Cell-Type-Specific Enhancement of Amyloid-β Deposition in a Novel Presenilin-1 Mutation (P117L)

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Abstract. The presenilin-1 (PS1) gene mutation (Pro117Leu), recently identified in a Polish family is characterized by the earliest reported onset (from 24–31 years) of Alzheimer disease (AD) and a very short duration of disease (4–6 years). The neuropathology of 2 subjects with this PS1 mutation (ages at death: 35 and 37 years) was compared to four Down syndrome (DS) patients (mean age at death: 62 years) and 4 sporadic AD patients (mean age at death: 79 years with a mean duration of disease of 18 years). The Polish familial AD (FAD) patients showed a marked increase in the amyloid burden of 2–6-fold in most areas of the brain. The entorhinal cortex was an exception where the amyloid burden was similar in each category of patient. Some brain regions of the Polish FAD patients showed a massive increase of amyloid, such as the molecular layer of the cerebellum where a 7- and 25-fold increase was noted, compared with DS and sporadic AD patients respectively. The cerebellar vessel amyloid burden was also greatly increased in the FAD patients, reflecting a vascular compartment specific increase of amyloid β deposition. The presence of this PS1 mutation has an even greater effect on both vascular and parenchymal amyloid deposition, than the overexpression of the amyloid β precursor protein present in DS patients, suggesting that PS mutations can be a critical factor determining amyloid deposition.

Key Words: Alzheimer disease; Amyloid-β; Mutation; Myocyte; Neuron; Presenilin.

INTRODUCTION

Alzheimer disease (AD) is an etiologically heterogeneous disorder, with both sporadic and familial forms of the disease. Three genes located on chromosomes 21 (β protein precursor, BPP), 14 (presenilin-1, PS1), and 1 (presenilin-2, PS2) are linked with familial Alzheimer disease (FAD). Six point mutations in the βPP gene are responsible for up to 1–2% of FAD cases (1–6). Two mutations have been found in the PS2 gene in 8 kindreds; 7 of them are of Volga German ancestry (7–9). However, the majority of early-onset FAD cases are associated with the over 43 mutations identified to date in the PS1 gene (10–18). All forms of AD are defined by the presence of amyloid β (Aβ) deposits in the brain parenchyma and cerebral vessels, neurofibrillary tangles and neuronal loss; however, the onset and duration of symptoms, as well as the distribution and quantity of amyloid may vary. Patients with PS1 mutations develop especially early and severe amyloidosis, with a mutation-specific pattern of pathological changes. In brains of patients with the PS1 gene mutation (Glu280Ala) an increase in Aβ42, but not in Aβ40, burden was found. Especially severe amyloidosis was observed in cerebellar parenchyma and vessels (19). The brain of a subject with the R269H mutation in the PS1 gene with onset of AD at 47 years-of-age and 9-year-long duration of AD had a higher Aβ1–42 burden. The latter case also showed a 1.5 fold higher number of NFTs compared to sporadic AD of matched duration, suggesting that PS1 mutations may also affect neurofibrillary degeneration (20).

We recently identified a novel PS1 mutation in a Polish FAD kindred (18) which is characterized by the earliest reported onset of dementia (24 years) and by very short duration of the disease (4–6 years). The aim of this study is to examine how this PS1 mutation (P117L) affects neuron and smooth muscle cell related Aβ deposition in this very aggressive form of AD.

MATERIALS AND METHODS

We compared the amyloid burden of 2 members of the Polish FAD kindred (who died at ages 35 and 37 years) with that of 4 patients with sporadic AD and 4 patients with DS. All the patients were matched clinically to be in the final stage of AD: GDS/FAST stage 7 (21). The duration of dementia in the PS1 mutation patients was only 6 years, while in the DS and sporadic AD groups the duration was on average 8 and 18 years respectively (Table 1). Sequence analysis of the DNA of both Polish FAD patients revealed a heterozygous CCA to CTGA mutation at codon 117 of PS1, producing a Pro to Leu amino acid substitution; no mutations in the PS2 or BPP genes were found (18). The subject with the PS1 mutation who died at the age of 37 years had the ApoE 3/3 genotype. As for the second patient, whose DNA could be isolated only from paraffin sections, all attempts to isotype ApoE have failed.

After at least 2 months' fixation in 10% buffered formalin, the brains were cut coronally into 5- to 10-mm-thick slabs,
TABLE 1
Case Descriptions

<table>
<thead>
<tr>
<th>Group</th>
<th>Case no.</th>
<th>Age at death (yr)</th>
<th>Sex</th>
<th>GDS/FAST</th>
<th>Duration of dementia (yr)</th>
<th>Cause of death</th>
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<tbody>
<tr>
<td>PS1-FAD</td>
<td>184-96</td>
<td>35</td>
<td>F</td>
<td>7d</td>
<td>6</td>
<td>Bronchopneumonia</td>
</tr>
<tr>
<td></td>
<td>185-96</td>
<td>37</td>
<td>F</td>
<td>7d</td>
<td>6</td>
<td>Bronchopneumonia</td>
</tr>
<tr>
<td>DS/AD</td>
<td>882-93</td>
<td>60</td>
<td>M</td>
<td>7d</td>
<td>10</td>
<td>Aspiration pneumonia</td>
</tr>
<tr>
<td></td>
<td>861-93</td>
<td>62</td>
<td>F</td>
<td>7e</td>
<td>4</td>
<td>Aspiration pneumonia</td>
</tr>
<tr>
<td></td>
<td>299-95</td>
<td>62</td>
<td>M</td>
<td>7d</td>
<td>12</td>
<td>Pulmonary edema</td>
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<tr>
<td></td>
<td>779-94</td>
<td>64</td>
<td>F</td>
<td>7d</td>
<td>7</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Sporadic AD</td>
<td>330-90</td>
<td>68</td>
<td>M</td>
<td>7b</td>
<td>13</td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>434-91</td>
<td>77</td>
<td>M</td>
<td>7e</td>
<td>19</td>
<td>NA</td>
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<tr>
<td></td>
<td>585-90</td>
<td>84</td>
<td>F</td>
<td>7c</td>
<td>17</td>
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<tr>
<td></td>
<td>Mean 79</td>
<td></td>
<td></td>
<td>Mean 18</td>
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</table>

processed, and embedded in paraffin. Serial 8-μm-thick sections were cut; stained with cresyl violet, thioflavin S, and Bielschowsky silver method; and immunostained with monoclonal antibody (mAb) 4G8 raised against the 17–24 amino acid sequence of Aβ protein (22), and with polyclonal antibodies (pAbs) R163, which recognizes Aβ residues 32–40, and pAb R165, which recognizes Aβ residues 32–42. The PS1 protein distribution was characterized by using mAb D3G6, which is specific for amino acid residues 160–168 of PS1 (23). The clinical diagnosis of AD was confirmed histopathologically according to CERAD criteria (24).

The amyloid load (percentage of the surface area of a given brain subdivision that is occupied by Aβ) in the hippocampal formation and the cerebral and cerebellar cortex was estimated as the measure of parenchymal amyloidosis-β. The measures of amyloid angiopathy are the numerical density of amyloid-positive profiles of arteries and veins (n/mm²) and the percentage of amyloid-positive vascular profiles (vascular amyloid load). The numerical density of Aβ-positive and -negative vessels in the leptomeninges was calculated per 1 millimeter of the leptomeningeal contour at 280× magnification. Cortical amyloid angiopathy was characterized by the numerical density (n/mm²) of amyloid-positive vessels. In the hippocampal complex subdivisions, amyloid deposits were examined in from 10–20 randomly selected test areas, and in the cerebral and cerebellar cortex, in more than 30 randomly selected test areas at 280× magnification. For morphometry, a digitizer (Numonics) and a morphometric program (Sigma Scan-Jandel Scientific) were used.

RESULTS

PS1 protein distribution in the brain

Monoclonal antibody D3G6 immunolabels neuronal perikarya and dendrites (Fig. 1a). Some neurons show only a weak reaction or none at all, such as some Purkinje cells. Nonstained Purkinje cells were more often in the DS group than in the sporadic AD or PS1 mutation groups. Ghost tangles are not stained (Fig. 1b). Rare plaques are labeled with mAb D3G6. The PS1 immunoreaction is detectable in neuronal processes in the plaque perimeter, but not in amyloid deposits (Fig. 1c). Oligodendroglia, microglia, and the majority of astrocytes are not stained. Strong immunopositivity is detectable in the cytoplasm of myocytes in the tunica media of arteries and veins (Fig. 1d).

Amyloidosis-β

In most brain areas there was a marked increase of Aβ immunoreactive structures in the PS1 patients compared to the DS and sporadic AD cases.

In the entorhinal cortex, hippocampal formation, neocortex, and cerebellar cortex, there is no significant difference in the amyloid load detected with mAb 4G8 and pAb R165 corresponding to Aβ42. The description of results is based on the morphometry of sections stained with pAb R165. In the majority of examined structures, the amount of Aβ40 was at least 76% less than that of Aβ42. In the cerebellar cortex, only a few deposits were Aβ40-positive. In cerebellar leptomeningeal vessels, amyloid load detected with mAb 4G8 and pAbs R163 and R165 was similar.

Entorhinal Cortex and Hippocampal Formation: The amyloid load of Aβ42 in the entorhinal cortex varies from 1.9% in Polish FAD patients to 2.9% in DS in the molecular layer, and from 7.2% in sporadic AD to 11.4% in the pyramidal layer of Polish FAD patients; however, the differences between FAD, DS, and sporadic AD are insignificant (Table 2). Amyloid load of Aβ40 is variable in specific layers but is always at least 76% less than that of Aβ42.

The topographic pattern of amyloidosis in the hippocampal formation subdivisions is similar in all 3 groups. Amyloid deposits are more numerous in the external zone of the molecular layer of the dentate gyrus (Fig. 1e) and in the stratum pyramidale and radiatum of the cornu Ammonis than in other layers. Morphometry shows that the amyloid load of Aβ42 in the stratum pyramidale and ra-
datum of subjects with the PS1 mutation (10.8% and 11.8%, respectively) is about 2 times higher than in the stratum oriens and lacunosum (4.0% and 5.5%, respectively). In all these hippocampal formation compartments, the amyloid load is several times more in the Polish FAD patients compared to DS or AD patients. The difference between the amyloid load in the DS and AD patients at the end stage of disease is insignificant.

**Neocortex:** The cerebral cortex of Polish FAD patients has many more amyloid deposits than in that of individuals with DS or sporadic AD. Morphometry shows that about 3–4% of the frontal, temporal, parietal, occipital, and limbic cortex of patients with DS or sporadic AD is infiltrated with Aβ42 (Table 3). In the PS1 mutation, the amyloid load increases to 7.2 ± 2.1% and 7.8 ± 3.5% in the frontal and limbic cortex, respectively, and to about 12–13% in the temporal, parietal, and occipital cortex.

The numerical density of the cerebral cortical Aβ positive vessels in the Polish FAD patients was slightly higher—2.7/mm²—vs 1–2/mm² among DS and AD patients; however, this difference is not statistically significant.

**Cerebellar Amyloid Angiopathy and Cortical Amyloidosis:** Almost all the profiles of leptomeningeal vessels of the cerebellum and numerous cortical cerebellar vessels in the Polish FAD patients are infiltrated by Aβ (Fig. 1f). The portion of the vascular network involved in amyloid deposition decreases in the molecular layer; however, often the whole length of the ramifications of leptomeningeal arteries penetrating the molecular layer of the cerebellar cortex also is occupied with amyloid (Fig. 1g). Relatively few vessels in the granular layer show amyloid deposits, whereas the vessels of white matter are free of amyloid.

Morphometry shows that there is no significant difference in the number of cerebellar leptomeningeal vessels per millimeter of the leptomeningeal contour detected with antibodies to Aβ42 (mAb 4G8 and pAb R165) and Aβ40 (pAb R163). The numerical density of amyloid-positive vessels immunolabeled with these 3 antibodies is about 2 times higher in the PS1 patients (4.5/mm ± 0.69/mm) than in the DS population (2.2/mm ± 1.2/mm), and almost 5 times higher than in sporadic AD (0.97/mm ± 0.54/mm) (Table 4).

The amount of amyloid-positive cerebellar cortical vessels is considerably less than in leptomeninges; however, the range of differences in the numerical density of vascular profiles with amyloid is larger. The numerical density of Aβ42-positive vessels in the molecular layer of the cerebellar cortex in the PS1 mutation (26.85/mm² ± 4.97/mm²) is 7 times more than in DS (3.84/mm² ± 3.83/mm²), and about 21 times more than in sporadic AD (1.06/mm² ± 1.87/mm²).

Vascular amyloidosis in the deeper layer of the cerebellar cortex is less than in the molecular layer in all 3 groups of subjects. The numerical density of Aβ42-positive vessels in the granular layer in the PS1 mutation (9.03/mm² ± 12.26/mm²) is almost 10 times more than in DS (0.93/mm² ± 2.03/mm²) and 14 times more than in sporadic AD (0.65/mm² ± 0.01).

In the PS1 mutation, DS, and sporadic AD, the numerical density of vessels in the molecular layer immunolabeled with pAb R163 to 32–40aa is 78%, 67%, and 76% less, respectively, than the numerical density of vessels detected with pAb R165. Similar proportions are seen also in the granular layer of the cerebellar cortex.

A remarkable portion of the cerebellar molecular layer in the Polish FAD patients is occupied by diffuse Aβ deposits present in 2 forms: as perivascular deposits and as amyloid deposits between dendritic processes of Purkinje cells (Fig. 1h). The deposits in DS and especially in sporadic AD are much less numerous than in PS1 mutation.

The portion of the molecular layer in the cerebellar cortex infiltrated by diffuse pAb R165-positive deposits varies in range from 0.15 ± 0.16% in sporadic AD to 4.54 ± 1.0% in DS and to 10.58 ± 5.19% in PS1 mutation. Amyloid load detectable with these 2 antibodies in the granular layer of the cerebellar cortex varies in range from 2.8 ± 4.9% in PS1 mutation, to 0.28 ± 0.30% in DS and 0.20 ± 0.06% in sporadic AD, but the differences are insignificant. Only a very few cerebellar diffuse amyloid deposits that are pAb R165-positive (0.01 ± 0.02%) are positive when stained with pAb R163 raised to Aβ residues 32–40.

**DISCUSSION**

We have conducted a comparison of the neuropathological changes in the brains of 2 Polish FAD patients with a PS1 P117L mutation, with 4 subjects each with DS and sporadic AD. All the patients were matched for the final stages of AD. Despite the fact that the duration of illness was far greater in both the DS and sporadic AD patients, we found a remarkable increase in the amyloid burden of the PS1 mutation patients in most areas of the brain, suggesting that PS play a very important role in the pathogenesis of AD.

In neocortical areas the Polish FAD patients had a 1.7–3-fold increase in the amyloid burden compared to either DS or sporadic AD. Interestingly in the molecular and pyramidal layers of the entorhinal cortex comparable levels of amyloid were seen in all 3 categories of patients. This suggests that the cerebral amyloid enhancing properties associated with this PS1 mutation have some brain regional specificity. Our prior ultrastructural studies have indicated that Aβ deposition in the brain parenchyma is associated with either neurons (25) or microglial cells (26, 27). Hence, it would seem that some neuronal or microglial populations are relatively resistant to the effects of this PS1 mutation or they have a plateau beyond.
Fig. 1. Immunodetection of PS1 with mAb D3G6 in the brain of subject with PS1 mutation (a--d). (a) Strong cytoplasmic reaction in the Purkinje cell body and a weaker reaction in dendritic tree (arrow). (b) Positive reaction in the cytoplasm of the pyramidal cells with neurofibrillary changes but no reaction in ghost tangles (arrows) (CA1 sector). (c) Weak immunoreactivity in the dystrophic neuronal processes (arrow) in plaque perimeter in the CA4 sector. Positive material in the pyramidal neuron (2 arrows) but no reaction in glial cells (small arrows). (d) Strong reaction in smooth muscle cells (arrow) in the wall of the leptomeningeal vessel.
TABLE 2
The Average Amyloid Load (%) in the Entorhinal Cortex, Dentate Gyrus, and Cornu Ammonis Subdivisions Detected With pAb R165 (± SD)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PS1 mutation</td>
</tr>
<tr>
<td>Entorhinal cortex</td>
<td>1.9 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>11.4 ± 13.6</td>
</tr>
<tr>
<td>Dentate gyrus</td>
<td>18.7* ± 3.2</td>
</tr>
<tr>
<td></td>
<td>1.5 ± 2.0</td>
</tr>
<tr>
<td>Cornu Ammonis</td>
<td>S. oriens</td>
</tr>
<tr>
<td></td>
<td>S. pyramidal</td>
</tr>
<tr>
<td></td>
<td>S. radiatum</td>
</tr>
<tr>
<td></td>
<td>S. lacunosum-molecular</td>
</tr>
</tbody>
</table>

* Significant difference between PS1 and both DS and sporadic AD (p < 0.01).

TABLE 3
The Average Amyloid Load (%) in the Neocortex Detected With pAb R165 (± SD)

<table>
<thead>
<tr>
<th>Cortical region</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PS1 mutation</td>
</tr>
<tr>
<td>Frontal (superior, middle, orbital, precentral gyrus)</td>
<td>7.2* ± 2.1</td>
</tr>
<tr>
<td>Temporal (superior, middle, inferior, fusiform gyrus)</td>
<td>12.1* ± 4.8</td>
</tr>
<tr>
<td>Parietal (superior, supramarginal, angular gyrus and precuneus)</td>
<td>12.9* ± 3.4</td>
</tr>
<tr>
<td>Occipital (lingual gyrus)</td>
<td>12.2* ± 1.9</td>
</tr>
<tr>
<td>Limbic (gyrus cinguli)</td>
<td>7.8* ± 3.5</td>
</tr>
</tbody>
</table>

* Significant difference between PS1 and both DS and sporadic AD (p < 0.01).

The mechanism by which PS1 mutations accelerate amyloid formation remains unclear. One possibility is by increasing Aβ42 production. The plasma of patients with PS1 mutations, who are presymptomatic and symptomatic, show increased Aβ42 (34). Furthermore, both cells transfected with PS1 mutations (35–38) and transgenic mice with PS1 mutations (35, 36, 39) show increased Aβ42 production. Our study shows a far greater increase

\[ \text{Detection of Aβ42 with pAb R165 (e–h). (e) Row of plaques in the external two-thirds of the molecular layer (M) of the dentate gyrus. G-granular layer; P-polymorphic layer. (f) Almost all profiles of the cerebellar leptomeningeal vessels are amyloid-positive. The molecular layer of the cerebellar cortex contains numerous amyloid deposits. A few clusters of amyloid (arrow) are detectable in the Purkinje cell layer and in the narrow rim of the granular layer close to the molecular layer. (g) The whole length of the branch of leptomeningeal vessel perforating the molecular layer is infiltrated by amyloid. (h) Amyloid between dendritic processes of Purkinje cell.} \]
in the Aβ42 immunoreactive deposits among the Polish FAD patients, consistent with this notion. In the entorhinal cortex or the hippocampus of the Polish FAD patients, less than 24% of the amyloid deposits were immunolabeled with pAb R163 (Aβ40 specific) compared to either mAb4G8 or pAb R165 (Aβ42 specific) immunolabeling. Increased Aβ42 or total soluble Aβ has been suggested to be a common mechanism by which all FAD linked mutations have their effect. The βPP mutation located just amino terminal to Aβ (βPP<sub>K<sup>670V,M<sup>671L</sub></sup></sub>) increases secretion of Aβ1–40 and Aβ1–42 (43), whereas the FAD-linked mutations carboxy terminal to Aβ (βPP<sub>V<sup>71L,F</sup> or G</sub>) selectively increase the concentration of Aβ1–42 (43) (40, 41). Hence some βPP and PS1 mutations can act through this common pathway. However, other possibilities exist for the effects of PS1 mutations. PS mutations are known to sensitive neural cells to apoptosis induced by trophic factor withdrawal, metabolic insults, and Aβ peptides (42). If increased apoptosis is the primary pathological mechanism of PS1 mutations, the increased Aβ42 production could represent a reactive process. An alternative hypothesis is that mutated presenilins could be an initiating factor for Aβ peptide fibrillogenesis (43, 44).

A striking finding was the extensive involvement of the cerebellum with Aβ deposition among the Polish FAD patients. In these 2 patients seven-fold more Aβ immunoreactivity was present in the molecular layer compared to DS and 25-fold more compared to sporadic AD. These molecular layer diffuse Aβ deposits are columnar (Fig. 1f), suggesting that the Purkinje cells or nerve endings on Purkinje cell dendrites may be a source of these deposits. These deposits are almost exclusively Aβ42 immunoreactive. Both immunochemistry with anti-PS1 antibodies (23) and in situ hybridization have shown that Purkinje cells belong to a group of neurons with strong expression of both PS1 and βPP (45).

The cerebellar blood vessels show even greater involvement with Aβ deposits. The Polish FAD patients show a 91% amyloid load in cerebellar leptomeningeal vessels, 7 times more amyloid-positive vessels in the molecular layer and 10 times more in the granular layer of the cerebellar cortex than in DS. Our prior ultrastructural studies have indicated that Aβ accumulates between smooth muscle cells of the tunica media and that myocytes are the source of Aβ (46). Smooth muscle cells encapsulated in amyloid coat die, and the wall of vessel becomes thinner and weaker. These changes can cause multiple cortical infarcts and hemorrhages (47–51). The absence of hemorrhages in brains of subjects with PS1 mutation and severe vascular amyloidosis may indicate that the loss of smooth muscle cells during the 6-year duration of the disease of relatively young people was less damaging than in elderly populations with almost 20-year duration of sporadic AD. Immunoreactivity with our anti-PS1 antibody (mAb D3G6) is particularly strong in the smooth muscle cells of the cerebellar leptomeningeal vessels (Fig. 1d). This high level of PS1 expression in this location may be related to the extensive Aβ deposits in the same sites.

The P117L PS1 mutation is associated with the most aggressive form of FAD reported so far, with an onset of disease at age 24 years. We document that the amyloid burden in this kindred is far greater than that seen in either sporadic AD or DS patients with much greater disease duration. The increased Aβ deposits are primarily Aβ42 immunoreactive, consistent with a possible role for PS1 in regulating γ-secretase function. However, the role of PS1 mutations in accelerating AD pathology remains uncertain and may be through other mechanisms. The effects of the P117L PS1 mutation show brain regional and cellular specificity. In the entorhinal cortex this PS1 mutation is not associated with any more amyloid then in sporadic AD or DS, while in the cerebellum there is a massive increase in the Aβ load, both in the molecular layer and in blood vessels. Interestingly, the Purkinje cells and smooth muscle cells associated with the deposits in the latter 2 locations show particularly strong PS1 immunoreactivity, suggesting a possible correlation between PS1 expression and Aβ deposition in this location. Our findings highlight the importance of local cellular and other factors in determining amyloid deposition, and also indicates an important role of PS1 in congophilic angiopathy.
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