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Density and spatial pattern of β-amyloid (Aβ) deposits in corticobasal degeneration

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Abstract

Corticobasal degeneration (CBD) is a rare, progressive movement disorder characterized neuropathologically by widespread neuronal and glial pathology including tau-immunoreactive neuronal cytoplasmic inclusions (NCI), oligodendroglial inclusions (GI), and astrocytic plaques (AP). However, β-amyloid (Aβ) deposits have been observed in the cerebral cortex and/or hippocampus in some cases of CBD. To clarify the role of Aβ deposition in CBD, the densities and spatial patterns of the Aβ deposits were studied in three cases. In two cases, expressing apolipoprotein E (APOE) genotypes 2/3 or 3/3, the densities of the Aβ deposits were similar to those in normal elderly brain. In the remaining case, expressing APOE genotype 3/4, Aβ deposition was observed throughout the cerebral cortex, sectors CA1 and CA2 of the hippocampus, and the molecular layer of the dentate gyrus. The densities of the Aβ deposits in this case were typical of those observed in Alzheimer's disease (AD). In the three cases, clustering of Aβ deposits, with clusters ranging in size from 200 to >6400 μm in diameter, was evident in 25/27 (93%) of analyses. In addition, the clusters of Aβ deposits were regularly distributed parallel to the tissue boundary in 52% of analyses, a spatial pattern similar to that observed in AD. These results suggest: (1) in some CBD cases, Aβ pathology is age-related, (2) more extensive Aβ deposition is observed in some cases, the density and spatial patterns of the Aβ deposits being similar to AD, and (3) extensive deposition of Aβ in CBD may be associated with APOE allele ε4.

Key words: *corticobasal degeneration (CBD), β-amyloid (Aβ), density, spatial pattern, Alzheimer's disease (AD), apolipoprotein E (APOE).*

Introduction

Corticobasal degeneration (CBD) is a rare, progressive movement disorder [29], the most characteristic clinical features of which include limb dysfunction [42,43,51], parkinsonism [49], apraxia [43], and dementia [49]. An individual patient, however, may exhibit a wide variety of clinical symptoms [46] including myoclonus [23], memory loss, behavioural change, speech, and gait problems [43].

Neuropathologically, CBD is characterized by a progressive cortical atrophy affecting the anterior cerebral cortex [46], the fronto-parietal region [33], and the superior temporal cortex [33]. As a consequence, the disease is regarded as a subtype of frontotemporal lobar degeneration (FTLD) [22]. There is atrophy of the basal ganglia, including the caudate nucleus [39,47] and substantia nigra (Kawasaki *et al.* 1996). In addition, widespread neuronal and glial

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pathology is present including ballooned neurons (BN) [41], neuropil threads [35], tau-immunoreactive neuronal cytoplasmic inclusions (NCI) [33], oligodendroglial inclusions (GI) [40], and astrocytic plaques (AP) [26]. CBD is therefore also classified as a tauopathy, a group of disorders that includes Alzheimer's disease (AD), Pick's disease (PiD), progressive supranuclear palsy (PSP), the NFT-predominant form of senile dementia (NFT-SD), argyrophilic grain disease (AGD), and the parkinsonism-dementia complex of Guam (Guam PDC) [28].

During a quantitative study of the pathology of 12 cases of CBD [17], β-amyloid (Aβ) deposits were observed in the cerebral cortex and/or hippocampus in three cases. Aβ deposits have been reported previously in CBD [43] and could represent the overlap or co-occurrence of CBD with AD [10,18]. Hence, to clarify the role of Aβ deposition in CBD, the density, distribution, and spatial pattern of the Aβ deposits were studied in these three cases and compared with previously reported data from normal elderly brains [2,3] and from AD [2,11,15].

Material and methods

Cases

The CBD cases (Table I) were obtained from the Brain Bank, Department of Neuropathology, Institute of Psychiatry, King's College London, UK. There is no specific clinical phenotype of CBD as diverse presentations of the disease are present [27]. However, the pathology of the cases was consistent with the criteria recommended by the National Institute of Health (NIH) Office of Rare Diseases for the pathological diagnosis of CBD [27]. First, NCI, GI and AP were present. Second, inclusions were present in the white and grey matter of various cortical and striatal regions. Third, neuronal loss was present in focal cortical areas and in the substantia nigra. CBD can be confused with PSP with cortical involvement and these two disorders were separated by the absence of 'tuft-shaped astrocytes' [50] and the lower density of inclusions in the subthalamic nucleus in CBD [48]. The apolipoprotein E (*APOE*) genotype of two of the cases (A, B) was 2/3 or 3/3 while the genotype of the third case (C) was 3/4.

Tissue preparation

After death, the consent of the next of kin was obtained for brain removal, following local Ethical Committee procedure and the 1995 Declaration of Helsinki (as modified Edinburgh, 2000). Tissue blocks were taken from the frontal cortex at the level of the genu of the corpus callosum to study the superior frontal gyrus (SFG) and motor cortex (MC), parietal cortex (PC) to study the superior parietal gyrus (SPG) at the level of the splenium of the corpus callosum, occipital cortex to study areas B17 and B18, and temporal cortex at the level of the lateral geniculate body. Within the temporal lobe, the superior temporal gyrus (STG) (B22), parahippocampal gyrus (PHG) (B28), hippocampus (HC), and dentate gyrus (DG) were investigated. Sequential tissue sections were stained by the following procedures: (1) haematoxylin and eosin (H/E), (2) ubiquitin, (3) phosphorylation-independent rabbit polyclonal antibody TP007 against tau [21], and (4) rabbit polyclonal antibody raised against the 12-28 amino acid sequence of the Aβ protein [45]. The three most common morphological subtypes of Aβ deposit were identified in the Aβ-immunolabelled sections using previously defined criteria [6,24]: (1) diffuse deposits were 10-200 μm in diameter, irregular in shape with diffuse boundaries, and lightly stained, (2) primitive deposits were 20-60 μm, well demarcated, more symmetrical in shape, and strongly stained, (3) classic deposits were 20-100 μm, had a distinct central 'core' surrounded by a 'corona' of dystrophic neurites, and (4) compact deposits comprised a condensed core of Aβ without the presence of a corona.

Table I. Demographic and gross brain features of the three corticobasal degeneration (CBD) cases studied

Case	Gender	Age	Onset	BW	BS/CB	Atrophy	*APOE*
A	F	55	44	1060	150	T	2/3
B	F	68	–	1082	129	F, P	3/3
C	F	69	65	1074	169	F, P, T	3/4

F – female, BW – total brain weight (gm), BS/CB – weight of brainstem and cerebellum (gm), T – temporal lobe, F – frontal lobe, P – parietal lobe, APOE – apolipoprotein E genotype

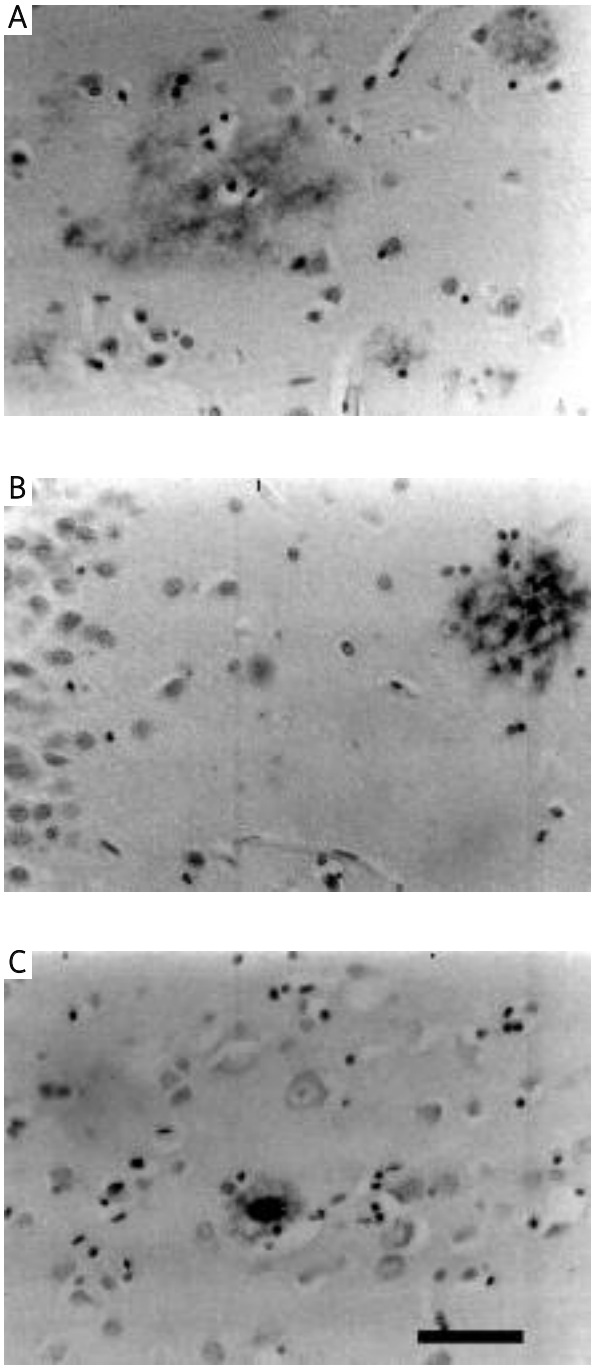

Fig. 1. β-amyloid (Aβ) deposits in a case of corticobasal degeneration CBD. **A)** Diffuse deposit in the frontal cortex, **B)** a primitive β-amyloid (Aβ) deposit in the molecular layer of the dentate gyrus, and **C)** a classic (cored) β-amyloid (Aβ) deposit in the parahippocampal gyrus. Compact deposits are very similar to cored deposits but without the surrounding corona (polyclonal antibody $A\beta_{12\text{-}28}$, Haematoxylin, bar = 50 µm).

Morphometric methods

In each cortical region, Aβ deposits were counted along a strip of tissue using 1000 × 200 µm contiguous sample fields, the short edge of the sample field being aligned with the pia mater [8,12]. Contiguous samples were located in the upper cortical laminae and included lamina I, II, and most of III, the short edge of the sample field being aligned with the surface of the pia mater. In the hippocampus, the lesions were counted from CA1 to CA4. From CA1 to CA3, the short dimension of the contiguous sample field was aligned with the alveus. Sampling was continued into sector CA4 using a guideline marked on the slide. In the DG, the sample field was aligned with the upper edge of the granule cell layer since Aβ deposits were present within the molecular layer.

Data analysis

The spatial pattern of the Aβ deposits in each brain region was studied using spatial pattern analysis described previously [1,5,9,12]. This method uses the variance-mean ratio (V/M) of the data to determine whether the Aβ deposits were distributed randomly (V/M = 1), regularly (V/M < 1), or were clustered (V/M > 1) along a strip of tissue. Counts of deposits in adjacent sample fields were added together successively to provide data for increasing field sizes, e.g., 200 × 1000 µm, 400 × 1000 µm, 800 × 1000 µm etc., up to a size limited by the length of the strip sampled and the V/M ratio calculated for each size. V/M was then plotted against field size to determine whether the clusters of a feature were regularly or randomly distributed and to estimate the mean cluster size parallel to the tissue boundary. A V/M peak indicates the presence of regularly spaced clusters while an increase in V/M to an asymptotic level suggests the presence of randomly distributed clusters. The statistical significance of a peak was tested using a 't' test [5].

Results

The three most common morphological types of Aβ deposit commonly found in AD, viz., diffuse, primitive, and classic deposits, were also observed in the CBD cases (Fig. 1). In addition, a smaller number of more 'compact' Aβ deposits were identified. Two of the cases (A, C) had all four types of Aβ deposit while case B had diffuse and classic-type deposits only.

The density of Aβ deposits in each brain region of each case is shown in Table II. In two cases (A, B), the density of the primitive, classic and compact Aβ deposits was generally low (<1 deposit per mm^2) and their distribution was restricted to either the frontal and motor cortex (case A) or to the occipital cortex (case B). Of these cases, case A had greater numbers of diffuse deposits in the frontal and motor cortex. In one case (case C), there was a greater density of Aβ deposits throughout the cerebral cortex and deposits were also present in the CA sectors of the hippocampus and molecular layer of the DG. In case C, the density of the diffuse deposits was greatest in the occipital and temporal cortex (16-18 deposits per mm^2), primitive deposits in the temporal cortex (14 deposits per mm^2), classic deposits in the frontal cortex (5.3 deposits per mm^2), and compact deposits in the parietal cortex (2.65 deposits per mm^2).

The spatial pattern of the Aβ deposits in each brain region is shown in Table III. Clustering of the Aβ deposits, with clusters ranging in size from 200 to >6400 µm in diameter, was evident in 25/27 (93%) of the brain areas analysed. In addition, clusters of Aβ deposits were regularly distributed parallel to the tissue boundary in 52% of the brain areas exhibiting clustering. In two cortical areas of case C, there was evidence of clustering at two scales, suggesting that the smaller clusters were aggregated into larger clusters. In the remaining analyses, large clusters of Aβ deposits were observed, of at least 6400 µm in diameter, but without evidence of regular spacing.

Discussion

Of the original 12 cases of CBD studied using quantitative methods [17], Aβ deposition was observed in three of the cases. In two cases, the density of the Aβ deposits was low and their distribution was restricted to a small number of cortical regions. The density of the Aβ deposit subtypes in these two cases was within the range reported for elderly non-demented brains [2,3]. Aβ pathology in the remaining CBD case, however, was more extensive and showed similarities to that previously reported in AD [2,13,15]. The densities of Aβ deposits in the frontal, occipital and temporal cortex were similar to AD [2-4] but the density in the parietal cortex was significantly lower than in AD. In addition, the spatial pattern of the Aβ deposits, i.e., clustering of deposits with a regular distribution of clusters parallel to the tissue boundary, was similar to that reported in AD [1,7,11].

A number of hypotheses could account for Aβ deposition in CBD. First, the presence of Aβ deposits could be age-related. The density and distribution of Aβ deposits in two of the CBD cases is similar to normal con-

Table II. Densities of the β-amyloid (Aβ) deposit subtypes (per mm^2) in brain regions where Aβ deposits were present in three cases of corticobasal degeneration (CBD)

		Aβ deposit subtypes			
Case	Region	Diffuse	Primitive	Classic	Compact
A	SFC	5.00	0.10	0.35	0.85
	MC	3.40	0.10	1.10	0.50
B	OC	0.13	0	0.10	0
C	SFC	3.06	4.55	5.30	0.55
	PC	0.10	0.25	0.80	2.65
	OC	16.45	4.40	1.50	0
	LOT	17.60	13.60	1.55	0
	PHG	16.10	11.05	1.45	0.10
	CA1/4	1.95	0.45	0.25	0.05
	DG	0.40	2.20	0	0

SFC – frontal cortex, MC – motor cortex, PC – parietal cortex, OC – occipital cortex, LOT – lateral occipitotemporal gyrus, PHG – parahippocampal gyrus, CA1/4 – hippocampus sectors CA1 to 4, DG – dentate gyrus

Table III. Spatial patterns of β-amyloid (Aβ) deposit subtypes in various brain regions in three cases of corticobasal degeneration (CBD)

		Aβ deposit subtypes			
Case	Region	Diffuse	Primitive	Classic	Compact
A	SFC	>3200	–	200	>3200
	MC	>3200	–	800	200
B	OC	R	–	–	–
C	SFC	>6400	400	200, 1600	>6400
	PC	–	R	800	>3200
	OC	3200	200, 800	800	–
	LOT	>6400	>6400	>6400	–
	PHG	>6400	1600	>6400	–
	CA1/4	>6400	200	200	–
	DG	–	1600	–	–

Data are the dimensions in μm of clusters of Aβ deposits measured parallel to the tissue boundary. >3200 etc represent the minimum size of large clusters without regular spacing. Remaining data represent the dimension of regularly distributed clusters. Where there are two figures, small clusters are aggregated into larger 'superclusters'. R = random distribution of deposits.
FC – frontal cortex, PC – parietal cortex, MC – motor cortex, OC – occipital cortex, LOT – lateral occipitotemporal gyrus, PHG – parahippocampal gyrus, CA1/4 – hippocampus sectors CA1 to 4, DG – dentate gyrus

trol brains [2,3], consistent with aging. A number of studies of Aβ pathology have demonstrated overlaps between AD and aging. Mann and Jones [38], for example, observed Aβ deposits in non-demented individuals older than 60 years, deposits being rare before this age. After 60 years of age, Aβ deposits were present in a variety of different disorders due to aging, especially in the temporal cortex [37]. In 14 non-demented elderly cases [3], Aβ deposits were present in the temporal lobe in eight cases, but only in cortical gyri, the CA sectors of the HC and DG being spared. In addition, there were variations in the density of Aβ deposits in control cases with a significant overlap with AD. The pattern of clustering of the Aβ deposits was also similar in control and AD cases, i.e., the deposits were aggregated into clusters that were regularly distributed parallel to the pia mater, suggesting that the formation of Aβ deposits was similar in AD and in aging [3]. In a further study of non-demented centenarians [25], Aβ deposits were recorded in the PHG, whether demented or not demented, but the hippocampus was spared, suggesting little relationship between lesion density and severity of mental deficits.

Secondly, in case C the density and distribution of the deposits were similar to those reported in AD [2,3] and therefore Aβ deposition in this case may be the result of the co-existence of AD and CBD [10,11,18]. The clinical syndrome of CBD is complex and variable and at least 50% of patients exhibit the signs and symptoms of an additional disorder, e.g., AD, PSP, or Parkinson's disease (PD) [43]. Typical AD cases, however, also have abundant neurofibrillary tangles (NFT). The paired helical filaments (PHF) of the inclusions present in CBD are wider than those of AD and have a longer periodicity [36]. In addition, PHF-tau in CBD is composed predominantly of 4-repeat (4R) tau [44] while abnormally aggregated tau from AD contains both 3R and 4R tau [30]. Hence, although the Aβ pathology in the present case resembles that of AD, there are differences in tau-immunoreactive pathology compared with AD.

Third, Aβ deposits in CBD could be associated with the development of capillary amyloid angiopathy (CAA), which often results in increased Aβ deposition [14]. The deposition of Aβ in capillary and arteriolar walls is a common pathological observation in AD and in unselected post-mortems with age [19]. There was no evidence in the present cases, however, of any significant Aβ deposition in relation to the vessel walls.

Fourth, Aβ deposition is also related to *APOE* genotype, enhanced deposition being observed in cases expressing the ε4 allele [20]. An increased frequency of allele ε4 has been recorded in cases of CBD, and in 5/7 patients expressing the ε4 allele, Aβ deposition was recorded in the hippocampus and cerebral cortex [43]. In the present study, case C had the highest densities and most widespread distribution of Aβ deposits and expressed genotype 3/4 whereas the other two cases with low densities of deposits expressed either genotype 2/3 or 3/3. Hence, it is hypothesized that enhanced Aβ deposition in case C represents the influence of *APOE* allele ε4.

In conclusion, in a quantitative study of 12 cases of CBD, three were shown to possess AD-type pathology in the form of Aβ deposits. The density of Aβ deposits in two of the cases was similar to that of elderly non-demented brains but in one case, the density and spatial patterns of the deposits resembled those of AD. Aβ pathology has now been shown to be associated with dementia with Lewy bodies (DLB) [16], amyotrophic lateral sclerosis (ALS) [31], Creutzfeldt-Jakob disease (CJD) [31], as well as CBD [43]. Hence, Aβ pathology can be observed in several distinct clinical contexts and it is possible that presence of the *APOE* ε4 allele is the common feature in these disorders enhancing Aβ deposition.

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