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Laminar distribution of β-amyloid (Aβ) peptide deposits in the frontal lobe in familial and sporadic Alzheimer's disease

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Abstract

To determine whether genetic factors influence frontal lobe degeneration in Alzheimer's disease (AD), the laminar distributions of diffuse, primitive, and classic β-amyloid (Aβ) peptide deposits were compared in early-onset familial AD (EO-FAD) linked to mutations of the amyloid precursor protein (APP) or presenilin 1 (PSEN1) gene, late-onset familial AD (LO-FAD), and sporadic AD (SAD). The influence of apolipoprotein E (Apo E) genotype on laminar distribution was also studied. In the majority of FAD and SAD cases, maximum density of the diffuse and primitive Aβ deposits occurred in the upper cortical layers, whereas the distribution of the classic Aβ deposits was more variable, either occurring in the lower layers, or a double-peaked (bimodal) distribution was present, density peaks occurring in upper and lower layers. The cortical layer at which maximum density of Aβ deposits occurred and maximum density were similar in EO-FAD, LO-FAD and SAD. In addition, there were no significant differences in distributions in cases expressing Apo E ε4 alleles compared with cases expressing the ε2 or ε3 alleles. These results suggest that gene expression had relatively little effect on the laminar distribution of Aβ deposits in the frontal lobe of the AD cases studied. Hence, the pattern of frontal lobe degeneration in AD is similar regardless of whether it is associated with APP and PSEN1, mutation, allelic variation in Apo E, or with SAD.

***Key words*:** *laminar distribution, β-amyloid (Aβ) peptide deposits, gene mutation.*

Introduction

The neuropathology of Alzheimer's disease (AD) is characterised by the formation of extracellular senile plaques (SP) and intracellular neurofibrillary tangles (NFT) [5,34]. The most important molecular constituent of the SP is β-amyloid (Aβ) [28], an approximately 4 kDa peptide arising by constitutive cleavage of a trans-membrane amyloid precursor protein (*APP*). A variety of Aβ peptides are formed as a result of secretase cleavage of *APP* [40]. The most common of these peptides is Aβ42, found largely in discrete Aβ deposits, whereas the more soluble Aβ40 is also found in association with blood vessels [37] and may develop later in the disease [21]. The discovery of Aβ led to the formulation of the 'amyloid cascade hypothesis' (ACH), one of the most important models of the molecular pathology of AD developed over the last 25 years [28]. Essentially, the ACH proposes that the deposition of Aβ is the initial pathological event in AD leading to the formation of NFT, cell death, and cortical degeneration [28].

At least four genetic loci are associated with AD: the *APP* gene on chromosome 21 [17,26], the prese-

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nilin *PSEN* genes on chromosome 14 (*PSEN1*) [47] and chromosome 1 (*PSEN2*) [32], and the apolipoprotein E (*Apo E*) gene on chromosome 19 [44]. *APP* and *PSEN* mutation may alter APP metabolism, resulting in increased deposition of Aβ peptide, while allelic polymorphism of *Apo E*, and especially the expression of allele ε4, may influence the proportion of the more fibrillogenic Aβ42 formed in the tissue [32,47]. These genetic factors, however, may not explain the majority of AD cases [27]. Hence, early-onset cases linked to *APP* and *PSEN* mutations may account for less than 5% of total AD [29]. Additional susceptibility genes and environmental factors are therefore likely to be involved, especially in sporadic AD (SAD) [38,39,41]. In isolated Amish communities, for example, 24 markers have been linked to dementia [33] and several other linkage studies have shown the presence of AD susceptibility genes on chromosomes 9, 10, and 12 [48]. Hence, a small number of AD cases have been linked recently to the chromosome 9 open reading frame 72 (*C9ORF72*) gene [55].

Three morphological subtypes of Aβ deposit are commonly observed in AD: 1) diffuse ('pre-amyloid') deposits, in which the Aβ is not in a fibrillar form with a β-pleated conformation, dystrophic neurites (DN) and paired helical filaments (PHF) being largely absent, 2) primitive ('neuritic') deposits, in which the Aβ is in a fibrillar form and is associated with DN and PHF, and 3) classic ('dense-cored') deposits, in which Aβ is highly aggregated to form a central amyloid plaque 'core' surrounded by a 'ring' of DN [3,8,10-12,20]. In the cerebral cortex in AD, Aβ deposits [2] and NFT [54] often exhibit significant variation in density across the cortex from pia mater to white matter, maximum density occurring within different layers [2,54]. The laminar distribution of Aβ deposits may be a consequence of degeneration of neural pathways that have their neurons of origin or axon terminals located within particular layers [22]. The main objective of this study was to determine whether genetic factors influence the laminar distribution of Aβ deposits and therefore result in a specific type of cortical degeneration in the frontal cortex in AD. Hence, laminar distributions of diffuse, primitive, and classic Aβ deposits were studied in three groups of cases: 1) early-onset familial Alzheimer's disease (EO-FAD) linked to mutations of either amyloid precursor protein (*APP717*) or presenilin 1 (*PSEN1: G209V*, *E280A*) genes, 2) late-onset familial AD (LO-FAD), and 3) sporadic AD (SAD). In addition, the influence of *Apo E* genotype on the distribution of Aβ deposits was studied.

Material and methods

Cases

Alzheimer's disease cases (N = 20; details in Table I) were obtained from the Brain Bank, Department of Neuropathology, Institute of Psychiatry, King's College, London, UK. Informed consent was given for the removal of all brain tissue according to the 1996 Declaration of Helsinki (as modified Edinburgh, 2000). Patients were clinically assessed and all fulfilled the 'National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association' (NINCDS/ADRDA) criteria for probable AD [52]. The histological diagnosis of AD was established by the presence of widespread neocortical SP consistent with the 'Consortium to Establish a Registry of Alzheimer Disease' (CERAD) criteria [34] and 'National Institute on Aging (NIA)-Reagan Institute' criteria [30,34]. The cases were divided into three groups: 1) EO-FAD (onset ≤ 65 years) (n = 4), 2) LO-FAD (≥ 65 years) (n = 6), and 3) SAD (n = 10) with no evidence of familial involvement.

Tissue preparation

A block of the frontal cortex was taken at the level of the genu of the corpus callosum to study the superior frontal gyrus (SFG). Tissue was fixed in 10% phosphate-buffered formal saline and embedded in paraffin wax. Both immunostaining and thioflavin S have been used to stain SP in AD [14,45]. Thioflavin S staining indicates that amyloid in these plaques contains fibrillar material with a β-pleated sheet conformation [14]. By contrast, immunohistochemistry generally reveals more plaques including diffuse Aβ deposits which are mainly thioflavin S-negative [14]. Hence, to label all types of plaque 7 µm coronal sections were immunolabelled with a rabbit polyclonal antibody (Gift of Prof. B.H. Anderton, Institute of Psychiatry, King's College London) raised to the 12-28 amino acid sequence of the Aβ protein and first used to identify Aβ deposit subtypes in Down's syndrome (DS) [50] but which also effectively distinguishes the major types of Aβ deposit in AD [4,6,7,10,50]. The antibody was used at a dilution of 1 in 1200 and the sections incubated at 4°C overnight. Sections were pretreated with

Table I. Demographic and genetic data of the Alzheimer's disease (AD) cases studied

Case	Sex	Age	Onset of disease	Group	Genetics	*Apo E*
1	M	65	–	EO-FAD	*APP717*	3/3
2	F	59	–	EO-FAD	*APP717*	3/3
3	F	61	–	EO-FAD	*PSEN1*	3/3
4	F	45	40	EO-FAD	*PSEN1*	2/3
5	F	72	66	LO-FAD	ND	2/3
6	F	86	80	LO-FAD	ND	3/4
7	F	77	72	LO-FAD	ND	3/3
8	F	79	68	LO-FAD	ND	3/4
9	F	85	76	LO-FAD	ND	3/3
10	F	89	–	LO-FAD	ND	3/3
11	M	80	77	SAD	–	3/3
12	F	87	82	SAD	–	3/4
13	F	64	59	SAD	–	4/4
14	F	91	83	SAD	–	3/4
15	M	73	66	SAD	–	2/3
16	F	82	75	SAD	–	ND
17	F	91	85	SAD	–	3/4
18	F	86	83	SAD	–	3/4
19	F	90	–	SAD	–	ND
20	M	82	78	SAD	–	3/3

Apo E – apolipoprotein E, APP – amyloid precursor protein, EO-FAD – early-onset familial Alzheimer's disease, LO-FAD – late-onset familial Alzheimer's disease, SAD – sporadic Alzheimer's disease, PSEN1 – presenilin 1, M – male, F – female, ND – not determined

98% formic acid for 6 minutes, which enhances Aβ immunoreactivity. Aβ was visualised using the streptavidin-biotin horseradish peroxidase procedure with diaminobenzidine as the chromogen. Sections were also stained with haematoxylin. Aβ deposits were identified in the sections using criteria published by Delaere *et al*. [20]: 1) diffuse deposits were 10-200 µm in diameter, lightly stained, irregular in shape, and with diffuse boundaries, 2) primitive deposits were 20-60 mm, well demarcated, symmetrical in shape, and strongly stained, and (3) classic deposits were 20-100 mm and had a distinct central amyloid core surrounded by a 'corona' of DN [20].

Morphometric methods

The distribution of the Aβ deposits in the SFG of each case was studied from the pia mater to white matter using methods described previously [23]. Five traverses from the pia mater to the edge of the white matter were located at random within each gyrus [9]. All deposits were then counted in 200 x 1000 µm sample fields arranged contiguously, the larger dimension of the field parallel with the surface of the pia mater. An eye-piece micrometer was used as the sample field and was moved down each traverse one step at a time from the pia mater to the edge of the white matter. Histological features of the section were used to correctly position the field. The mean of the counts from the five traverses was calculated to study variations in density of histological features across each cortical gyrus.

Data analysis

No attempt was made to locate precisely the boundaries between individual cortical layers. First, the degree of cortical degeneration present in many

gyri made laminar identification difficult. Second, identification was especially difficult in the frontal cortex because it exhibits a heterotypical structure, i.e., six layers cannot always be clearly identified and vary in prominence from case to case. Third, Aβ deposits appeared to exhibit complex patterns of distribution across the cortex rather than being confined to specific layers. Hence, variations in density of Aβ deposits with distance across the cortex were analysed using a polynomial curve-fitting procedure (STATISTICA software, StatSoft Inc., 2300 East 14th St, Tulsa, OK, 74104, USA) [2,49]. For each gyrus, polynomials of order 1, 2, 3 up to the 4th order were fitted successively to the data. Hence, second-order curves are parabolic, third-order curves are 'S' shaped, and fourth-order curves are double-peaked (bimodal). With each fitted polynomial, the correlation coefficients (Pearson's '*r*'), regression coefficients, standard errors of the mean (SEM), values of *t*, and the residual mean square were obtained. At each stage, the reduction in the sums of squares (*SS*) was tested for significance. A polynomial was accepted as the best fit using the procedure described by Snedecor and Cochran [49], viz. when either a non-significant value of *F* was obtained or there was little gain in explained variance. The distributions of the Aβ deposits across the cortex were classified initially into three groups: 1) a single density peak was present (unimodal distribution), peak density being located in either upper or lower layers, 2) two density peaks were present (bimodal distribution), density peaks occurring in upper and lower layers, and 3) there was no significant change in density across the cortex, Aβ deposits not being confined to particular layers. Bimodal distributions were then classified further according to whether the density peaks in the upper and lower layers were of similar or different magnitude. To study the effect of *Apo E* genotype, cases were classified into two groups: those not expressing allele ε4, i.e., genotypes ε2/3 and ε3/3, and those expressing at least one allele ε4, i.e., genotypes ε3/4 and ε4/4. In addition, the location of peak density and the maximum density of deposits were compared in EO-FAD, LO-FAD, and SAD. Hence, the point of maximum density (peak density) was identified for each deposit type for each gyrus while location of the peak was determined as the distance from the pia mater to that of the maximum density of Aβ deposits, expressed as a percentage of the total distance from the pia mater to the edge of the white matter.

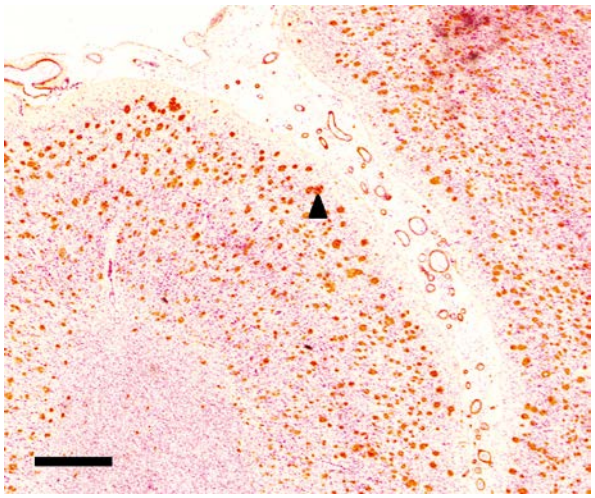

Fig. 1. Distribution of β-amyloid (Aβ) peptide deposits (arrowhead) in the superior frontal gyrus (SFG) in a case of early-onset familial Alzheimer's disease (EO-FAD) (*PSEN1* mutation). Aβ deposits occur across the cortex in all layers but with a greater density of larger-sized deposits in the upper layers. Aβ immunohistochemistry, haematoxylin, bar = 0.75 mm.

Results

Examples of the distribution of Aβ peptide deposits across the SFG are shown in Figures 1 and 2. In a case of EO-FAD (Fig. 1) (*PSEN1* mutation), Aβ deposits occurred across the cortex with a greater density of larger deposits in the upper layers. By contrast, in a case of SAD (Fig. 2), Aβ deposits occur largely in the lower layers.

Examples of the laminar distribution of the diffuse, primitive, and classic Aβ deposits in the SFG of a single EO-FAD case (case 2, *APP* mutation) is shown in Figure 3. The distribution of the diffuse deposits was fitted by a first-order (linear) regression ($r = 0.82$, $p < 0.01$) consistent with greater densities of diffuse deposits in the upper layers and a linear decrease in density across the cortex from pia mater to white matter. The distribution of the primitive Aβ deposits was fitted by a third-order polynomial ($r = 0.91$, $p < 0.001$) with a large density peak in the upper layers, while the classic deposits were also fitted by a third-order polynomial ($r = 0.82$, $p < 0.01$) with slightly higher densities adjacent to the pia mater and in the lower layers.

A comparison of the laminar distributions is shown in Table II. In FAD, diffuse Aβ deposits exhib-

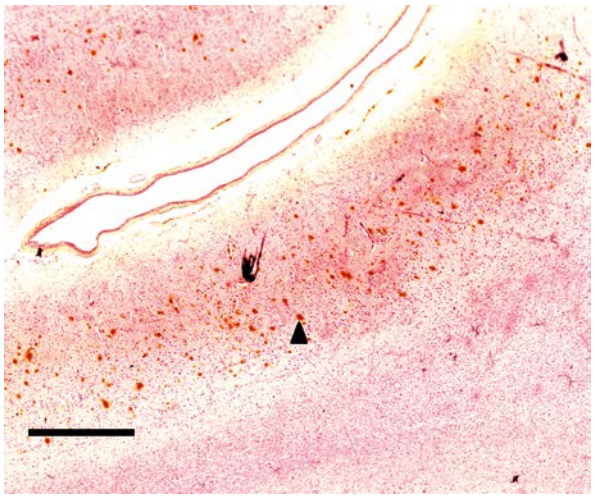

Fig. 2. Distribution of β-amyloid (Aβ deposits) (arrowhead) across the superior frontal gyrus (SFG) in a case of sporadic Alzheimer's disease (SAD). Aβ deposits occur largely in the lower layers. Aβ immunohistochemistry, haematoxylin, bar = 0.75 mm.

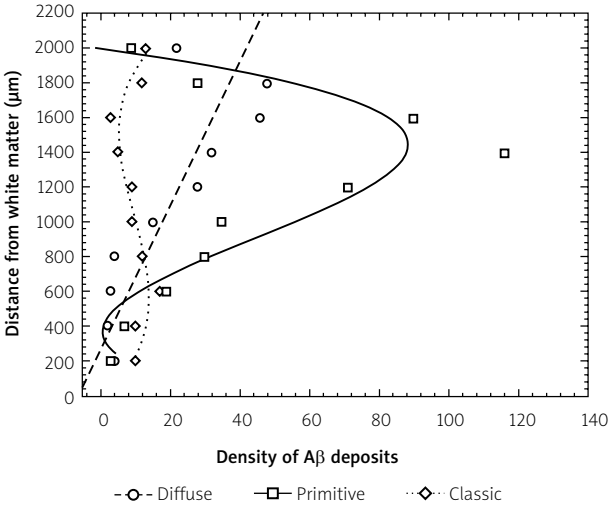

Fig. 3. Examples of the laminar distribution of the diffuse, primitive, and classic β-amyloid (Aβ deposits) in frontal lobe of a case of early-onset familial Alzheimer's disease (EO-FAD) (case 2, amyloid precursor protein (*APP*) gene mutation).

ited a density peak in the upper layers in 6/10 cases, and the primitive deposits did so in 9/10 cases. The distribution of the classic deposits was more variable; in 6/10 cases there was either a density peak in lower cortex or a bimodal distribution was present with density peaks in upper and lower layers. In SAD, diffuse and primitive Aβ deposits exhibited a density peak in the upper cortex in 7/10 cases and 9/10 cases respectively. Distribution of the classic Aβ deposits was more variable, a density peak in the lower layers or a bimodal distribution being present in 5/10 cases. The frequency of the various types of distribution of the diffuse (χ^2 = 3.74, p > 0.05), primitive (χ^2 = 0.71, p > 0.05), and classic (χ^2 = 11.18, p > 0.05) Aβ deposits was similar in EO-FAD, LO-SAD, and SAD.

Comparison of the mean location of maximum density and peak density of deposits among the three groups of cases is shown in Table III. Although there were significant differences in the layers at which peak density occurred among Aβ deposit subtypes (F = 4.44, p < 0.01), there were no significant differences among EO-FAD, LO-FAD, or SAD (F = 0.89, p > 0.05). In addition, there were no significant differences in peak density of Aβ deposits (F = 3.28, p > 0.05) among patient groups.

A comparison of the distributions exhibited by the Aβ deposits in cases classified according to *Apo E* genotype groups is shown in Table IV. There were no significant differences in distribution of diffuse (χ^2 = 2.55, p < 0.05), primitive (χ^2 = 0.003, p < 0.05), or classic (χ^2 = 3.41, p < 0.05) Aβ deposits in cases expressing *Apo E* genotypes ε2/3 and ε3/3, compared with those expressing genotypes ε3/4 and ε4/4.

Discussion

The objective of this study was to determine whether genetic factors were associated with a specific pattern of cortical degeneration, as revealed by the deposition of Aβ deposits in the frontal cortex in AD. The data confirm the need for quantitative assessment of Aβ deposition in different layers of cortex as deposits often occur over many layers with variation in abundance across the cortex. This study demonstrated: 1) laminar distributions of diffuse, primitive, and classic Aβ deposit subtypes were essentially similar in EO-FAD, LO-FAD, and SAD, 2) within FAD, laminar distributions were similar in *APP/PSEN1* cases compared with LO-FAD, and 3) laminar distributions were similar in cases expressing *Apo E* ε4 alleles compared with cases expressing ε2 or ε3 alleles.

The data suggest no significant differences in Aβ deposit density in EO-FAD, LO-FAD, and SAD or when cases were classified according to *Apo E* genotype. Previous quantitative studies comparing SP or Aβ

Table II. Comparison of the frequencies of different types of laminar distribution of β-amyloid (Aβ) deposits in superior frontal gyrus (SFG) in three groups of cases: early-onset familial Alzheimer's disease (EO-FAD), late-onset familial AD (LO-FAD), and sporadic AD (SAD). Data are the number of cases in which a particular type of laminar distribution is present

Group	Deposit type	Type of laminar distribution			
		UL	LL	B	NS
EO-FAD	Diffuse	3	0	1	0
	Primitive	4	0	0	0
	Classic	2	0	2	0
LO-FAD	Diffuse	3	1	1	1
	Primitive	5	0	0	1
	Classic	0	4	0	2
SAD	Diffuse	7	1	0	2
	Primitive	9	0	0	1
	Classic	2	4	1	3

Comparison of frequencies between groups: χ^2 contingency tables: diffuse deposits $\chi^2 = 5.09$ (6 DF, $p > 0.05$), primitive deposits $\chi^2 = 0.74$ (2 DF, $p > 0.05$), classic deposits $\chi^2 = 11.26$ (6 DF, $p > 0.05$)
UL – maximum Aβ deposit density occurred in upper cortical layers, LL – maximum Aβ deposit density occurred in lower cortical layers, B – bimodal distribution with peaks of density in upper and lower layers, NS – no significant change in density of Aβ deposits across the cortex

Table III. Comparison of mean peak location, i.e., percentage distance from the pia mater at which maximum density of β-amyloid (Aβ) deposits occurred expressed as a percentage of the width of the gray matter, and mean peak density, i.e., the actual density of deposits at the peak (mm^2) in the superior frontal gyrus (SFG) in three groups of cases: early-onset familial Alzheimer's disease (EO-FAD), late-onset familial AD (LO-FAD), and sporadic AD (SAD). Standard errors of the mean (SEM) are in parentheses

Group		Aβ deposit subtype		
		Diffuse	Primitive	Classic
EO-FAD	Peak location	32.5 (12.11)	21.3 (5.98)	40.0 (12.54)
	Peak density	36.5 (6.39)	86.5 (21.85)	12.3 (2.19)
LO-FAD	Peak location	39.5 (9.89)	31.7 (4.88)	51.7 (10.24)
	Peak density	28.0 (5.22)	70.3 (17.84)	8.17 (1.79)
SAD	Peak location	32.0 (9.66)	27.20 (3.69)	55.10 (6.09)
	Peak density	20.8 (3.20)	38.3 (10.76)	10.3 (1.50)

Analysis of variance (ANOVA): 1) Peak location: patient group $F = 0.89$ ($p > 0.05$), deposit type $F = 4.44$ ($p < 0.01$), interaction $F = 0.22$ ($p > 0.05$); 2) Peak density: patient group $F = 3.28$ ($p > 0.05$), deposit type $F = 18.73$ ($p < 0.001$), interaction $F = 1.36$ ($p > 0.05$)

deposit abundance in FAD and SAD have been controversial [16,18,24,36]. Hence, no significant differences in severity scores of SP were observed in FAD and SAD [36], and Aβ 'load' in the frontal cortex and temporal isocortex was similar in SAD and FAD cases linked to the APP_{717} mutation [16]. Nevertheless, cultured cells expressing a double mutation in *APP* produced six times more Aβ than normal cells [18]. In addition, other studies have reported increased amyloid deposition in individuals expressing allele ε4 [24]. However, it is possible that Aβ deposition could be more widely distributed across the cortical layers of the SFG in FAD, but with similar peak densities.

In the SFG of both SAD and FAD, maximum density of the diffuse and primitive Aβ deposits occurred most frequently in the upper layers. By contrast, the distribution of the classic deposits was more variable, peak densities occurring either in the lower lay-

Table IV. Comparison of frequencies of different types of laminar distribution of Aβ deposits in superior frontal gyrus (SFG) of Alzheimer's disease (AD) cases divided into two groups according to apolipoprotein (*Apo E*) genotype, i.e., those expressing genotypes ε2/3 and ε3/3 compared with those expressing genotypes ε3/4 and ε4/4. Data are the number of cases in which a particular type of laminar distribution is present

Group	Aβ deposit subtype	Laminar distribution			
		UL	LL	B	NS
ε2/3, ε3/3	Diffuse	8	0	2	1
	Primitive	10	0	0	1
	Classic	3	4	2	2
ε3/4, ε4/4	Diffuse	7	0	0	0
	Primitive	7	0	0	0
	Classic	1	5	0	1

Chi-square (χ^2) contingency tables: diffuse deposits $\chi^2 = 2.29$ (2 DF, $p > 0.05$), primitive deposits $\chi^2 = 0.006$ (1 DF, $p > 0.05$), classic deposits $\chi^2 = 2.69$ (3 DF, $p > 0.05$) UL – maximum Aβ deposit density occurred in upper cortical layers, LL – maximum Aβ deposit density occurred in lower cortical layers, B – bimodal distribution with peaks of density in upper and lower layers, NS – no significant change in density of Aβ deposits across the cortex

ers, or in both upper and lower layers. Similar results have been reported in studies of the laminar distribution of SP [15,19], Apo E-immunoreactive SP [53], neuritic plaques (NP) [42], and Aβ deposits in AD [2], which are frequently abundant in layers II and III. In addition, in a transgenic mouse model expressing the APP_{717} mutation, Aβ deposits were most abundant in layers II and III, similar to AD [51]. However, aged dogs often show a different distribution of Aβ deposits to humans, being usually abundant in the deep cortical layers but with evidence of spread to superficial cortical layers with increasing age [43].

Various hypotheses could explain the laminar distribution of Aβ deposits in the SFG in AD. First, mRNA of APP is preferentially expressed by the large pyramidal neurons in layers III and V [13]. Degeneration of these neurons could then result in increased secretion of APP and formation of Aβ deposits within these layers [4]. Second, interleukin-immunoreactive microglia (IL-Mg) have a similar laminar distribution as APP-immunoreactive NP [46]. Hence, the laminar distribution of microglia could be a factor determining the distribution of the Aβ deposits. Third, the laminar distribution of the classic deposits could be spatially related to blood vessels [2,37]. Large blood vessels often exhibit a bimodal distribution in the cortex, whereas smaller capillaries occur at maximum density in the deeper layers [2]. In addition, Akiyama *et al*. [1] found that Aβ deposits accumulated vertically in columns, with blood vessels often occurring perpendicular to the column and penetrating its centre. Previous studies suggest, however, that although classic Aβ deposits are clustered around blood vessels in SAD [6], there are fewer spatial associations with blood vessels in FAD [7].

Laminar distributions of Aβ deposits in frontal lobe AD are essentially similar in the FAD and SAD cases examined and similar whether *Apo E* allele ε4 was present or not [31]. In addition, among FAD cases, there was no evidence that a specific type of laminar distribution was influenced by genetic subtype. Hence, neither *APP/PSEN1* mutations nor the presence of *Apo E* allele ε4 uniquely determines Aβ deposition and therefore the pattern of frontal lobe degeneration in AD. Uchihara *et al*. [53] found that Apo E labelled a subset of deposits in lamina III with more Apo E-immunoreactive diffuse deposits in the deeper layers. However, only a proportion of the diffuse deposits were Apo E-immunoreactive, suggesting that Apo E was not involved in the process of cortical degeneration but immunoreactivity was acquired by certain deposits later in the disease. Hence, pathological changes initiated by the various genetic changes in FAD and, by other causes in SAD, appear to follow a parallel course resulting in very similar patterns of cortical degeneration in the SFG.

In conclusion, there were no essential differences in the laminar distribution of the Aβ deposits in the SFG between FAD and SAD, or between different subtypes of FAD. Hence, *APP* and *PSEN1* mutations and the presence of *Apo E* genotype ε4 appear to have little influence on laminar distribution. Although the

mechanism of generating fibrillogenic species of Aβ may differ among disease subtypes, gene expression appears to have little effect on the pattern of degeneration of the frontal lobe in AD.

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Disclosure

Author reports no conflict of interest.

References

1. Akiyama H, Yamada T, McGeer PL, Kawamata T, Tooyama I, Ishii T. Columnar arrangement of beta-amyloid deposits in the cerebral cortex of patients with Alzheimer's disease. Acta Neuropathol 1993; 85: 400-403.
2. Armstrong RA. β-amyloid (Aβ) deposits and blood vessels: laminar distribution in frontal cortex of patients with Alzheimer's disease. Neurosci Res Comms 1996; 18: 19-28.
3. Armstrong RA. β-amyloid plaques: stages in life history or independent origin? Dement Geriatr Cogn Disord 1998; 9: 227-238.
4. Armstrong RA. Diffuse β-amyloid (Aβ) deposits and neurons: in situ secretion or diffusion of Aβ? Alz Rep 2001; 3: 289-294.
5. Armstrong RA. Plaques and tangles and the pathogenesis of Alzheimer's disease. Folia Neuropathol 2006; 44: 1-11.
6. Armstrong R. Classic β-amyloid deposits cluster around large diameter blood vessels rather than capillaries in sporadic Alzheimer's disease. Curr Neurovasc Res 2006; 3: 289-294.
7. Armstrong RA. Spatial correlations between β-amyloid (Aβ) deposits and blood vessels in familial Alzheimer's disease. Folia Neuropathol 2009; 46: 241-248.
8. Armstrong RA. A spatial pattern analysis of β-amyloid (Aβ) deposition in the temporal lobe in Alzheimer's disease. Folia Neuropathol 2010; 48: 67-74.
9. Armstrong RA. Quantitative methods in neuropathology. Folia Neuropathol 2010; 48: 217-230.
10. Armstrong RA. Spatial patterns of β-amyloid (Aβ) deposits in familial and sporadic Alzheimer's disease. Folia Neuropathol 2011; 49: 153-161.
11. Armstrong RA. β-amyloid (Aβ) deposition in cognitively normal brain, dementia with Lewy bodies, and Alzheimer's disease. Folia Neuropathol 2012; 50: 130-139.
12. Armstrong RA. Size frequency distributions of β-amyloid (Aβ) deposits: a comparative study of four neurodegenerative disorders. Folia Neuropathol 2012; 50: 240-249.
13. Bahmanyar S, Higgins GA, Goldgaber D. Localization of amyloid β protein messenger RNA in brains from patients with Alzheimer's disease. Science 1987; 237: 77-80.
14. Bussiere T, Bard F, Barbour R, Grajeda H, Guido T, Khan K, Schenk D, Games D, Seubert P, Buttini M. Morphological characterization of thioflavin-S-positive plaques in transgenic Alzheimer mice and effect of passive Aβ immunotherapy on their clearance. Am J Pathol 2004; 165: 987-995.
15. Braak H, Braak E, Kalus P. Alzheimer's disease: areal and laminar pathology in the occipital isocortex. Acta Neuropathol 1989; 77: 494-506.
16. Cairns NJ, Chadwick A, Lantos PL, Levy R, Rossor M. βA4 protein load in familial Alzheimer's disease with the mutation in codon 717 of the βA4 amyloid precursor protein gene and sporadic Alzheimer's disease. Neurosci Lett 1993; 149: 137-140.
17. Chartier-Harlin MC, Crawford F, Houlden H, Warren A, Hughes D, Fidani L, Goate A, Rossor M, Rocques P, Hardy J, Mullan M. Early onset Alzheimer's disease caused by mutations at codon 717 of the β-amyloid precursor protein gene. Nature 1991; 353: 844-846.
18. Citron M, Oltersdorf T, Haass C, McCoulogue L, Hung AY, Seubert P, Vigo-Pelfrey C, Lieberburg I, Selkoe DJ. Mutation of β-amyloid precursor protein in familial Alzheimer's disease increases β-protein production. Nature 1992; 360: 672-674.
19. Delaere P, Duyckaerts C, Brion JP, Poulain V, Hauw JJ. Tau, paired helical filaments and amyloid in the neocortex: A morphometric study of 15 cases with graded intellectual status in aging and senile dementia of the Alzheimer type. Acta Neuropathol 1989; 77: 645-653.
20. Delaere P, Duyckaerts C, He Y, Piette F, Hauw JJ. Subtypes and differential laminar distribution of β/A4 deposits in Alzheimer's disease: relationship with the intellectual status of 26 cases. Acta Neuropathol 1991; 81: 328-335.
21. Delacourte A, Sergeant N, Champain D. Wattez A, Maurage CA, Lebert F, Pasquier F, David JP. Nonoverlapping but synergetic tau and amyloid precursor protein pathologies in sporadic Alzheimer's disease. Neurology 2002; 59: 398-407.
22. De Lacoste M, White CL III. The role of cortical connectivity in Alzheimer's disease pathogenesis: a review and model system. Neurobiol Aging 1993; 14: 1-16.
23. Duyckaerts C, Hauw JJ, Bastenaire F, Piette F, Poulain C, Rainsard V, Javoy-Agid F, Berthaux P. Laminar distribution of neocortical senile plaques in senile dementia of the Alzheimer type. Acta Neuropathol 1986; 70: 249-256.
24. Gearing M, Schneider JA, Robins RS, Hollister RD, Mori H, Games D, Hyman BT, Mirra SS. Regional variations in the distribution of Apolipoprotein E and Aβ in Alzheimer's disease. J Neuropath Exp Neurol 1995; 54: 833-841.
25. Glenner GG, Wong CW. Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein, Biochem Biophys Res Commun 1984; 122: 1131-1135.
26. Goate R, Chartier-Harlin M-C, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, Mant R, Newton P, Rooke K, Roques P, Talbot C, Pericak-Vance, Roses A, Williamson R, Rossor M, Owen M, Hardy J. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature (London) 1991; 349: 704-706.
27. Grazini M, Prabas J, Silva F, Oliveira S, Santana I, Oliveira C. Genetic basis of Alzheimer's dementia: role of mitochondrial DNA mutations. Genes, Brain, and Behaviour 2006; 5 (Suppl 2): 92-107.

28. Hardy JA, Higgins GA. Alzheimer's disease: The amyloid cascade hypothesis. Science 1992; 256: 184-185.
29. Hoenicka J. Genes in Alzheimer's disease. Revista de Neurolgia 2006; 42: 302-305.
30. Jellinger KA, Bancher C. Neuropathology of Alzheimer's disease: a critical update. J Neural Transm 1998; 54: 77-95.
31. Kida E, Pluta R, Lossinsky AS, Golabek AA, Choimiura NH, Wisniewski HM, Mossakowski MJ. Complete cerebral ischemia with short-term survival in rat induced by cardiac-arrest. II. Extracellular and intracellular accumulation of apolipoproteins E and J in the brain. Brain Res 1995; 674: 341-346.
32. Levy-Lahad E, Wijsman EM, Nemens E, Anderson L, Goddard KA, Weber JL, Bird TD, Schellenberg GD. A familial Alzheimer's disease locus on chromosome 1. Science 1995; 269: 970-973.
33. McCauley JL, Hahs DW, Jiang L, Scott WK, Welsh-Bohmer KA, Jackson CE, Vance JM, Pericak-Vance MA, Haines JL. Combinatorial Mismatch Scan (CMS) for loci associated with dementia in the Amish. BMC Med Genet 2006; 7: 19.
34. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, van Belle G, Berg L, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathological assessment of Alzheimer's disease. Neurology 1991; 41: 479-486.
35. Newell KL, Hyman BT, Growden JH, Hedley-Whyte ET. Application of the National Institute on Aging (NIA)-Reagan Insitute criteria for the neuropathological diagnosis of Alzheimer's disease. J Neuropathol Exp Neurol 1999; 58: 1147-1155.
36. Nochlin D, Van Belle G, Bird TD, Sumi SM. Comparison of the severity of neuropathologic changes in familial and sporadic Alzheimer's disease. Alz Dis Assoc Dis 1993; 7: 212-222.
37. Pluta R, Barcikowska M, Januszewski S, Misicka A, Lipkowski AW. Evidence of blood-brain barrier permeability/leakage for circulating human Alzheimer's beta-amyloid-(1-42)-peptide. Neuroreport 1996; 7: 1261-1265.
38. Pluta R, Jabłoński M, Czuczwar SJ. Postischemic dementia with Alzheimer phenotype: selectively vulnerable versus resistant areas of the brain and neurodegeneration versus β-amyloid peptide. Folia Neuropathol 2012; 50: 101-109.
39. Pluta R, Kocki J, Maciejewski R, Ulamek-Koziol M, Jabłoński M, Bogucka-Kocka A, Czuczwar SJ. Ischemia signalling to Alzheimer-related genes. Folia Neuropathol 2012; 50: 322-329.
40. Pluta R, Furmaga-Jablonska W, Maciejewski R, Ulamek-Koziol M, Jablonski M. Brain ischaemia activates beta- and gamma-secretase cleavage of amyloid precursor protein: Significance in sporadic Alzheimer's disease. Mol Neurobiol 2013; 47: 425-434.
41. Pluta R, Jablonski M, Ulamek-Koziol M, Kocki J, Brzozowska J, Januszewski S, Furmaga-Jablonska W, Bogucka-Kocka A, Maciejewski R, Czuczwar S. Sporadic Alzheimer's disease begins as episodes of brain ischemia and ischemically dysregulated Alzheimer's disease genes. Mol Neurobiol 2013; 48: 500-515.
42. Rafalowska J, Barcikowska M, Wen GY, Wisniewski HM. Laminar distribution of neuritic plaques in normal aging, Alzheimer's disease and Downs syndrome. Acta Neuropathol 1988; 77: 21-25.
43. Satou T, Cummings BJ, Head E, Nielson KA, Hahn FF, Milgram NW, Velaquez P, Cribbs DH, Tenner AJ, Cotman CW. The progression of beta-amyloid deposition in the frontal cortex of the aged canine. Brain Res 1997; 774: 35-43.
44. Saunders A, Strittmatter W, Schmechel D, St. George-Hyslop P, Pericak-Vance M, Joo S, Rose B, Gasella J, Crapper-MacLachan D, Albersts M, Hulette C, Crain B, Goldgaber D, Roses A. Association of apolipoprotein E allele e4 with late-onset familial and sporadic Alzheimer's disease. Neurology 1993; 43: 1467-1472.
45. Serrano-Pozo A, Mielke ML, Muzitansky A, Gomez-Isla T, Growdon JH, Bacskai BJ, Betensky RA, Frosch MP, Hyman BT. Stable size distribution of amyloid plaques over the course of Alzheimer's disease. J Neuropath Exp Neurol 2012; 71: 694-701.
46. Sheng JG, Griffin VST, Roystan MC, Mrak RE. Distribution of interleukin-1-immunoreactive microglia in cerebral cortical layers: implications for neuritic plaque formation in Alzheimer's disease. Neuropath Appl Neurobiol 1998; 24: 278-283.
47. Sherrington R, Rogaev E, Liang Y, Rogaeva E, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K, Tsuda T, Mar L, Foncin J, Bruni A, Moulese M, Sorbi S, Rainero I, Pinessi L, Nee L, Chumakov I, Pollen D, Brookes A, Sauseau P, Polinski R, Wasco, R, Dasilva H, Haines J, Pericak-Vance M, Tanzi R, Roses A, Fraser P, Rommens J, St George-Hyslop P. Cloning of a gene bearing missense mutations in early onset familial Alzheimer's disease. Nature 1993; 375: 754-760.
48. Sillén A, Forsell C, Lilius L, Axwlman K, Björk B, Onkamo P, Kere J, Winblad B, Graff C. Genome scan on Swedish Alzheimer disease families. Mol Psychiatry 2006; 11: 182-186.
49. Snedecor GW, Cochran WG. Statistical Methods. Iowa State University Press, Ames 1980.
50. Spargo E, Luthert PJ, Anderton BH, Bruce M, Smith D, Lantos PL. Antibodies raised against different proteins of A4 protein identify a subset of plaques in Down's syndrome. Neurosci Lett 1990; 115: 345-350.
51. Su Y, Ni BH. Selective deposition of amyloid-beta protein in the entorhinal-dentate projection of a transgenic mouse model of Alzheimer's disease. J Neurosci Res 1998; 53: 177-186.
52. Tierney MC, Fisher RH, Lewis AJ, Zorzitto ML, Snow WG, Reid DW, Nieuwstraten P. The NINCDS-ADRDA work group criteria for the clinical diagnosis of probable Alzheimer's disease. Neurology 1988; 38: 359-364.
53. Uchihara T, Duyckaerts C, Lazarini F, Mokhtari K, Seilhean D, Amouyel P, Hauw JJ. Inconsistent apolipoprotein (Apo E)-like immunoreactivity in amyloid beta protein deposits: relationship with Apo E genotype in aging brain and Alzheimer's disease. Acta Neuropathol 1996; 92: 180-185.
54. Van Hoesen GW, Parvizi J, Chu CC. Orbitofrontal cortex/pathology in Alzheimer's disease. Cerebral Cortex 2000; 10: 243-251.
55. Wallon D, Rovelet-Lecrux A, Deramecourt V, Pariente J, Auriacombe S, Le Ber I, Schraen S, Pasquier F, Campion D, Hannequin D. Definite behavioural variant of frontotemporal dementia with C9ORF72 expansions despite positive Alzheimer's disease cerebrospinal fluid biomarkers. J Alz Dis 2012; 32: 19-22.