Astrocytic degeneration relates to the severity of disease in frontotemporal dementia

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Summary
The main unifying feature of cases with frontotemporal dementia (FTD) is the pattern of brain atrophy. Surprisingly, there are a variety of underlying histopathologies in cases with the clinical features and typical pattern of atrophy characterizing FTD. This suggests that the degenerative mechanism(s) associated with pyramidal cell loss and gliosis in FTD is likely to be similar in the different histopathological forms of the disease. In this study we tested this hypothesis by analysing a common cell death mechanism, apoptosis, in cases of FTD with either Pick’s disease (PiD) (n = 9) or frontotemporal lobar degeneration (FTLD) (n = 7) compared with normal controls (n = 10).

Tissue sections from previously analysed cases were stained using anti-activated caspase-3 immunohistochemistry, TUNEL, propidium iodide, and cell- and pathology-specific labels. These markers of apoptosis identified both astrocytes and neurons in regions vulnerable to degeneration in all cases of FTD. However, neuronal apoptosis was rare (<2% of neurons), even at early disease stages where there is considerably less frontotemporal atrophy or pyramidal cell loss. This suggests that other cell death mechanisms account for the progressive neuronal loss in FTD. In contrast, astrocytes with beaded processes and other apoptotic features were very frequent in both PiD and FTLD, with the severity of astrocytosis and astrocytic apoptosis correlating with both the degree of neuronal loss and the stage of disease. These findings provide evidence that astrocytic apoptosis occurs as an early event in different histopathological forms of FTD. Furthermore, this astrocytic apoptosis directly relates to the degree of degeneration in FTD, and becomes the overwhelming pathological feature as the disease progresses.

Keywords: apoptosis; disease stage; frontotemporal dementia; frontotemporal lobar degeneration; Pick’s disease

Abbreviations: ANOVA = analyses of variance; FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; GFAP = glial fibrillary acidic protein; PiD = Pick’s disease; TUNEL = terminal deoxynucleotide transferase-mediated dUTP nick end labelling.


Introduction
Frontotemporal dementia (FTD) is the preferred clinical term for the spectrum of non-Alzheimer dementias characterized by focal atrophy of frontal and anterior temporal regions. Unlike other neurodegenerative syndromes, there is no consistency in the type of underlying histopathology, with a variety of histological changes characterizing FTD (McKhann et al., 2001). The most common of these histopathologies include neuronal loss with tau-positive intracellular Pick body inclusions (Pick’s disease, PiD; Fig. 1A); neuronal loss with marked gliosis and microvacuolation but no other histopathology (frontotemporal lobar degeneration, FTLD; Fig. 1B); neuronal loss with a variety of other tau-positive intracellular structures; or neuronal loss with ubiquitin-positive, tau-negative intracellular motoneuron disease-like inclusions (McKhnann et al., 2001). Variability in FTD extends to the pattern and degree of gross atrophy and degeneration found in different cases, although our recent work has established that this variability relates to the duration and severity of clinical dementia (Broe et al., 2003). Surprisingly, there is no difference in the degree of atrophy, pyramidal cell loss or reactive gliosis between FTD cases with different histopathologies if they are examined at the same disease stage (Broe et al., 2003; Schofield et al., 2003). This suggests that (i) there is great variability in an individual’s capacity to survive with FTD (see Hodges et al., 2003) and (ii) the basic tissue mechanisms associated with the pyramidal cell loss and gliosis are likely to
be similar across FTD cases at the same disease stages despite variability in the presence and type of different intracellular inclusions.

To date, there have been no studies analysing histological evidence of apoptosis in the different pathological subtypes of FTD at different stages of disease. In previous studies analysing FTLD cases, classical features of apoptosis were found in both neurons and astrocytes (Su et al., 2000; Martin et al., 2001; Nichol et al., 2001). However, studies analysing PiD have shown that neurons with tau inclusions do not undergo apoptosis (Gleckman et al., 1999; Atzori et al., 2001). The differences between such studies may be related to the disease stage (and therefore the degree of neuronal loss) of the cases examined and/or the types of cells selected for analysis.
Comparison of the degree of apoptosis at different disease stages in different subtypes of FTD may identify a common disease mechanism.

Material and methods

Cases

FTD cases were selected as previously published (Broe et al., 2003; Schofield et al., 2003) from a neuropathological series of 125 patients with dementia recruited via a brain donor program in Sydney, Australia, between October 1993 and February 2002. For the present analysis, behavioural variant FTD cases with either PiD (n = 9) or FTLD (n = 7) were selected, and 10 age- and sex-matched controls, without significant neurological or neuropathological abnormality were chosen for comparison from our brain donor program. Two cases with tau-positive PiD had a parent with dementia, but both had negative tau gene mutation screening tests. Consent for autopsy was obtained for all cases and the program was approved by the Human Ethics Committees of the Central and South Eastern Sydney Areas Health Services and The Universities of Sydney and New South Wales. Case demographics are provided in Table 1, including disease stage as previously published for this cohort (Broe et al., 2003). Cases with PiD were older at death, but had similar disease duration and staging severity (Table 1). As we have described previously (Broe et al., 2001), certain agonal events and long post mortem delay can decrease tissue pH, which increases terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling (TUNEL) (although not necessarily apoptosis) of neuronal nuclei. We evaluated the causes of death and post mortem delay and found that they did not significantly differ between the groups (Table 1).

Tissue preparation

Blocks from the superior frontal gyrus, orbitofrontal gyrus, inferior temporal gyrus, hippocampal CA1 and primary visual cortex were paraffin-embedded, serially sectioned at 10 μm, mounted onto slides coated with 3-aminopropyl-trimethoxysilane (TESPA; #A1435; Sigma, St Louis, MO, USA) and stained for markers of apoptosis using peroxidase immunohistochemistry with anti-activated caspase-3 (#556425, clone CPP32; Becton Dickinson, Franklin Lakes, NJ, USA; diluted 1:750) as well as the peroxidase-enhanced TUNEL method using the In Situ Cell Death Detection Kit (#1684817; Boehringer Mannheim, Germany). The fluorescent DNA marker propidium iodide (PI; #P4170; Sigma; used at 0.5 μg/ml) was also used (Broe et al., 2001). All sections were counterstained with 0.5% cresyl violet (#C1791; Sigma) to identify cell structures and sections were viewed on an Olympus M081 microscope with bright field and fluorescence attachments.

Evaluation of astrocytes for the degree of degeneration and apoptosis

In order to detect astrocytic apoptosis, double labelled immunohistochemistry for glial fibrillary acidic protein (GFAP; #Z0334; DAKO, Glostrup Denmark; diluted 1:1750, NovaRED detection) and activated caspase-3 were also labelled with either TUNEL or PI. GFAP-positive astrocytes double-labelled for apoptotic markers and with abnormal processes were further analysed for beading of their processes (Fig. 1C) as evidence of apoptosis (Martin et al., 2001). As ~25% of astrocytes in PiD also contain abnormal tau immunoreactivity (Dickson, 1998; Komori, 1999; Schofield et al., 2003), tau-positive astrocytes (Fig. 1D) were also assessed in each region.

Table 1 Case details

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>Cause of death</th>
<th>Post mortem delay (h)</th>
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F = female; M = male.
severity of astrogliosis was graded as previously described (Schlofield et al., 2003) into none (0), mild (+), moderate (++) or severe (+++).

Evaluation of neurons for the degree of degeneration and apoptosis

All neurons were identified in counterstained sections using the following criteria, and only labelled nuclei larger than glial nuclei were included in the analysis, ensuring the exclusion of astrocytes and microglia (Fig. 1F and G). This may underestimate the degree of neuronal apoptosis in these cases. TUNEL-positive neurons were not considered apoptotic if they had an intact nucleus and cytoplasm (Fig. 1E) (Su et al., 1994; Broe et al., 2001) and no activated caspase-3 immunoreactivity (Lassmann et al., 1995; Lucassen et al., 1997; Ferrer, 1999; Gleckman et al., 1999). TUNEL-positive neuronal nuclei were apoptotic when they had margination and condensation of DNA, and no visible nucleolus. These type 2+ nuclei had a visible neuronal cytoplasm that contained activated caspase-3 immunoreactivity (Fig. 1F), while type 2− nuclei had no visible cytoplasm (Fig. 1G) (Broe et al., 2001). In order to detect the neuronal types undergoing apoptosis, sections labelled immunohistochemically with 200 kDa neurofilament proteins (phosphorylated: #MAS330; Seralab, Loughborough, UK; diluted 1:200; and non-phosphorylated: SMI32; Sternberger Monoclonals, Maryland, USA; diluted 1:1000) or tau (AT8, #MN1020; Pierce Biothechnology Rochford, IL, USA; diluted 1:20 000; and tau-2, #T5530; Sigma; diluted 1:10 000) were also labelled with fluorescent PI, as described previously (Broe et al., 2001).

Quantitation of normal and apoptotic neurons (Fig. 1E–G) was performed as described previously (Broe et al., 2001). Briefly, in each cortical region, two fields containing the highest densities of TUNEL-positive neuronal nuclei were sampled at 200 × magnification (i.e. five regions × two samples × 26 cases = 260 cortical fields sampled) and all neuron types counted. Counts by two investigators, or those repeated by the same investigator, differed by <5%. The average density of all normal neurons in affected frontotemporal regions was calculated and the data normalized to mean control densities for each region. The data were converted to a percentage of the total normal and abnormal neurons counted for that region by calculating the proportion of all neuronal nuclei with either normal or apoptotic morphology.

Statistical analysis

Spearman rank correlations were used to identify any relationships between disease stage, neuronal and glial changes. For these analyses, the more rapidly progressive early stages 1 and 2 were combined, and the later, more variable stages 3 and 4 were combined (Broe et al., 2003). Group differences were identified using analyses of variance (ANOVA) with post hoc Fisher’s least square difference tests. Two-way ANOVAs and post hoc testing were used to determine any differences between: (i) the regional pattern of neuronal and glial changes in the different groups; and (ii) the pattern of neuronal and glial changes at different stages in the different groups.

Results

Apoptotic markers identify both glia and neurons in FTD

All FTD cases, regardless of histopathological group, had evidence of apoptotic glial and neuronal cells, although not in any of the samples taken from the visual cortex. A small number of controls also had occasional apoptotic glial or neuronal cells. No evidence of neuronal necrosis or inflammatory reaction around neurons was observed in any case at any stage. In PiD, neurons with histopathological evidence of degeneration (tau-positive or phosphorylated 200 kDa neurofilament-positive immunohistochemistry) did not have apoptotic nuclei (Fig. 2A–D). Non-phosphorylated 200 kDa neurofilament-positive pyramidal neurons also did not have evidence of apoptosis in either PiD (Fig. 2E and F) or FTLD (not shown).

In all FTD cases, many glial nuclei were darkly positive with TUNEL (Fig. 3A) and brightly stained with PI, indicating apoptosis. However, using double-labelling immunohistochemistry, only GFAP-positive astrocytes had apoptotic nuclei and activated caspase-3-positive cytoplasm (Fig. 3B). While other glial types (oligodendroglia and microglia) may still be apoptotic, these cells were not analysed in detail due to the lack of confirmatory cytoplasmic evidence for apoptosis (they have minimal associated cytoplasm). In both PiD and FTLD, apoptotic astrocytes differed in their morphology. Some had ‘curly’ rather than straight processes (prominent at the pial surface; Fig. 3C), while others had beaded processes (prominent in layer VI, at the grey/white matter junction and in the white matter; Fig. 3D). In PiD the astrocytes with beaded processes were tau-positive (Fig. 3E), although these tau-positive astrocytes were not caspase-3 immunoreactive.

The degree of degeneration in FTD relates to disease severity rather than underlying histopathology

Analysis of neuronal density in controls revealed regional differences. Slightly higher neuronal densities were observed in the CA1 region and layer III of orbitofrontal cortex compared with layer III in the superior frontal and inferior temporal cortices (Table 2; ANOVA = 8.9, P = 0.0001; post hoc P-values <0.02). However, the degree of neuronal loss in FTD was equivalent in proportion in all regions analysed with no difference between PiD and FTLD (Table 2; ANOVA_region = 0.82, P = 0.49; ANOVA_diagnosis = 507, P < 0.0001; ANOVA_interaction = 0.42, P = 0.87; PiD versus FTLD post hoc P = 0.10). The FTD disease stage related to the degree of neuronal loss with significant progression of overall neuronal loss across all regions in FTD compared with controls (82% loss of neurons in stages 1–2; 90% loss in stage 3–4; ANOVA_region = 2.5, P = 0.06; ANOVA_stage = 9.9, P = 0.003; ANOVA_interaction = 0.21, P = 0.89).

Astrocytic apoptosis increases with disease progression while neuronal apoptosis remains constant

The type and extent of apoptosis in neurons and glia at different stages of FTD was analysed. In affected regions, there
Fig. 2 Representative paired micrographs of sections from a PiD case showing double-labelling for neuronal and apoptotic markers. The scale in B is equivalent for A and the scale in F is equivalent for C–E. (A, B) Hippocampal dentate gyrus. Tau-positive Pick bodies (A) did not have abnormal nuclei either morphologically or with enhanced PI labelling (B). (C, D) Superior frontal cortex. Phosphorylated neurofilament-positive pyramidal neurons (C) did not have abnormal nuclei either morphologically or with enhanced PI labelling (D). (E, F) Superior frontal cortex. Non-phosphorylated, neurofilament-positive ballooned neurons (E) did not have abnormal nuclei either morphologically or with enhanced PI labelling (F).

Fig. 3 Apoptotic markers in glia. All sections are counterstained with Cresyl Violet. The scale in E is equivalent for B–D. (A) The orbitofrontal cortex of a PiD case double-labelled with GFAP-immunohistochemistry and TUNEL. Strongly labelled TUNEL nuclei were seen in many GFAP-positive astrocytes (arrows). (B) The hippocampal CA1 region of a PiD case labelled with TUNEL, GFAP- and caspase-3-immunohistochemistry. Only GFAP-positive astrocytes were double-labelled using anti caspase-3 immunohistochemistry and TUNEL. (C, D) The superior frontal cortex of a FTLD case double-labelled with GFAP-immunohistochemistry and TUNEL showing ‘curly’ astrocytic processes (C, arrows) and beaded and severely degenerated processes (D, arrows). (E) The orbitofrontal cortex of a PiD case double-labelled with tau-immunohistochemistry and TUNEL showing an astrocyte with tau-positive beaded processes (arrows) and a TUNEL-positive nucleus (asterisk).
was no significant difference observed. Apoptotic neurons were only identified in cases with FTD (1.7–2.5% of neurons), with no difference between disease stages (ANOVA = 8.1, P = 0.0006; control versus early or late stages post hoc P < 0.05; early versus late FTD stage post hoc P = 0.27).

In the early FTD stages, many GFAP- and TUNEL-positive astrocytes in cortical laminae I, II and IV and at the grey/white matter junction had enlarged cytoplasm and processes (density range + to ++). Some TUNEL-positive astrocytes at the pial surface had ‘curly’ GFAP- and activated caspase-3-immunopositive processes (Fig. 3C) and others in deeper pyramidal layers had TUNEL-positive nuclei with beaded processes (Fig. 3D). In PiD, few astrocytes were tau-positive at early disease stages.

At late disease stages, cortical GFAP-positive astrocytes (also tau-positive in PiD) seemed less ‘activated’ and more apoptotic, as fewer of their processes were visible with either GFAP or activated caspase-3 antibodies. Despite this, in both PiD and FTLD the number of GFAP/TUNEL-positive astrocytes appeared to have increased (density ++++) due to the large loss of normal neurons and tissue by these stages. By end-stage, those astrocytes remaining had lost their stellate morphology and had shrunken cytoplasm with beaded degenerated processes. The increase in astrocytosis and astrocytic apoptosis was related to the neuronal loss over the stages of disease for both PiD and FTLD (rho = −0.35, P < 0.05).

The numbers of apoptotic astrocytes correlated with disease stage, with increasing evidence of astrocytic apoptosis with progression of FTD (rho = 0.56, P = 0.045).

**Discussion**

The present study shows that the degree of frontotemporal atrophy in FTD is related to the degree of astrocytic apoptosis. Both changes are independent of underlying histopathology and we have previously shown in the same cases that the degree of atrophy is related to clinical severity and disease duration (Broe et al., 2003). This suggests that a unifying pathological feature of clinical decline and tissue atrophy in FTD is astrocytic apoptosis. While astrocytic apoptosis has been previously identified as a potentially important pathogenic mechanism in FTLD (Su et al., 2000; Martin et al., 2001; Nichol et al., 2001), its relationship to disease stage has not been defined. Far fewer studies have described astrocytic apoptosis in PiD, with most studies concentrating on neuronal apoptosis and the lack of overlap with abnormal tau deposition (Gleckman et al., 1999; Atzori et al., 2001).

Our data show that astrocytic apoptosis occurs at the earliest disease stages in both FTLD and PiD when there is only very mild frontotemporal atrophy, and that the degree of astrocytic apoptosis increases and correlates with the degree of neuronal loss and atrophy. This suggests that with ongoing tissue destruction, previously quiescent astrocytes become involved in the process, until by end-stage most remaining astrocytes participate in these changes. At this stage there is little remaining tissue with activated microglia the other major cell type involved (Schofield et al., 2003).

In the present study, many glial cells appeared to be undergoing apoptosis in FTD, but only astrocytes had significant expression of cleaved caspase-3, as reported previously (Su et al., 2000). In contrast, disease-associated neuronal apoptosis was rare, as described previously (Gleckman et al., 1999; Atzori et al., 2001). It has recently been shown that exposure to a limited insult can protect cells by preconditioning them, a process that activates caspase-3 binding to caspase-binding proteins, and prevents caspase activation leading to apoptosis (McLaughlin et al., 2003). Such a mechanism may play a role in the glial changes observed in the present study.

Activation of caspase-3 initially occurred in astrocytes found in cortical layers I, II and VI and the grey/white matter border (main synaptic layers for pyramidal cell dendrites; Peters and Jones, 1984; Thomson et al., 2002) and cortical layer IV (thalamic input layer; Thomson et al., 2002). At this stage, the majority of these astrocytes appear to be upregulated with increased GFAP-positive cytoplasm, although the fragmentation of some GFAP-immunoreactive processes heralds the increasing breakdown of their cytoskeletons over time. The laminar distribution of these early astrocytic changes is broader than the neurodegeneration at this time. Abnormal tau deposition is not an early feature of this astrocytic degeneration in PiD. The increasing astrocytic apoptosis with increasing disease stage and greater tissue loss is consistent with more significant axonal and white matter involvement over time in FTD, and has been shown to correlate directly with the degree of hypoperfusion (Martin et al., 2001). In PiD, abnormal tau accumulation appears within the degenerating processes of the astrocytes late in the disease process, displacing the activated caspase-3 immunoreactivity. We have previously shown that ~25% of GFAP-positive astrocytes accumulate abnormal tau in these cases, and that more astrocytes survive in these PiD cases compared with the FTLD cases studied (Schofield et al., 2003). Importantly, the death of astrocytes and the loss of their support mechanisms would significantly compromise surrounding neurons and may be the main mechanism of ongoing neuronal degeneration.

Overall, we provide novel evidence that astrocytic apoptosis occurs early in FTD, relates directly to the degree of degeneration and becomes the overwhelming pathological feature as the disease progresses and substantial tissue is lost. This change appears to be independent of the
histopathological type of FTD and suggests that the neuro-degenerative mechanisms in FTD are assisted or precipitated by the loss of astrocytic support.

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**References**


