Virchows Archiv A Pathol Anat (1992) 420:243–252

Virchows Archiv A
Pathological Anatomy and Histopathology

Peculiar axonal debris with subsequent astrocytic response (foamy spheroid body)

A topographic, light microscopic, immunohistochemical and electron microscopic study

Nobutaka Arai[1], Saburo Yagishita[2], Kazuaki Misugi[3], Masaya Oda[4], Kenji Kosaka[5], Toshio Mizutani[6], and Yoshio Morimatsu[1]

[1] Department of Clinical Neuropathology, Tokyo Metropolitan Institute for Neurosciences, 2–6 Musashidai, Fuchu, Tokyo 183, Japan
[2] Department of Pathology, Kanagawa Rehabilitation Centre, Atsugi, Japan
[3] Department of Pathology, Yokohama City University School of Medicine, Yokohama, Japan
[4] Department of Pathology, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan
[5] Department of Neuropathology, Psychiatric Research Institute of Tokyo, Tokyo, Japan
[6] Department of Neuropathology, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

Received March 26, 1991 / Received after revision and accepted August 5, 1991

Summary. Foamy spheroid bodies (FSBs) are described, as newly identified pathological structures occurring in human brain. FSBs favoured the substantia nigra pars reticulata (SNPR) and/or globus pallidus (GP) in degenerative conditions especially postencephalitic parkinsonism, progressive supranuclear palsy, pallido-nigro-luysial atrophy and multiple system atrophy. No FSBs were observed anywhere in the presence of substantia nigra pars compacta (SNPC) degeneration, such as occurs in idiopathic Parkinson's disease, or luysio-pallidal system degeneration, such as found in dentato-rubro-pallido-luysial atrophy or Joseph's disease. FSBs were also occasionally identified in the substantia nigra (SN) and/or GP of aged persons. In addition to SN and GP lesions, FSBs were seen in diffuse axonal lesions of long fibre tracts (the corpus callosum, the superior cerebellar peduncle) after non-missile head injuries, and in peri-infarct lesions. Under the light microscope, FSBs appear as slightly eosinophilic, foamy and nearly round objects with vague outlines, measuring approximately 10–50 μm in diameter. Some FSBs contain coarse, eosinophilic clusters at their periphery. FSB stained black when stained by the Gallyas silver method. Some FSBs were immunohistochemically positive for synaptophysin and 68 kDa neurofilament. Glial fibrillary acidic protein-positive fibres were observed alongside and/or inside some FSBs. Electron microscopically, FSBs were found to consist of collections of neuritic debris containing a variety of dense bodies and a small number of both mitochondria and neurofilaments. Some such collections were surrounded by astrocytic processes. These findings strongly suggest that FSBs are collections of small axonal debris destined for removal by astrocytes in due course. A variety of factors (degeneration of the SNPR and/or the GP, injury, infarction, ageing) seemed to be responsible for the histogenesis of FSBs.

Key words: Axon – Astrocyte – Synaptophysin – Glial fibrillary acidic protein – Foamy spheroid body

Offprint requests to: N. Arai

Introduction

We recently described numerous foamy spheroid bodies (FSBs) in the substantia nigra (SN) of a patient with a narcolepsy-like condition (Arai et al. 1988). In our review of the literature, these FSBs seemed to be identical to structures referred to by the vague term "grumose degeneration" (Trétiakoff 1919), earlier described as a characteristic pathological structure in the SN of patients with parkinsonism. Until the 1950s, this term was sometimes mentioned and interpreted as cellular change of unknown nature (Greenfield and Bosanquet 1953; Greenfield 1958). As far as we know, however, no subsequent studies have been performed focusing on its histopathological nature, and some have misinterpreted the bodies to be single axonal swellings (so-called spheroids) in spite of a lack of evidence (for review, see Arai et al. 1989). Thus, this study was conducted firstly to identify the histological properties of FSBs by means of immunohistochemical and electron microscopic methods and secondly to determine the regions in which FSBs tend to appear in a variety of typical neurological diseases.

Materials and methods

This study was mainly conducted on clinicopathologically established cases (Table 1) exhibiting degeneration in the SN and the basal ganglia. Elderly persons (cases 29–33) were also examined. Two cases of non-missile head injury (Mizutani et al. 1990; Arai et al., in press) and three cases of cerebral infarction were also examined (Table 2).

Each brain was fixed in 10% formalin immediately after autopsy and various regions were cut after 2–4 weeks' fixation. Paraffin-embedded blocks were stained with various methods including haematoxylin and eosin (H & E), luxol fast blue, Nissl, Bodian silver, modified Bielschowsky, Gallyas silver, periodic acid-Schiff (PAS) before/after diastase digestion, Best's carmine, alcian blue and von Kossa. Formalin-fixed frozen sections were used for fat stains including Sudan III, Sudan black B, oil red 0 and Nile blue.

Formalin-fixed paraffin-embedded tissues containing FSBs were immunostained by the SAB method using various antibodies shown in Table 3. Immunostaining procedures were performed us-

Table 1. Clinicopathological summary

Case no.	Age (years)/sex	Diagnosis	SNPC		SNPR		GP	
			Damage	FSB	Damage	FSB	Damage	FSB
1	62/M	IdioP	+++	−	−	−	−	−
2	73/F	IdioP	++	−	−	−	−	−
3	66/M	IdioP	+++	−	−	−	−	−
4	58/M	IdioP	++	−	−	−	−	−
5	56/F	IdioP	++	−	−	−	−	−
6	78/M	PostP	+++	−	+++	**	++	−
7	78/F	PostP	+++	−	+++	*	+	−
8	68/F	PostP	+++	−	+++	*	+	−
9	76/M	VascP	++	−	++	*	−	−
10	72/F	VascP	++	*	+	−	−	−
11	68/F	PNLA[a]	+++	*	+++	***	+++	**
12	50/M	HSCD[b]	++	−	++	**	+	−
13	57/M	HSCD[b]	++	−	+	−	+	−
14	50/M	HSCD[b]	+	−	+	−	+	−
15	63/F	MSA	++	−	+	−	+	−
16	52/M	MSA	++	−	++	**	+	*
17	50/M	MSA	+	−	−	−	−	−
18	69/M	PSP[c]	++	−	++	−	+	−
19	62/F	PSP[c]	++	−	++	**	+	−
20	65/M	PSP[c]	++	−	++	−	+	−
21	63/M	PSP[c]	++	−	++	**	+	−
22	72/M	PSP[c]	++	−	++	**	+	−
23	40/F	JD[b]	++	−	++	−	+	−
24	48/F	JD[b]	+	−	+	−	++	−
25	55/M	DRPLA[d]	−	−	−	−	+++	−
26	24/F	DRPLA[d]	−	−	−	−	+++	−
27	59/M	HC	−	−	−	−	−	−
28	52/M	HC	−	−	−	−	−	−
29	70/F	Cancer	+	−	−	−	+	−
30	77/M	Pneumonia	−	−	+	**	+	*
31	89/M	Pneumonia	+	−	+	−	+	−
32	91/F	Pneumonia	−	−	+	*	+	*
33	99/F	Cancer	+	−	−	−	+	−

IdioP, Idiopathic Parkinson's disease; PostP, postencephalitic parkinsonism; VascP, vascular parkinsonism; PNLA, pallido-nigro-luysial atrophy; HSCD, hereditary spinocerebellar degeneration; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; JD, Joseph's disease; DRPLA, dentato-rubro-pallido-luysial atrophy; HC, Huntington's chorea, SNPC, substantia nigra pars compacta; SNPR, substantia nigra pars reticulata; GP, globus pallidus; FSB, foamy spheroid body; +, mild; ++, moderate; +++, severe; −, unremarkable or not detected; *, small number; **, many; ***, numerous

[a] Kosaka et al. (1981); [b] Iwabuchi et al. (1990); [c] Amano et al. (1990); [d] Iwabuchi et al. (1987)

Table 2. Clinicopathological summary

Case no.	Age (years)/sex	Diagnosis	Location of FSBs
34	78/M	Protracted head[a] injury (22 years)	Corpus callosum
35	51/F	As above[b] (6.5 years)	Superior cerebellar peduncle
36	66/M	Old cerebral infarction	Frontal cortex
37	70/M	Old cerebral infarction	Parietal cortex
38	72/F	Old cerebellar infarction	Cerebellar white matter

[a] Arai et al. (1992); [b] Mizutani et al. (1990)

ing the Histofine SAB-PO Kit (Nichirei, Tokyo, Japan), using 3,3-diaminobenzidine as a chromogen. Counterstaining was performed using methyl green.

For electron microscopic examination fresh samples obtained at autopsy were fixed at 4° C overnight in 3% glutaraldehyde. The samples were post-osmificated, dehydrated and embedded in an epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate.

Results

FSBs are ill-defined, foamy and nearly round objects measuring about 10–50 μm in diameter (Fig. 1A). Such FSBs have often been observed in the substantia nigra pars reticulata (SNPR) and/or the globus pallidus (GP) as described below. Interestingly, FSBs were occasionally observed beneath the pia (Fig. 1B) and along small capillaries (Fig. 1C, D). Some FSBs contained small, eo-

Table 3. Immunohistochemical analysis of foamy spheroid bodies

Antibodies	Source	Dilution	FSBs
Neurofilament-68 kDa (Sigma St. Louis, USA)	Mouse	1: 40	+ (very weak)
Neurofilament-160kDa (Sigma)	Mouse	1: 40	−
Neurofilament-200 kDa (Sigma)	Mouse	1: 40	−
MAP-2 (Sigma)	Mouse	1:200	−
Alpha-tubulin (Sigma)	Mouse	1:200	−
Beta-tubulin (Sigma)	Mouse	1:200	−
Tau (Sigma)	Mouse	1:200	−
Synaptophysin (BMY Mannheim, FRG)	Mouse	1:200	++ (granular)
NSE (Dako Copenhagen, Denmark)	Mouse	prediluted	−
GFAP (Dako)	Rabbit	prediluted	++ (mesh-like)
MBP (BMY)	Rabbit	1:100	−
Human LCA (Dako)	Mouse	prediluted	−
Ferritin (Cosmo Saitama, Japan)	Mouse	1:100	−
HLA-DR (Dako)	Mouse	1:800	−
Transferrin (Dako)	Rabbit	1: 50	−

MAP, Microtubule-associated protein; NSE, neuron specific enolase; GFAP, glial fibrillary acidic protein; MBP, myelin basic protein; LCA, leucocyte common antigen

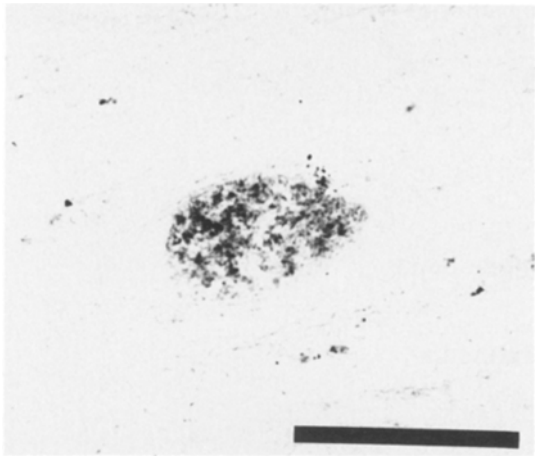


Fig. 2. Gallyas silver method stained FSBs black. ×580; *bar*= 50 μm

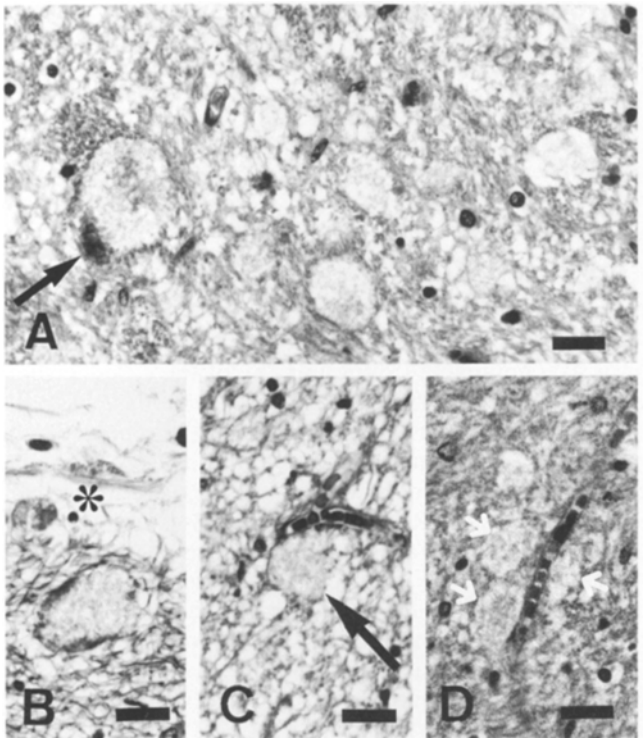


Fig. 1A–D. Light microscopic features of foamy spheroid bodies (FSBs). **A** FSBs are nearly round objects showing foamy, slightly eosinophilic appearances. Some FSBs contained coarse and eosinophilic clusters (*arrow*) in their periphery. Substantia nigra from progressive supranuclear palsy. H & E, ×330; *bar*=30 μm. **B** Some FSBs were noted beneath the subpial region. Mid-brain, *asterisk* indicates subarachnoid space. H & E, ×330; *bar*=30 μm. **C, D** Some FSBs (*white arrows*) were sometimes noted along small capillaries. Substantia nigra. H & E, ×330; *bar*=30 μm

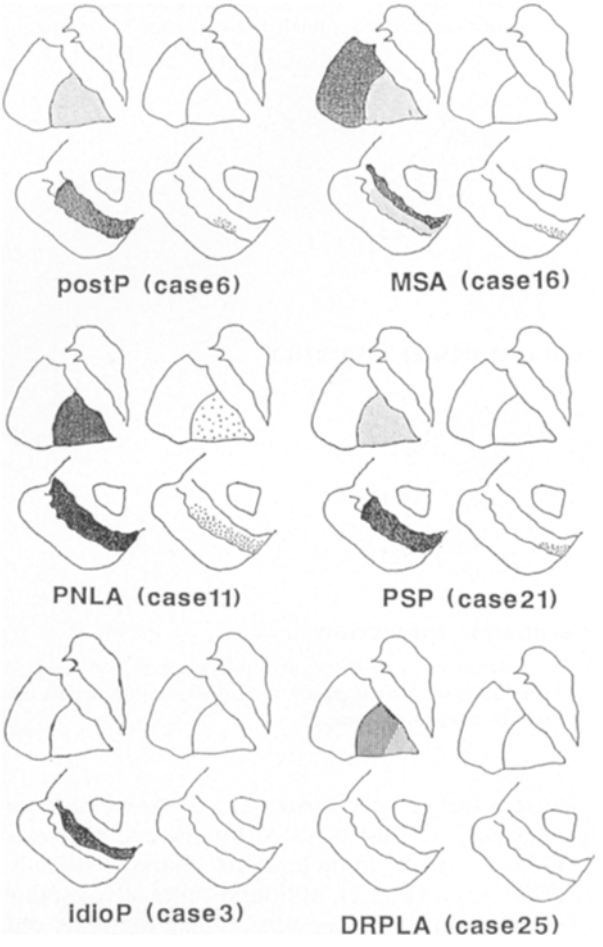
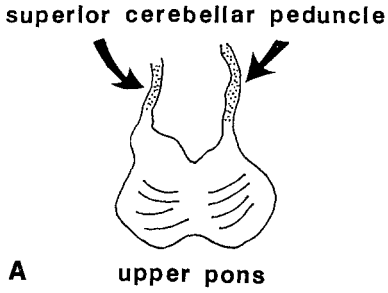


Fig. 3. Representative regional distribution of FSBs. Intensity of degeneration is demonstrated by dark shadow (severe) or light shadow (mild to moderate) in each left side of illustration of the basal ganglia (*top*) and the substantia nigra (*bottom*). *Dots* in each right side represent distributional pattern and amount of FSB in each case. *post*P, Postencephalitic parkinsonism; *MSA*, multiple system atrophy; *PNLA*, pallido-nigro-luysial atrophy; *PSP*, progressive supranuclear palsy; idio*P*, idiopathic parkinsonism; *DRPLA*, dentato-rubro-pallido-luysial atrophy



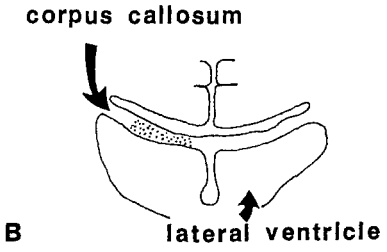
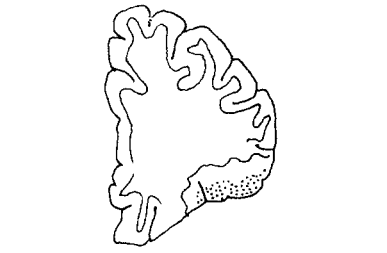


Fig. 4A, B. Illustration of FSBs occurring in cases of non-missile head injuries. *Dots* represent FSBs. **A** Corpus callosum lesion in case 34. **B** Superior cerebellar peduncle lesion in case 35



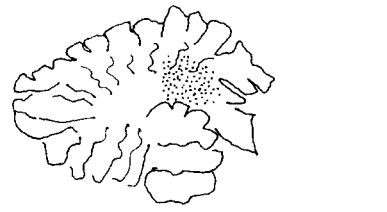


Fig. 5A, B. Illustration of FSBs occurring in cases of old cerebral or cerebellar infarction. **A** Frontal cerebral infarct lesion in case 36. **B** Cerebellar infarct lesion in case 37

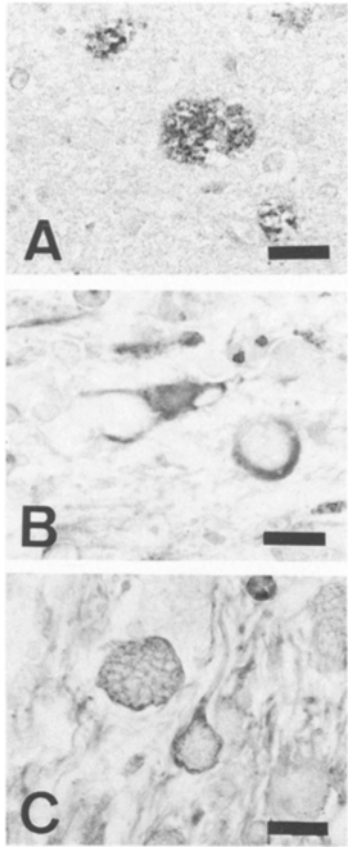


Fig. 6A–C. Immunohistochemical features of FSBs. **A** Some of FSBs stained with anti-synaptophysin monoclonal antibody. Note granular positive pattern. ×330; *bar*=30 μm. **B** Glial fibrillary acidic protein (GFAP) was shown along FSB. A GFAP-positive astrocyte is seen near FSB, ×330; *bar*=30 μm. **C** GFAP was noted not only along FSBs but inside FSBs in a mesh-like appearance. ×330, *bar*=30 μm

sinophilic, relatively coarse clusters (Fig. 1 A) which were weakly PAS-positive (not digested by diastase pretreatment). Gallyas silver impregnation characteristically stained FSBs black (Fig. 2), although other silver stains did not demonstrate argyrophilia. Other methods did not stain FSBs.

In Fig. 3, the typical regional distribution of FSBs was mapped by placing dots on the right side of drawings of the basal ganglia (top) and the SN (bottom), and the degree of degeneration (neuronal loss and gliosis) is indicated by the density of the shadow on the left side of the illustrations. FSBs occurred most frequently in the medial part of the SNPR, especially along the border region between the SNPR and the cerebral peduncle, while few FSBs were seen in the substantia nigra pars compacta (SNPC) in any of the cases, except case 10 (vascular parkinsonism; vascP) and case 11 (pallido-nigro-luysial atrophy; PNLA). FSBs appeared not only in the SNPR but also in the GP (diffusely), though few in number, in cases in which there were a number of FSBs in the SNPR. In summary, FSBs were frequently observed in postencephalitic parkinsonism (postP; 3 of 3 cases, frequently and in great numbers in the SNPR and occasionally in the GP), in the one case of PNLA (numerous in both the SN and the GP), often in progressive supranuclear palsy (PSP; 3 of 5 cases, with many in the SNPR), in multiple system atrophy (MSA; 1 of 3 cases, a small number in both the SNPR and the GP), in hereditary spinocerebellar degeneration (hSCD; 1 of 3 cases, many in the SNPR), vascP (1 of 2 cases, a small number in the SN), elderly persons (2 of 5 cases, occasionally in the SNPR). No FSBs, however, were seen anywhere in another cases, including idiopathic Parkinson's disease, dentato-rubro-pallido-luysial atrophy (DRPLA) or Joseph's disease (JD).

Figure 4 shows the regional distribution of FSBs in

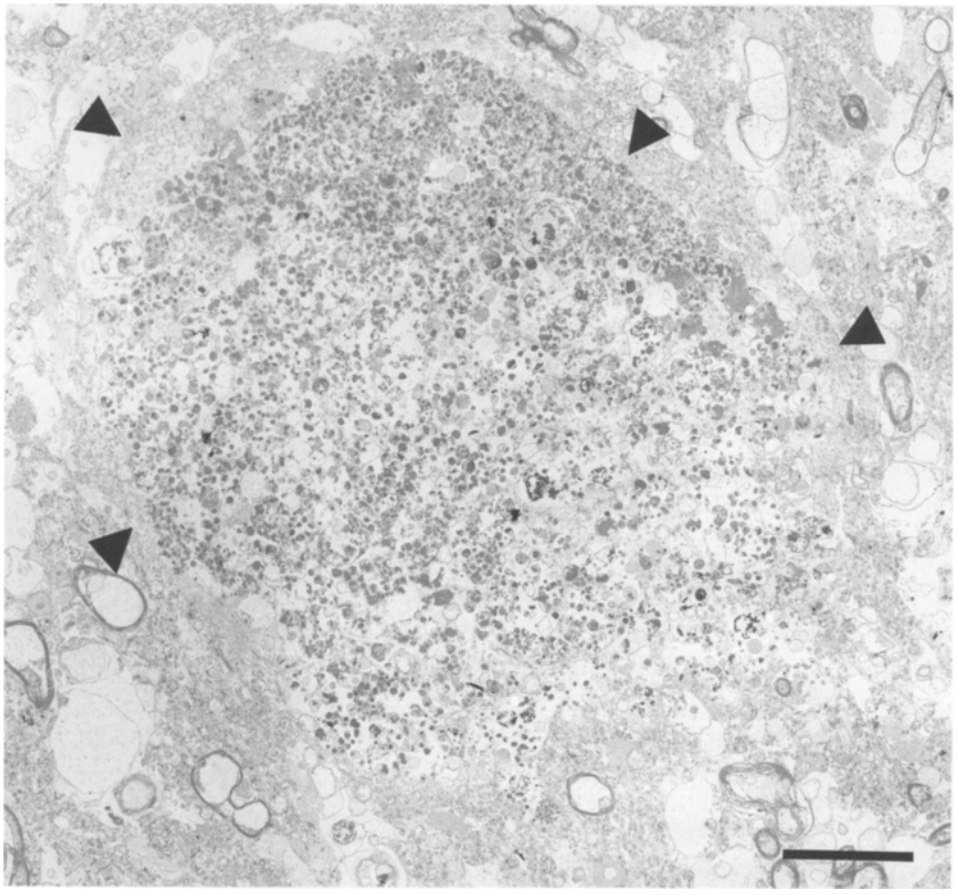


Fig. 7. Electron microscopic profile. FSBs mainly consisted of various appearances of dense bodies. ×3840; *bar* = 5 μm

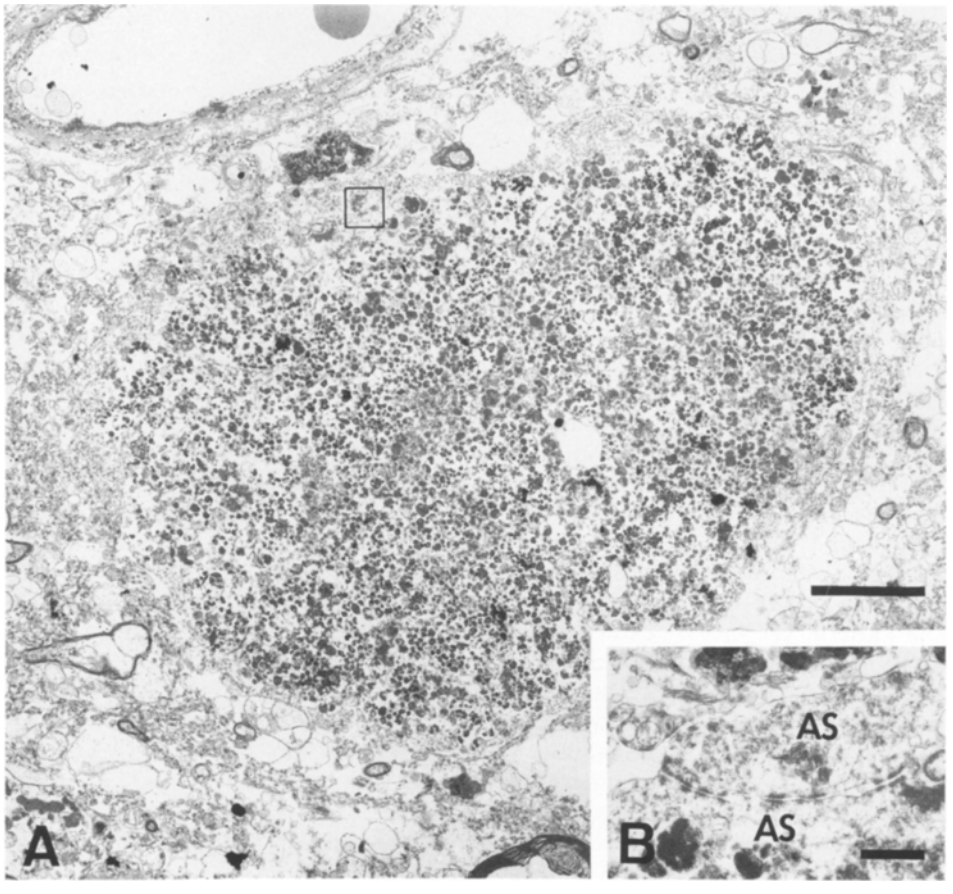


Fig. 8. **A** electron microscopic profile. ×3370; *bar* = 5 μm. **B** High magnification of a square in Fig. 4A. Astrocytic punctate adhesion was focally noted along the periphery of FSB, revealing that such a FSB was a part of the astrocyte (*AS*). ×9470; *bar* = 1 μm

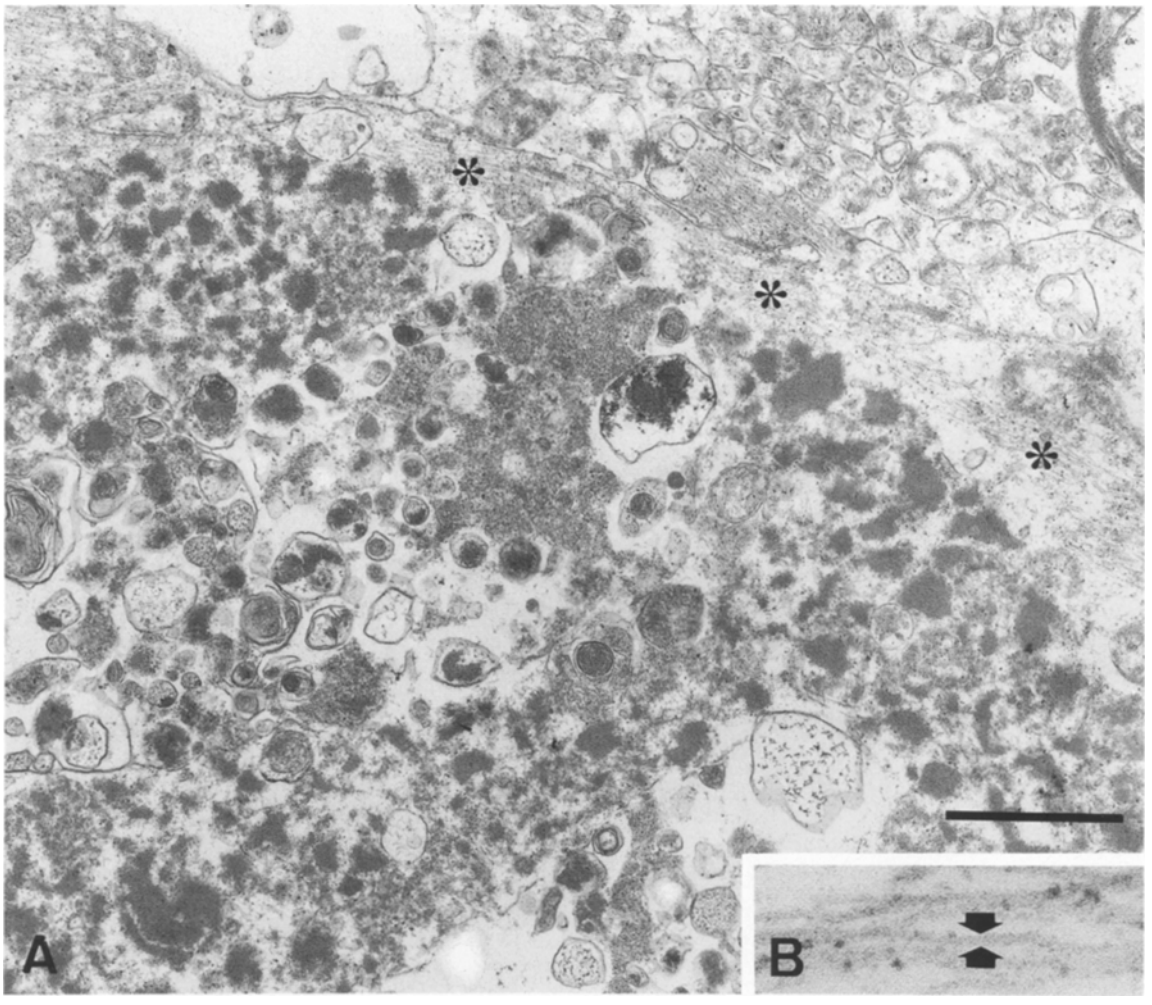


Fig. 9. A Dense bodies in FSBs showed various profiles. Some were strongly condensed and some were relatively amorphous. Bundles of glial fibrils were seen in the periphery of FSBs (*asterisks*). ×27,000; *bar* = 1 μm. **B** High magnification of the glial fibrils. Between *arrows* = 85 nm

two cases of protracted non-missile head injury. FSBs were incidentally observed in diffusely injured axonal lesions in the long tracts, such as the corpus callosum (case 34) and the superior cerebellar peduncle (case 35). Figure 5 shows the appearance of FSBs in old peri-infarct lesions (cases 36 and 37).

FSBs showed immunoreactivities (IR) to neurofilament (NF) 68 kDa, synaptophysin (SYP) and glial fibrillary acidic protein (GFAP). The intensity of 68 kDa NF staining was very weak. SYP-IR showed a granular pattern in some FSBs (Fig. 6A). However, no SYP-IR was found in FSBs in the long tract lesions in cases of non-missile head injury (cases 34 and 35). GFAP, however, exhibited a different staining pattern; GFAP-IR was strongly demonstrated along the margins of the FSBs (Fig. 6B, C) and inside the FSBs in a mesh – like pattern (Fig. 6C).

FSBs showed complex electron microscopic profiles consisting of neuritic and astrocytic elements, as described below. FSBs constituted collections of degenerating debris mainly consisting of a number of various kinds of dense bodies (DB) (Figs. 7, 8A). The DBs varied in shape and ranged from 0.1 to 1.0 μm in diameter (Fig. 9A). Some of the DBs were strongly condensed, while some were amorphous. Most of the DBs were scattered randomly throughout the FSBs, but some DBs were surrounded by a continuous membrane, though the number varied (Fig. 10A, B). In addition to these DBs, a very small number of mitochondria was also seen in the FSBs (Fig. 10C). Continuous myelinated or non-myelinated membranes were not noted along any of the FSBs, but several areas of the periphery of the FSBs were covered by a membrane (Fig. 9A). Inside this membrane, bundle-like aggregates of astroglial fibrils (85 nm in diameter) were observed (Fig. 9B). Astrocytic punctate adhesions were also observed in some peripheral regions of the FSBs (Fig. 8B). In other words, FSBs were surrounded by astrocytic processes or perikarya. Possible early FSBs (Fig. 11) consisted of such DBs and a small number of NFs but no astrocytic elements were associated with these early FSBs. Late FSBs (Figs. 12, 13), which mainly consisted of strongly condensed DBs, were surrounded by dense bundles of astroglial fibrils.

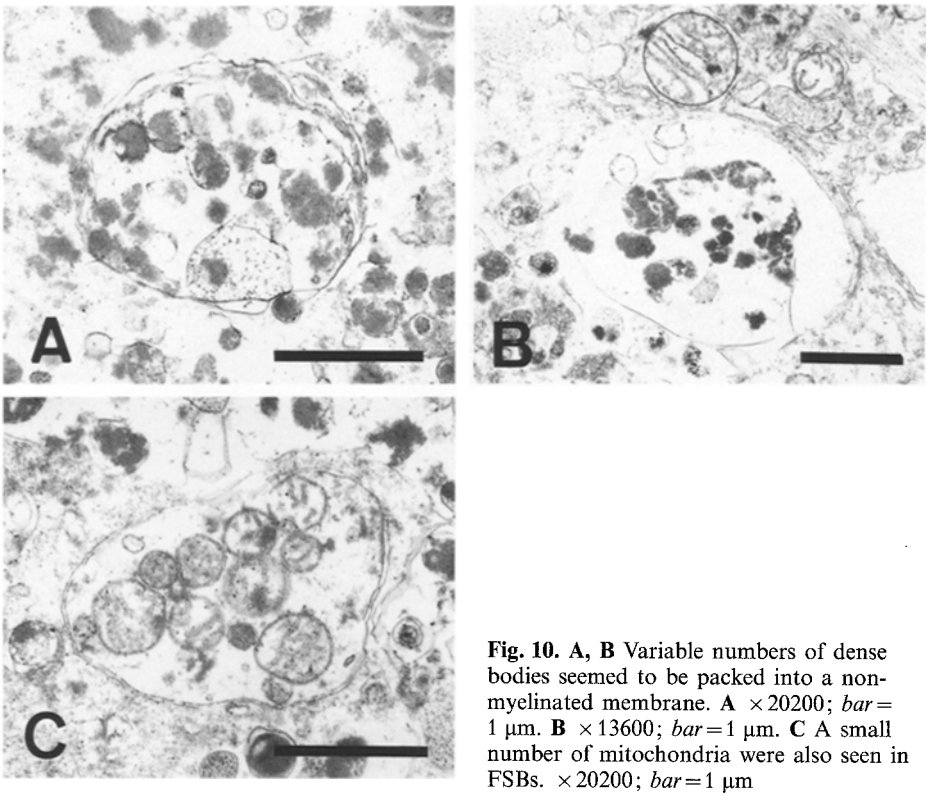


Fig. 10. A, B Variable numbers of dense bodies seemed to be packed into a non-myelinated membrane. **A** ×20200; *bar* = 1 μm. **B** ×13600; *bar* = 1 μm. **C** A small number of mitochondria were also seen in FSBs. ×20200; *bar* = 1 μm

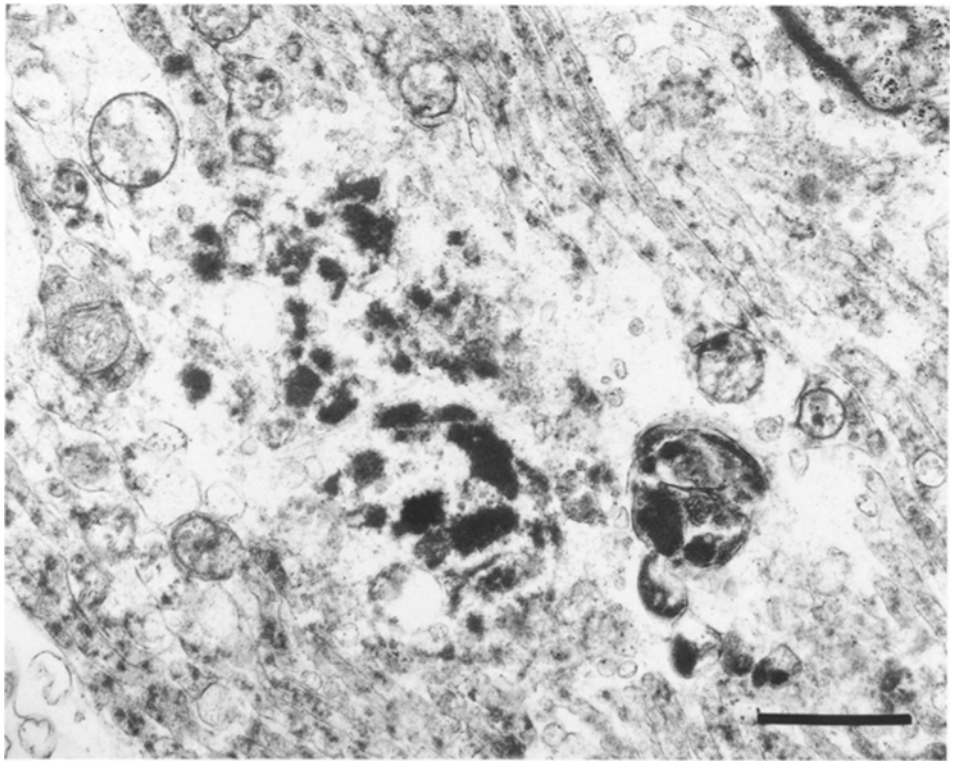


Fig. 11. Possible early FSB, consisting of dense bodies and a small number of neurofilaments. ×20000; *bar* = 1 μm

Discussion

FSBs are quite different from so-called spheroids (axonal swellings), which are a familiar form of axonal pathology. Spheroid is a term referring to a single axon which has become pathologically or physiologically swollen. Light microscopically, spheroids are homogeneously eosinophilic and exhibit compact argyrophilia in response to Bodian staining. FSBs, however, are foamy and amorphous and do not exhibit argyrophilia when exposed

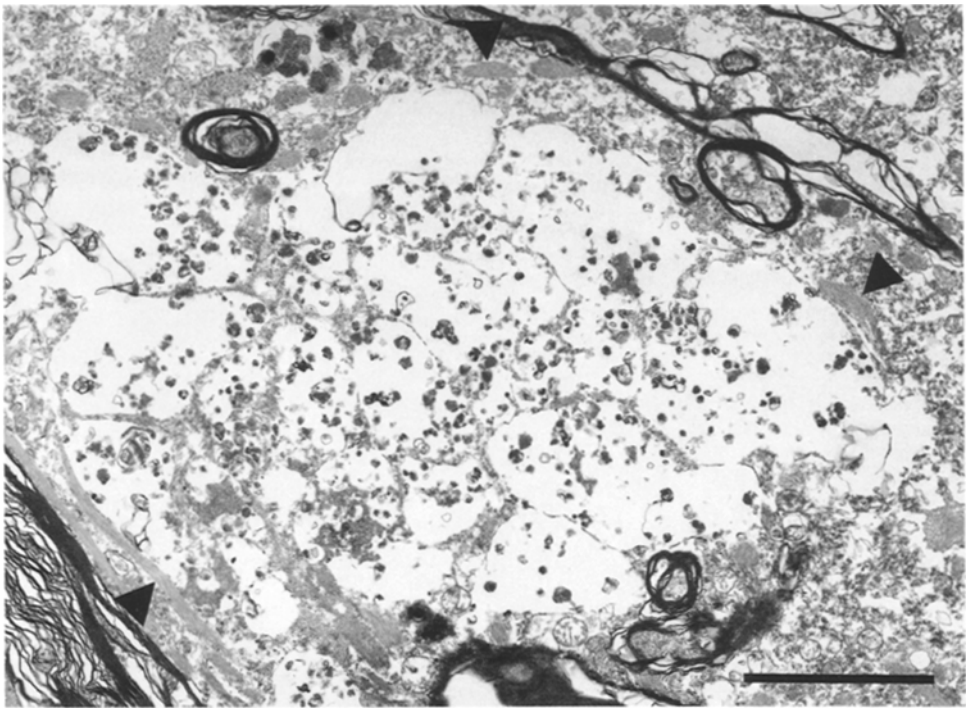


Fig. 12. Late FSB. Note dense glial bundles (*arrowheads*) along and/or inside FSBs. ×5870; *bar* = 5 μm

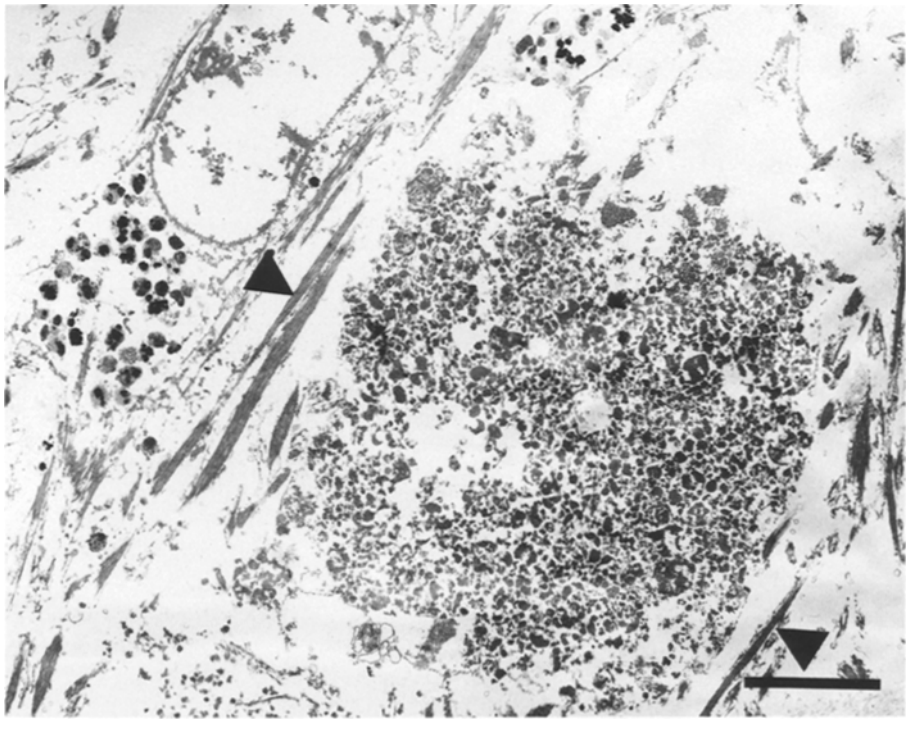


Fig. 13. Late FSB. An astrocytic nucleus and dense astroglial bundles (*arrowheads*) were seen. ×3590; *bar* = 5 μm

to the Bodian stain. The Gallyas silver method, however, stained the FSBs strongly but failed to stain typical spheroids (data not shown). Electron microscopic studies have shown that spheroids are usually surrounded by a continuous non-myelinated or myelinated membrane, even in autopsy material (Lampert 1967; Yagishita 1978). No continuous limiting membranes, however, were noted along any of the FSBs examined here. Hence, FSBs seem not to consist of single axonal swellings but to be collections of degenerating axonal debris, as demonstrated in a possible early FSB. The electron microscopic content of the FSBs was different from that of spheroids, which consist of an accumulation of a variable number of NFs, interconnected tubules, layered membranes, grouped mitochondria and degenerating organelles (Lampert 1967; Yagishita 1978), although a

very small number of NFs and mitochondria were noted in the FSBs. The DBs seen in FSBs have not been identified in spheroids. The source of the DBs in FSBs is unknown at present and may be degenerated axonal organelles.

Characteristically some FSBs reacted with an antibody to SYP, a major synaptic vesicle protein present in the axon terminals of the mammalian brain (Wiedenmann and Franke 1985). Hence, demonstration of SYP-IR in FSBs strongly suggests their neuritic, probably axonal origin. Two of the specimens examined here were obtained from long tract lesions after typical non-missile head injury causing diffuse axonal (of course not dendritic) injury. It is quite reasonable to assume that the FSBs occurring in such long tract lesions originate from injured axons, although, of course, no SYP was found in the FSBs in the long tracts. This evidence strongly supports the hypothesis of an axonal origin of FSBs. Furthermore, FSBs contained no IR to MAP-2, one of the microtubule-binding proteins present in both neural somas and dendrites and absent in axons (Bernhardt and Matus 1984). No expression of MAP-2 in FSBs suggests a paucity of dendritic elements. Taking this into consideration, most FSBs may occur in different parts of axons. In this respect, FSBs are also different from dystrophic axons, a special type of spheroid occurring exclusively in axon terminals (Lampert 1967; Seitelberger 1973).

It is also interesting that GFAP-positive fibres were seen alongside FSBs as though FSBs were surrounded by astrocytes. The present electron microscopic study confirmed this. On the other hand, FSBs did not display any IR to either oligodendroglial markers, including transferrin (Connor and Fine 1986), or reactive microglial markers, including leucocyte common antigen (McGeer et al. 1989) and HLA-DR (McGeer et al. 1988). Thus, it appears that FSBs are related to astrocytes, and not to oligodendroglia or microglia. Some FSBs were noted in the subpial region and along the veins where astrocytic processes are plentiful. This provides additional evidence that FSBs are closely associated with astrocytes. It is hypothesized that FSBs represent axonal debris destined to be cleared away in due course by astrocytes.

When clinicopathological reports were reviewed, it was found that FSB-like structures in the SN and/or the GP have at times been described in cases of postP (Trétiakoff 1917; Greenfield and Bosanquet 1953), PSP (Steele et al. 1964), PNLA (Takahashi et al. 1977; Kosaka et al. 1981), amyotrophic lateral sclerosis-Parkinson-dementia complex (Shiraki and Yase 1975), an unusual narcolepsy-like case (Arai et al. 1988). Regarding this point, our study clearly confirmed that FSBs favour the SNPR and the GP in neurodegenerative diseases. Such appearance of FSBs is considered pathognomonic of SNPR-GP dysfunction in such neurodegenerative diseases. Luysio-pallidal dysfunction, nevertheless, does not seem to be responsible for the appearance of FSBs in the SN or GP, since no FSBs have been observed in cases of DRPLA or JD, both of which are characterized by marked luysio-pallidal system degeneration. Nor were FSBs detected anywhere in idiopathic Parkinson's disease exhibiting SNPC degeneration, suggesting that primary SNPC degeneration is not responsible for the development of FSBs in the SN or GP. In cases of MSA with striatonigral degeneration, however, a variable number of FSBs are sometimes found in the SNPR and in the GP. The FSBs in the SN and the GP in cases of SND are thought to be by-products of degenerating efferents from the putamen to the SNPR passing through the GP. Thus, in addition to the possibility of SNPR-GP dysfunction, FSBs may be produced in secondary GP and SNPR degeneration in association with degeneration of putaminal efferents to the SNPR passing through the GP.

The precise mechanism of the development of FSBs is still unknown. Considering the fact that FSBs appear under a variety of circumstances including infectious disease (postP), system degenerations (PNLA, MSA, hSCD), multiple "degenerative" disorders (PSP), vascular disorders (vascP), normal ageing, injury and infarction, heterogeneous factors are thought to be responsible for their development.

Acknowledgements. The authors wish to express appreciation to Dr. N. Amano and Dr. K. Iwabuchi for providing some of the cases; to Ms R. Umitsu for the immunohistochemical technique; to Mr. Y. Ito, Ms H. Eguchi and Mr. T. Ohyoshi for the electron microscopy technique; and to Ms. K. Suzuki for assistance with the photography.

References

Amano N, Yagishita S, Yokoi S (1990) Progressive supranuclear palsy. On the neurofibrillary tangles observed in Ammon's horn and cerebral cortices. Neuropathology 10:83–95

Arai N, Honda Y, Amano N, Yagishita S, Misugi K (1988) Foamy spheroid bodies in the substantia nigra: report of an unusual case with recurrent attacks of peculiar twilight state. J Neurol 235:330–334

Arai N, Yagishita S, Amano N, Iwabuchi K, Misugi K (1989) "Grumose degeneration" of Trétiakoff. J Neurol Sci 94:319–323

Arai N, Nishimura M, Oda M, Morimatsu Y (1992) A necrobiotic form of astrocyte appeared in a case of non-missile head injury – an immunohistochemical study. Neuropathology (in press)

Bernhardt R, Matus A (1984) Light and electron microscopic studies of the distribution of microtubule-associated protein 2 in rat brain: a difference between the dendritic and axonal cytoskeletons. J Comp Neurol 226:203–221

Connor JR, Fine RE (1986) The distribution of transferrin immunoreactivity in the rat central nervous system. Brain Res 368:319–328

Greenfield JG (1958) System degenerations of the cerebellum, brain stem and spinal cord. In: Greenfield JG, Blackwood W, et al. (eds) Greenfield's neuropathology, 1st edn. Arnold, London, pp 529–549

Greenfield JG, Bosanquet FD (1953) The brain-stem lesions in parkinsonism. J Neurol Neurosurg Psychiatry 16:213–226

Iwabuchi K, Yagishita S (1990) Re-examination of autosomal dominant hereditary cerebellar ataxia with the degeneration in olivo-ponto-cerebellar system. Shinkei Kenkyu no Shinpo (Adv Neurol Sci) 34:134–147

Iwabuchi K, Amano N, Yagishita S, Sakai H, Yokoi S (1987) A clinicopathological study on familial cases of dentatorubropallidoluysial atrophy (DRPLA) (in Japanese). Rinsho Shinkei (Clin Neurol) 27:1002–1012

Kosaka K, Matsushita M, Oyanagi S, Uchiyama S, Iwase S (1981) Pallido-nigro-luysial atrophy with massive appearance of corpora amylacea in the CNS. Acta Neuropathol (Berl) 53:169–172

Lampert PW (1967) A comparative electron microscopic study of reactive, degenerative, regenerating and dystrophic axons. J Neuropathol Exp Neurol 26:345–368

McGeer PL, Itagaki S, Boyes BE, McGeer EG (1988) Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology 38:1285–1291

McGeer PL, Akiyama H, Itagaki S, McGeer EG (1989) Immune system response in Alzheimer's disease. Can J Neurol Sci 16:516–527

Mizutani Y, Hayakawa K, Takizawa T, Matsumoto M, Morimatsu Y (1990) Non-missile head injury: report of a patient surviving for 6 years. Neuropathol Appl Neurobiol 16:431–435

Seitelberger F (1973) Neuropathological conditions related neuroaxonal dystrophy. Acta Neuropathol (Berl) [Suppl V]:17–29

Shiraki H, Yase Y (1975) Amyotrophic lateral sclerosis in Japan. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology, vol 22. North-Holland, Amsterdam, pp 353–419

Steele JC, Richardson JC, Olszewski J (1964) Progressive supranuclear palsy. Arch Neurol 10:333–359

Takahashi K, Nakashima R, Takao T, Nakamura H (1977) Pallidonigro-luysial atrophy associated with degeneration of the centrum medianum: a clinicopathologic and electronmicroscopic study. Acta Neuropathol (Berl) 37:81–85

Trétiakoff C (1919) Étude histopathologique du locus niger dans 54 cas de maladies du systeme nerveux. In: Contribution à l'étude de l'anatomie pathologique du locus niger. Thesis, Paris, pp 29–56

Wiedenmann B, Franke WW (1985) Identification and localization of synaptophysin, an integral membrane glycoprotein of Mr 38000 characteristic of presynaptic vesicles. Cell 41:1071–1028

Yagishita S (1978) Morphological investigations on axonal swellings and spheroids in various human diseases. Virchows Arch [A] 378:181–197