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# Astrocytes expressing hyperphosphorylated tau protein without glial fibrillary tangles in argyrophilic grain disease

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**Abstract** Argyrophilic grain disease (AgD), a frequent type of late onset dementia, is characterized by the occurrence of Gallyas-stained neuropil grains in the hippocampus, entorhinal cortex, amygdala and hypothalamus. High numbers of neurons containing hyperphosphorylated tau protein, but devoid of tangles, are encountered in areas rich in argyrophilic grains (ArGs). A third type of change consists of slender argyrophilic and tau-immunoreactive cytoplasmic inclusions in white matter oligodendrocytes, the coiled bodies. We now extend earlier studies on glial pathology in AgD (20 cases) and compare the results with glial changes in old age (10 cases) and Alzheimer's disease (AD; 7 cases). Numerous non-argyrophilic, non-neuronal tau-positive stellate cells in the amygdala and anterior entorhinal cortex were consistently found in all of the 20 AgD cases but not in AD cases. Double-labelling experiments performed on paraffin sections with phosphorylation-dependent anti-tau antibody AT8, anti-glial fibrillary acidic protein and anti-CD44, revealed coexpression of these markers in stellate cells. The high expression of CD44 indicate that they probably correspond to reactive astrocytes. Unlike astrocytic plaques in corticobasal degeneration (CBD), where AT8 reactivity is accumulating in distal astrocytic processes, tau reactivity in AgD was found in all astrocytic cell compartments. The absence of glial fibrillary tangles further distinguished tau-labelled astrocytes in AgD from astrocytic plaques in CBD and tufted astrocytes in progressive supranuclear palsy (PSP). In contrast to AD and aged non-demented control cases tau-positive non-argyrophilic astrocytes represent a consistent finding in anterior limbic structures in AgD. Our findings point to a more widespread pathology of the glial cell population in AgD than previously supposed, and will be of further help in differentiating AgD from other neurodegenerative disorders, including AD, PSP, CBD and Pick's disease.

**Key words** Argyrophilic grain disease · Hyperphosphorylated tau protein · Glial fibrillary tangles · Astrocytes

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## Introduction

Argyrophilic grain disease (AgD) constitutes a frequent type of late onset dementia pathologically characterized by abundant Gallyas-stained and tau-immunoreactive argyrophilic grains (ArGs) in the neuropil of the amygdala, entorhinal cortex, subiculum, sector CA1 of the hippocampus and some hypothalamic nuclei [4, 5]. Most patients with ArGs show concomitant development of Alzheimer-type changes, mainly in the shape of neurofibrillary lesions corresponding to early entorhinal and limbic Braak stages [6], whereas senile plaques (SP) were reported to be absent in about one third of AgD cases [7, 34, 35, 38]. We have recently shown that tau protein is hyperphosphorylated in up to 80% of nerve cells in areas rich in ArGs and that at least a subset of grains are formed within dendrites and dendritic side-branches of neurons containing hyperphosphorylated tau [35, 37]. Moreover, tau- and αB-crystallin-expressing ballooned neurons (BNs) have been reported as a constant finding of the amygdala in AgD cases [33]. In addition to neuronal tau inclusions, argyrophilic and tau-immunoreactive deposits are regularly found in white matter oligodendrocytes adjacent to cortical areas rich in ArGs, either termed coiled bodies [5, 20] or oligodendroglial microtubular masses [39]. However, astrocyte pathology has not been considered to be a significant feature in AgD [7, 9, 22, 23].

We recently observed tau-reactive non-argyrophilic astrocytes in gray matter areas rich in ArGs, and therefore decided to investigate in detail a higher number of our AgD cases to determine whether astrocytic pathology constitutes a regular finding in AgD. Tau-positive non-argyrophilic stellate astrocytes were consistently found in

**Table 1** Astrocytic pathology in AgD, AD and control cases [*AgD* Argyrophilic grain disease, *AD* Alzheimer's disease, *Lb* Lewy bodies, *vl* vascular lesions (small lacunar infarcts), *AT8⁺Gall⁻* AT8-positive Gallyas-negative astrocytes, *AT8⁺Gall±* AT8-positive Gallyas-positive or -negative astrocytes, *am/ec* amygdala/entorhinal cortex, *wm* white matter, *se* subependymal, – absent, + few, ++ moderate, +++ abundant]

| Case | Sex | Age | Dementia | Braak stages | Other lesions | Astrocytic pathology | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | AT8⁺Gall⁻ am/ec | AT8⁺Gall± | |
| | | | | | | | wm | se |
| AgD | | | | | | | | |
| 1 | M | 87 | Yes | I | vl | ++ | + | – |
| 2 | F | 89 | Yes | III | vl | ++ | – | – |
| 3 | M | 71 | Yes | III | vl | + | – | – |
| 4 | F | 94 | Yes | III | – | ++ | + | – |
| 5 | M | 84 | Yes | III | vl | +++ | ++ | + |
| 6 | F | 87 | Yes | III | – | +++ | + | – |
| 7 | F | 85 | Yes | I | vl | +++ | – | – |
| 8 | M | 100 | Yes | III | vl | ++ | – | + |
| 9 | M | 82 | Yes | III | – | +++ | + | – |
| 10 | F | 78 | Yes | I | vl | ++ | + | + |
| 11 | M | 86 | Yes | II | – | ++ | – | – |
| 12 | M | 87 | Yes | III | Lb | + | + | + |
| 13 | F | 93 | Yes | III | vl | +++ | +++ | +++ |
| 14 | M | 69 | Yes | II | vl | + | + | + |
| 15 | F | 88 | Yes | I | vl | + | ++ | + |
| 16 | F | 69 | Yes | I | Lb | ++ | ++ | – |
| 17 | F | 86 | Yes | II | – | + | – | – |
| 18 | M | 87 | Yes | II | – | + | + | – |
| 19 | M | 94 | Yes | III | – | ++ | ++ | ++ |
| 20 | M | 88 | No | III | – | + | ++ | ++ |
| AD | | | | | | | | |
| 21 | F | 89 | Yes | VI | vl | – | – | – |
| 22 | F | 94 | Yes | V | vl | – | – | + |
| 23 | M | 68 | Yes | VI | – | – | – | – |
| 24 | F | 90 | Yes | V | vl | – | ++ | + |
| 25 | M | 82 | Yes | VI | – | – | – | + |
| 26 | M | 83 | Yes | V | vl | – | +++ | – |
| 27 | F | 87 | Yes | VI | – | – | – | – |
| Control cases | | | | | | | | |
| 28 | M | 91 | No | II | – | – | + | ++ |
| 29 | F | 87 | No | III | – | – | + | – |
| 30 | M | 90 | No | III | – | – | – | – |
| 31 | F | 82 | No | I | – | – | – | – |
| 32 | F | 90 | No | IV | vl | – | – | – |
| 33 | F | 83 | No | II | – | + | – | – |
| 34 | M | 66 | No | II | – | – | – | – |
| 35 | M | 90 | No | I | – | – | – | – |
| 36 | F | 77 | No | II | – | – | – | – |
| 37 | F | 90 | No | II | – | – | – | – |

the amygdala and anterior entorhinal cortex in all our AgD cases but were absent in brains from AD and aged non-demented subjects. Our finding points to more extensive glial pathology in AgD than previously supposed, and will be of help in further distinguishing AgD from AD and other neurodegenerative disorders.

## Materials and methods

Brains from 20 subjects with AgD (11 males, 9 females, age range 69–100 years, mean age 85.2 ± 8.17 years), 7 subjects with AD (3 males, 4 females, age range 68-94 years, mean age 84.33 ± 9.18 years) and from 10 control subjects without neurological disorders (4 males, 6 females, age range 66–90 years, mean age 84.6 ± 8.00 years) were investigated (Table 1). A progressive dementia was clinically documented in 19 AgD cases and in all of the 7 AD cases according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [2]. Routine neuropathological examination was performed in all cases. After fixation in 4% buffered formaldehyde (pH 7.2) for 2 weeks, representative tissue blocks were embedded in paraffin. Deparaffinized 4-μm-thick sections were stained with hematoxylin and eosin, periodic acid methenamine silver and the Gallyas silver technique [13]. For the present study we used blocks containing the amygdala with the adjacent anterior entorhinal cortex, and the anterior, middle and posterior parts of the hippocampus with the adjacent entorhinal or parahippocampal cortices on both sides. Immunohis-

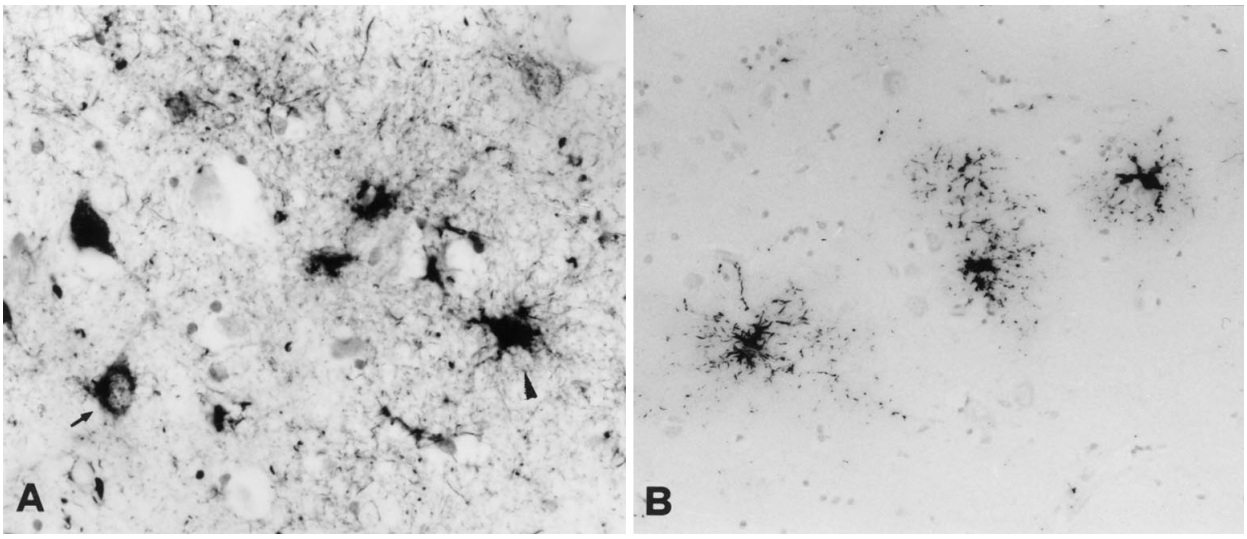


**Fig. 1** **A** AT8-immunostained section of the amygdala showing tau-positive argyrophilic grains, "pretangle" neurons *(arrow)* and tau-immunoreactive Gallyas-negative bush-like astrocytes *(arrowhead)*. **B** Cluster of AT8-immunoreactive bush-like astrocytes in the amygdala (AgD, case 20) (*AgD* argyrophilic grain disease). **A** × 350, **B** × 175

tochemistry was performed on 4-μm paraffin sections according to standard procedures using avidin-biotin-peroxidase (Vectastain, Elite kit, Vector Laboratories). The antibodies used included monoclonal phosphorylation-dependent anti-tau antibodies AT8 (phosphorylated serine 202 and threonine 205; dilution 1 : 1000) [16] and PHF-1 (phosphorylated serine 396 and 404; dilution 1 : 500) [18, 30], the phosphorylation-independent anti-tau antiserum N-Tau 5 (directed against the N terminus of tau; dilution 1 : 1000) [17], an antiserum against glial fibrillary acidic protein (GFAP, DAKO; 1 : 100), an anti-CD44 monoclonal antibody (kindly provided by Dr. K. Günthert, Basel Institute of Immunology, Basel; 1 : 10) recognizing surface glycoprotein of reactive astrocytes [15], an anti-ubiquitin (polyclonal, DAKO; 1 : 500) and an anti-αB-crystallin antibody (polyclonal, Novocastra; 1 : 1000). Consecutive sections were stained with AT8, anti-ubiquitin, anti-GFAP, anti-CD44 and anti-αB-crystallin in that order. In addition, double and consecutive staining experiments were performed on single sections of the amygdala and anterior entorhinal cortex. For double immunostaining 3,3′-diaminobenzidine (DAB) and V-VIP substrate kits (Vector Laboratories) were used as chromogens. For consecutive staining, sections were first stained with AT8 using amino-ethyl-carbazole (AEC, Sigma) as chromogen. The cells of interest were photographed and drawn using a drawing tube attached to a microscope (Zeiss Axioplan) under an oil immersion 100× objective, and exactly localized in the section using cross-sectioned vessels as a landmark. The stained sections were subsequently bleached in decreasing grades of ethanol and then immunostained with the anti-GFAP antibody. The same bleaching procedure was applied to the GFAP-stained sections and the sections then stained with anti-CD44 as a third antibody. In the amygdala the densities of AT8-positive astrocytes were estimated semi-quantitatively (Table 1).

## Results

### Histology

Light microscopical examination of AgD cases revealed high densities of ArGs throughout the CA1 subfield of the hippocampus, entorhinal cortex and amygdala (Fig. 1 A). Gallyas-positive coiled bodies were found within the white matter close to the areas rich in ArGs. Various numbers of BNs were present in the amygdala of AgD cases, but their numbers did not correlate with the density of ArGs in this nucleus, thus confirming our previous observations [33]. Neurofibrillary tangles (NFTs) and neuropil threads (NTs) were found in a distribution corresponding to early entorhinal or limbic Braak stages (stages I–III) (Table 1). In the cognitively normal control cases, the distribution of neurofibrillary lesions corresponded to Braak stages I–IV, and no ArGs were found. AD cases were characterized by Braak stages V–VI and abundant SP (mainly of the neuritic type) in the neocortex. Additional neuropathological findings in AgD, AD and control cases are listed in Table 1.

### Immunohistochemistry

In addition to ArGs, coiled bodies and "pretangle" neurons (Fig. 1 A), AT8-stained sections of AgD cases revealed high numbers of AT8-immunoreactive astrocytes with abundant hair-like branching processes sprouting from the cell body, giving the cell a bush-like appearance (Figs. 1, 2). Generally, there was stronger staining of the cell soma than of the cell processes (Fig. 2 B). Some of these astrocytic processes displayed a few small AT8-immunoreactive dilatations. Double or consecutive labelling on single sections revealed colocalization of AT8 and CD44 staining in the same cell (Fig. 2 C, D). Furthermore, the same cells immunoreactive for AT8 and CD44 were shown to be positive for GFAP (Fig. 2 C), thus confirming their astrocytic nature. Many more astrocytic processes were found on AT8-stained sections than those labelled for CD44 or GFAP, and some astrocytes showed complex branches of thin AT8-stained fibers superimposed on a GFAP-stained backbone. High numbers of AT8-positive astrocytes were found in the amygdala and the anterior parts of the entorhinal cortex, but in the more posterior parts of the entorhinal cortex and the hippocampus. With

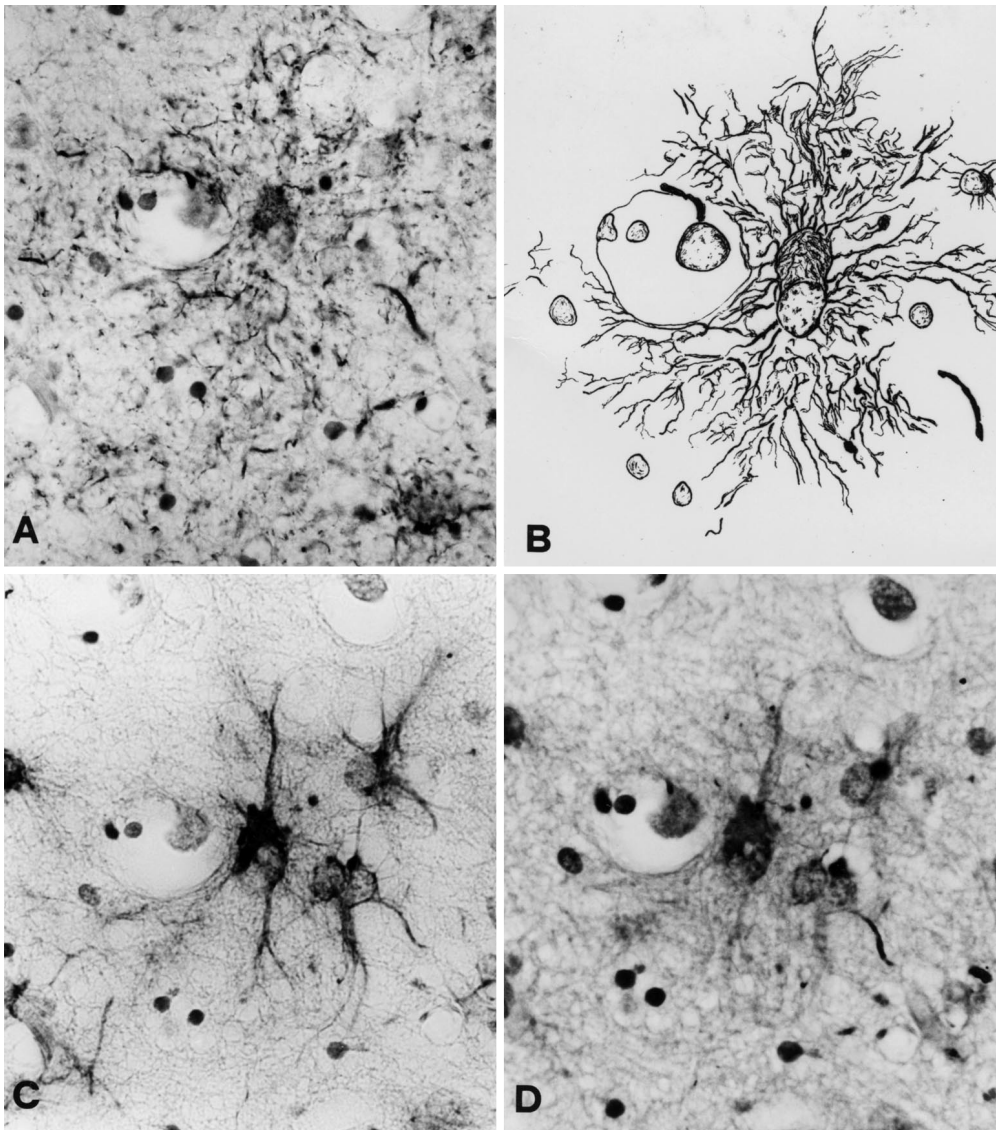


**Fig. 2 A–D** A single AT8-positive non-argyrophilic highly branched astrocyte in the amygdala of an AgD case. **A** AT8-immunostained astrocyte. Counterstain with hematoxylin. **B** Camera lucida drawing showing the same AT8-stained cell in more detail. Note the high number of long, hair-like branching cell processes. Some small dilatations may be observed along these processes. The same cell immunostained for glial fibrillary acidic protein (**C**) and CD44 (**D**) after bleaching the AT8 staining. **A**–**D** × 810

few exceptions these astrocytes remained unstained using the Gallyas silver technique and failed to stain for ubiquitin and αB-crystallin.

A second type of astrocytic pathology in all AgD cases consisted of hypertrophic, highly branched CD44-positive astrocytes which were found in the amygdala and entorhinal cortex either as individual cells or in clusters surrounding some of the few SP. When comparing sections stained for AT8 and CD44, only a small subset of CD44-positive cells were found to coexpress hyperphosphorylated tau, and may, therefore, represent an earlier stage of the aforementioned AT8- and CD44-immunoreactive bush-like astrocytes. Again, these astrocytes were not stained with the anti-ubiquitin and αB-crystallin antibodies. Few AT8- and CD44-immunoreactive astrocytes were also found in one of the aged control cases (case 33) but not in AD cases (Table 1). BNs strongly stained for anti-tau and anti-αB-crystallin antibodies but not for CD44.

A third type of AT8- and CD44-immunoreactive astrocytes had a typical “thorn-shaped” appearance [21]. They were found in a strip of white matter ventral to the amygdala in 14 AgD, 2 AD and 2 control cases. Less than 10% of these cells were argyrophilic and did not stain for ubiquitin. Similar astrocytes, characterized by their predominant perivascular location and their numerous perivascular foot processes, were found in the periventricular subependymal white matter along the inferior horn, lateral to the amygdala. These astrocytes were found in 9 AgD, 3 AD and 1 control case (Table 1).

In one of the control cases (case 32) a subacute encephalomalacia was found in the parieto-occipital lobe. Numerous reactive astrocytes in the vicinity of the lesion were strongly stained with GFAP and CD44; however, they remained consistently unstained with the anti-tau antibodies used. All types of AT8-stained astrocytes were also found when using antibody PHF-1 and antiserum N-Tau 5. However, strongest staining intensity was obtained with the phosphorylation-dependent anti-tau antibodies.

## Discussion

We report here the finding of non-argyrophilic astrocytes expressing hyperphosphorylated tau epitopes as a constant feature of the amygdala and anterior entorhinal cortex in AgD cases. Coexpression of GFAP and strong CD44-antigen reactivity was found together with tau expression, indicating that these abnormal cells are reactive astrocytes [15]. These cells were further characterized by the presence of a high number of tiny AT8- and to a lesser extent CD44- and GFAP-positive ramifications of cell processes.

In AgD, oligodendroglial pathology in the shape of argyrophilic, tau-expressing and ubiquitin-positive intracytoplasmic inclusions, termed coiled bodies [5, 20], has been well documented, but astrocytes have been considered not, or only occasionally, to be affected [7, 9, 22, 23]. Our present findings point to a more widespread pathology of the glial cell population in AgD than previously admitted. The tau-immunoreactive non-argyrophilic astrocytes we now describe in AgD have to be considered together with other features differentiating AgD from AD, including widespread expression of hyperphosphorylated tau protein in non-argyrophilic neurons, tau- and αB-crystallin-coexpressing BNs in the amygdala and a significantly lower amyloid plaque load in brains from AgD compared to AD subjects [33, 35, 38]. Moreover, in contrast to AD, two independent studies have recently shown that the apolipoprotein E ε4 allele does not constitute a risk factor for the development of AgD [14, 36].

Argyrophilic tau-positive inclusions in glial cells, also termed glial fibrillary tangles (GFTs), have been described in many neurodegenerative disorders in which there is also tangle pathology in neurons. Morphologically, glial tangle pathology includes tufted astrocytes, thorn-shaped astrocytes, astrocytic plaques, coiled bodies as well as interfascicular and white matter threads (for review see [9]). None of these morphological subtypes seem to be specific for a particular disease, and various subtypes of GFTs may be present in one particular disorder, such as in progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) or Pick's disease (PD).

The tau-positive non-argyrophilic astrocytes in the amygdala and anterior entorhinal cortex of AgD cases share some features with tufted astrocytes mainly observed in basal ganglia and cortical regions of PSP [1, 19, 31, 40], with tau-positive astrocytes in the neocortex and subcortical white matter of PD [12, 41, 42] and with astrocytic plaques of CBD [11]. However, in contrast to all these glial inclusions, there are no argyrophilic GFTs in tau-immunoreactive astrocytes of AgD. The absence of GFTs in tau-positive astrocytes of AgD cases may also explain the fact that this particular glial pathology has been overlooked in the past. AT8 immunostaining was found in all cell compartments of affected astrocytes in AgD, which contrasts with astrocytic plaques of CBD where tau protein is mainly concentrated in distal cell processes, and with tufted astrocytes of PSP where tau immunoreactivity is mainly confined to proximal and distal processes with relative sparing of the cell soma. Abnormal tau-containing astrocytes in PSP have been shown to contain 7–8-nm glial filaments and aggregates of 15-nm straight tubular profiles, similar to those of neurofibrillary tangles of PSP [21, 29, 32]. Although nothing is known about the ultrastructural features of non-argyrophilic astrocytes expressing hyperphosphorylated tau epitopes, we suppose that any fibrillary component will be lacking except the glial filaments.

Accumulation of hyperphosphorylated tau protein without evidence for tangle formation has been well documented in AD and considered an initial step of tau pathology leading to the formation of NFTs in neurons [3, 8]. Abnormal phosphorylation of tau also constitutes an important feature in limbic neurons of AgD where they are mainly found in cortical regions rich in ArGs [35, 37]. However, to the best of our knowledge, the presence of "pretangle" glial cells has not yet been demonstrated, although Ikeda et al. [22], in a recent study on glial tau pathology, speculated about their existence. Most neurons containing hyperphosphorylated tau in AgD probably do not further evolve to a stage of tangle-bearing cells, but instead, to the formation of ArGs within their dendrites and dendritic side branches [37]. Tau-expressing astrocytes in AgD, like their neuronal counterpart, are likely to remain in a state of tau hyperphosphorylation without tendency to aggregate fibrillary tau, as shown by the absence of Gallyas staining.

The astrocytic pathology we now report in AgD shares some important features with tufted astrocytes of PSP, except that the latter are argyrophilic. Morphological evidence indicates that expression of hyperphosphorylated tau protein takes place in a subset of reactive astrocytes and that a progressive new formation of cell processes occurs with increasing tau content in these cells. Such an association was also suggested by the morphology of tufted astrocytes in PSP [31], and by in vitro experiments showing that overexpression of tau and other microtubule-associated proteins in non-neuronal cells, including astrocytes, constitutes an important prerequisite for the formation of cell processes [10, 24].

In summary, we describe novel non-argyrophilic tau-immunoreactive astrocytes as a constant feature in the amygdala and anterior entorhinal cortex of AgD cases. This observation will be of help to further distinguish AgD from other neurodegenerative disorders, including AD, CBD, PD and PSP. PD and PSP cases have been shown to be associated with ArGs and some authors therefore suggested to classify AgD within the broad spectrum of these disorders [26–28]. We now demonstrate that astrocytic pathology in AgD clearly differs from tufted astrocytes in PSP, astrocytic plaques in CBD and tau-expressing astrocytes in PD. Moreover, an elegant study by Komori et al [25] recently showed that PSP and CBD cases can be distinguished by their astrocytic pathology in that astrocytic plaques and tufted astrocytes do not coexist in these two disorders. Therefore, careful evaluation of glial pathology in neurodegenerative disorders constitutes an important tool for differential diagnosis.

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