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Posterior parahippocampal gyrus pathology in Alzheimer's disease

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Abstract

The posterior parahippocampal gyrus (PPHG) of the non-human primate brain has a distinct dual role in cortical neural systems. On the one hand, it is a critical link in providing the entorhinal cortex and hippocampal formation with cortical input, while on the other hand it receives output from these structures and projects widely by disseminating the medial temporal lobe output to the cortex. Layer III of TF and TH areas (temporal areas F, H of von Economo and Koskinas (1925) and von Bonin and Bailey (1947) largely mediate the former (input) while layer V mediates the latter (output). We have examined areas TF and TH in the normal human brain and in Alzheimer's disease (AD) using pathological stains (Nissl, Thioflavin S) and phenotype specific stains non-phosphorylated neurofilament protein (SMI-32) and parvalbumin (PV). Seven clinically and pathologically confirmed AD cases have been studied along with six age-compatible normal cases. Our observations reveal that neurofibrillary tangles (NFTs) heavily invest the area TF and TH neurons that form layers III and V. In both cortical areas, the large pyramids that form layer V contain a greater number of NFTs. These changes, and possibly, pyramidal cell loss, greatly alter the cytoarchitectural picture and diminish SMI-32 staining patterns. Layer III of area TH loses the majority of SMI-32 immunoreactivity, whereas this change is more conspicuous in layer V of area TF. PV-staining in both areas is largely unaffected. Normal cases contained no evidence of pathology or altered cytoarchitecture. These observations reveal a further disruption of memory related temporal neural systems in AD where pathology selectively alters both the input to the hippocampal formation and its output to the cortex.

Keywords

Alzheimer's disease; neurofibrillary tangles; posterior parahippocampal gyrus; hippocampal formation; memory; laminar pattern

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Introduction

The posterior parahippocampal gyrus (PPHG) is part of a system of structures in the medial temporal lobe that are anatomically interconnected to the hippocampus, while segregated and involved in memory processing functions. These cortical areas show atrophic and neuropathological changes in AD (Krasuski et al., 1998, Teipel et al., 2006, Whitwell et al., 2007). AD is a devastating degenerative dementia characterized neuropathologically by abundant neurofibrillary tangles (NFTs), neuritic plaques and the loss of neurons in the cerebral cortex. However, NFT pathological changes are not uniform throughout the cerebral cortex. Some cytoarchitectural areas are affected higher than others and, more specifically, deviations can be seen in different layers within these areas. The predominantly affected NFTs in AD are medium to large sized pyramidal neurons in the layers III, V and VI of the PPHG. The loss of these neurons that form corticocortical association systems are affected in AD (Morrison and Hof, 2002).

The first major connectional study in monkeys demonstrated that the corticocortical connections of the caudal portion of the parahippocampal gyrus receives massive convergent input from visual, auditory and somatosensory association cortices (Jones and Powell, 1970). In addition, layer III of the PPHG (areas TF and TH) provides input to the entorhinal cortex and hippocampal formation. These structures reciprocate the entorhinal cortex and hippocampal projection and areas TF and TH of layers III, V and VI then project widely to cortical limbic and association area (Zola-Morgan et al., 1989, Suzuki and Amaral, 1994a, b, Blatt and Rosene, 1998, Huther et al., 1998, Insausti et al., 1998b, Fernandez et al., 1999, Yukie, 2000, Munoz and Insausti, 2005). Furthermore, several other studies have addressed the organization of the cortical connections of the PPHG in non-human primates (Zola-Morgan et al., 1989, Suzuki and Amaral, 1990, Squire and Zola-Morgan, 1991, Suzuki and Amaral, 1994a, b, Suzuki, 1996).

A cytoarchitectonic study of von Economo and Koskinas divided the caudal medial temporal lobe in the human brain into medially positioned TH and TF areas (von Economo and Koskinas, 1925). Also, (von Bonin and Bailey, 1947) noted the same nomenclature and parcellated the posterior medial temporal lobe into areas TH and TF in a monkey. Other cytoarchitectonic studies in monkeys have defined that the parahippocampal cortex was made up of two areas (TH and TF), the medially located area TH and further area TF subdivided into two portions, laterally situated TF1 or TF lateral area and TF2 or TF medial area (Tranel et al., 1988, Blatt and Rosene, 1998, Yukie, 2000). However, connectional and cytoarchitectonic studies from this (Van Hoesen and Pandya, 1975a, Van Hoesen and Pandya, 1975b, Kondo et al., 2005, Saleem et al., 2007) and several other investigators (Amaral et al., 1987, Suzuki and Amaral, 1994b, a, Insausti et al., 1998a, Suzuki and Amaral, 2003) demonstrate clear cytoarchitecture differences between the anterior and posterior portions of the ventral medial temporal lobe.

In addition to the connectional studies in non-human primates, many other non-invasive functional neuroimaging studies in humans have shown that the PPHG is closely involved with memory related cognitive and object recognition functions (Fernandez et al., 1999, Harasty et al., 1999, Rombouts et al., 1999, Stark and Squire, 2000, Weniger and Irle, 2006).

The parahippocampal gyrus in the medial temporal lobe contains the greatest quantity of NFT pathology in AD (Arnold et al., 1991) although most investigations to date have focused on parahippocampal gyrus anterior components, mainly the entorhinal cortex and hippocampus. Our present study is to focus on the neuropathological changes observed in the PPHG in AD. This cortex is thought to play a crucial role in several of the memory processing associated behaviors in AD.

EXPERIMENTAL PROCEDURES

Brain tissue samples and histology

We used seven AD donor brains with dementia (Table. 1) and compared them with six, age matched controls with no history of neurological or psychiatric disease. The autolysis time for all of the cases was less than 6 hrs. For all cases, the ventromedial temporal lobe was dissected, and the tissue samples were immediately immersed in cold solution of 4% paraformaldehyde, 15% picric acid and 0.1 M phosphate buffer (PB), for 24 hours at 4°C. After 24 hrs, the blocks were placed in 30% sucrose in PB solution at 4° C until they sank. Thereafter, the blocks were cut on a freezing microtome at a thickness of 50 µm and the sections were collected in PB. The sections were mounted on the gelatin-coated slides.

Nissl staining and Thioflavin-S histochemistry

The sections were stained with thionin for Nissl substance and Thioflavin-S for NFTs and neuritic plaques (Van Hoesen et al., 1991, Thangavel et al., 2007). Nissl substance stained sections were observed under the microscope (Leitz, Diaplan). Thioflavin-S (0.1%, Sigma, St. Louis, MO, USA) stained sections for NFTs were used to examine the diameter of layer III and V in the area TH. The NFTs diameters were measured using Neurolucida software (MicroBrightField Inc., Colchester, VT). A microscope equipped with a camera and the image analysis software Neurolucida were used to chart the laminar location and distribution of NFTs in sections stained with Thioflavin-S histochemistry.

Immunohistochemistry

Series of frozen sections were processed for immunohistochemistry (Thangavel et al., 2007). The monoclonal antibody SMI32 (Sternberger Monoclonal, Baltimore, MD), which recognizes non-phosphorylated neurofilament protein epitopes and calcium binding protein parvalbumin (mouse anti-PV; Swant, Switzerland) was used. These antibodies were used at a dilution of 1:5000 5% normal rabbit serum in KPBS containing 0.4% Triton X-100 and incubated for 48 hrs at 4°C. Also, for the abnormally hyperphosphorylated tau protein, we used the AT8 antibody (dilution at 1:1000; Innogenetics, Ghent, Belgium). They were incubated with the corresponding biotinylated second antibody (1:1000, Jackson) for 1 h at room temperature. The sections were then processed with the avidin-biotin method using a Vectastain ABC kit (Vector Laboratories, Burlingame, CA). 3, 3'- diaminobenzidine (DAB, Sigma) was used as a chromogen to obtain a brown reaction product. Some sections were incubated in DAB with nickel ammonium sulfate to yield a black reaction product. For negative control experiments, sections were incubated in parallel by omission of the primary antibody. Finally, the sections were mounted, dehydrated, cleared with xylene, and coverslipped. The localization of PV and SMI-32 immunolabeling in relation to cytoarchitectonically identified structures was determined by viewing sections under the microscope.

Result

Topography

The parahippocampal gyrus can be subdivided into two parts: the anterior component which includes the entorhinal cortex and the posterior part which contains the isocortical area TF and proisocortical area TH fields. The boundaries and other delineation's of these areas were identified with the aid of Brodmann's and Von Economo maps (Fig. 1). Macroscopically, the entorhinal cortex can be visualized by small bumps on the external surface of the control human brain called the Verrucae gyri hippocampi (Fig. 2 A). Gross examination of the PPHG in the ventromedial temporal lobe showed severe atrophic changes in AD (Fig. 2 B). The PPHG is located caudal to the entorhinal cortex and perirhinal cortex at the level of the lateral geniculate

nucleus; the PPHG occupies the area immediately adjacent to the parasubiculum. Ventrolaterally, the PPHG ends at the collateral sulcus. Laterally, it adjoins the temporal isocortex. In the posterior, the anterior most tips of the calcarine sulcus cuts into the parahippocampal gyrus (Van Hoesen et al., 2000).

Microscopic examinations

The caudomedial temporal lobe has been partitioned into two different cytoarchitectonic areas in the PPHG. The medial and lateral subdivisions, corresponding to TH and TF areas of PPHG. Also, TH and TF areas encompassed posterior or caudal area 35 and rostrocaudal area 36 of Brodmann's map (Brodmann, 1909). Anteriorly, at the level of the lateral geniculate nucleus when the entorhinal cortex narrows, the parasubiculum moves medially and exposes the posterior part of the PPHG. Caudally, at the level of posterior pulvinar nucleus is the internal landmark for reliable delineation of the PPHG. Microscopically analyzed cytoarchitectonic areas of proisocortex –area35 or TH and TF were compared with a normal control (Fig. 4 A).

Area TH

Observations of the PPHG included its two sub regions (areas TH and TF). The cortical layers of areas TH and TF were identified in Nissl preparations (Fig. 4A). Area TH is a caudal continuation of the perirhinal cortex. At the level of the lateral geniculate nucleus, the proisocortical field of area TH is located along the medial portion parahippocampal cortex immediately adjacent to the parasubiculum. Area TH has lack of granule cells in the layer IV and layers V and VI are not clearly differentiated. Layer II is accentuated having an admixture of small and slightly larger neurons and has a dark staining, patchy appearance. Layer III is broader and well-developed but less dense population of large size pyramidal cells. There is a little separation between layers II and III in area TH. Layer III and V contained the mixed populations of pyramidal neurons in area TH. There is no clear gap between these two layers. Layer IV contains small pyramidal cells and layer V consists of large pyramidal neurons structurally closer to the isocortex. Nearing to the boundary of TF, the area TH has layers II and IV. Layers V and VI are merged together with dense populationsof large pyramidal neurons.

Area TF

The posterior part (adjacent to the TH) of the parahippocampal cortex is called area TF. Area TF is located directly lateral to the rhinal sulcus and perirhinal cortex. Area TF is an isocortical, larger and approximately corresponds to area 36 of Brodmann's map. The lateral boundary is caudal continuation of area 20 (area TE). Area TF contains well-differentiated layers including a granular layer IV. One of the most identifiable features is the patchy appearance of layer II cells. Layer V neurons are prominent in appearance and consist of large pyramidal cells that merge with layer VI. There is relatively broader layer III which contains large number of cells. The differentiation of layers V and VI is very distinct in TF area.

Nissl staining observations in AD

In AD cases, Nissl staining revealed a diffuse neuronal loss in layers III and V of the PPHG. The cytoarchitectonic appearance is not well preserved in the cortical fields (areas TH and TF) of the PPHG in AD (Fig. 4 B). Layer IV did not show much significant change in either areas TH and TF. In addition to laminar alterations, the cortical layer thickness, neuronal shape and neuronal size are easily observable in AD. Layer II is darkly stained and appeared as a thin band like structure in the area TF. In some cases, the patches disappeared and showed a weak staining in layer II. The marked cell loss is observed in layers III, IV and V. Gliosis were also noticed in both areas TH and TF. Layer IV clearly showed a dark staining because of less staining intensity in III and V of area TF.

Laminar Distribution and Topography of NFT pathology in PPHG

The PPHG is vulnerable to NFT pathology in AD. Microscopically, NFTs were densely distributed in cortical layers III and V in the PPHG in AD cases. The laminar distribution and topography of NFTs in the PPHG of one AD case is illustrated in Figure 3. NFTs first appeared in the perirhinal cortex which is corresponding to Braak's transentorhinal region (Braak and Braak, 1991). In AD, in the proisocortical portion of area 35 (TH), layer III contains medium to large size NFTs. The large pyramidal cells in layer III were heavily degenerated in this area. Layer V contained larger sized NFTs like other isocortical area. A selective population of pyramidal neurons in layers III and V are heavily damaged by NFTs of TH and TF. In long duration AD cases, the NFTs distribution, which was charted in the cross-sections, mimicked the pattern of pathology primarily found in cortical layers III and V in entire TF and TH areas (Fig. 3). Moreover, TH and TF cortical regions were heavily damaged throughout its long anterior-posterior course of NFTs in layers III and V in advanced AD. Particularly in layers III and V, large numbers of NFTs occurred in the PPHG. However, only a few NFTs were observed in layers II and VI. Also, we observed the mean diameter of NFTs in layer III of TH area was 9.43 μm and layer V was 12.06 μm . However, in TF cortex the mean diameter of NFTs in layer III was 9.8 μm and layer V was 12.25 μm . These results revealed that the mean diameter of NFTs in layers III and V of TH field varies from the layers III and V of TF area.

SMI32 Immunostaining

Non-phosphorylated neurofilament protein labeling with the antibody SMI32, recognizes the only specific subpopulation of pyramidal neurons in the PPHG of normal (Fig. 5 A) and AD brains (Fig. 6 A). The distribution of SMI32 immunoreactive neurons were located in layers II through VI of PPHG in control brains, but predominates in layers III and V, which contained the largest and strongest-labeled pyramidal cells. The variability of SMI32 staining intensity noticed in the deep portion of layer III and the superficial part of layer V contains the large strongly stained pyramidal cells. The long apical dendrites of SMI32 immunoreactive neurons were elongated towards the cortical surface. A high density of SMI32 immunoreactive neurons were distributed in bilaminar pattern layers III and V of area TF of the PPHG (Fig 7 A, C, and E). In AD groups, we have observed that the PPHG displays a considerable loss of SMI32 containing cells in layers III and V. The staining intensity of the SMI32 immunoreactive large pyramidal neurons was moderately reduced in AD cases. Marked loss of pyramidal neurons in both layers III and V was observed in areas TH and TF (Fig. 7 B, D, and F). However, when compared to layer V, a dramatic loss of pyramidal cells was observed in layer III of area TF in AD (Fig. 7 B, D).

PV-Immunostaining

In the present study, we have chosen the calcium binding protein PV, an immunocytochemical neuronal marker, which characterizes the neurochemical neurons in the PPHG of the control (Fig. 5 B) and AD brain (Fig. 6 B). PV-labels the small interneuron's cell body, axon and proximal dendrites which showed a unipolar morphology. Also, PV-immunolabeled neurons were distributed on layers II through VI of the PPHG. However, the PV-labeling shows a dark band of immunoreactivity more in the middle layers (layers III and IV) of area TF (Fig. 8). Some of the PV-immunoreactive cells have multipolar morphology and their neuronal soma was darkly stained. Two distinct patterns of PV-immunoreactivity are observed in the areas of TH and TF of PPHG in control and AD cases. The density of PV-immunoreactive cell bodies in the deep layer III in the area TF of PPHG was high. Area TH contains only a dispersed few and faintly PV-immunopositive cells in control and AD cases. No dark band-like structures appeared in the TH field. Moreover, the PV-immunoreactive cells were densely located and the band enlarged when approaching the area 20 in the fusiform gyrus. In our AD cases, PV-

immunopositive neurons did not show any major morphological alterations in their perikarya and dendritic processes in these cortical fields.

AT8 immunohistochemistry

AT8 immunostaining of adjacent serial sections of the ventromedial temporal lobe of an AD brain shows the cortical NFT lesions (Fig. 9) and laminar distribution pattern in areas TH (Fig 10 A, B) and TF (Fig. 10 C, D) of the PPHG. AT8 immunoreactive neurons and their processes were very strongly stained in layers III, V and VI. Also, we observed that the bilaminar pattern of AT8 immunostaining in these cortical layers of the PPHG. But the density of AT8 lesions was heavy in layer III of areas TH and TF. Also, AT8 immunostained NFTs appeared as cluster patterns in layers III and V of the PPHG. It should be noted that, very thick clusters were observed in area TH.

DISCUSSION

In the present study, we demonstrate that a severe neuronal loss occurred in layers III and V of areas TH and TF where NFTs appeared to be most numerous. Specifically, the NFT pathology predominates in layer III and V in both areas. The cortical areas that are closely interconnected with the limbic regions have the greatest vulnerability to NFT formation (Braak and Braak, 1991). Similarly, the interconnectivity of the PPHG with hippocampal formation and other associated cortical areas throughout the neocortical regions is crucial for memory (Van Hoesen et al., 1972, Van Hoesen and Pandya, 1975b, Morrison and Hof, 1997, Yukie, 2000). In this context, NFT formation in the PPHG may represent a critical stage of the neuropathological process, and a critical determinant of the clinical presentation of dementia in AD.

Although, (Brodmann, 1909) parcellated into medially located area 35, called the perirhinal cortex, and a more laterally situated area 36, designated as the entorhinal cortex in the human medial temporal lobe. In contrast, the entirely different nomenclature adopted to label the caudal medial temporal lobe in the human brain into TH and TF areas is based on their cytoarchitectural study (von Economo and Koskinas, 1925). Also, they labeled the medial temporal lobe as a rostral area TG. Similarly, von Bonin and Bailey 1947, also followed the same description of von Economo and Koskinas, and partitioned the posterior medial temporal lobe into areas TH and TF in monkeys. After re-examination of the cytoarchitectonic features of the monkey parahippocampal cortices in the context of their connectional studies of the medial temporal lobe (Van Hoesen and Pandya, 1975a, Van Hoesen and Pandya, 1975b). They also appreciated areas TH and TF, as originally described in the very early cytoarchitectural study (von Economo and Koskinas, 1925), and these areas are cytoarchitectonically different from other regions. We maintained the same nomenclature (Van Hoesen and Pandya, 1975a, Van Hoesen et al., 1975) which was originally from an earlier study (von Economo and Koskinas, 1925) and divided these regions into areas TF and TH; these two areas together were called the PPHG. Finally, more recent studies have shown that the cytoarchitectonic and chemoarchitectonic characteristics of the PPHG in non-human primate species are relatively similar to humans (Blaizot et al., 2004, Saleem et al., 2007).

The monkey parahippocampal cortex showed lesser staining intensity and distribution pattern of PV-immunolabeled neurons (Pitkanen and Amaral, 1993). This result would enable its homologue to identify the structures in the human parahippocampal cortex by PV-immunolabelling. As previous studies have demonstrated, PV-immunoreactive neurons in the neocortex are largely resistant to vulnerability and do not form the NFTs in AD (Hof et al., 1991, Hof, 1997, Sampson et al., 1997). There was no prominent loss of PV-immunopositive neurons in the PPHG of our AD cases. There was no obvious change in PV-immunoreactivity, especially in the area TF of PPHG, although there may be some loss or degeneration of PV-

immunoreactive neurons in these cortical fields. One study showed the PV-immunoreactive neurons were affected by regional variability in the parahippocampal gyrus of the patients with AD (Inaguma et al., 1992, Solodkin and Van Hoesen, 1996, Solodkin et al., 1996, Brady and Mufson, 1997).

In AD, the distributions of NFTs are predominantly in layers III and V in the PPHG (TH and TF areas). In these cortical areas, SMI32 primarily labels the medium to large sized pyramidal neurons, predominantly located within layers III and V in control the brain. In AD brain, we observed a reduced staining intensity of SMI32 immunoreactive pyramidal neurons of these layers in the PPHG, indicating that the alteration of these cytoskeletal proteins may take place during the course of the disease process. The laminar distribution pattern of NFTs in the PPHG strongly indicates that there is a clear association of this lesion with pyramidal neurons. Specifically, large pyramidal cells in layers III and V represent most of the affected cell types in these cortical areas. This suggests that these pyramidal neurons are long corticocortical projections originating from these layers and are likely to be selectively affected in AD (Morrison and Hof, 1997).

In summary, layers III and V of PPHG (area TF and TH) are heavily affected by NFT pathology in AD. Also, in both cortical areas the large pyramids that form layer V contain a greater number of NFTs. These changes and possibly, pyramidal cell loss, greatly alter the cytoarchitectural picture and diminish the SMI-32 staining patterns. Layer III of areas TH and TF loses the majority of SMI-32 immunoreactive pyramidal neurons, whereas this change is more conspicuous in layer V of area TF. Cortical pathology in AD selectively affects the memory-related temporal neural structures both in the input to the hippocampal formation and in its output to the cortex.

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Abbreviations

AD, Alzheimer's disease; NFTs, Neurofibrillary tangles; SMI32, non-phosphorylated neurofilament protein; PV, Parvalbumin; PPHG, Posterior parahippocampal gyrus, TF and TH areas (temporal areas F, H of von Economo and Koskinas (1925) and von Bonin and Bailey (1947); PB, Phosphate buffer.

Fig. 1. Brodmann's map of the human cerebral cortex in (A) lateral and (B) medial views. Von Economo and Koskinas' map of the human cerebral cortex in (C) lateral and (D) medial views. Note on the medial view that the ectorhinal cortex, which is approximately area 36 as assigned by Brodmann, corresponds to area TF of Von Economo and Koskinas (1925). This area adjoins the perirhinal cortex (area 35) on the lateral bank of the collateral sulcus and extends onto the PPHG. Area TH is a caudal continuation of the perirhinal cortex (area 35).

Fig. 2. Medial view of an age imaged control human brain (A) and AD brain (B) showing the external morphology. Notice the severe atrophic changes, shrunk and pitted appearance in the PPHG of the temporal lobe in the AD brain (B). Abbreviations: RS = rhinal sulcus, TP = temporal pole, EC = entorhinal cortex, CS = collateral sulcus, PPHG = posterior parahippocampal gyrus, CaS = calcarine sulcus

Fig. 3.

Neurolucida chartings of the distribution and topography of NFTs at the level of the PPHG in an AD case, showing the bilaminar and cluster pattern of NFTs distribution in layers III and V of area TF and a very dense distribution of NFTs in layer III and V of area TH. Note the heavy involvement of NFTs in layer V in both areas. The borders between the areas TH and TF in the PPHG are indicated by arrowheads. Abbreviations: CS=collateral sulcus, V=ventricle, S=subiculum, PaS=parasubiculum, DG=dentate gyrus

Fig. 4.

Nissl substance stained cross-section through the PPHG of the temporal lobe of the normal human brain (A) at the levels of lateral geniculate nucleus illustrates the comparison of cytoarchitectural organization of the PPHG (areas TF and TH) with a section from the medial temporal lobe of an AD brain (B). CS=Collateral Sulcus, DG=dentate gyrus, V=ventricle, PrS=presubiculum, PaS=parasubiculum, CaS= calcarine sulcus, LGN= lateral geniculate nucleus, MGN=medial geniculate nucleus, CA1=hippocampus, TH and TF = Von Economo and Koskinas cytoarchitectonic mapping areas

Fig. 5.

Photograph showing the immunohistochemical localization pattern of (A) SMI32 and PV (B) in the PPHG of control human brain. Sections were immunostained with primary antibodies against mouse monoclonal PV and SMI32 and were visualized by the ABC method. Notice in A the SMI32 immunostained pyramidal neurons distribution in layers III, V and VI throughout the cortex. Also, note that in B, PV immunoreactive neurons distribution pattern of areas TH and TF. Abbreviations: CA1, CA3=hippocampus, PrS=presubiculum, PaS=parasubiculum, S=subiculum, DG=dentate gyrus

Fig. 6.

SMI32 (A) and PV (B) immunostained temporal lobe coronal sections through the PPHG of an AD brain demonstrating the distribution pattern of SMI32 and PV-immunoreactive neurons in areas of TH and TF. Like the control, the very light PV-immunostaining pattern was shown in area TH. Note that there is an absence of the dark middle layers band in PV-immunostaining in this area. Abbreviations: CA1, CA3=hippocampus, PrS=presubiculum, PaS=parasubiculum, S=subiculum, DG=dentate gyrus

Fig. 7. Photograph showing TF area of control human brain (A, C) and AD brain (B, D) immunostained with SMI32 antibody. In AD brain, (B, D) there was a severe loss of SMI32 pyramidal neurons in layer III of areas TH and TF when compared to the control. But layer V SMI32 immunostained pyramidal neurons were not severely altered. E, area TH of control brain stained with SMI32 and F, showing the TH area of AD brain from fig. 6. Note the loss of large pyramidal neurons in layers III and V in areas TH and TF. However, the prominent loss of pyramidal cells was shown in layer III of both TH and TF areas. (A) A, B, E, F 10x Scale bar 100µm, C and 20x Scale bar 100 µm

Fig. 8. PV-immunostaining depicting the location and laminar distribution pattern of PV-immunoreactive neurons and fibers in the area TF of the PPHG in control human brain (A) and AD. Note the clear morphology of PV-immunoreactive neurons and their preservation as well as the dense band of immunoreactivity in middle layers. 10x scale bar 100μm.

Fig. 9.

The temporal lobe of an AD brain section immunostained for AT8 antibody showing the severe involvement of NFT pathology confined to areas TH and TF of the PPHG. Note, bilaminar distribution of AT8 stained neurons in layers III/V of areas TH and TF; numerous NFTs and neuropil threads; and dystrophic neurites.

Fig. 10. Neuropathological alterations in areas TH (A, C) and TF (B, D) of the PPHG visualized by AT8 immunostaining. These changes were distributed in layers III, V and VI of areas TH and TF. Also, note that the distribution of high density of AT8 immunoreactive neurons and fibers in layers III of area TH. Scale bar indicates 250 μ m (A, C, and 4 X) and 100 μ m (B, D 10X).

TABLE 1

SUMMARY OF CASES

Case no.	Age (years)	Sex	Autolysis (hours)	Dementia (years)	Brain weight (grams)
A 580	78	F	5	7	1100
A 578	76	F	4	8	1200
A 571	70	M	5	9,2	1246
A 569	89	M	3,45	10	1220
A 568	87	F	3	10	800
A 528	81	M	3,30	10	1190
A 504	72	M	3	12	875