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Spatial correlations between β-amyloid (Aβ) deposits and blood vessels in familial Alzheimer's disease

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Abstract

In sporadic Alzheimer's disease (SAD), the classic ('dense-cored') β-amyloid (Aβ) deposits are aggregated around the larger blood vessels in the upper laminae of the cerebral cortex. To determine whether a similar relationship exists in familial AD (FAD), the spatial correlations between the diffuse, primitive, and classic β-amyloid (Aβ deposits and blood vessels were studied in ten FAD cases including cases linked to amyloid precursor protein (APP) and presenilin (PSEN) gene mutations and expressing apolipoprotein E (apo E) allele E4. Sections of frontal cortex were immunolabelled with antibodies against Aβ and with collagen IV to reveal the Aβ deposits and blood vessel profiles. In the FAD cases as a whole, Aβdeposits were distributed in clusters. There was a positive spatial correlation between the clusters of the diffuse Aβdeposits and the larger (>10 μm) and smaller diameter (<10 μm) blood vessels in one and three cases respectively. The primitive Aβ deposits were spatially correlated with larger and smaller blood vessels each in four cases and the classic deposits in three and four cases respectively. Apo E genotype of the patient did not influence spatial correlation with blood vessels. Hence, spatial correlations between the classic deposits and larger diameter blood vessels were significantly less frequent in FAD compared with SAD. It was concluded that both Aβ deposit morphology and AD subtype determine spatial correlations with blood vessels in AD.

Key words: *clustering, frontal cortex, blood vessels, diffusion, perivascular clearance, spatial correlation.*

Introduction

The involvement of the cerebral microcirculation in the pathogenesis of the β-amyloid (Aβ deposits in Alzheimer's disease (AD) is controversial [11]. In the cerebral cortex of cases of sporadic AD (SAD), Aβ deposits often occur in clusters that are regularly distributed parallel to the pia mater [7]. Of the three morphological subtypes of Aβ deposit common in AD, viz., the diffuse ('pre-amyloid'), primitive ('neuritic'), and classic ('dense-cored') deposits [2,17], clusters of the classic Aβ deposits, which consist of a solid amyloid core surrounded by a 'corona' of dystrophic neurites [2], is the only subtype to exhibit a consistent spatial relationship with the blood vessels [5,9]. Hence, in SAD, the classic deposits are often aggregated around the larger diameter (>10 μm) blood vessels and especially the vertically penetrating arterioles in the upper cortical laminae [5]. In addition, the density of the classic deposits declines exponentially with distance from the larger vessels, suggesting that proteins diffusing from the

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vessels may be involved in the pathogenesis of the classic deposits in SAD [5].

Vascular pathology may also be involved in the pathogenesis of Aβ deposits in the much rarer cases of familial AD (FAD). Hence, plasma Aβ may be increased in cases of FAD as well as in some SAD cases [33]. In addition, as in SAD, a proportion of FAD cases are associated with cerebral amyloid angiopathy (CAA), viz., the deposition of Aβ in and around the major blood vessels. Mutations of the amyloid precursor protein (*APP*) gene [14,20] within the Aβ region are often associated with familial CAA [29] while *APP* mutations outside the Aβ region are associated with a pathology deficient in $A\beta_{40}$ and with lower levels of CAA [22]. A larger group of FAD cases are linked to the presenilin (*PSEN*) genes *PSEN1* [28] and *PSEN2* [23] with selective *PSEN* mutations promoting CAA [22]. In addition, the apolipoprotein E (*apo E*) gene is an important risk factor associated with late-onset familial and sporadic FAD [27,32]; possession of one or more E4 alleles significantly increases the risk of the disease, and could also be linked to vascular pathology. For example, in transgenic mice, apo E markedly promotes CAA-associated vessel damage [19]. Hence, the objective of this study was to determine the spatial correlations between the diffuse, primitive, and classic Aβ deposits and blood vessels in a group of FAD cases and to compare the pattern of correlations with previously studied SAD cases [5,9].

Material and Methods

Cases

Ten cases of FAD (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's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD [34]. The histological diagnosis of AD was established by the presence of widespread neocortical senile plaques (SP) consistent with the Consortium to Establish a Registry of Alzheimer's Disease (CERAD) criteria [25]. Four of the cases were early-onset FAD (onset ≤65 yrs), two linked to the APP_{717} mutation and two to PSEN1 mutations. All early-onset cases had apo E genotypes 2/3 or 3/3. The remaining six FAD cases were of late-onset (≥65 yrs), two of which expressed the E4 allele. The remaining four late-onset FAD cases were not linked to any of the known genes and had apo E genotypes 2/3 or 3/3. All cases exhibited mild to moderate CAA in the frontal cortex and in the occipital cortex, the cortical region most significantly affected in AD [10].

Table I. Details of familial Alzheimer's disease (FAD) cases

Case	Sex	Age	Cause of death	Genetic link	Apo E	CAA
A	M	61	Bronchopneumonia	APP_{717}	3/3	Mild
B	F	52	Bronchopneumonia	APP_{717}	3/3	Mild
C	F	37	Bronchopneumonia	PSEN1	3/3	Mild/Mod
D	F	57	Bronchopneumonia	PSEN1	2/3	Mild/Mod
E	F	86	Bronchopneumonia	ND	3/4	Mod
F	F	79	Bronchopneumonia	ND	3/4	Mod
G	F	89	Bronchopneumonia	ND	3/3	Mild
H	F	75	Bronchopneumonia	ND	2/3	Mild
I	F	69	Bronchopneumonia	ND	3/3	Mild
J	F	72	Ischaemic heart disease	ND	3/3	Mild

M – male, F – female, APP – amyloid precursor protein, PSEN – presenilin, Apo E – apolipoprotein E genotype, ND – FAD not linked to any of the known genes, CAA – cerebral amyloid angiopathy, Mod – moderate.

Histological methods

A block of the superior frontal cortex was removed from each case at the level of the genu of the corpus callosum. Coronal sections, 7 µm in thickness, were stained with a rabbit polyclonal antibody (Gift of Prof. B.H. Anderton) raised against the 12-28 amino acid sequence of the Aβ protein [30] to reveal the deposits. The antibody was used at a dilution of 1 in 1200 and incubated at 4°C overnight. Sections were pretreated with 98% formic acid for 6 minutes to enhance immunoreactivity. Aβ was visualised using the streptavidin-biotin horseradish peroxidase procedure with diaminobenzidine as the chromogen. Sections were also immunostained with collagen type IV antiserum (Europath Ltd, U.K.) to reveal the microvessels [5,21,24]. The antiserum was used at 1:500 dilution following protease digestion of the section with a solution of 0.04% pepsin. Collagen type IV stains a component of the cerebrovascular basement membrane [37] and hence reveals arterioles, venules, precapillaries, and capillaries [5]. The three most common morphological types of Aβ deposit were identified using previously published criteria [2,17]. Hence, diffuse deposits were 10-200 µm in diameter, irregular in shape with diffuse boundaries and lightly stained. Primitive deposits were 20-60 µm, well demarcated, more symmetrical in shape, and strongly stained, while the classic deposits were 20-60 µm, and had a distinct central 'core' surrounded by a 'corona' of dystrophic neurites.

Clustering of Aβ deposits and blood vessels

The spatial patterns of the Aβ deposits and blood vessels were studied parallel to the pia mater in the upper 1 mm of the cortex using a magnification of ×100. Aβ deposits occur at high density and the vertically penetrating arterioles are especially prominent in this region [5,12]. A strip of cortex 17600 to 25600 µm in length, and which included a sulcus and a gyrus, was studied using 1000 × 200 µm contiguous sample fields, the short dimension of the field being aligned with the surface of the pia mater. Between 64 and 128 contiguous sample fields were used to sample each gyrus. A micrometer grid with grid lines at intervals of 10 µm was used as the sample field. The number of Aβ deposits was counted manually in each field. The frequency of the larger diameter (>10 µm) and smaller diameter (<10 µm) blood vessels in a field was estimated separately by 'lattice sampling', i.e. by counting the number of times a vessel profile intersected the grid lines of the field [3].

Statistical analysis

The data were analysed by spatial pattern analysis [1,6]. Essentially, the variance/mean (V/M) ratio is used as an index of non-randomness and determines whether the Aβ deposits and blood vessel profiles were distributed randomly (V/M = 1), regularly (V/M < 1), or in clusters (V/M > 1) along the strip of cortex parallel to the pia mater. V/M ratio is calculated at various field sizes, e.g. 200 × 1000 µm (the original field size) and then at 400 × 1000 µm, 800 × 1000 µm, etc., up to a size limited by the length of cortex sampled. The V/M ratio is plotted against the increasing field size to reveal the spatial pattern. If the deposits or blood vessels were clustered, then the analysis indicates whether the clusters themselves are randomly or regularly distributed and provides an estimate of the mean dimension of the clusters parallel to the pia mater. There were too few cases to compare spatial patterns between APP and PSEN cases, but cases expressing different apo E genotypes were compared using analysis of variance (ANOVA).

The degree of correlation between the density of each Aβ deposit subtype and the larger and smaller diameter blood vessels was tested at each field size using Pearson's correlation coefficient [4]. Correlations at small field sizes (≤400 µm) indicate a close spatial relationship between individual blood vessels and Aβ deposits while correlations at larger field sizes only (≥1600 µm) probably reflect the general abundance of blood vessels and deposits in a region of tissue [4,21,24].

Results

Examples of the spatial patterns exhibited by the Aβ deposits in the upper laminae of the frontal cortex are shown in Fig. 1. The diffuse deposits in the APP717 case exhibited a V/M peak at a field size of 3200 µm, suggesting the presence of clusters of deposits 3200 µm in diameter regularly distributed parallel to the pia mater. In the PSEN1 case, the V/M ratio increased with field size without reaching a peak, suggesting large scale clustering of the classic deposits (≥6400 µm in diameter).

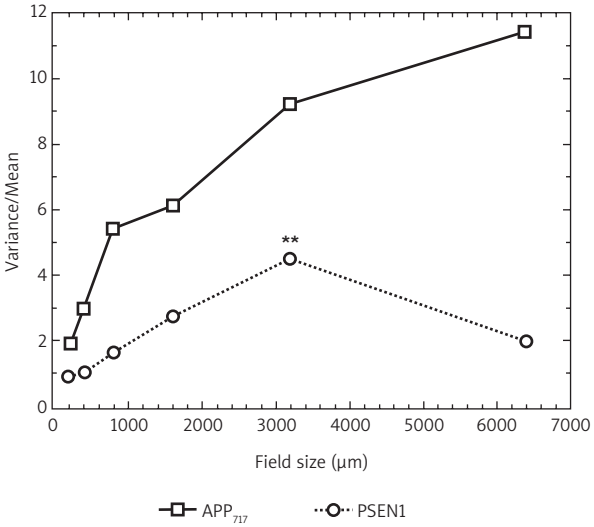

Fig. 1. The spatial distribution of the diffuse-type β-amyloid deposits along the upper laminae of the frontal cortex of a patient (Case A) with familial Alzheimer's disease (FAD, APP_{717}) and of the classic deposits in a case linked to a PSEN1 mutation as revealed by spatial pattern analysis (** indicates significant V/M peak)

Table II. Mean cluster sizes (µm) of the diffuse, primitive, and classic β-amyloid (Aβ) deposits and the larger diameter (>10 µm) and smaller diameter (<10 µm) blood vessels in ten cases of familial Alzheimer's disease (FAD)

Case	Diffuse	Primitive	Classic	>10 µm	<10 µm
A	3200	3200	≥6400	≥6400	3200
B	3200	≥6400	3200	400	≥6400
C	400	≥6400	≥6400	≥6400	200
D	≥6400	3200	≥6400	200	400
E	3200	1600	–	800	6400
F	1600	≥6400	≥6400	200	400
G	≥6400	≥6400	1600	200	≥6400
H	≥6400	3200	3200	800	≥6400
I	≥6400	6400	1600	400	≥6400
J	6400	≥6400	6400	200	3200

Data preceded by ≥ indicate large scale clustering of Aβ deposits or blood vessel profiles of at least 6400 µm. Data not preceded by ≥ indicate clusters that are regularly distributed parallel to the pia mater. (-) density of classic deposits was too low to determine spatial pattern. Comparison of cluster sizes: Analysis of variance (ANOVA): Aβ deposits: Genetic group, F = 1.88 (p>0.05), Blood vessel type F = 0.48 (p>0.05), Interaction F = 0.53 (p>0.05); Blood vessels: Genetic group, F = 1.10 (p>0.05), Blood vessel type F = 2.79 (p>0.05), Interaction F = 2.14 (p>0.05).

The spatial patterns of the Aβ deposits and blood vessel profiles in each of the ten FAD cases are summarized in Table II. The diffuse, primitive, and classic Aβ deposits occurred in clusters, the diffuse deposit clusters being regularly distributed along the cortex parallel to the pia mater in six cases, and the primitive and classic deposits each in five cases. In the remaining cases, the Aβ deposits occurred in larger clusters (diameter ≥6400 µm) without evidence of regular spacing. The large and small diameter blood vessels were also clustered, the larger vessels being regularly distributed parallel to the pia mater in eight cases and the smaller blood vessels in six cases. There were no significant differences in the mean cluster sizes of the Aβ deposits in cases expressing different apo E genotypes ($F = 2.87$, $p>0.05$).

Correlations between the diffuse Aβ deposits and blood vessel profiles for a single case (Case A, APP_{717}) are shown in Fig. 2. The diffuse deposits were positively correlated with the larger diameter blood vessels at field sizes 200-800 µm inclusive but there were no significant correlations with the smaller blood vessels at any field size. Spatial correlations between the densities of the Aβ deposits and blood vessels in the data as a whole are shown in Table III. There was a positive spatial correlation between the clusters of the diffuse

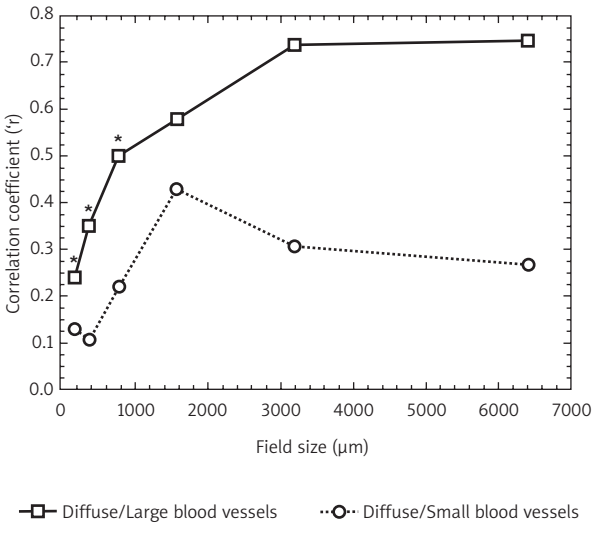

Fig. 2. Spatial correlations (Pearson's 'r') between the diffuse-type β-amyloid deposits and blood vessels along the upper laminae of the frontal cortex of a patient (Case A) with familial Alzheimer's disease (FAD, APP_{717}) (* indicates significant positive spatial correlation)

Aβ deposits and the larger (>10 μm) and smaller diameter (<10 μm) blood vessels in one and three cases respectively. The primitive Aβ deposits were spatially correlated with larger and smaller blood vessels each in four cases and the classic deposits in three and four cases respectively. There were no differences in the frequency of spatial correlation in cases expressing different apo E genotypes (χ^2 = 3.73, 2DF, p>0.05).

A comparison of the spatial correlations in FAD with previously published data for SAD is shown in Table IV. The frequency of spatial correlation of the diffuse and primitive deposits with the larger and smaller diameter blood vessels is similar in SAD and FAD. By contrast, the classic deposits were highly spatially correlated with the larger blood vessels in all 11 cases of SAD but more weakly correlated in only three FAD cases (χ^2=8.61, p<0.01), the majority of FAD cases showing no significant correlation with blood vessels.

Discussion

Spatial correlations between the Aβ deposits and the blood vessels were present in a small number of the FAD cases studied. The frequency of significant spatial correlations between the diffuse and primitive types of deposit and the blood vessel profiles in FAD was similar to previously published SAD data [9]. The most significant difference between FAD and

Table III. Spatial correlations between the diffuse (D), primitive (P), and classic (C) β-amyloid (Aβ) deposits and the larger diameter (>10 μm) and smaller diameter (<10 μm) blood vessels in 10 cases of familial Alzheimer's disease (FAD)

Case	Large blood vessels (>10 μm)			Small blood vessels (<10 μm)		
	D	P	C	D	P	C
A	1*,2*,4*	NS	2*,4*,8*	NS	NS	2*,4**,8*
B	NS	2*,4*	NS	NS	1***,2**,4**	1**,2**,4*
C	NS	1*,4*	NS	NS	NS	NS
D	NS	NS	NS	NS	NS	NS
E	NS	NS	1*,2*	1*,2*	NS	NS
F	NS	NS	NS	2*	1*,2*	2*,4*
G	NS	1*,2*	NS	NS	NS	16*
H	NS	NS	NS	1**	1*,2*,4*	NS
I	NS	NS	1*	NS	NS	NS
J	NS	1*,2*	NS	NS	4*,8**	NS

*Data show the field size (1 – 200 μm, 2 – 400 μm, 4 – 800 μm, 8 – 1600 μm) at which a significant spatial correlation occurred (*p<0.05, **p<0.01), NS – no significant correlations at any field size.*

Table IV. Comparison of the frequency of significant spatial correlations between Aβ deposits and the large (>10 μm) and small (<10 μm) blood vessels (BV) in familial Alzheimer's disease (FAD) and previously published data for sporadic Alzheimer's disease (SAD) (P – probability level)

Aβ type	P	FAD		SAD	
		>10 μm BV	<10 μm BV	>10 μm BV	<10 μm BV
Diffuse	<0.05	1	3	1	4
	<0.01	0	0	0	0
Primitive	<0.05	4	3	2	1
	<0.01	0	1	0	0
Classic	<0.05	3	3	0	0
	<0.01	0	1	11	4

Comparison of proportion of cases in FAD and SAD in which classic deposits show a significant spatial correlation with larger diameter (>10 μm) blood vessels (χ^2 = 8.61, p<0.01).

SAD involved the correlation of the classic deposits and the larger diameter vessels. In FAD, three cases showed a significant spatial correlation at a relatively low level of probability ($p<0.05$) while in SAD, all 11 cases studied showed a highly significant spatial correlation ($p<0.01$ or $p<0.001$) with the larger diameter blood vessels [5]. There were no significant differences in the mean densities of the classic deposits in FAD and the previously reported SAD cases ($t=1.27$, $p>0.05$) [5]. The mean cluster size of the classic Aβ deposits, however, was significantly greater in FAD ($t=3.56$, $p<0.01$). Hence, clusters of classic deposits in FAD are larger but less dense than in SAD.

A number of hypotheses could explain the difference in spatial correlation between the classic Aβ deposits and larger diameter blood vessels in FAD and SAD. First, spatial correlations might reflect differences in the pattern of the vasculature in SAD and FAD. However, neither the mean cluster size ($t=1.57$, $p>0.05$) nor the spatial pattern of the blood vessels differed in the FAD and SAD cases [5]. Hence, if amyloid deposition limits or reduces capillary density leading to the observation of less amyloid deposition in relation to capillaries but more in relation to the larger vessels [5], then this effect is similar in the FAD and SAD cases.

Second, variations in the pattern of spatial correlation could result from differences in patient age. Haem-rich deposits (HRD) <200 μm in diameter associated with blood vessels and with Aβ deposits, for example, are more common in individuals older than 50 years [16]. In addition, Aβ deposition around the larger blood vessels (CAA) could reflect impaired drainage since extracellular fluid is drained from the brain to the cervical lymph nodes via the perivascular channels [35] and there may be more resistance to this drainage in older patients. However, there were no overall differences in mean age between the FAD and SAD patients [5] ($t=1.48$, $p>0.05$). In addition, in FAD, there were no differences in the pattern of spatial correlation with blood vessels in those patients where age at death was <65 yrs compared with those >65 yrs ($\chi^2=0.39$, $p>0.05$).

Third, the severity of CAA may vary between the FAD and SAD cases and influence the spatial correlation with blood vessels. For example, the density of the classic Aβ deposits in proportion to the diffuse deposits is significantly greater in cases with pronounced CAA [8]. In addition, there is an inverse relationship between parenchymal load of Aβ and degree of CAA [13,36]. Hence, a greater degree of CAA in the SAD cases could lower the load of Aβ in the brain parenchyma but increase it in the region closer to blood vessels, resulting in enhanced formation of the classic deposits. However, there were no significant differences in the degree of CAA in the occipital or frontal cortex in the FAD and SAD cases studied.

Fourth, differences in spatial correlation could be associated with apo E genotype and specifically the number of E4 alleles expressed by the patient [13]. There were no differences, however, in apo E genotype profile of the SAD and FAD cases studied and in addition, within the FAD group, no difference in the pattern of spatial correlation in cases expressing different apo E genotypes.

Fifth, in FAD, the pathogenesis of the classic deposits may be more closely related to specific genetic abnormalities than in SAD. AD genotype, for example, may have a profound effect on the morphology of Aβ deposits. High densities of classic deposits associated with severe CAA are features of specific PSEN1 mutations [18], while a PSEN1 deletion resulted in non-congophilic Aβ and 'cotton-wool' type plaques [31]. In addition, APP692 mutations result in extensive CAA and numerous classic deposits with especially large cores clearly distinct in morphology from those of SAD [15,26]. Hence, the most likely explanation is that differences in spatial correlation with blood vessels reflect differences in pathogenesis of the classic Aβ deposits in SAD and FAD, being closely linked to the microvasculature in SAD and more directly linked to patient genotype in FAD.

In conclusion, the classic Aβ deposits are significantly less spatially related to blood vessels in FAD than in SAD. This difference is unlikely to be attributable to differences in the microvasculature, patient age, apo E genotype, or degree of CAA. It is possible that the classic deposits have a distinctly different pathogenesis in FAD than in SAD, being more closely linked to patient genotype, and less dependent on the microcirculation. Hence, at least two factors determine the spatial correlations of Aβ deposits with blood vessels in AD, viz., deposit morphology and AD subtype, and may explain the controversy in the literature [11].

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