Neuropathological and Clinical Phenotype of an Italian Alzheimer Family with M239V Mutation of Presenilin 2 Gene

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Abstract. Presenilin 1 and 2 are 2 highly homologous genes involved in familial Alzheimer disease. While more than 100 mutations in presenilin 1 are known to segregate with the disease in familial Alzheimer disease, only 9 mutations of presenilin 2 have been identified to date. We report the clinical and neuropathological phenotype of FLO10, the large Italian Alzheimer kindred associated with methionine to valine substitution at residue 239 of presenilin 2. The patients showed a remarkable variability in age of onset of symptoms, disease duration, and clinical presentation. The neuropathological study of 2 patients revealed peculiar features in addition to neurofibrillary changes and Aβ amyloid deposits in the neuropil and vessel wall. Ectopic neurons in the subcortical white matter, often containing neurofibrillary tangles, were found in both patients, one of whom presented with epilepsy. Furthermore, 1 patient showed an unusually high number of ghost tangles in the cerebral cortex. These observations indicate that the Alzheimer kindred FLO10 associated with M239V mutation of presenilin 2 is characterized by some peculiarities of the clinical and neuropathological phenotype compared to sporadic Alzheimer disease.

Key Words: Aβ; Alzheimer disease; Ectopic neurons; Epilepsy; Ghost tangles; Mutation; Presenilin 2.

INTRODUCTION

Presenilin familial Alzheimer disease (FAD) is inherited as an autosomal dominant condition, associated with defects in at least 3 different genes: β-precursor protein (BPP) (1) and 2 highly homologous genes, presenilin 1 (PSEN1) (2) and presenilin 2 (PSEN2) (3). More than 100 missense mutations in PSEN1 are known to segregate with the disease in families of different national and ethnic origins accounting for about 50% of FAD (http://molgen-www.uia.ac.be/ADMutations/) and some PSEN1 mutations are associated with clinical symptoms and neuropathological lesions not typically observed in sporadic Alzheimer disease (AD). One of these lesions is the presence of ectopic white matter neurons, which has been reported previously in FAD linked to S169L mutation of PSEN1 (4).

On the other hand, only 9 missense mutations of PSEN2 have been identified to date. Moreover, 5 of them—R62H (5), T122P (6), V148I (7), T430M (8) and D439A (9)—have been reported in single patients. The other 4 PSEN2 mutations are N141I in the extended Volga German kindred (3, 10), M239I in a family from northern Italy (11), S130L in a family from central Italy (12), and M239V in a large Italian pedigree indicated as FLO10. This mutation has been identified in 1995 (10) and further genetic and clinical data were reported later (13).

Neuropathological studies of FAD linked to PSEN2 mutations are few (14–17). This report is the first to describe the neuropathology associated with the M239V mutation of PSEN2. Peculiar features in addition to the characteristic Alzheimer lesions were numerous ectopic neurons in the subcortical white matter, often containing neurofibrillary tangles (NFTs), and an unusually high number of extracellular (“ghost”) NFTs immunoreactive for Aβ40. Our results show that ectopic white matter neurons occur in FAD associated with a genetic defect of PSEN2 and provide further evidence of phenotypic heterogeneity of FAD linked to presenilin mutations.

MATERIAL AND METHODS

Pedigree

FLO10 was initially studied in 1989, following an in-patient evaluation of the proband (IV-16) for early-onset dementia. We reconstructed a pedigree consisting of 134 members over 5 generations. Figure 1 shows an abbreviated version of the pedigree, in which the subjects of the fifth generation have been omitted because they are all younger than 40 years (still below the mean age of onset of the disease) and clinically unaffected. Most members of FLO10 live in Friuli Venezia-Giulia, a northeastern Italian region, with small branches in France and Great Britain. For patients of the first, second, and third generations, information on the affected members were obtained by parish registers, historical archives, medical records, and conducting interviews with relatives; while for 3 of the 5 patients of the fourth generation (IV-16, IV-18, IV-29) the clinical evidence of...
Morphometric analysis of Aβ burden (percentage area occupied by Aβ immunoreactivity) was carried out on 10-μm-thick sections of the cerebral cortex immunostained with polyclonal anti-Aβ42 antibody, using a Nikon Eclipse E800 microscope (Nikon, Tokyo, Japan) equipped with a color video camera (Nikon DXM 1200) and a computer-based image analysis system (Lucia Measurement, version 4.60, Laboratory Imaging, Prague, Czech Republic). After establishing a density threshold, the software calculated the percentage area occupied by the reaction product by dividing the area of immunopositivity by the total area. Briefly, using a ×10 objective, we measured 25 contiguous fields across the entire cortical thickness in the frontal, temporal, and parietal lobes.

Morphometric analysis of white matter ectopic neurons was carried out on sections immunostained with antibody anti-repeat region of tau, using a Nikon Eclipse E800 microscope. We selected the white matter areas randomly avoiding directly subcortical and periventricular regions in the frontal, parietal, and temporal lobes. The neurons were counted in 100 consecutive fields using a ×40 objective (each measuring 0.11 mm²) in the selected areas.

**Molecular Genetics**

Following the genetic study of the proband that showed an A-to-G mutation at nucleotide 1080 of PSEN2 resulting in methionine to valine substitution at residue 239 (10), the analysis was extended to 22 unaffected and 8 affected family members. DNA for the genetic studies was obtained from peripheral leukocytes.

**RESULTS**

**Clinical Features**

Eighteen members of FLO 10 (7 men and 11 women) over 4 generations developed progressive dementia fulfilling the criteria for the clinical diagnosis of AD (23). The mode of inheritance was consistent with an autosomal dominant disorder with high penetrance (Fig. 1). The mean age of onset was 60.1 ± 10.0 years (range 45 to 83), based on 15 affected members for whom this information was considered reliable. The mean age at death was 71.1 ± 9.6 years (range 59 to 87), and the mean duration of the disease was 11.3 ± 4.7 years (range 4 to 22) (Table 2).

Detailed clinical data for 3 patients revealed a striking variability of the clinical picture and preliminary data of the personality assessment in 3 mutated unaffected subjects showed no differences in affective, personality, and imaging profiles in comparison with control (nonmutated) members of the family (24).

**Patient IV-16: Proband**

At age 45 this patient started to complain of memory loss, difficulty concentrating, and depressive mood. Three years later the disease was characterized by a serious impairment of memory, aphasia, and disorientation in time and place. Neurological examination showed brisk tendon reflex, rigidity of lower and upper limbs, and grasp reflex. Computed tomography (CT) scan of the head showed supratentorial atrophy with ventricular enlargement. She was always calm and never required neuroleptic medications. Five years after the onset the patient was incontinent and unable to communicate. The disease then progressed to a condition characterized by severe dementia and spastic tetraparesis and the patient died at age 59.

**Patient IV-18: Brother of Patient IV-16**

At age 52 the patient started to complain of depressive mood and presented a generalized convulsive epileptic seizure. One year later he developed memory loss and disorientation in time and place. The progression of the
TABLE 1

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Antigen/Epitope</th>
<th>Type</th>
<th>Pretreatment (fixation)</th>
<th>Source/Reference</th>
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<tr>
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</tr>
<tr>
<td>6F3D</td>
<td>Aβ 8–17</td>
<td>m</td>
<td>formic acid 98%, 15 min (formalin)</td>
<td>DakoCytomation</td>
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<tr>
<td>4G8</td>
<td>Aβ 17–24</td>
<td>m</td>
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<tr>
<td>EM2</td>
<td>Aβ x-40</td>
<td>p</td>
<td>formic acid 98%, 15 min (formalin)</td>
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</tr>
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<td>p</td>
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<td>Innogenetics (20)</td>
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<tr>
<td>ubiquitin</td>
<td>ubiquitin</td>
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<td>Sigma</td>
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<td>nonphospho-NF</td>
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<td>SMI31</td>
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<tr>
<td>α-synuclein</td>
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<td>22C11</td>
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<td>m</td>
<td>none (Carnoy)</td>
<td>Chemicon</td>
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<tr>
<td>CR3/43</td>
<td>β-chain of MHC-II</td>
<td>m</td>
<td>none (Carnoy)</td>
<td>DakoCytomation</td>
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</table>

Abbreviations: m, monoclonal antibody; p, polyclonal antibody; βPP, β-precursor protein; GFAP, glial acidic fibrillary protein; phospho-tau, phosphorylated tau; nonphospho-NF, nonphosphorylated neurofilament; phospho-NF, phosphorylated neurofilament; MHC-II: major histocompatibility complex class II antigen.

Locations of sources/references: DakoCytomation, Carpinteria, CA; Senetek PLC, Napa, CA; Dr. Blas Frangione, New York University School of Medicine, New York, NY; Dr. Peter Davies, Albert Einstein College of Medicine, Bronx, NY; Innogenetics, Gent, Belgium; Bio-Rad, Hercules, CA; Sigma, St. Louis, MO; Sternberger Monoclonals, Lutherville, MD; Dr. Bernardino Ghetti, Indiana University School of Medicine, Indianapolis, IN; Chemicon, Temecula, CA.

TABLE 2

<table>
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<th>Duration of disease</th>
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<tr>
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<td>60</td>
<td>11</td>
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<tr>
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<td>60</td>
<td>75</td>
<td>15</td>
</tr>
<tr>
<td>III-21</td>
<td>62</td>
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<td>5</td>
</tr>
<tr>
<td>III-22</td>
<td>60</td>
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<td>III-25</td>
<td>73</td>
<td>84</td>
<td>11</td>
</tr>
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<td>45</td>
<td>59</td>
<td>14</td>
</tr>
<tr>
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<td>48</td>
<td>61</td>
<td>13</td>
</tr>
<tr>
<td>IV-18</td>
<td>52</td>
<td>63</td>
<td>11</td>
</tr>
<tr>
<td>IV-29</td>
<td>58</td>
<td>(born 1942)</td>
<td>2 (alive)</td>
</tr>
<tr>
<td>IV-33</td>
<td>66</td>
<td>(born 1931)</td>
<td>3 (alive)</td>
</tr>
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</table>

The onset of the disease at age 58 was dominated by important behavioral signs, such as persecutory delusions, verbal and physical aggressive behaviors against the daughter, and psychomotor agitation. She also had loss of memory and disorientation in time and place. One year later a cerebral MRI was normal, while a SPECT showed bilateral hypoperfusion of the occipital lobes and the left basal ganglia. The neurologic examination was unrevealing. Treatment with cholinesterase inhibitors did not change the clinical picture, while neuroleptic treatment (olanzapine 10 mg/day) improved the psychiatric symptoms.

Genetics

The A-to-G transition at nucleotide 1080 causing methionine to valine substitution at residue 239 of PSEN2 was present in 8 affected and absent in 14 unaffected members of the family. Eight healthy subjects of generation IV and V (range 30 to 51 years) carried the M239V...
mutation of PSEN2 (not shown in Fig. 1 for ethical reasons). No demented patients without PSEN2 mutation were identified in the family.

Neuropathology

Both patients showed diffuse cerebral atrophy, the weight of the fresh brain being 950 g in patient IV-16 and 1,030 g in patient IV-18. Microscopically, AD was recognized by the presence of senile plaques and NFTs in the neuropil. In both brains the quantity of these lesions was consistent with the diagnosis of definite AD by the CERAD criteria, with stage VI of Braak and Braak of neurofibrillary pathology and of high likelihood AD using the NIA-Reagan criteria (25–27).

Patient IV-18

Severe neuronal loss and gliosis was present throughout the cortex. Fluorescence microscopy after thioflavine S treatment revealed amyloid deposits in the cerebral cortex and in several subcortical nuclei as well as amyloid-laden vessels in the cerebral cortex parenchyma and in the leptomeninges of the cerebral hemispheres and cerebellum (Fig. 2A, B).

Anti-Aβ42 and 4G8 labeled the largest number of amyloid and preamyloid deposits in the cerebral cortex (Fig. 2C–E). Aβ burden measured in sections immunostained with the Aβ42 antibody was 15.0%, 14.4%, and 17.1% in the frontal, temporal, and parietal cortex, respectively. Aβ deposits were also abundant in the caudate nucleus, putamen, claustrum, thalamus (Fig. 2F), and the brainstem. Anti-Aβ42 and 4G8 also immunostained diffuse subpial deposition of Aβ in the cerebral cortex (Fig. 2C, E) and numerous preamyloid deposits in the molecular layer of the cerebellum (Fig. 2G, H). Anti-Aβ40 labeled a small fraction of amyloid deposits in the neuropil of the cerebral cortex, whereas 6F3D labeled most of them. Amyloid-laden vessels were strongly immunolabeled by anti-Aβ40, 4G8, and 6F3D, but not by Aβ42 antibody.

Bielschowsky and Bodian silver impregnations, thioflavine S, and anti-tau immunohistochemistry revealed the presence of abundant NFTs and senile plaques in the neocortex and mesial temporal structures (Fig. 3A–C). Immunolabeling with anti-tau antibodies was intense in the cerebral cortex in the form of NFTs, neuropil threads, and degenerating neurites surrounding Aβ deposits (Fig. 3C). Tau immunoreactivity showed a laminar pattern of intracortical distribution, being more represented in the external and internal pyramidal layers. NFTs and neuropil threads were also prominent in claustrum, thalamus, substantia nigra, and locus coeruleus and were consistently absent in the cerebellum (Table 3).

A remarkable finding was the presence of ectopic neurrons in the white matter of the centrum semiovale in the absence of consistent immunopositivity for Aβ. They were identified by cresyl violet staining for Nissl substance and on the basis of immunoreactivity for MAP2 and neurofilaments. Most of them showed a bipolar morphology and contained argyrophilic and tau-immunoreactive NFTs (Fig. 3D, E).

The number of white matter neurrons immunoreactive for the antibody against the repeat region of tau was higher in the frontal lobe (74/100 fields) than in the temporal and parieto-occipital lobe (14/100 fields and 27/100 fields, respectively).

Patient IV-16

Microscopically, neuronal loss and gliosis were very severe throughout the cerebral cortex, with marked thinning of the cortical ribbon and loss of distinction of cortical layers. In the neuropil, parenchymal amyloid deposits revealed by thioflavine S were abundant in the cerebral cortex and were present also in the caudate nucleus, putamen, thalamus, globus pallidus, and several brainstem nuclei. The wall of numerous vessels in the leptomeninges of the occipital lobe and cerebellum were thickened and intensely fluorescent after thioflavine S treatment, but no amyloid angiopathy was detected in the parenchymal vessels. Anti-Aβ42 and 4G8 labeled parenchymal amyloid and preamyloid deposits. A burden in sections immunostained with anti-Aβ42 was 11.4% in the frontal, 11.7% in the temporal, and 12.8% in the parietal cortex. Anti-Aβ40 decorated amyloid-laden vessels and a subset of amyloid deposits in the neuropil. In the cerebellum, preamyloid deposits were present in the molecular layer but were less numerous than in case IV-18. 6F3D labeled amyloid in the brain parenchyma and vessels but not preamyloid deposits.

NFTs revealed by Bodian silver impregnation and thioflavine S were numerous in the frontal, temporal, cingulate, insular, parietal, and occipital cortex, as well as in the hippocampus and entorhinal cortex (Table 3). In
Fig. 3. Patient IV-18. A: Immunoreactivity for phosphorylated tau was diffuse in all areas of the cerebral cortex and its extent and distribution can be evaluated by direct observation of the large hemispheric section (AT8, ×1.35). B: Silver impregnation revealed NFTs in the neocortex (Bodian stain, frontal cortex, ×620). C: Anti-tau antibodies labeled NFTs, neuropil threads, and degenerating neurites of senile plaques (AD2, frontal cortex, ×210). D, E: Numerous ectopic neurons with neurofibrillary pathology were present in the white matter of the centrum semiovale (D, AT8, ×125) and most of these neuronal cells were bipolar, often with tau-immunoreactivity extending into the proximal neuronal processes (E, AT8, ×620).
Another remarkable finding was the presence of ectopic neurons in the white matter of the frontal, temporal, and parieto-occipital lobes. Most of these neurons contained NFTs that were labeled by the antibody against the repeat region of tau but not by AT8 or Alz50 antibodies (Fig. 4F, G). The number of neurons immunoreactive for the former in the white matter was 89/100 fields in the frontal lobe and 46/100 fields in the parieto-occipital lobe.

In both cases, Lewy bodies were absent in cortical and subcortical structures, no α-synuclein immunoreactive inclusions were detected, and no cotton-wool plaques were observed. Many of the Aβ amyloid deposits in the cerebral cortex were associated with cellular profiles immunoreactive with antibodies against ubiquitin, βPP and synaptophysin, and were surrounded by GFAP-positive astrocytic processes and activated microglial cells recognized by CR3/43 antibody.

DISCUSSION

In contrast to the high frequency of PSEN1 mutations in AD families, screening of a large number of AD patients revealed that PSEN2 mutations are very rare (13). FLO10 is the second largest AD family with PSEN2 mutation, with the Volga-German kindred considered the largest.

From a clinical standpoint the most remarkable finding of FLO10 is the high variability of age of onset, disease duration, and presenting symptoms. Environmental or genetic factors other than the PSEN2 mutation are therefore likely to influence the expression of the disease. One genetic determinant believed to affect the age of onset of sporadic AD is the presence of APOE4 allele(s), although this influence has been excluded in FAD associated with mutations of presenilins, including this family (28). The wide range of age of onset and disease duration in FLO10 are similar to those of patients of the Volga-German kindred (29) and differ from most families with PSEN1 mutations characterized by a “malignant” form of AD with early onset and rapid progression (30–32). A major peculiarity of FLO10 was the clinical onset with epileptic seizures before the dementia in 1 patient (IV-18). It is noteworthy in this that generalized seizures and myoclonus were reported in Volga-German kindred in the course of the disease (15).

The neuropathologic analysis revealed some analogies with previously reported cases of FAD associated with PSEN2 mutations, but also findings that have not been previously described in PSEN2 families. However, until now, detailed neuropathological descriptions of patients with PSEN2 mutations were only available for the Volga-German family. One of the similarities was represented by the cerebral Aβ deposition that mainly involved the Aβ42 form and was characterized by a degree of severity higher than in sporadic AD. In FLO10 patients, the Aβ burden in the cerebral cortex ranged from 11.4% to 17.1%, a value similar to those found in FAD associated with PSEN1 and PSEN2 mutations and higher than in

\[
\begin{array}{|l|c|c|c|c|c|}
\hline
\text{Cerebrum} & \text{NFT (AT8)} & \text{NFT (anti-repeat region of tau)} \\
\hline & IV-16 & IV-18 & IV-16 & IV-18 \\
\hline
\text{frontal cortex} & 1 & 3 & 3 & 3 \\
\text{cingulate cortex} & 1 & 3 & 3 & 3 \\
\text{temporal cortex} & 1 & 3 & 3 & 3 \\
\text{parietal cortex} & 1 & 3 & 3 & 3 \\
\text{insular cortex} & 1 & 3 & 3 & 3 \\
\text{occipital cortex} & 1 & 2 & 3 & 2 \\
\text{hippocampus} & 1 & 2 & 3 & 3 \\
\text{dentate gyrus} & 1 & 1 & 3 & 2 \\
\text{subiculum} & 2 & 3 & 3 & 3 \\
\text{entorhinal cortex} & 1 & 3 & 3 & 3 \\
\text{caudate nucleus} & 1 & 1 & 1 & 1 \\
\text{putamen} & 1 & 1 & 1 & 1 \\
\text{claustrum} & 1 & 2 & 2 & 2 \\
\text{globus pallidus} & 1 & 0 & 1 & 0 \\
\text{thalamus} & 1 & 1 & 2 & 2 \\
\hline
\text{Cerebellum} & & & & \\
\text{molecular layer} & 0 & 0 & 0 & 0 \\
\text{granular layer} & 0 & 0 & 0 & 0 \\
\text{dentate nucleus} & 0 & 0 & 0 & 0 \\
\hline
\text{Midbrain} & & & & \\
\text{substantia nigra} & 1 & 1 & 1 & 1 \\
\text{red nucleus} & 1 & 1 & 1 & 1 \\
\hline
\text{Pons} & & & & \\
\text{tegmentum} & 1 & 2 & 1 & 2 \\
\text{basis} & 0 & 0 & 0 & 0 \\
\hline
\text{Medulla} & & & & \\
\text{hypoglossal nucleus} & 0 & 0 & 1 & 0 \\
\text{inferior olive} & 0 & 0 & 0 & 0 \\
\hline
\end{array}
\]

Legend: 0 = absent; 1 = rare; 2 = moderate; 3 = frequent.

the same areas, immunolabeling with the polyclonal antibody against the repeat region of tau was intense under the form of NFTs, neuropil threads, and degenerating neurites surrounding Aβ deposits.

In addition, this patient showed some unusual distinctive features. The NFTs labeled by AT8 were much less than expected on the basis of immunostaining with the antibody against the repeat region of tau but not by AT8 or Alz50 antibodies.

**TABLE 3**

Distribution of tau-Immunoreactive Lesions

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<th>NFT (AT8)</th>
<th>NFT (anti-repeat region of tau)</th>
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<td>IV-18</td>
</tr>
<tr>
<td></td>
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<td>IV-18</td>
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<tr>
<td>Cerebrum</td>
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<tr>
<td>frontal cortex</td>
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most cases of sporadic AD (33, 34). Moreover, Aβ de-
positions were present in the molecular layer of the cere-
bellum of both FLO10 patients, similar to the Volga-Ger-
man kindred and with most PSEN1-associated FAD cases
(4, 16, 35, 36). On the basis of the high homology of the
2 genes, these findings support the view that PSEN1 and
PSEN2 mutations influence the AD pathology in a similar
way.

An important neuropathological finding in FLO10 is
the presence of numerous ectopic neurons with NFTs in
the subcortical white matter, a feature not reported pre-
viously in FAD associated with PSEN2 mutations. This
change has been described in one patient with S169L
mutation of PSEN1, leaving doubt as to whether this ab-
normality represented a coincidental finding or was part
of the neuropathological phenotype associated with this
mutation (4). In the light of our present findings the latter
possibility seems more likely, and it can be argued that
the presence of ectopic neurons in white matter is asso-
ciated with mutations of both presenilins, further sug-
gesting a link between presenilins and neuronal differ-
entiation and migration. Supporting this view,
PSEN1-deficient mice develop a disorder of neuronal mi-
gration (37) and it has been suggested that premature
neuronal differentiation may be the underlying basis of
this embryonic defect (38). Moreover, in Drosophila, pre-
senilins are required for signaling through the Notch re-
ceptor, important for cell survival and fate during devel-
opment (39, 40).

On the other hand, the possibility that the presence of
ectopic white matter neurons in AD is more frequent than
previously thought is suggested by a recent study where
ectopic degenerating neurons in the white matter were
found in more than half of a series of 66 brains from
patients with sporadic AD (41). However, the quantity of
ectopic white matter neurons in sporadic AD was much
lower than in the PSEN1 patient described by Takao et
al (4) and in the FLO10 patients reported here.

The presence of ectopic neurons in the white matter
may be the neuropathological substrate of seizures since
they have been shown in cases of generalized epilepsy
(42). Epilepsy was observed in the patient described by
Takao carrying the PSEN1 S169L mutation as well as in
a patient with L166P mutation of PSEN1 (4). However,
a close relationship between ectopic white matter neurons
and epilepsy is challenged by the fact that ectopic neu-
rons were present in the white matter of both patients of
FLO10 family and that they were even more abundant in
the nonepileptic patient (IV-16). For this reason the epi-
lepsy in presenilin-mutated patients can be considered a
multifactorial syndrome in which the presence of white
matter ectopic neurons represents a condition favoring
the development of seizures.

In addition, one of the FLO10 patients (IV-16) was
remarkable for the presence of many ghost tangles in the
neocortex, which are recognized by specific tinctorial
and immunohistochemical properties (fluorescence after thio-
flavine S treatment, argyrophilia, immunoreactivity with
antibodies to the repeat region of tau, and lack of im-
munoreactivity with AT8 antibody) likely related to re-
moval of fuzzy coat and exposure of epitopes of the
paired helical filaments when they became extracellular
(43, 44). The “aging” of NFTs is associated not only
with loss of some tau epitopes but also with the appear-
ance of Aβ immunoreactivity (45, 46). Accordingly,
many Aβ-40-immunoreactive NFTs were observed in sev-
eral neocortical regions, a picture that was not found ei-
ther in a large series of sporadic AD patients in whom
extracellular tangles were confined to the mesial temporal
structures (GG, unpublished observation) nor in the other
patient (IV-18) of this family, characterized by a shorter
disease duration. These findings indicate that PSEN2
M239V mutation represents a condition favoring the evo-
lution of NFT in ghost tangles by molecular mechanisms
that are largely unknown.

This study demonstrates that the PSEN2 FAD kindred
FLO10 is characterized by a wide range of age of onset
and duration of disease associated with some peculiarities
of the clinical and neuropathologic phenotype, involving
not only Aβ deposition but also neuronal pathology such
as the development of ectopic white matter neurons and
the evolution of NFTs. The analysis of the brain of 2
FLO10 patients showed that differences in the neuro-
pathological features may be relevant even among family
members with identical mutations of presenilins, further
suggesting a phenotypic modulation by other genetic and/
or environmental factors.

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REFERENCES


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