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Commentary

The Dichotomy of Alzheimer's Disease Pathology: Amyloid-β and Tau

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Abstract. In this issue, an article by Tiepolt et al. shows that PET scanning using [^{11}C]PiB can demonstrate both cerebral blood flow (CBF) changes and amyloid-β (Aβ) deposition in patients with mild cognitive dysfunction or mild dementia of Alzheimer's disease (AD). The CBF changes can be determined because the early scan counts (1–9 minutes) reflect the flow of the radiotracer in the blood passing through the brain, while the Aβ levels are measured by later scan counts (40–70 minutes) after the radiotracer has been cleared from regions to which the radiotracer did not bind. Thus, two different diagnostic measures are obtained with a single injection. Unexpectedly, the mild patients with Aβ positivity had scan data with only a weak relationship to memory, while the relationships to executive function and language function were relatively strong. This divergence of findings from studies of severely impaired patients highlights the importance of determining how AD pathology affects the brain. A possibility suggested in this commentary is that Aβ deposits occur early in AD and specifically in critical areas of the neocortex affected only later by the neurofibrillary pathology indicating a different role of the amyloid-β protein precursor (AβPP) in the development of those neocortical regions, and a separate component of AD pathology may selectively impact functions of these neocortical regions. The effects of adverse AβPP metabolism in the medial temporal and brainstem regions occur later possibly because of different developmental issues, and the later, different pathology is clearly more cognitively and socially devastating.

Keywords: Alzheimer's disease, amyloid, cerebral blood flow, cognition, neuroplasticity, pathology

In this issue, Tiepolt et al. [1] present a PET scan study showing that early scan counts, obtained in the time-frame of 1 to 9 minutes after injection of [^{11}C]PiB, reflect cerebral blood flow (CBF). Pittsburgh compound B (PiB) is an extensively studied radiotracer marker whose late scan counts reveal the distribution of cerebral amyloid-β (Aβ) [2], a protein deposited in the brains of patients with Alzheimer's disease (AD). This study presented the early PiB count distribution and showed that distribution pattern is substantially similar to the pattern of CBF loss seen in AD patients using established scanning techniques [3, 4]. This finding is important because it shows that a single PET tracer injection can be used to determine both the pattern of CBF change in patients with cognitive impairment as well as testing for the presence of Aβ. The study provides further potentially even more important data challenging the association of memory changes with early AD and Aβ deposition. The relationship between the CBF changes and various cognitive factors, in the presence or absence of cerebral Aβ, in this relatively mildly impaired population, suggests the need for better understanding of AD pathology.

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ESTABLISHMENT OF AD PATHOLOGY

AD is a complex condition first described by Alois Alzheimer in 1906 in which neurofibrillary tangles (NFTs) and neuritic plaques (NPs) affect the brain in association with progressive cognitive impairment and dementia [5]. The modern awareness of AD began in 1968 when Blessed, Tomlinson, and Roth showed in elderly individuals that the NFTs correlated with the severity of the dementia, though the NPs, which contain Aβ, did not [6]. A major advance in understanding AD pathology was the demonstration that AD pathology predominantly affects the posterior-temporal, inferior parietal, posterior cingulate, and medial temporal regions [7], with a characteristic pattern of progression beginning in the entorhinal cortex involving neurofibrillary (NF) and microtubule associated protein-tau (tau) pathology rather than senile plaque and Aβ pathology [8], consistent with the earlier findings of Blessed, Tomlinson, and Roth. This progression of AD NF/NFT/tau pathology is clearly reflected by both CBF [3] and cerebral metabolism [9, 10], as well as by PET tracers targeting tau [11, 12], with characteristic regional and stage-specific variations [12]. These changes in the brain are closely related to the impairments of memory function that are so typical of the dementia associated with AD and its progression [13, 14]. This pattern has strongly suggested that AD pathology selectively attacks those neuroplastic brain systems which perform the functions of episodic memory [15, 16].

The NPs and Aβ are consistent components of AD pathology [17], which is the predominant cause of dementia. However, the distribution pattern of Aβ pathology, which is found at least as early and diffusely in the neocortex as the tau pathology, is found first in most regions of the neocortex [18], but is generally not or much less related to cognitive changes than the tau pathology [19–23].

UNDERSTANDING AD PATHOPHYSIOLOGY AND DEMENTIA CAUSATION

The key issue related to the development of dementia in AD is thought to be the loss of synapses [24], leading to decreases in energy metabolism [25], with a direct secondary loss of CBF. This process, as noted above, is closely related to tau pathology and likely results from clogging of neuritic processes [26] leading to NF pathology, amputation of neurites, and synaptic slaughter [27]. The Tiepolt et al. study [1] shows that the CBF change can be demonstrated with PiB by examining the early passage of the radiotracer to the brain. The actual tagging of Aβ requires scanning 40 to 70 minutes after the injection, due to the dynamics of brain binding to the compound, specifically the clearance of PiB from regions where there is no Aβ for it to tag. The data presented by Tiepolt et al. [1] confirm that the estimated CBF is consistent with cognitive changes associated with loss of cerebral metabolism in AD, but associated cognitive changes vary according to the Aβ presence and the overall severity.

The important inconsistency revealed by the Tiepolt et al. study [1] is the lack of a strong relationship in the mildly-impaired Aβ-positive patients between CBF measurement and episodic memory, while CBF shows better relationships with executive and language functions. Thus, there is a critical issue as to whether there may be a separate process early in the development of AD, which disrupts the executive and language functions of the frontal, temporal, and parietal neocortical regions, where Aβ is chiefly deposited [28–30], that is not related to the effect of AD on episodic memory, which occurs later in the disease progression and does correspond to dementia severity.

AD AND THE ROLE OF THE AMYLOID-β PROTEIN PRECURSOR AND Aβ

There has been a long and contentious perspective that AD is specifically a disease beginning with Aβ deposition that causes the development of the tau pathology, which is directly related to the dementia [31–33]. Yet this "amyloid cascade hypothesis" has yielded no AD therapeutic benefits in 25 years [34–36].

While the concept that the Aβ molecule directly leads to the tau pathology is weak and circumstantial, it has become progressively clearer that the amyloid-β protein precursor (AβPP) plays a central role in all forms of Alzheimer-type dementia, and each type begins with an early deposition of Aβ [37]. The first advance in this area of understanding related to the occurrence of Alzheimer-type dementia in Down syndrome, linked to trisomy of chromosome 21. When Aβ was sequenced and related to a gene on chromosome 21, AβPP, the first link to a causative mechanism of AD was established [38]. Deposition

of Aβ occurs early in Down syndrome as well [39]. Many of the early onset AD cases are related to mutations in AβPP or a component of the gamma-secretase (PSEN1 and PSEN2) [40], and each of these cases is associated with a typical age of onset of dementia [41] and an early deposition of Aβ in the typical pattern of AD [42]. The relationship of early changes related to the apolipoprotein E (APOE) gene and Aβ, which is the strongest genetic factor leading to AD [43, 44], is specifically related to Aβ as well [4, 45–47]. A major question in the field is the basis of the APOE relationship, which could be through a direct stimulation of the transcription of AβPP [48], though other theories have been posited related to Aβ, and APOE affects hundreds of cellular mechanisms [49], so the specific molecular biology is not yet known. Further there are several other genetic factors which affect AD occurrence and are associated with early Aβ levels [50, 51]. Additionally, environmental factors likely play a role in the age at which AD develops and are likely also associated with early Aβ deposition [52].

Extensive efforts have led to the development of PET ligands such as PiB to image Aβ in the brain, which have confirmed that Aβ is deposited first generally in neocortical regions, with a predilection for the lateral temporal cortex, the orbito-frontal cortex, and the precuneus, beginning well before symptoms of dementia develop and consistent with the anatomical pathology. Yet these measurements are not or minimally related to cognitive decline or dementia and removal of these deposits does not slow the progress of AD. Yet Aβ is somehow integrally involved with AD, including that it is closely related to specific young-onset genetic factors [40] and the genotype of Apolipoprotein E (APOE) [4, 53–55]. In view of the major questions about the role of Aβ in the development of dementia in AD [36], there is a need for an analysis of the basic pathology of AD with regard to brain changes and cognitive deterioration.

The amyloid hypothesis has been problematic for many reasons [56], but one issue has been that the distribution of the amyloid changes is predominantly neocortical, with tendencies to involve frontal and lateral temporal areas early, which does not correspond to the distribution of the CBF, cerebral metabolic, or tau changes in the brain early or late [19]. Further, the Aβ changes are not related to the cognitive dysfunction of the dementia of AD, and they have a time-course that precedes the dementia by decades [53, 54]. So, there remains the question of whether the Aβ pathology is directly associated with any cognitive impairment, and if so, what impairment. Since the Aβ pathology occurs so early and affects several key neocortical regions including the frontal lobes, it is reasonable to consider that it may have an effect on executive and language functions, as described in the Tiepolt et al. paper [1]. A similar finding was found as well in another recent study examining normal elderly and individuals with mild cognitive impairment with the Montreal Cognitive Assessment and a computerized cognitive test, which included processing speed [57], a factor more related to Aβ than the tau-related pathology [45]. Another study found a relationship between Aβ positivity and executive impairment, that was not independently related to the APOE genotype [47].

The dementia of AD is specifically characterized by highly correlated impairments of memory and other cognitive functions and activities of daily living [58]. The AD-dementia corresponds to the metabolic impairment mostly located in the posterior temporal and inferior parietal neocortical regions, with limited frontal lobe involvement [10], the secondary loss of CBF [3], and tau pathology [8]. However, Aβ changes can be severe yet not be associated with dementia or any well-characterized cognitive impairment [59]. Thus, Aβ deposition might be a separate process unrelated to the relentlessly progressive tau pathology of AD and its dementia. Determining exactly how the Aβ and tau pathologies are related is probably essential to understand AD and develop an approach to AD prevention.

THE ROLE OF AβPP IN NEUROPLASTICITY

Given the central relationship of several genetic factors to AβPP, Aβ, and AD, there is a clear need to understand the specific properties of the AβPP, its proteolysis, and its pervasive role in brain function. AβPP appears be controlled by a variety of molecular processes related to the establishment of new synaptic organizations underlying the formation of new memory, particularly in the temporal and parietal lobes [16, 60]. Of great potential relevance, the beta-cleavage and gamma-cleavage product from AβPP produces, in addition to Aβ, an equal amount of an intracellular domain protein (AICD), which has important roles in intracellular signaling [61–63]. The alpha-cleavage products appear to have separate properties [64]. One possible role of AICD is to stimulate transcription of intracellular factors [65],

which may include tau phosphorylation. Of further relevance, there are several cellular mechanisms for controlling AβPP proteolysis, and the control of the alpha-secretase, ADAM-10 [66]. These systems may play an important role in AβPP management. Further, AβPP may be managed differently in various cortical regions and have multiple critical roles, with pathological processing in some regions leading to Aβ deposition and in others leading to abnormal tau phosphorylation.

It is possible that AβPP may have a specific role in the neocortex and particularly the frontal lobes which has not yet been delineated. AβPP could play a central role in pruning synapses, producing Aβ as a natural synaptic toxin, during critical neocortical periods, and the late and prolonged critical period of the frontal lobes may make parts of that region particularly susceptible to dysfunction, thus predisposing to Aβ deposition there. The critical period of the frontal lobes, which occurs in late adolescence and early adulthood, is associated with the development of schizophrenia [67, 68]. Particular brainstem neurons which project to the neocortex, including the frontal lobes, norepinephrine and serotonin, are also known to augment AβPP alpha-secretase activity, decreasing Aβ production [66, 69], and these neurons are known to degenerate early in AD [70, 71], potentially leading to an excess of beta-cleavage of AβPP and an excess production of Aβ. Accordingly, some AβPP related mechanisms which have an early, adverse effect on the function of the frontal lobe could lead to symptoms of mild behavioral impairment, including personality changes, apathy, and depression, which are related to prodromal and mild AD [72, 73]. In further support of this concept, these behavior changes are linked to genetic loci associated with AD [74]. However, even in the case of psychiatric symptoms, tau pathology, particularly in the brainstem, appears to be more closely related to all dysfunctions than Aβ pathology [75].

Alternatively, in the temporal lobe (hippocampus, amygdala, posterior convexity), inferior parietal lobe, and posterior cingulate, neuroplasticity is a life-long function, leading to progressively longer dendrites [76, 77]. Neuroplasticity may depend on AβPP to either grow neurites or cause them to retract, through induction of tau de-phosphorylation or phosphorylation, respectively [16]. Accordingly, disturbances of AβPP metabolism, without Aβ deposition, could lead to neuritic pathology [26] and synaptic slaughter [27], resulting in dementia.

IMPORTANCE OF BETTER COGNITIVE ASSESSMENT

A point emphasized by the Tiepolt et al. paper [1] is the importance of cognitive assessment. Analysis of CERAD data has led to improvements in cognitive screening for AD. For example, data from CERAD was analyzed, and the most efficient components were identified to construct the Brief Alzheimer Screen [78]. Yet, one of the deficiencies of the CERAD test battery is the lack of power for assessment of episodic memory. Indeed, more powerful assessment of episodic memory is critical to improving the assessment of AD, particularly in very mild impairment. Computerized testing is a probable direction for developing more precise assessments which can increase the sensitivity for measuring not just memory function, but executive, language, and visuo-spatial functions. Improved measures will provide a better assessment of the cognitive impairments early in the course of AD and the continuum of deterioration of cognition leading into dementia [57].

Another issue which should be addressed in considering brain scans in general is the costs and risks of the scans, including the expense of frequent repetitions to determine longitudinal changes. Given the relationship between genetic factors and Aβ deposition, including the early deposition of Aβ in Down syndrome, early onset AD, specific APOE genotype, and polygenic risk factors, it may be that the relationship between age and established age time-lines can provide as much information about the amount of Aβ deposited in the brain as does a brain scan [53, 55]. In the course of establishing such time-lines, there should also be further investigation of environmental factors and medications which affect age of Aβ deposition. Ultimately, the goal is to determine the course of AD in any individual non-invasively and efficiently.

While there has been an exhaustive search for biomarkers of AD, ultimately, the best measures, potentially reflecting every aspect of pathology, will be more precise cognitive assessment of several relevant but different domains. Certainly, cognitive assessment performed by computer can provide greater precision than paper and pencil tests and be considerably cheaper and have less side-effects than brain scanning. As better brain scanning approaches develop, as exemplified by the Tiepolt et al. paper [1], the best outcome may be improvement of neurocognitive assessment.

DISCLOSURE STATEMENT

The author's disclosure is available online (https://www.j-alz.com/manuscript-disclosures/18-1198r1).

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