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Review - Part of the Special Issue: Alzheimer's Disease - Amyloid, Tau and Beyond

The complexities of the pathology–pathogenesis relationship in Alzheimer disease

Rudy J. Castellani [a,*], George Perry [b]

[a] Division of Neuropathology University of Maryland School of Medicine Baltimore, MD, USA
[b] College of Sciences University of Texas, San Antonio San Antonio, TX, USA

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ABSTRACT

Current pathogenic theories for Alzheimer disease (AD) and aging favor the notion that lesions and their constituent proteins are the initiators of disease due to toxicity. Whether this is because structural pathology is traditionally viewed as deleterious, and whether this, in turn, is a fundamental misinterpretation of the relationship between pathology and pathogenesis across the spectrum of chronic diseases, remains to be determined. As more and more detailed information about the biochemical constituents of AD lesions becomes available, it may also be argued that just as much knowledge of cellular physiology as pathophysiology has been gained. Indeed, essentially all major proteins in AD lesions are derived from molecular cascades, which are in turn highly conserved across cells, tissues, and species. Moreover, the lesions themselves are observed in the cognitively intact, and sometimes in large numbers, while major consensus criteria indicate that an extent of pathology is normal with advanced age. As the medical science community continues to pursue lesion targeting for therapeutic purposes, the notion that AD pathology is indicative of an active host response or environmental adaptation, and therefore a poor target, is becoming clearer.

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1. Introduction

The neuropathology of dementia has been the subject of numerous investigations since the original description of the plaque by Blocq and Marinesco [1]. These studies have generally attempted to crystallize relationships between two parameters – clinical phenotype and pathological expression – in order to establish disease entities and, hopefully, gain insight into disease pathogenesis. In parallel with these efforts, however, has been the recognition that pathological lesions occur in cognitively intact elderly. Recognition of this fact initially led to the pursuit of qualitative differences in lesions between disease and control, *e.g.*, differences in the phosphorylation of tau [2], or overrepresentation of amyloid-β (Aβ) isoforms or assembly states [3]. To date, however, there are no known differences between neuritic plaques and neurofibrillary degeneration as observed in the cognitively intact elderly versus those that occur in the setting of Alzheimer's disease (AD). Since putative biomarkers such as cerebrospinal fluid Aβ and phospho-tau (ptau), or imaging techniques such as positron-emission tomography for Pittsburgh Compound B (PiB), are most likely extensions and reflections of pathology, these analyses will necessarily suffer from the same uncertainties that

* Corresponding author.
E-mail address: rcastellani@som.umaryland.edu (R.J. Castellani).

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are inherent in pathologic examination, namely that AD pathology is a poor predictor of cognitive state short of end-stage disease.

Complicating the issue further is the existence of two distinct hallmark lesions, the senile plaque and the neurofibrillary tangle, each associated with accumulation of cellular proteins of normal primary structure, amyloid-β and tau, respectively, and each a product of metabolic processes that are highly preserved across ontogeny and phylogeny. The post-translational processing of both proteins, which is poorly understood, and the structural lesions into which they deposit, represent departures from normal much more than the proteins, or protein levels, themselves. The question of etiology is therefore much more complex, in comparison with the relationship between lesion and clinical disease, which is more a study of statistical correlations than investigation of pathogenesis *per se*.

In this brief review, we examine some of the quantitative data and suggest that the pathology of neurodegeneration, especially with respect to AD and senile dementia, is a productive response to the generally deleterious passage of time, the proper understanding of which is hampered, we believe, by equating lesional proteins with toxicity [4].

2. Familial versus sporadic ad: Are they the same?

The justification for placing Alzheimer's disease (AD) in the lexicon of dementing illnesses was based not on the discovery of lesions in dementia, but by an early age at onset and atypical clinical signs [5,6]. It was separated from senile dementia, a well-known entity in Alzheimer's day, only with difficulty and considerably deliberation [7]. In the end, it was the young age that was the most compelling for Emil Kraepelin, who named AD in the 8th edition of his Textbook of Psychiatry [8]. The neuropathological findings of AD were initially thought to be overall more severe compared to senile dementia, although subsequent studies have not elucidated consistent differences between presenile dementia (AD as originally defined) and senile dementia (sporadic AD as viewed currently) that reliably predict one or the other.

That being said, it is of some interest that the original AD patient, Auguste D, has recently been show to carry a presenilin 1 (*PSEN1*) mutation [9]. This provides some justification for the assertion of Kraepelin and Alzheimer that this was a new disease, distinct from senile dementia. Patients with *PSEN1* mutations show substantial heterogeneity in their clinical and pathological presentations [10]. Seizures, spastic paraparesis, and focal neurological signs have been described as prominent features [11]. Pathologically, such cases may have prodigious amyloid burden and tau throughout the neuraxis with, in some instances, widespread "cotton wool plaques" which are only rarely seen in sporadic AD and differ in structure from neuritic plaques. Most likely, AD was uncovered by the appearance of familial early onset disease in Auguste D. Such cases often present a diagnostic challenge and show little clinical resemblance to senile dementia aside from the overall progressive deterioration. In Alzheimer's words: "after all we are dealing with a 56 year old woman, and in Perusini's case a 46 year old man, in whom no one would make the diagnosis of senile dementia" [5].

Such differences between familial and sporadic AD dating back to the original description are relevant to the present discussion of therapeutics, since constructs for preclinical studies are based entirely on pathogenic mutations, and yet the targeted patient population is sporadic AD which, by definition, lacks pathogenic mutations. This raises the important question of whether familial and sporadic AD are essentially the same condition, or sufficiently similar such that preclinical studies are applicable to both groups, and predict success equally. Given the repeated failures of therapeutic approaches that specifically target the amyloid cascade, be it the amyloid-β output or the enzyme processing, familial AD and sporadic AD appear to be pathogenically distinct entities. Indeed, all seven clinical trials designed specifically to target the amyloid cascade have failed to show therapeutic benefit, including solanezumab which, while described in mainstream press as showing benefit, showed only a marginal reduction in the rate of decline, quantitatively insufficient for the threshold required to demonstrate clinical benefit in trials [12]. As an aside, we have previously raised concerns about this type of reporting, specifically that if enough trials are performed enough times, marginal data that is objectively negative will otherwise appear as a "flicker" of positivity, and justify continued pursuit of a paradigm that is flawed both theoretically (highlighted here) and in practice (multiple failed clinical trials) [13].

Some issues with pathogenic mutations are worth noting, however, the most basic of which is that they are anti-evolutionary. Although familial disease may take several decades to surface, AD mutations are 100% penetrant provided patients live long enough [14]. So despite cellular physiology involving processing of tens of thousands of proteins at any given time, processing of the product of a single pathogenic mutation within this cellular milieu invariably leads to disease given enough time. The aberrant nature of the cellular environment of pathogenic mutation has further been shown by metabolic labeling studies [15], where trafficking and processing of mutated APP differ markedly from that of the wild type. Posttranslational processing in the Golgi and ER, glycosylation, metal binding capabilities, signal transduction, and overall housekeeping function of APP are all altered. The result is premature neurologic deterioration that includes not only simple cortical decline and hallmark pathology, but also diverse clinical signs encompassing atypical cortical signs and symptoms, focal neurological signs, and spastic paraparesis [16], as well as widely variable pathological changes, sometimes encompassing Lewy bodies, Pick bodies [17], and innumerable cotton wool plaques [11]. This tends to substantiate the first impression that familial AD is worthy of a different name.

It should also be kept in mind that genuine familial AD, *i.e.*, autosomal dominant AD with pathogenic mutation, is exceedingly rare. When one considers that AD worldwide numbers in the tens of millions, and that familial AD is limited to only several hundred families (http://www.molgen.ua.ac.be/ADMutations/), it becomes clear that the amyloid cascade concept is based on an aberration, and its wholesale extrapolation to sporadic AD questionable. This view becomes even more questionable in light of several large genome wide association studies, which highlight a host of new genetic associations that relate to amyloid metabolism only with considerable difficulty or with a pre-ordained conclusion that Aβ causes disease [18,19].

3. Ad lesion quantitation and consensus guidelines

Lacking convincing evidence for qualitative differences, scientists have generally deferred to clinicians to point out the biologically important processes *in vivo*. Given the long recognized presence of lesions in normal, aged brains, quantitation assumes greater importance. Attempts at quantitation not surprisingly date to the inception of the AD nomenclature. Simchowitz was among the first to look carefully at quantity over quality as a means of separating AD from simple aging. Still the evidence for potential qualitative differences tended to dominate the literature for several decades hence. Gellerstadt published an important study in 1933, in which he noted senile plaques and neurofibrillary change in the overwhelming majority of well-preserved older individuals [20]. Although the changes tended to be scant by semiquantitative terms, some patients showed changes just as intense as those with senile dementia. Similar findings by Grunthal suggested to him