsonism, orthostatic hypotension
6	61	M	53	Parkinsonism → cerebellar atrophy, pyramidal
7	63	F	51	Parkinsonism → cerebellar atrophy
8	59	M	54	Parkinsonism → orthostatic hypotension pyramidal
9	50	M	35	Orthostatic hypotension → parkinsonism → pyramidal

Cerebellar, Cerebellar signs and symptoms; pyramidal, pyramidal tract sign

Thus, all cases satisfied the criteria for the neuropathology of OPCA or MSA.

Light microscopically, the corticopontine tract was considerably degenerate at the level of the crus cerebri in three cases (Fig. 1), less markedly so in two cases, and was spared in four cases. The tract was more severely affected at the level of the pons than the crus cerebri (Figs. 2, 4). The tract degeneration was also present at the limb of the internal capsule in three cases (Figs. 3, 5).

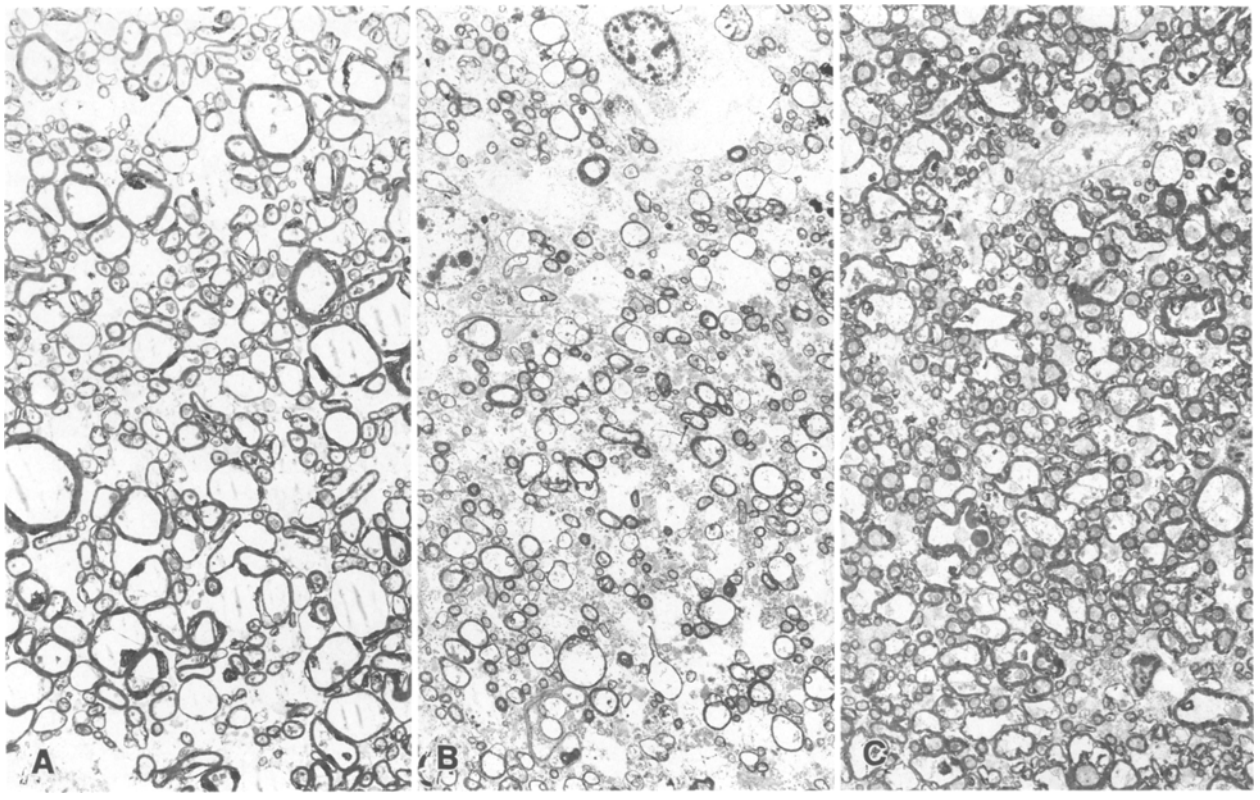

Fig. 6A–C. Electron micrograph of the frontopontine tract at the level of the midbrain. Myelinated fibres are less in number and small. Large fibres are missing associated with astrogliosis (**B**), compared with control (**A**). Myelinated fibres are atrophic but dense in their population, and each axon appears to be encased by a disproportionally thick myelin sheath in dentatorubropallidoluysian atrophy (DRPLA), suggestive of diffuse axonal atrophy (**C**).

In the cases showing degeneration of the tract, the longer the clinical course was, the more severely affected was the corticopontine tract (Table 3). The pontine neurons were completely lost in all cases but case 5.

Ultrastructurally, most myelinated fibres were small and the majority of large myelinated fibres were lost selectively, compared with the control, so that the density of myelinated fibres was greatly decreased (Fig. 6b). However, all myelinated fibres were considerably atrophic and encased by disproportionally thick myelin sheath in the DRPLA case (Fig. 6c).

Morphometrically, most axons of myelinated fibres were attenuated and selective loss of large fibres was predominant in OPCA: the number of fibres over 3 μm in axonal area was 364 of 40000 fibres measured, in comparison with 984 of 40000 in controls. The histogram of frequency distribution of axonal areas of myelinated fibres in OPCA is very similar to that of DRPLA. However, in the latter there seemed to be no loss of fibres and each axon was ensheathed by a relatively thick myelin, suggestive of axonal atrophy (Fig. 7).

Discussion

Degeneration of the corticopontine tract was observed histologically in five of nine cases of OPCA examined. Only a few authors (Noica et al. 1936; Geary et al. 1956) have reported degeneration of the tract. The reason why degeneration of this tract has rarely been reported up to now is considered to be due to considerable distortion of myelin sheaths in a routine paraffin-embedded preparation and the great difficulty of distinguishing each myelinated fibre histologically, since most fibres are too small to identify by light microscopy. The tract appeared to be more severely affected in the longstanding cases than in the cases with a short clinical episode (Table 2). The fact that more severe degeneration of the fibres at the level of the pons than at the level of the cerebral peduncle indicates that degeneration of the fibres may start axodistally.

Morphometrically, the axonal areas were as a whole decreased and large fibres were shifted into the smaller group in the frequency distribution of axonal areas, and in addition, remaining large fibres did show normal cylindrical outline. There were no irregular foldings and loss of circularity of the myelin sheath in transverse sections nor relative thickening of the myelin sheath. Thus, these findings suggest the selective loss of large myelinated fibres but not atrophy of the fibres (Clark et al. 1980; O'Neill et al. 1984; O'Neill and Gilliatt 1987). Although in DRPLA all the fibres were small in axonal areas and its histogram on frequency distribution of myelinated fibres is at first glance virtually identical to that of OPCA, all fibres, small as well as large, were ensheathed by a relatively thick myelin lamellae, so it is reasonable

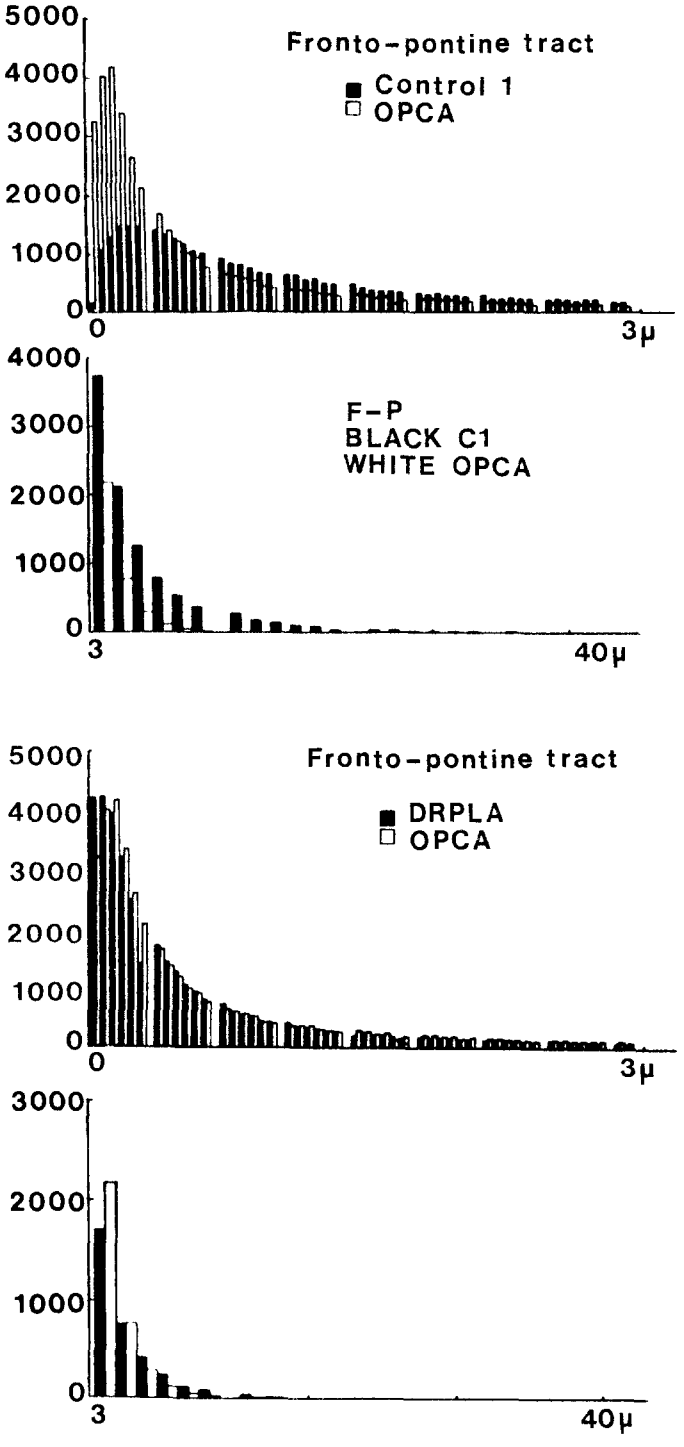

Fig. 7. Histograms of frequency distribution of axonal areas of myelinated fibres. All fibres seem to be atrophic, with low density of myelinated fibres, especially of large fibres in olivopontocerebellar atrophy (OPCA) (*top*). The histogram in OPCA is superficially similar to that of DRPLA (*bottom*)

to consider that all myelinated fibres have undergone axonal atrophy without apparent loss of the fibres. Thus, the degenerative pattern in the corticopontine tract in OPCA differs from that in DRPLA.

It is of great importance whether degeneration of the tract is secondary to neuronal loss of the pontine nuclei (retrograde transsynaptic degeneration) or a primary tract degeneration. In our experience from many autopsies, secondary neuronal loss in the pontine nuclei does not occur for many years after fibre loss in the corticopontine tract. It is thus unlikely that loss of neurons in the pontine nuclei is secondary to fibre loss in the corticopontine tract and represents a secondary antegrade transsynaptic neuronal degeneration. Furthermore, the corticopontine tract appears not to degenerate easily in old infarcts in the pons. Transsynaptic degeneration of the tract and/or neurons occurs readily in young animals but not in the adult, including Man (Goldby et al. 1957; Kupfer et al. 1965). Degeneration of the corticopontine tract in this adult degenerative disease is not, in our view, secondary to neuronal loss in the pontine nuclei.

In this connection, both the primary and secondary neurons usually degenerate in amyotrophic lateral sclerosis but the cases in which only the primary neurons are involved in the degenerative process are very rare. There is no case report which shows involvement of the corticopontine tract only in cerebellar ataxia.

Acknowledgement. The present study was supported in part by a grant from the Ataxia Research Group of the Japanese Welfare and Health Ministry. We are indebted to Miss K. Ito for her skillful technical assistance.

References

Clark AW, Griffin JW, Price DL (1980) The axonal pathology in chronic IDPN intoxication. J Neuropathol Exp Neurol 39:42–55

Eadie MJ (1975) Olivo-ponto-cerebellar atrophy (Déjérine-Thomas type). In: Vinken PJ, Bruyn GW (eds) Textbook of clinical neurology, vol. 25. North-Holland publishing company Amsterdam, pp 415–431

Geary GR, Earl KM, Rose AS (1956) Olivo-ponto-cerebellar atrophy. Neurology 6:218–224

Goldby F (1957) A note on transneuronal atrophy in the human lateral geniculate body. J Neurol Neurosurg Psychiatry 20:202–207

Kupfer C (1965) The distribution of cell size in the lateral geniculate nucleus of man following transneuronal cell atrophy. J Neuropathol Exp Neurol 24:653–511

Noica D, Nicolesco J, Banu E (1936) Contribution a l'étude de l'atrophie olivo-onto-cérébelluse. Rev Neurol (Paris) 66:285–306

O'Neill JH, Gilliatt RW (1987) Adaptation of the myelin sheath during axonal atrophy. Acta Neuropathol (Berl) 74:62–66

O'Neill H, Jacobs JM, Gilliatt RW, Baba M (1984) Changes in the compact myelin of single internodes during axonal atrophy. Acta Neuropathol (Berl) 63:313–318

Oppenheimer DR (1983) Neuropathology of progressive autonomic failure. In: Bannister R (ed) Autonomic failure. Oxford University Press, Oxford, pp 267–283

Oppenheimer DR (1984) Disease of the basal ganglia, cerebellum and motor neurons. In: Adams JM, Corsellis JAM, Duchen LW (eds) Greenfield's neuropathology. E Arnold, London, pp 699–747

Truex RC, Carpenter MB (1969) Human neuroanatomy, 6th edn. Williams and Wilkins, Baltimore, p 578