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Thorn-shaped astrocytes: possibly secondarily induced tau-positive glial fibrillary tangles

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Abstract Argyrophilic and tau-positive abnormal structures occurring in glial cells are called glial fibrillary tangles. In the astrocyte, a conspicuous tau-positive structure is known to appear in progressive supranuclear palsy (PSP). In this report, another type of argyrophilic and tau-positive astrocytes is reported. The morphology of this new type is quite different from that of the previously reported tau-positive astrocyte in PSP and they are designated here as thorn-shaped astrocytes (TSA). TSA have an apparently argyrophilic cytoplasm with a few short processes and often have a small eccentric nucleus, whose appearance resembles that of a reactive astrocyte. Immunohistochemically, TSA are positive to anti-tau antibodies but are negative for ubiquitin. Simultaneous immunostaining revealed the coexistence of tau and glial fibrillary acidic protein epitopes in the same cytoplasm. Electron microscopically, bundles of 15-nm straight tubules were included in the cytoplasm together with abundant glial filaments. In the vicinity of a cluster of TSA, related structures of perivascular or subpial tau-positive linings, which correspond to astrocytic end-feet, are sometimes observed. In almost all cases, a few TSA are generally located in a confined area of subpial and subependymal regions. Although TSA appear to be intimately associated with some diseases, they are also found in a wide range of cytoskeletal disorders including the aged brain with neurofibrillary tangles. TSA are presumed to be a secondarily induced product in relation to astrocytic reaction.

Key words Thorn-shaped astrocyte · Glial fibrillary tangles · Tau · Astrocyte · Straight tubules

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Introduction

Recently, the observation of tau-positive abnormal structures in glial cells, called glial fibrillary tangles (GFT), was reported in some cytoskeletal disorders [2, 13, 14]. GFT found in oligodendroglia are referred to as 'coiled bodies' [3] or 'oligodendroglial microtubular masses' [16] and are reported to appear in considerable numbers in dementia with argyrophilic grains [3, 10], progressive supranuclear palsy (PSP) [16], corticobasal degeneration [9, 15] or subacute sclerosing panencephalitis (SSPE) [11, 12]. Tau-positive astrocytes are also reported in PSP and have been described as 'tufts of abnormal fibers ' [7] or 'star-like tufts of fibers' [17, 18] according to their conspicuous features. These tau-positive astrocytes are regarded to appear almost exclusively in PSP, with the frontal cortex or striatum as their preferential site. We noted another type of tau-positive astrocytes, which morphologically differ from 'tufts of abnormal fibers'. Our survey of this new type of tau-positive astrocytes in various diseases revealed their presence in a wide range of cytoskeletal disorders. We conducted immunohistochemical and electron microscopical studies to clarify the features of this type of astrocytes. We designated this new type of tau-positive astrocytes as thorn-shaped astrocytes (TSA), while we refer to 'tufts of abnormal fibers' as tuft-shaped astrocytes.

Materials and methods

Samples from TSA-positive cases were subjected to morphological examination. These included one each of postencephalitic parkinsonism of Economo-type (Economo) (84-year-old male), dementia pugilistica (77-year-old male), PSP (63-year-old male) and senile dementia of Alzheimer's type (SDAT) (77-year-old female). Formalin-fixed and paraffin-embedded 10-mμ sections including TSA-positive areas were stained with hematoxylin-eosin (H & E), Holzer, conventional Bodian, and modified Gallyas-Braak (G-B) methods [4, 10]. Additionally, TSA were compared with another type of GFT, tuft-shaped astrocytes and coiled bodies in oligodendroglia. The latter two types were found in cases of PSP. Morphological information as to tau pathology was obtained from sections stained by procedures described below.

For immunohistochemical examination, a small brain block from the hippocampal-head region of one case each of PSP (66-year-old male) and of diffuse Lewy body disease (DLBD) (78-year-old male) was obtained at autopsy and fixed in 4% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4 (postmortem delay 4 and 4.5 h, respectively). The block was cut into 30-μm sections on a freezing microtome. The sections were incubated with the primary antibodies overnight and then incubated with a secondary biotinylated antibody followed by the reaction with diaminobenzidine (DAB) containing nickel ammonium sulfate. The primary antibodies for tau were: Alz-50 (1:200, mouse monoclonal, 1–10); M4 (1:1000, mouse monoclonal, 231); human-tau (pool 2) (1:50000, rabbit polyclonal, 299–385); C5 (1:1000, mouse monoclonal, 396); and tau6 (1:500, rabbit polyclonal, 420–429). M4 and C5 recognize the proline-directed phosphorylation sites in tau. The last number inside the parentheses represents the amino acid sequence of each tau epitope according to the numbering system of human tau presented by Goedert et al. [6]. Antibodies against ubiquitin (1:1000, rabbit polyclonal, Dako), DF2 (1:200, mouse monoclonal to ubiquitin), glial fibrillary acidic protein (GFAP; 1:10000, mouse monoclonal), neurofilament (NF) 200K (1:50, rat monoclonal), microtubule-associated protein (MAP) 1 (1:1000, mouse monoclonal, Sigma), MAP 2 (1:1000, mouse monoclonal, Sigma), and MAP 5 (1:1000, mouse monoclonal, Chemicon) were also used. Paraffin sections from one case each of Economo (midbrain section from the 84-year-old male) and dementia pugilistica (temporal section from the 77-year-old male) were also subjected to immunostaining using the series of tau antibodies.

For double immunostaining, serial sections from the hippocampal-head region of the PSP case in the 66-year-old male were used. In the first cycle, sections were stained with Alz-50 (mouse IgM). The nickel-intensified DAB reaction yielded a dark-purple precipitate in the first cycle. Following treatment with 0.5% H_2O_2 solution in PBS for 30 min, sections were incubated with anti-GFAP (rabbit) or anti-C4d (mouse IgG) antibodies. The second immunohistochemical cycle was carried out similarly to the first except that nickel ammonium sulfate was eliminated from DAB solution, yielding a yellow precipitate in the second cycle [1].

For electron microscopic examination, a small block from the hippocampal region in one case each of DLBD (78-years-old male) and Pick's disease (67-year-old male) was obtained at autopsy and fixed with 0.05% glutaraldehyde, 3% paraformaldehyde, and 0.2% picric acid in 0.1 M phosphate buffer, pH 7.4 (postmortem delay, 4 and 6 h, respectively). The blocks were cut into 50-μm sections on a vibratome, and the sections with and without staining by the modified Gallyas-Braak method were embedded in epoxy resin. Sections of 30 μm in thickness from the same blocks were pretreated with 0.1% DMSO followed by 0.1% Triton X-100 and then incubated with Alz-50 for 3 days at 4°C, and visualized by avidin-biotin method using DAB as the chromogen. The sections were osmified and embedded in Epon. Ultrathin sections with heavy mental staining were observed with a JEOL-100CX electron microscopy.

For the survey of the incidence of TSA in various diseases, formalin-fixed and paraffin-embedded 10-μm sections of cerebral hemisphere through the hippocampal region and, additionally, sections of the involved area in each case, were subjected to study. Modified G-B method was used for the study because it most clearly revealed the TSA. The diagnosis (number of cases) was as follows: Alzheimer's disease (AD; 8 cases), SDAT (10 cases), dementia pugilistica (8 cases), Economo (4 cases), myotonic dystrophy (1 case), SSPE with (2 cases) and without neurofibrillary tangles (NFT; 2 cases), PSP (8 cases), corticobasal degeneration (3 cases), Pick's disease with (8 cases) and without Pick bodies (7 cases), dementia with argyrophilic grains (3 cases), DLBD (4 cases), Parkinson's disease (3 cases), hepatic encephalopathy with Alzheimer type II glia (3 cases), oligodendroglioma grade II (2 cases), astrocytoma grade II (2 cases), herpes simplex encephalitis (3 cases), adrenoleukodystrophy (3 cases), tuberous sclerosis (1 case) and aged brain without central nervous system involvement (12 cases).

The study of cases of dementia pugilistica was confined only to the temporal region. In all cases of Economo there was a clinical history of over 50 years. The diagnosis in all cases examined had been corroborated by the findings of neuropathological evaluation.

Results

Morphology and distribution

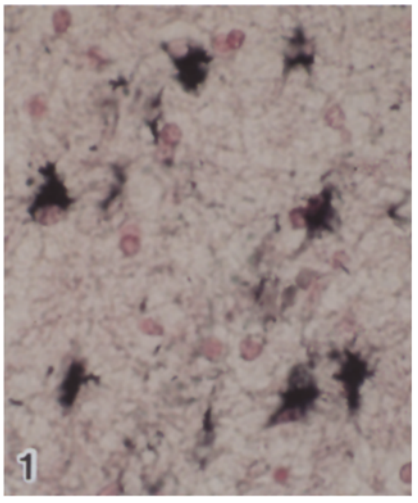
TSA could be visualized by conventional Bodian method but were not visualized by H&E. Modified G-B method, which most clearly reveals all types of GFT, also clearly revealed the astrocytic appearance of TSA. TSA showed conspicuous cytoplasm with a few short and thick processes. The cytoplasm showed partial or total argyrophilia and often contained a relatively clear eccentric nucleus (Fig. 1). Thus, the morphological features resembled those of reactive astrocytes. Such an appearance is quite different from that of tuft-shaped astrocytes in PSP, which are characterized by many fine radiating fibers but no apparent cytoplasm (Fig. 2). Many argyrophilic 'coiled bodies' [3], whose appearance also differed from that of TSA, were scattered predominantly in the white matter in PSP. These have been identified as oligodendroglia by simultaneous immunostaining [16], and we also confirmed their oligodendroglial origin (see Fig. 6). Hitherto, three types of argyrophilic and tau-positive 'tangles' could be differentiated in GFT.

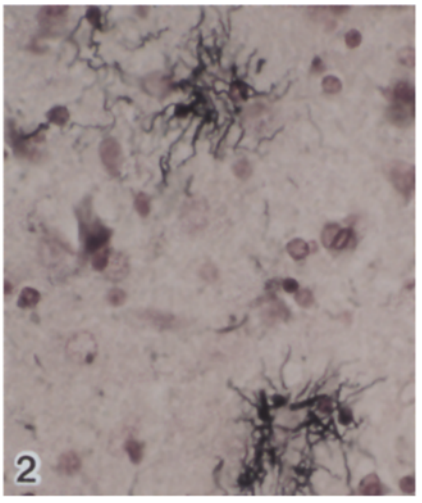
TSA differ from tuft-shaped astrocytes not only in their morphology but also in their distribution in the brain. Except for the occasional presence in the deep cortical layer, TSA were generally confined to the subpial and subependymal regions of the gray and white matter. They were frequently found in the clefts of gyri as well as in the basal brain and brain-stem (see Fig. 7). The occurrence of TSA coincides well with the distribution of prominent marginal gliosis. Holzer staining revealed gliosis in the same areas in which TSA were distributed. In contrast, tufts-shaped astrocytes were scattered throughout all of the cortical layers of the frontal lobe, striatum and other gray matter in cases of PSP, but they were found seldom in the white matter.

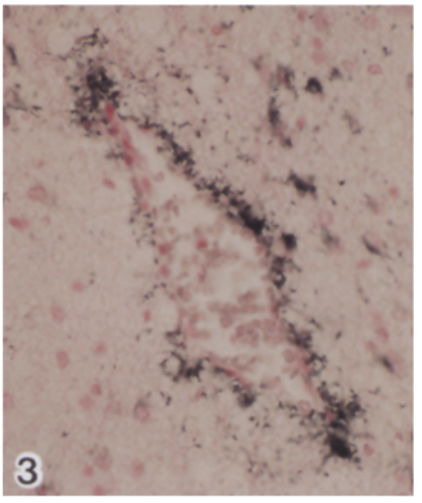
In the vicinity of a cell cluster of TSA, argyrophilic and tau-positive perivascular (Fig. 3) or subpial (Fig. 4, arrows) irregular linings were sometimes observed. Based on their features, these TSA-related structures are thought to correspond to the astrocytic end-feet.

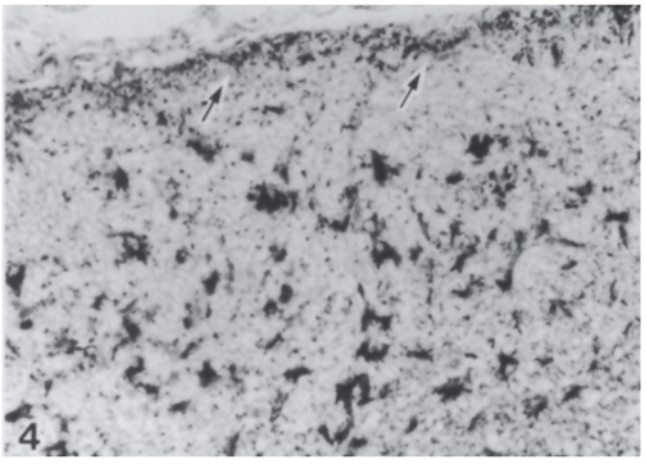
Immunohistochemistry

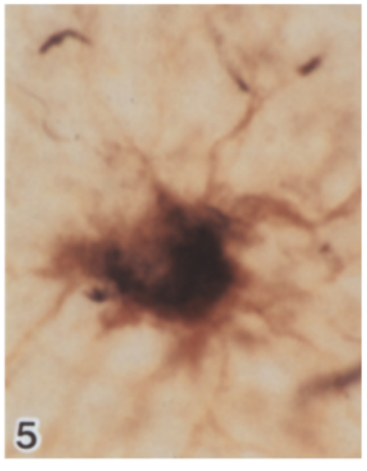
Immunohistochemically, the TSA were reactive to all of the anti-tau antibodies examined, but were negative for ubiquitin, NF 200K and MAP 1, 2 and 5. Small cells presented tau-positive cytoplasm with a few short and thick processes, and the reactive site ranged from being ubiquitous to representing only a part of the cell bodies and processes (Fig. 4). Thus, the tau-positive astrocytes showed

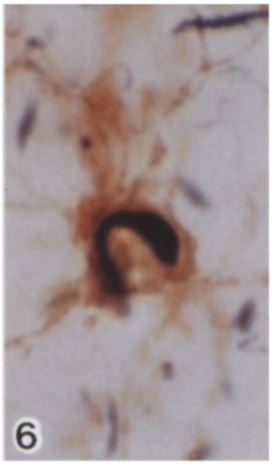


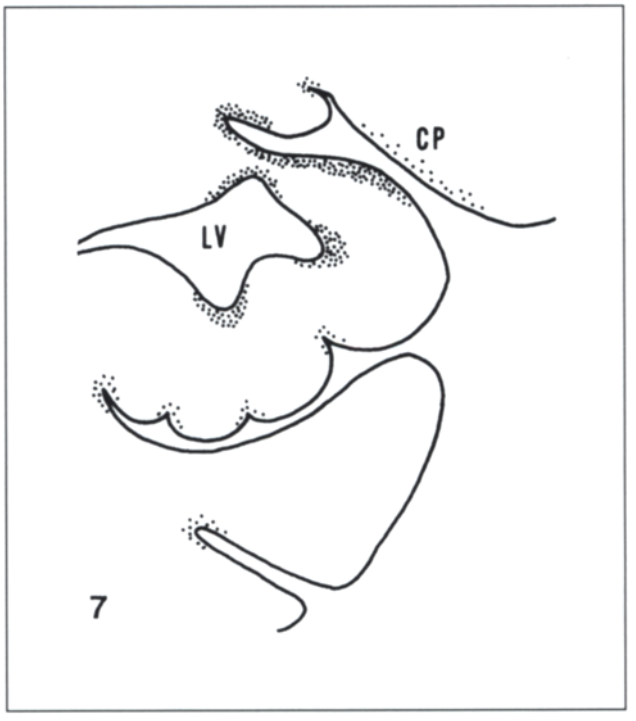












Figs. 1–3 Micrographs of materials treated with modified Gallyas-Braak (G–B) method counterstained with Kernechtrot

Fig. 1 Subependymal white matter of senile dementia of Alzheimer type. Thorn-shaped astrocytes (TSA) have prominent argyrophilic cytoplasm and a few short processes with an occasional eccentric small clear nucleus, and their appearance resembles that of a reactive astrocyte. × 520

Fig. 2 Frontal cortex of progressive supranuclear palsy. Unlike TSA, tuft-shaped astrocytes exhibit no apparent cytoplasm but have tufts of argyrophilic long fine radiating fibers. × 520

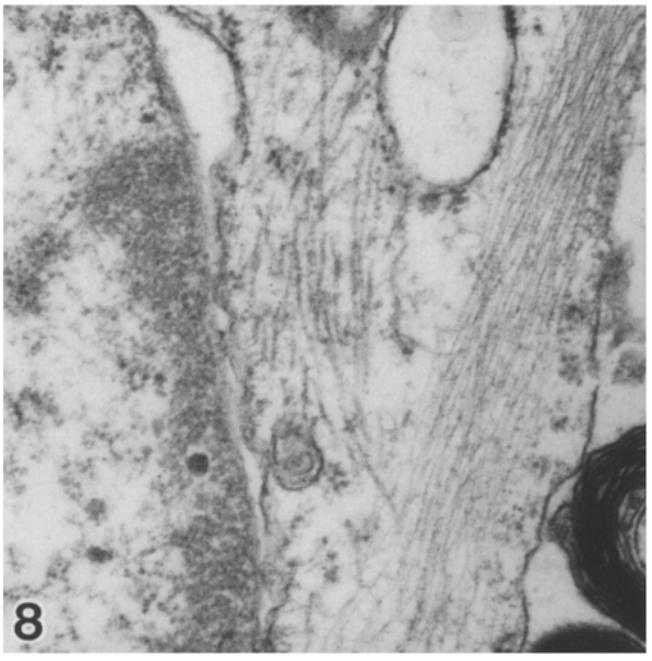
Fig. 3 White matter in the vicinity of temporal horn of lateral ventricle of postencephalitic parkinsonism of Economo type. In the vicinity of a cell cluster of TSA, perivascular irregular argyrophilia is sometimes observed, the features of which correspond to astrocytic end-feet. × 260

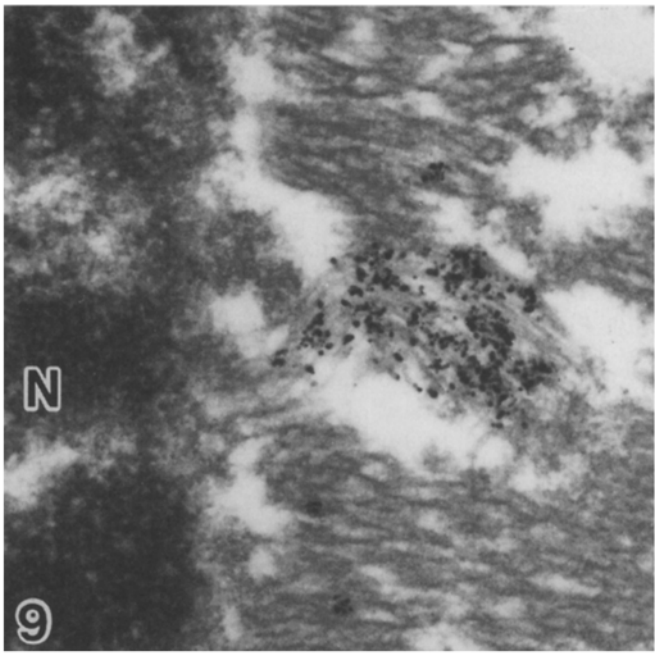
Fig. 4 Cerebral peduncle of postencephalitic parkinsonism of Economo type. The many tau-positive TSA and subpial tau-positive irregular linings *(arrows)* are consistent with the features illustrated by modified G-B method. Human-tau (pool 2) × 260

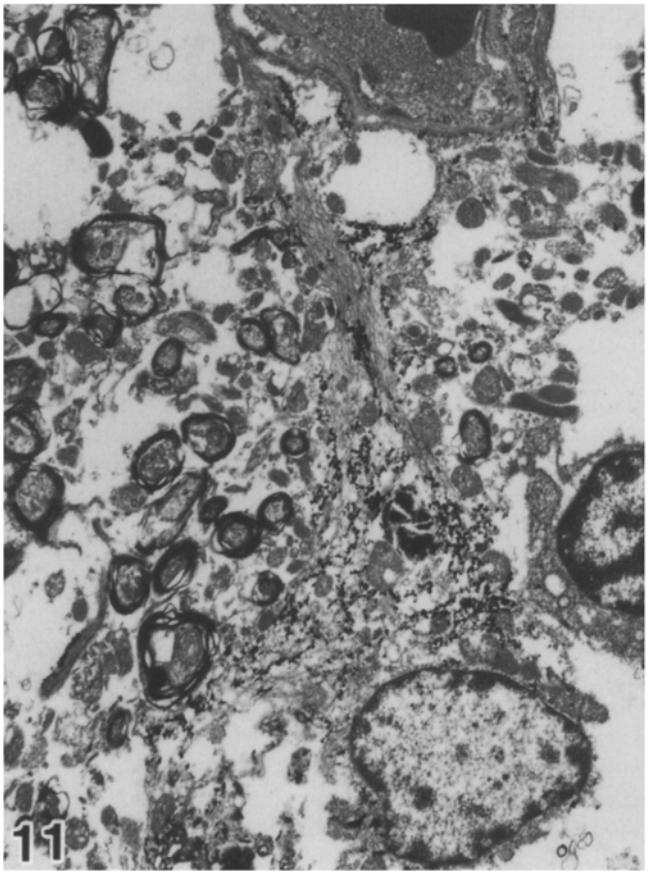
Fig. 5 Double immunostaining of TSA using Alz-50 and anti-GFAP antibodies reveals the purple-stained Alz-50 portion within the yellow-colored GFAP-positive area. × 1300

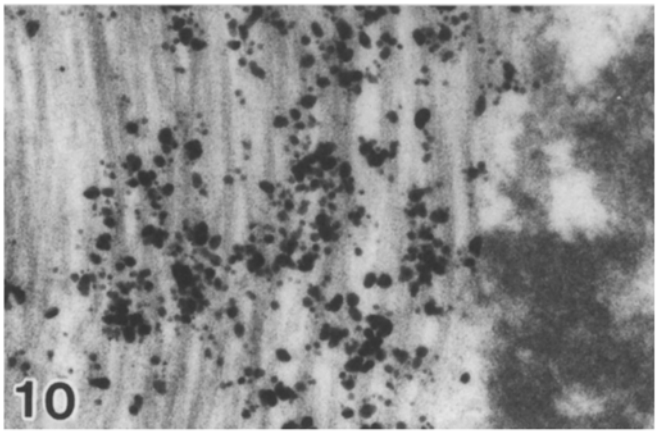
Fig. 6 Double immunostaining of coiled bodies using Alz-50 and anti-C4d antibodies reveals that the purple-stained Alz-50-positive tangle within the yellow-colored C4d-positive area, which is confirmed to represent complement-activated oligodendroglia. × 1300

Fig. 7 Distribution of TSA in the mediobasal temporal cortex. The number of dots represents the incidence of TSA. They are also found in other regions with prominent gliosis (*LV* lateral ventricle, *CP* cerebral peduncle)









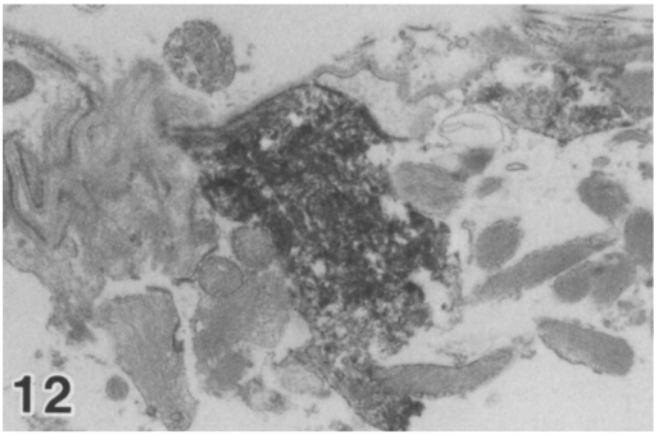


Fig. 8 A conventional electron micrograph reveals the coexistence of 15-nm straight tubules and intermediate filaments within the cytoplasm of the same astrocyte. × 48 000

Fig. 9 Silver particles specifically deposited on juxtanuclear 15-nm tubules, which are surrounded by the bundles of glial filaments. (*N* nucleus, Electron microscopy treated by modified G-B method). × 72 000

Fig. 10 Higher magnification of a bundle of straight tubules of TSA showing silver particle deposition. × 120 000

Fig. 11 The processes of a G-B-positive astrocyte protrude to a vessel wall and consist of end-feet. Modified G-B method applied electron microscopy. × 7200

Fig. 12 Tau-positive astrocytic processes attached to the basal lamina of a vessel correspond to the perivascular end-feet. × 12 000

an appearance similar to that seen on staining with the modified G-B method. The coexistence of Alz-50 and GFAP-positive epitopes in this cell type observed by simultaenous immunostaining confirmed the TSA to be of astrocytic origin (Fig. 5). In contrast, double immunostaining using Alz-50 and C4d revealed tau-positive coiled bodies within the C4d-positive area (Fig. 6); C4d is known to recognize complement-activated oligodendroglia and its processes [16]. NFT observed in the same sections were also positive for all of the examined anti-tau and some of the NFT were reactive to anti-ubiquitin antibodies. The main immunohistochemical difference between GFT and NFT lies in the reaction against anti-ubiquitin.

The related structures of irregular argyrophilic linings of perivascular and subpial region presented the same immunoreactivity as the TSA.

Electron microscopy

Observation with conventional electron microscopy revealed the coexistence of 15-nm straight tubules and intermediate filaments within the cytoplasm of the same cell in the subpial white mater (Fig. 8). Application of modified G-B method to Epon-embedded sections disclosed scattered G-B-positive cells, whose appearance coincided with that of TSA. The cell body and processes contained various degrees of G-B-positive staining. On electron microscopy, silver particles were observed deposited on the bundles of 15-nm straight tubules (Figs. 9, 10), which coincided with the tubules observed in the astrocytes examined by conventional electron microscopy. Silver particles were sometimes recognized on amorphous substances but not on glial filaments. G-B-positive astrocytes often presented processes with silver particles protruding to the vessel wall and composing perivascular astrocytic end-feet (Fig. 11). The sections subjected to immunoelectron microscopy from the same areas presented findings consistent with the G-B electron microscopy observations. A tau-positive structure was seen in both the astrocytic cytoplasm and its processes. An identical tau-positive structure was occasionally found attached to the basement membrane of the vessel forming the perivascular end-feet (Fig. 12).

Disease specificity

This survey of a variety of cytoskeletal disorders, some other diseases with non-cytoskeletal pathological glia, and control aged cases disclosed that the presence of a neuronal cytoskeletal abnormality seems to be a necessary condition for the formation of TSA. However, as no case of AD had any apparent TSA, the severity of the cytoskeletal abnormality does not play an important role. Although TSA appear to be intimately associated with the Economo (4 positive cases out of 4 cases studied) and dementia pugilistica (5/8), they were also observed in some cases of SDAT (2/10), PSP (3/8), Pick's disease with Pick body (2/8), and DLBD (1/4) as well as in the aged controls (2/12). The two positive control cases also showed NFT in the hippocampal region. In other cases, including cases with non-cytoskeletal pathological glial cells, TSA could not be found. Except for in one case of Economo, a small number of TSA were always found in a confined area in each positive case. These results indicate that TSA, in contrast to tuft-shaped astrocytes, have no apparent disease specificity.

Discussion

Tau-positive TSA morphologically resemble the thorn-like astrocytes in PSP reported by Nishimura et al. [13], who were the first to refer to the argyrophilic and tau-positive glial structure as 'glial fibrillary tangles (GFT)'. We have followed their designation and also refer to tau-positive glial structures generically as GFT.

The morphology and distribution of TSA are quite different from those of tuft-shaped astrocytes in PSP. Thus, at least two types of tau-positive astrocytes can be differentiated. Very recently, Feany and Dickson [5] have reported an unusual cluster of tau-positive fibers in corticobasal degeneration and termed it an astrocytic plaque. Astrocytic plaques also appear in some PSP patients (manuscript in preparation). Most astrocytes that form astrocytic plaques lack detectable amout of GFAP, suggesting that they originate from protoplasmic astrocytes and are an entity more closely related to tuft-shaped astrocytes. An important dissimilarity between TSA and tuft-shaped astrocytes is the specificity for diseases. Tuft-shaped astrocytes are reported to appear almost exclusively in PSP [2], while TSA, although they seem to be somewhat more common in Economo and and boxer's brain, were also detected in other cytoskeletal disorders and in the aged brain showing a normal range of NFT. There was no relation between the degree of NFT and TSA, because GFT were rather sparse in AD and related diseases. In most positive cases, there were only a few TSA and these were found in a localized area. These observations indicate that TSA are neither essential nor specific to any cytoskeletal disorders.

The role of TSA can be presumed to be based on their morphology and distribution. Except for the occasional presence in the deep cortical layer, the distribution of TSA is confined to the subpial or subependymal regions, where strong marginal gliosis is known to generally occur. TSA showed cytoplasm and short processes which resemble those of the reactive astrocyte. As noted in boxer's brain and other diseases, TSA tend to form in the cleft of the gyrus, where the damage due to cerebral edema would be more prominent than that at the crest of the gyrus. It can be deduced that the repeated mechanical damage probably provokes frequent cerebral edema and would result in gliosis in this region in dementia pugilistica. A similar hypothesis could also be applicable in Economo cases with long survival. In this disease, most TSA are found in the midbrain, but always in the marginal region where the

gliosis is most prominent [8]. In other diseases TSA are also generally confined to the marginal region of the tissue. These observations indicate that the abnormally phosphorylated tau are formed in the reactive astrocytes under the condition of the presence of, to a greater or lesser degree, some cytoskeletal disorder. Unlike tuft-shaped astrocytes, TSA have the aspect of a secondary product. GFT may be produced by multiple genesis, as NFT formation is considered to be a type of degradation process caused by the aging process or viral, mechanical or other involvements.

Both the TSA and tuft-shaped astrocytes were strongly positive to all tau antibodies examined, from Alz-50 to tau-6, including the phosphorylation-dependant tau monoclonal antibodies, but were negative to anti-ubiquitin. This result suggests that the full-length of abnormally phosphorylated tau is an important component of the astrocytic tangles. The poor ubiquitination also seems to be, unlike the case in NFT, a common feature of tau-positive structures reported in oligodendroglia, i.e., the coiled bodies [12] and argyrophilic thread-like structures, which are presumed to be a tau-positive abnormality of inner and outer loop of oligodendroglia [9]. However, there is debate as to the ubiquitination of GFT [13, 16], specifically of the ultrastructure of the tubules constituting GFT. TSA consist of 15-nm straight tubules and show an ultrastructure similar to the astrocytic tangles in PSP reported by Nishimura et al. [13], as well as the astrocytic straight tubules in a case of Pick's disease described by Yamazaki et al. [19], whereas coiled bodies are reported to consist of 25-nm smooth tubules in not only PSP [16, 17] but also in dementia with argyrophilic grains [10]. Yamada et al. [16] suspected a microtubule origin for astrocytic tubules based on the similarity of the width. Wakabayashi et al. [15], however, reported that the oligodendroglial inclusions in corticobasal degeneration comprised 15-nm smooth tubules and the coiled bodies observed in SSPE had irregular woven tubules of approximately 14 ~ 25 - nm in diameter [11]. This information concerning GFT requires more detailed comparative studies in the various cytoskeletal disorders accompanying GFT. Not only the morphological or histochemical differences of GFT, but also the role as a possible glial counterpart of NFT, must be elucidated.

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