Distribution of pathology in frontal variant Alzheimer's disease

Author:

Blennerhassett, Richard; Lillo, Patricia; Halliday, Glenda; Hodges, John R; Kril, Jillian J

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Running title: Frontal variant Alzheimer's disease

Richard Blennerhassett[a], Patricia Lillo[b], Glenda M Halliday[b, c], John R Hodges[b, c], Jillian J Kril[a, d]

Disciplines of [a]Pathology and [d]Medicine, Sydney Medical School, The University of Sydney, Sydney NSW, [b]Neuroscience Research Australia, Barker St, Randwick NSW, [c]University of New South Wales, Kensington, NSW.

Address for correspondence
Professor Jillian Kril
Discipline of Pathology
The University of Sydney
Sydney NSW 2006
Ph: – 61-2-9036 7118
Fax: 61-2-9351 3429
Email: jillian.kril@sydney.edu.au

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Summary (248 words)

Atypical presentations of Alzheimer's disease (AD) have been described, including a "frontal" variant (fvAD), which presents with personality change and executive dysfunction similar to that seen in behavioral variant frontotemporal dementia (bvFTD). This clinical variation is thought to reflect the regional distribution of pathology, although few reports include autopsy confirmation. We compared three clinicopathological groups matched for age at diagnosis and disease duration; those with possible bvFTD who at autopsy had only AD (fvAD), those with typical AD clinically and pathologically, and those with typical clinical bvFTD confirmed pathologically. The density of neurons and AD-type pathology was quantified in the frontal association, occipital association, and entorhinal cortices and hippocampal CA1 regions. Immunohistochemistry for phosphorylated tau and amyloid-β deposition was used to detect neurofibrillary tangles and plaques.

Of the six core clinical features of the International Consensus Criteria, disinhibition, stereotyped behaviors and executive dysfunction were most common, occurring in five of the six fvAD patients. Other features were rare. While there was no significant difference in neuron density between groups for any of the four regions, when the ratio of frontal:occipital pathology was examined, neuronal density in fvAD was significantly less than AD but similar to bvFTD. The frontal:occipital ratio of AD-type pathology was also greater in fvAD than AD. The findings of this study suggest a frontal variant of AD exists with features that mimic bvFTD and that this reflects a differential distribution of neurodegeneration with more marked pathology in the frontal cortex compared with the occipital cortex.

Introduction:

In Alzheimer's disease (AD) neurodegeneration and the hallmark pathology of neurofibrillary tangles (NFTs) and amyloid-β (Aβ) plaques follow a well-established, and relatively stereotypical, anatomical spread [1]. Degeneration occurs first in the medial temporal lobe and then spreads through limbic regions to the association and then primary cortices. This progression of pathology is reflected in the evolution and increasing severity of clinical deficits that underpin the diagnosis and staging of AD [2].

Despite this relative homogeneity, in recent years, there has been a growing number of reports of atypical presentations of AD [3-7]. These include patients with visual and language presentations [8-10] as well as a rarer group with impairment of frontal lobe function similar to that seen in behavioral variant frontotemporal dementia (bvFTD) [3, 4, 6, 7, 11, 12]. A number of case reports and small series confirm the presence of AD pathology in such patients which has led to the use of the term "frontal variant AD" (fvAD) [3, 7, 11, 12].

In Alladi and colleagues [6] study of 100 patients with progressive focal syndromes, 34% had AD pathology including 2 of 28 (7%) with a diagnosis of bvFTD. The clinical features of these patients were dominated by behavioral changes without the presence of memory impairment for 1-3 years after the initial syndrome onset. Another study compared the pathological profile of three patients with AD and disproportionate frontal lobe dysfunction to three typical AD patients and found a greater density of NFTs in the frontal lobe, but no difference in plaque pathology [3]. Neuronal loss was not assessed in this study. While there is general acceptance of the concept of fvAD and that the clinical profile is as a result of an altered distribution of pathology [3, 13], pathological studies are rare and have not examined the range of pathology in these cases. Moreover, it is not clear that patients with a clinical label of fvAD would meet strict criteria for a diagnosis of bvFTD. In this study we examined six

patients with fvAD defined as meeting the recently validated International Consensus Criteria for bvFTD [14, 15] and pathological criteria for AD [16] to determine the distribution and severity of pathology.

Materials and Methods:

Patient selection:

This project was approved by the Human Research Ethics Committee of the University of Sydney. Cases with a pathological diagnosis of AD [16] and clinical information from the treating physician suggesting behavioral features consistent with bvFTD were selected from the Sydney Brain Bank. Of the 16 cases reviewed by two behavioral neurologists (PL, JRH; see below), six were considered to have possible bvFTD using the recently revised consensus criteria [15]. These were matched for age at diagnosis and death, and mean duration of disease with six patients with typical amnestic AD and six with bvFTD and pathologically confirmed frontotemporal lobar degeneration (FTLD) of the FTLD-TDP type [17].

Clinical classification of fvAD cases:

Case notes held by the Sydney Brain Bank were reviewed by an experienced behavioral neurologist (PL) blind to the pathological diagnosis and the presence or absence of the key clinical features of the International Consensus Criteria for bvFTD [15] at any time during the course of illness noted. For all donated cases prospective consent for research is obtained from the donor and/or senior next-of-kin and the program holds approval from the Sydney South Eastern Sydney Local Health Network and the University of New South Wales. Following enrolment in the program initial, and then annual, updates of medical and lifestyle information are obtained from treating physicians, general practitioners and next-of-kin. These are in the form of standardised questionnaires based on commonly used instruments to assess cognitive, behavioral and movement disorders.

All cases included in this study had evidence of a progressive deterioration in behavioral and/or cognitive function. Symptoms of possible bvFTD listed in the International Consensus Criteria for bvFTD [15] were scored according to the definitions provided with the exception of "IIF Neuropsychology profile" where, due to either the absence of neuropsychological testing or, where present, the variability in application of tests, the presence of executive dysfunction with preservation of memory and visuospatial skills was assessed from notes. Because of the retrospective nature of the assessment, patients endorsing two or more of the six symptoms, rather than three or more, were considered to have possible bvFTD and included in this study as fvAD. The presence of other common clinical features (memory impairment, language deficit, parkinsonism, gait abnormality, delusion and hallucinations) was also recorded. Limb apraxia was not seen in any of the AD or fvAD patients studied. Of the ten possible fvAD cases not included in this study, four had familial AD, while the remainder endorsed only one symptom or symptoms were not present early in the disease course [15].

Pathological characterisation of cases:

Cases were prepared according to the standardized procedures of the Sydney Brain Bank (GH Ref). Briefly, sections of the prefrontal, anterior cingulate, inferior temporal, primary motor and occipital cortices, hippocampus, basal ganglia, brainstem and cerebellum were examined using hemotoxylin and eosin stain, silver impregnation (modified Bielschowsky) and immunostains for hyperphosporylated tau, Aβ, α-synuclein, TDP-43 and ubiquitin or p62, and if ubiquinated or p62 inclusion pathology was found that was not accounted fro by tau, α-synuclein or TDP-43, additional immunostains were performed (eg. FUS). No subjects with pathological evidence of Lewy body disease, significant cerebrovascular disease, cerebral trauma or any other neurodegenerative disease were included. All AD and fvAD cases had either intermediate or high AD neuropathologic changes (new AD ref); one AD case had

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intermediate AD neuropathologic changes with a Braak neuritic stage of IV (B2), a CERAD plaque score of frequent (C3) and a Thal amyloid phase score of at least 3 ($\geq$A2); while all other AD and fvAD cases had high AD neuropathologic changes with Braak neuritic stages V/VI. Semiquantitative assessment of neuropil threads revealed differences between regions and cases, but no systematic difference in staining pattern between AD and fvAD, consistent with their similar Braak neuritic stages. Notably, none of the fvAD cases had coexisting TDP-43 pathology in either the dentate gyrus or frontal cortex. Of the AD cases two had sparse TDP-43-positive intracytoplasmic inclusions in the dentate gyrus and neurites in the frontal or entorhinal cortex (one case each). The TDP pathology in the bvFTD cases was type A in three cases, B in two and C in one {Mackenzie, 2011 #185}.

Tissue samples:

Formalin fixed and paraffin embedded blocks from three regions, the frontal (BA9) and occipital (BA19) association cortices and hippocampal formation, were sectioned at 10μm using a rotary microtome. Samples were from the left hemisphere for all cases except one fAD and one AD case. Two sections per region were slide mounted and stained, one for visualising neurons and NFTs using tau immunohistochemistry and a cresyl violet counterstain, and the other for visualising Aβ plaques. Briefly, immunohistochemistry was performed as previously described [18] using antibodies to Aβ (monoclonal mouse anti-human beta-amyloid M0872, DakoCytomation, Denmark; 1:500) and AT8 tau (anti-human PHF Tau monoclonal antibody MN1020, Thermo Scientific, Rockford IL; 1:1,000). Reactions were visualised using biotinylated anti-mouse antibody (IgG BA-2000, Vector Lab, Burlingmae CA), ABC elite (avidin-biotin complex, kit PK6100, Vector Lab, Burlingame CA) and diaminobenzadine as a chromogen.

Quantification of neurons and pathology:

Neuron and AD-type pathology were quantified in a manner similar to that described previously [19, 20]. For neurons and NFT quantitation in cortical regions (frontal, occipital and entorhinal), three randomly selected strips, perpendicular to the pial surface and spanning the cortical ribbon to the grey-white junction, were examined at 200x magnification using a graticule eyepiece with exclusion/inclusion borders. For the CA1 region of the hippocampus, three randomly spaced fields were counted for each section. The total number of neurons and the number of neurons containing NFTs were counted when the nucleolus was visible in the plane of section. Densities (number per mm^2) for each were calculated using the sum of the area of the strips/fields counted. The same counting grid was used to determine the areal fraction of Aβ staining at 100x magnification. The number of intersection points of the grid falling on an area of Aβ staining as a percentage of the total number of intersection points was determined. For the cortex three strips were counted, for the hippocampus three non-overlapping fields.

All counts were performed by one person (RB) blinded to the case type. Intra-rater reliability was determined by re-counting 10 randomly selected sections. An independent samples t-test for equality of means demonstrated no significant difference between the original and second counts. Previous studies using the methods employed here have demonstrated a co-efficient of error in the range of 0.07 to 0.23 [19, 21].

Data Analysis:

Analysis was performed using JMP 10.0.0 (SAS Institute inc). Non-parametric tests (Kruskall Wallis) were used for continuous variables with Mann-Whitney U posthoc tests performed when significance was reached. Chi squared tests were used for categorical data.

Results:

The demographic details of the three groups can be seen in table 1. There are no significant differences between the groups for the gender, age at diagnosis, age at death, disease duration or cerebrum volume.(see table 1 for p values)

The clinical features of each fvAD patient are list in table 2. Disinhibition was present in all patients and perseverative, stereotyped or ritualistic behaviors were seen in all but one patient. Similarly, executive dysfunction occurred in five of the six patients. In contrast, the remaining features (apathy, loss of empathy and altered diet) were only seen in a single patient. Of the other symptoms scored, parkinsonism or gait disturbance was present in five of the six patients, and the remaining features in only two or three patients. Interestingly, all of the patients with recorded parkinsonism also had language disorders. Memory impairment at the time of presentation was recorded in four of the six patients, including one patient who died within one year of presentation. In the remaining two cases, memory deficits were recorded 2 years and 6 years after presentation. Of the typical AD cases, one developed behavioral change 8 years after presentation and one perseverative behaviors 5 years after presentations. No other features of bvFTD were noted.

The mean density of neurons and NFTs and areal fraction of Aβ deposition for each group are shown in table 3. No significant difference in neuron density was identified for any region, although there is a large variance in most measures. As might be expected AD-type pathology was either absent or at a reduced density in the pathologically confirmed bvFTD group compared with the two AD groups. No difference was identified between the fvAD and AD group in any of the measure. Given the relatively small number of cases and the variance in the results from individual subjects, two ratios were calculated for each measure for each of

the fvAD and typical AD cases; (i) a frontal to occipital ration, and (ii) a frontal to entorhinal cortex ratio. Ratio of neuron density was also calculated for the bvFTD cases.

When the ratio of frontal to occipital neuron density is considered the fvAD and bvFTD groups show values approximately half of the AD group (p=0.009) suggesting greater frontal degeneration in the former groups and greater occipital degeneration in AD (figure 1). The mean for ratio Aβ plaques in fvAD is also significantly different to AD (p= 0.03) being around 30 times greater (figure 1). The ratio of NFTs is also greater but this does not reach significance (figure 1). One case (fvAD-3) showed a much higher NFT ratio (24.4 compared with between 0.05 to 3.1 in other cases) due to the very low number of NFTs in the occipital region. The comparison remained non-significant when this case was excluded from the analysis. Taken together these findings support the suggestion of greater frontal pathology in fvAD compared with typical AD that has more occipital neurodegeneration.

When the ratio of frontal to entorhinal neuron density is considered no significant difference is seen (figure 1). Similarly, no significant difference in AD pathology is seen between the fvAD and AD groups, although the mean NFT ratio is larger and the standard error greater. These results suggest no difference in medial temporal lobe pathology between the two AD groups.

Discussion:

The six patients reported here represent the largest series of pathologically proven AD with behavioral features severe enough to meet consensus criteria for bvFTD. Previous studies have suggested that such clinical features might be due to an irregular anatomical distribution of pathology, or perhaps more likely to the coexistence of both AD and FTLD [22-24]. We excluded patients with dual pathologies and quantified neuronal loss and AD type pathology

to determine whether the anatomical distribution of pathology could alone be responsible for such clinical features. Patients with fvAD were found to have greater depletion of neurons and higher density of Aβ plaques in the frontal compared to the occipital lobe than patients with clinically typical AD. Mean NFT ratio was also increased, but failed to reach significance. Importantly, we matched the AD groups for age and disease duration to allow direct comparison. The results of this study provide support for the concept of fvAD which can be mistaken for bvFTD and reflects an atypical distribution of AD pathology. In our autopsy series, such cases represent approximately 2% (6/272) of cases with pathologically confirmed AD referred to the Sydney Brain Bank, and 6/16 (37%) of cases with AD presenting with some features of a bvFTD-like syndrome. It should be noted that this represents a relatively rare cause of bvFTD given that 83 cases with pathologically proven FTLD have been seen over the same period.

The pattern of clinical symptoms observed in the fvAD cases reported here is strongly weighted towards deficits in executive function, disinhibition and preservative/stereotypical behaviors, while the other symptoms notably apathy, loss of empathy and dietary changes were identified infrequently. This may be due to an ascertainment bias secondary to the inherent nature of retrospective selection via review of case notes and questionnaires. It is highly likely that less intrusive or disturbing features such as reduced empathy were recorded less frequently. Although this seems an unlikely explanation for the absence of changes in satiety and food preference which tend to be prominent features in pathologically verified FTLD [25] suggesting that the difference in symptom profile may reflect differences in the distribution of pathology. For instance, disinhibition in bvFTD has been mapped using neuroimaging to medial frontal regions [26]. In contrast, apathy in FTD has been correlated with changes in the caudate nucleus and temporoparietal regions [27] while changes in eating habits result from hypothalamic pathology [25]. Interestingly, loss of empathy in FTD has

been correlated with bifrontal and left anterior temporal deficits [28] suggesting this symptom might be expected to be seen in fvAD. Interestingly 5/6 fvAD cases demonstrated parkinsonism or gait disturbance without evidence of co-existing Lewy body disease. A more extensive review of the distribution and nature of pathology in these patients is required to better understand the neural substrates of the range of deficits seen.

Previous studies of fvAD have reported pathological findings in only a small number of cases. Taylor and colleagues [7] reported an atypical distribution of AD pathology in a single case study. They described a high density of NFTs, extracellular (ghost) NFTs, neuropil threads and plaques in the frontal lobe and significant pathology in the entorhinal cortex, albeit with fewer extracellular NFTS. In a study of three patients with fvAD compared with three typical AD patients, Johnson *et al.* [3] showed higher NFT load in the frontal cortex, but similar values for the entorhinal cortex. No difference in Aβ plaque load was identified. In the present study we found no difference in the frontal to entorhinal ratio of pathology, but a significantly difference in the degree of neuronal loss between frontal and occipital regions. Johnson and colleagues [3] found higher NFT density in the frontal cortex compared with the entorhinal cortex in 30% of the 63 cases reviewed. In a large study of 889 AD patients Murray and colleagues [29] used an algorithm derived from ratios of density measures of pathology from cortical and hippocampal regions to classify AD into typical (75%), limbic predominant (14%) and hippocampal sparing (11%). When the clinical profiles of each of these groups were analysed the groups differed on age at onset (hippocampal sparing < typical < limbic predominant) and rate of decline (hippocampal sparing > typical > limbic predominant). Interesting, the prevalence of a clinical diagnosis other than AD ("atypical" diagnosis) was also significantly different between groups (hippocampal sparing > typical > limbic predominant). In the hippocampal sparing group 30% of cases had an atypical clinical diagnosis including 11/27 (12%) with a diagnosis of bvFTD. Similarly, Gefen and colleagues found a left sided

dominance of NFTs in AD patients with primary progressive aphasia when compared with amnestic AD [10]. However, unlike the present study, these studies did not examine neuronal loss rather they concentrated on the density of AD-type pathology. Neuronal loss and NFT number in the CA1 region of the hippocampus, entorhinal and frontal cortices have previously been shown to account for 79-87% of the variance in Mini-Mental State Examination scores in AD [30] suggesting neuronal loss is a major determinate of clinical dysfunction.

The Braak staging scheme for AD pathology proposes a relatively stereotypical evolution of AD pathology in most cases of AD [1]. There is, however, growing evidence for atypical cases which clearly do not follow this pattern, including those with progressive visual deterioration or posterior cortical atrophy [6] and with the logopenic form of primary progressive aphasia [10, 31, 32]. This present study adds further evidence for the existence of a frontal form of AD which can be mistaken for bvFTD. Given the retrospective nature of the study which relied of case note review we relaxed the consensus criteria for bvFTD to allow the inclusion of cases with two core features (most frequently disinhibition and executive dysfunction) although it should be noted that four of the six cases met strict criteria of three key features accompanied by evidence of progressive deterioration and impaired activities of daily living.

The findings from this study have a number of implications for the diagnosis and management of patients with dementia. While at present no targeted therapies are available for patients with bvFTD, patients with AD are general offered symptomatic treatment with acetylcholinesterase inhibitors. Failure to identify this subset of clinically diagnosed bvFTD patients as having AD pathology may influence treatment choices for these patients. Although the *in vivo* identification of certain $A\beta$ pathology with positron emission tomography [33, 34] is now available, the availability of such imaging is still limited. Furthermore, the duration and course of deficits, and features influencing management such as those that contribute to

caregiver stress [35] are likely to be similar to those for bvFTD rather than typical AD. The small numbers of reports together with declining autopsy rates among patients with dementia make it difficult to amass a sufficient number of cases to undertake studies on the natural course of fvAD. Finally, the findings have relevance to the specificity of the International Consensus criteria for bvFTD [15] and suggest that some symptoms, such as changes in eating behavior, may carry greater weight than others, although these speculations require verification by a prospective study.

Figure legend

Figure 1.

Frontal to Occipital (F:O) and Frontal to Entorhinal (F:E) ratios were calculated for pathology measures for each group using Kruskul Wallis test and Mann-Whitney U posthoc. Mean (±SEM) values for each ratio are shown. (A) F:O neuron ratio in fvAD is lower than AD and equivalent to bvFTD (# p=0.01) suggesting a frontal focus to neurodegeneration in these cases. No significant difference is seen for F:E ratio. (B) For AD-type pathology both the NFT and Abeta ratio for F:O is higher in fvAD than AD, although this only reaches significance for Abeta (* p=0.03). No significant differences are seen for F:E ratio. ^ fvAD-3 showed an extremely high F:O NFT ratio (24.4) due to the very low number of NFTs in the occipital region and was excluded from the analysis.

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Table 1. Demographic characteristics of each group. Mean (standard deviation)

	fvAD	AD	bvFTD	P value[1]
Number of cases	6	6	6	
Mean age at death (SD), y	74 (11)	75 (12)	72 (7)	0.96
Sex (M:F)	4:2	2:4	4:2	0.41
Age at diagnosis (SD), y	68 (14)	68 (15)	67 (8)	0.97
Duration of illness (SD), y	6.7 (3.2)	6.7 (4.5)	6.8 (4.8)	0.99
Cerebrum volume (SD), mL	877 (110)	794 (179)	695 (170)	0.13
Braak neuritic stage, /6[3]	5-6	4-6	0	<0.001

[1] Significance using Chi^2 for gender and Kruskul Wallis test for continuous variables
[3] Braak ref or new AD criteria ref here?

Table 2. Clinical features of fvAD cases. The International Consensus Criteria of Rascovsky et al (2011) were used applied retrospectively to the review of the case records. All cases showed evidence of a progressive deterioration of behaviour and/or cognition.
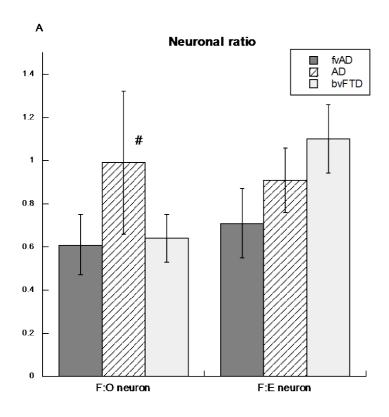
Clinical features	fvAD-1	fvAD-2	fvAD-3	fvAD-4	fvAD-5	fvAD-6
bvFTD*						
Disinhibition	Y	Y	Y	Y	Y	Y
Apathy/inertia				Y		
Loss of empathy				Y		
Perseverative behaviours	Y		Y	Y	Y	Y
Dietary changes				Y		
Executive deficit	Y	Y	Y	Y		Y
Other features						
Language deficit		Y		Y	Y	
Parkinsonism		Y		Y	Y	
Falls/gait abnormality	Y		Y			
Delusions			Y	Y		
Hallucinations		Y		Y	Y	

 * see (Rascovsky et al., 2011) for definitions of features of bvFTD

Table 3: Quantitative pathology. Mean (standard deviation)

	fvAD	AD	bvFTD	P value[1]
Neuron density (N/mm^2)				
Frontal	39 (12)	52 (20)	50 (17)	0.36
Occipital	66 (20)	55 (22)	78 (20)	0.26
CA1^	114 (20)	113 (48)	79 (67)	0.40
ERC^	63 (26)	62 (26)	49 (19)	0.51
NFT density (N/mm^2)				
Frontal	6 (6)	3 (3)	0#	0.005
Occipital	9 (10)	7 (4)	0*	0.006
CA1^	51 (10)	56 (37)	0.44 (1.09)*	0.004
ERC^	20 (15)	16 (16)	0.80 (1.09)#	0.076
Aβ area (%)				
Frontal	0.50 (0.46)	0.28 (0.23)	0#	0.011
Occipital	0.19 (0.15)	0.12 (0.23)	0	0.030
CA1^	0.46 (0.87)	0.11 (0.17)	0	0.224
ERC^	0.41 (0.30)	0.16 (0.35)	0.04 (0.09)	0.074

ERC= entorhinal cortex; ^ hippocampal section not available for one fvAD case; [1] Significance using Kruskul Wallis test; * significantly different from fvAD and AD groups using posthoc Mann-Whitney U test; # significantly different from fvAD using posthoc Mann-Whitney U test

A

Neuronal ratio

B

AD pathology ratio