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Amyloid Imaging in Atypical Presentations of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is thought to progress in a fairly stereotyped manner with episodic memory loss being the first and most salient domain of impairment reflecting the early pathology in structures supporting this function. However, there is considerable heterogeneity in the relative involvement of different cognitive domains and at the extreme are three syndromes associated with AD pathology: 1) Logopenic Progressive Aphasia, 2) Posterior Cortical Atrophy, and 3) Frontal Variant of AD. As each of these syndromes is variably associated with non-AD pathology and clinically overlaps with other presentations more commonly associated with different etiologies of neurodegeneration (e.g. progressive non-fluent aphasia), the use of amyloid imaging for detection of the molecular pathology of AD is of significant clinical value. The current manuscript will review several amyloid imaging studies of these populations which support autopsy case series and reveal a dissociation between the spatial distribution of amyloid pathology and clinical phenotype.

Keywords

atypical dementia; logopenic progressive aphasia; posterior cortical atrophy; frontal variant of Alzheimer's disease; amyloid imaging

I. Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative condition that results in both cognitive and functional decline. Episodic memory loss has traditionally been considered the cardinal feature of the disease, as it is thought to be the first and most salient domain of cognition affected. Indeed, long-standing diagnostic criteria for AD emphasize the requirement for the presence of amnesia associated with at least one of several additional domains of impairment, including executive or visuospatial function, language and praxis [1]. However, heterogeneity in the clinical and pathoanatomic presentation of AD has become increasingly appreciated [2–5]. Indeed, the recently updated clinical criteria for AD proposed by the National Institute on Aging-Alzheimer's Association workgroup

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Compliance with Ethics Guidelines

Conflict of Interest

David A. Wolk has been a consultant for GE Health Care, Inc. and Exponent, Inc.; has received funding for two studies using novel amyloid imaging tracer from GE Healthcare, Inc.; and has received payment for development of educational presentations including service on speakers' bureaus from Haymarket Medical Education.

Human and Animal Rights and Informed Consent

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incorporates non-amnestic presentations of the disease as potentially satisfying the core clinical features [6]. Three types of non-amnestic phenotypes in particular are considered by these criteria: (1) a language presentation, (2) a visuospatial presentation, and (3) executive dysfunction.

These “presentation” types correspond to three clinical syndromes that have been increasingly well-defined and strongly associated with AD-related pathology. While a variety of different names have been used to describe these syndromes, the following have become accepted terms in the literature and clinical practice: (1) logopenic primary progressive aphasia (LPA), (2) posterior cortical atrophy (PCA), and (3) frontal variant of Alzheimer’s disease (FvAD). A particular challenge diagnostically for these syndromes is their overlap with other non-AD dementias. For example, LPA shares features of progressive non-fluent aphasia, a condition generally thought associated with tau-based frontotemporal dementia (FTD) pathology [7, 8]. While relatively sophisticated cognitive testing may help differentiate these AD-associated conditions from non-AD dementias, it is unclear that these distinctions will be easy to apply outside of specialty clinics. These patients underscore the value of *in vivo* molecular measures of AD pathology, including cerebrospinal markers (CSF) amyloid-beta (A β) and amyloid imaging.

The current manuscript will review these three syndromes, particularly focusing on data from studies that have applied amyloid imaging to these populations. In addition to providing support about the underlying etiology, these data provide perspective on the relationship between the distribution of amyloid plaque pathology and the clinico-anatomic features of the syndromes, which has implications for disease pathophysiology. Imaging results will be compared to autopsy findings when available.

II. Amyloid Imaging

A definitive diagnosis of AD requires pathologic confirmation, and new criteria for this assessment were recently published [9]. Clinically, the underlying pathology has generally been inferred based on the cognitive and behavioral features of the presentation and supported by the presence of neuroimaging measures of neurodegeneration (e.g. hippocampal atrophy, posterior cingulate hypometabolism) commonly associated with AD. The emergence of biofluid and imaging methodologies to provide more direct measures of the molecular pathology *in vivo* has been one of the major achievements of the field over the last decade and has contributed significantly to our understanding of the disease process [10] and inspired new targets for therapeutic intervention (e.g. preclinical AD; [11]).

Particularly compelling has been the emergence of amyloid imaging with positron emission tomography (PET) that allows for visualization of fibrillar A β plaques. The first widely used ligand for this purpose was ¹¹C-labelled Pittsburgh Compound-B (PiB-C11; [12]). PET imaging with PiB-C11 has consistently demonstrated the ability to discriminate between cognitively normal adults and patients with AD, predict progression in both preclinical and mild cognitive impairment (MCI) populations, and correlate with *ex vivo* histological measurements of A β plaque burden ([13–15]; for review, see [16]). While the main limitation of PiB-C11 is the short half-life of carbon-11 (~20 minutes) that prevents its widespread clinical use, several “second-generation” ligands that use the radiotracer fluorine-18 (F-18) have been developed and display similar results in patient populations, including correlation with histology obtained by biopsy or autopsy [17–19]. Indeed, florbetapir F-18, or Amyvid, is the first amyloid imaging ligand to be approved for clinical use by the U.S. Food and Drug Administration (FDA) last year.

III. Logopenic Primary Progressive Aphasia

For the last several decades two main forms of progressive aphasia have been described, which have carried the monikers of semantic dementia (SD) and progressive non-fluent aphasia (PNFA) [20, 21]. Both of these syndromes have traditionally been considered types of primary progressive aphasia (PPA) and are generally thought to be associated with the frontotemporal dementia (FTD) spectrum of pathology. Indeed, a number of studies have linked SD with ubiquitin-positive, TAR DNA-binding protein 43 (TDP-43) pathology, a major subtype of FTD-related pathology [7, 22–24]. Alternatively, PNFA is most commonly reported to be associated with non-AD, tau-positive pathology [7, 22, 25, 26]. Nonetheless, a number of clinico-pathologic series of PPA patients have reported relatively frequent cases with primarily AD pathology. As more focused analysis of these cases were pursued, a relatively distinct language phenotype emerged and this group has more recently been classified as logopenic progressive aphasia (LPA) [8, 27].

LPA is characterized by prominent word-finding deficits, both in free speech and with naming. While these patients can often speak with fluent utterances, there are frequent word-finding pauses. A hallmark feature is the presence of impaired repetition of speech, particularly for longer phrase lengths and sentences, reflecting the notion that a reduction in phonologic working memory is a major driver of the cognitive presentation. In distinction from SD and PNFA, respectively, these patients have intact single word comprehension and grammar. Structural and functional imaging with MRI and FDG PET have demonstrated consistent involvement of posterior temporal and parietal perisylvian regions in the left hemisphere [27–29]. Based on still relatively limited autopsy data with most prior to recent formal accepted diagnostic criteria [8], AD appears to be the most common underlying pathology in these patients, but non-AD pathologies have also been reported [7, 25]. Nonetheless, LPA is often considered an atypical variant of AD.

There have now been several amyloid imaging studies of PPA, all with PiB-PET [28, 30–32]. Consistent with the autopsy literature, these studies have reported that the vast majority of these patients have evidence of amyloid plaque deposition, marked by increased uptake of PiB-C11. Remarkably, the pattern of amyloid uptake in these cases was not clearly different from typical AD comparison groups. That is, despite the prominence of language symptoms and evidence of more focal left hemisphere neurodegenerative change, these patients did not display asymmetry in amyloid plaque distribution measured by PiB-PET. For example, Leyton and colleagues reported very similar levels of uptake in the left and right temporal and parietal lobes in the LPA patients [30]. Lehmann et al. demonstrated significant left hemisphere hypometabolism on FDG-PET in LPA patients, but, again, bilateral and symmetric uptake with PiB-PET [32]. In a “PiB-positive” PPA case, Wolk and colleagues noted 19% decreased left relative to right hemisphere metabolism with FDG PET, but, if anything, greater PiB uptake (~4%) in the right hemisphere [31].

While the finding of symmetric amyloid distribution in patients with evidence of much more focal left hemisphere involvement may be unexpected, autopsy data has provided similar findings. Mesulam and colleagues performed both qualitative and quantitative analyses of both neuritic amyloid plaques and neurofibrillary tangles (NFT) in PPA patients with AD pathology [7]. They found no evidence of asymmetry in amyloid plaque burden, comparable to typical AD patients and consistent with the above amyloid imaging data. However, they did report increased NFT burden in left hemisphere language regions, but this was not a universal finding among these patients. The finding that amyloid pathology does not strongly reflect the clinical phenotype is consistent with long-standing data demonstrating poorer correlation of amyloid plaque burden with cognitive severity relative to NFTs [33]. Nonetheless, the fact that NFT pathology also does not always demonstrate concordance

with the focused language impairment in these patients adds to the mystery of the pathophysiology [7, 34, 35]. Importantly, autopsy studies have not revealed additional FTD-spectrum pathology in these cases and, thus, it is unlikely that the AD pathology represents an incidental finding.

Finally, the fact that LPA is not *always* associated with AD pathology while SD and PNFA may be in a minority of the cases, as reported in both autopsy and amyloid imaging studies [28, 30, 36], accentuates the potential role of amyloid imaging in these populations. Even detailed assessments of language and other cognitive function do not predict AD pathology at an individual level in more than a probabilistic manner. Furthermore, these reports have come from dementia specialty clinics, and the granular language assessments applied may not be feasible in more general clinical practice.

IV. Posterior Cortical Atrophy

The entity of posterior cortical atrophy (PCA) was first formally described by David Cogan and then expanded on by Benson and colleagues ~25 years ago [37, 38], but had not received much attention until the last decade. The syndrome is generally defined by a striking impairment of higher order visual processing function out of proportion to other cognitive domains. Most cognitive deficits are attributable to occipito-parietal and occipito-temporal dysfunction, including impairment of visuospatial processing, elements of Bálint's and Gerstmann's syndromes, alexia, apraxia, and impairment of face/object visual recognition [39, 40]. While significant atrophy in the above brain regions is frequently present on structural imaging, such "posterior atrophy" is not always observed in spite of the name. Functional imaging with FDG PET often reveals prominent hypometabolism in parietal and occipital cortex [32, 41]. It is notable that there is significant overlap of the structural and functional cortical involvement in PCA with typical AD making these conditions difficult to discriminate purely based on neuroimaging [40].

Currently, there is not consensus on diagnostic criteria for PCA, but proposed criteria emphasize the presence of visual processing deficits in the face of relatively preserved episodic memory and language function [42, 43]. Age of onset is also a diagnostic consideration, as these patients tend to present at a relatively young age, usually before 65 years old, but this is by no means exclusionary. Perhaps related, in part, to the lack of definitive consensus criteria, PCA reflects a heterogeneous condition with regard to underlying pathoetiology. While there is some variability across the literature, the majority of these cases do appear to have AD-related pathology [35, 36, 42, 44]. However, a variety of other conditions have also been associated with this syndrome, including corticobasal degeneration (CBD), dementia with Lewy Bodies (DLB), and prion disease. It is not clear presently whether specific clinical features and structural or functional imaging aid in prediction of the underlying pathology. Interestingly, in those with AD pathology, NFT burden has been reported to be increased in primary visual cortex and visual association regions relative to other more typical structures affected by AD (e.g. hippocampus) [42, 45, 46]. However, whether or not amyloid plaques are also of greater density in these regions has been inconsistent in the still limited autopsy literature with some studies reporting increases and others a more typical distribution of senile plaques.

Given that there is pathoetiologic heterogeneity and the fact that prominent and relatively focal parietal dysfunction is not rare in AD (~5–10% in one series; [3]), molecular imaging has potentially significant utility in the diagnostic process. There are now several case reports and small series of patients with PCA who have undergone amyloid imaging (all with PiB-PET). These studies have been consistent with the notion that a majority of patients with this phenotype do have evidence of AD pathology [31, 47–52]. However, it is

worth noting that DLB, a condition marked by parkinsonism, visual hallucinations, and cognitive fluctuations, is also often associated with the presence of cortical amyloid plaques and positive amyloid imaging [53], in addition to the synuclein pathology, and, thus, some proportion of these cases may have underlying DLB.

Several reports have indicated increased PiB uptake in occipital regions relative to typical AD [31, 48, 49, 52]. For example, in “PiB positive” PCA patients (n=3), Wolk and colleagues described a lower ratio of anterior-to-posterior PiB uptake relative to typical AD with the opposite pattern for FDG PET, the latter consistent with the lower posterior metabolism in PCA [31]. Lehmann et al. also reported some evidence of increased visual association cortex PiB uptake in PCA and a somewhat more constrained distribution within the visual network. However, as with the pathological data, evidence of greater visual system amyloid plaque burden has not been a universal finding as assessed with amyloid imaging [47, 51].

V. Frontal Variant of AD

While somewhat less studied and less clearly defined than LPA and PCA, it is apparent that AD can sometimes present with a more prominent dysexecutive or behavioral phenotype [54–57]. Furthermore, a number of groups have reported some proportion of clinical FTD patients with primary AD pathology on autopsy [36, 58]. In particular, FvAD has been associated with early onset cases of AD (<65 years old) in which a subset display structural and/or metabolic evidence of a predilection for neurodegeneration in frontal-control networks [2, 32, 59].

The most comprehensive pathologic description of FvAD is the report of 3 cases by Johnson and colleagues [57]. They selected these patients from a series of 63 pathologically proven AD cases based on disproportionate impairment on psychometric measures that measure executive function. Interestingly, they reported a 10-fold increase in NFT pathology in frontal cortical regions disproportionate with other structures. In contrast, they did not find differences in amyloid plaque burden. This group has also described a dysexecutive subtype of mild cognitive impairment and has reported greater frontal AD pathology in one of these patients that was autopsied at this disease stage, suggesting that FvAD can be differentiated from typical AD in prodementia stages [60, 61].

There have not been systematic studies with amyloid imaging of individuals with suspected FvAD. However, studies of clinical diagnosed FTD patients have revealed some proportion that demonstrate positive amyloid scans, including those with primarily executive or behavior symptoms (as opposed to SD or PNFA) [62]. These individuals are likely best classified as FvAD. In a study in which patients were classified as having “possible AD” (n=7) due to atypical presentations with more prominent non-memory cognitive or behavioral symptoms, or were classified as “dementia of uncertain etiology (DUE)” (n=10) with many having significant executive/behavioral symptoms contributing to their diagnostic confusion, 7 had positive amyloid scans. In particular, DUE patients tended to have greater hypometabolism of anterior regions based on FDG PET consistent with their phenotype and suggestive of FvAD. Nonetheless, with the exception of one patient, there was no evidence of greater amyloid uptake in anterior brain regions (frontal cortex, anterior cingulate) in these cases. Finally, studies of early onset AD with associated FDG PET frontal-control network neurodegeneration do not display evidence of more significant amyloid deposition in these regions based on PiB PET. Thus, the amyloid imaging data parallels the findings of Johnson et al. who found an increase in the density of NFTs, but not amyloid plaques, in the frontal cortex of these patients.

VI. Conclusions

The above atypical presentations underscore the potential utility of biomarkers that are specific for the molecular pathology of AD, such as amyloid imaging. While LPA, PCA, and FvAD represent somewhat circumscribed syndromes, their clinical presentation is still associated with varying degrees of uncertainty with regard to the underlying pathoetiology. Further, diagnostic criteria are still limited and in evolution, with LPA being the most developed and FvAD being the least, and the relative sensitivity and specificity of these designations remains largely unknown. As noted above, application of these criteria also may be more challenging outside of dementia specialty clinics. Thus, in addition to enhancing our understanding of these conditions, amyloid imaging is likely to provide critical information with regard to etiology in these cases in the clinical setting. Of course, the value of diagnostic accuracy will be greatly enhanced by the development of more disease specific interventions.

It is also worth noting that these three syndromes represent probable ends of the spectrum with regard to the heterogeneity of AD and that there are certainly cases that would be classified as “atypical”, but defy an obvious syndromic category, that may ultimately have underlying AD pathology as the primary driver of their cognitive impairment. As an example, the case series described above by Wolk and colleagues included 17 patients that were either given a designation of possible AD due to atypical features or dementia of uncertain etiology in which no consensus could be reached by an experienced team of clinicians at an Alzheimer’s Disease Research Center [31]. Of these patients, 7/17 (41%) were considered “positive” for cerebral amyloid as measured by PiB PET, suggesting that this is a mixed group in which amyloid imaging can provide increased diagnostic certainty. Further, a number of clinicopathologic series have suggested that phenotypes, which are traditionally thought to be associated with non-AD dementia, have a significant minority of cases associated with AD histopathology [36, 58]. While the actual proportion of AD cases that have an atypical course or presentation is difficult to determine, some studies have suggested anywhere from 10 to 25% of patients will not follow the classic AD pattern of cognitive deficits [3, 63]. While biomarkers of neurodegeneration, such as FDG PET and structural MRI may offer additional insight into the likely etiology, they tend to recapitulate the pattern of the clinical phenotype rather than resolve the molecular pathology. In these instances, amyloid imaging is likely most valuable, as also suggested by recent “Appropriate use criteria for amyloid PET” proposed by the Amyloid Imaging Task Force, the Society for Nuclear Medicine and Molecular Imaging, and the Alzheimer’s Association [64], criteria developed in the context of FDA approval for Amyvid.

In addition to the potential clinical role of amyloid imaging in these atypical phenotypes, it also offers some insight into the pathobiology of AD. Particularly striking is the generally “normal” appearance of the distribution of amyloid plaques despite the sometimes very focal nature of these presentations. While the notion that amyloid plaques, as opposed to NFTs, do not correlate well with cognition is not a new one [33], these cases offer extreme examples. In light of the generally accepted antecedent nature of amyloidogenesis, the question remains why NFT pathology and neurodegenerative change occur more selectively in these focal cases despite a typical amyloid plaque distribution. Recent work has suggested that while default mode network involvement is common to both typical and atypical cases, different networks display additional more focal involvement in, for example, LPA (left language network) versus PCA (higher visual network) [32, 59]. What drives this differential selectivity may help unlock keys to the progression of not only these atypical cases, but also AD more generally.

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