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Uncertain Influences: Genetics, Pathology, and Alzheimer’s Disease

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Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disease that primarily affects individuals above the age of 65 and is often associated with memory loss, one of its chief symptoms. Although it was first discovered by Alois Alzheimer in 1906, AD has only recently garnered attention proportionate to the impact it is expected to have as the world’s population ages at increasing rates (National Institute on Aging, 2016). Despite the certainty of this its importance, there is much the medical and scientific communities do not know about the etiology of this disease. This paper will discuss a few of the reasons for this lack of knowledge by specifically describing the definite but unclear influence of genetics and pathology on the clinical symptoms of AD.

As previously mentioned, its hallmark symptom is memory loss, specifically the inability to retain novel information (National Institute on Aging, 2016). Other symptoms include disorientation, problems with speaking and swallowing, and behavioral changes, the last of which are often the most burdensome on the individual’s relationships with others (National Institute on Aging, 2016). AD is the most common type of dementia, and currently affects over 5 million Americans (National Institute on Aging, 2016).

Understanding the Disease

Given its current and expected future prevalence, there is a clear need for an understanding of the underlying causes of this disease, for it is what occurs within (and beyond) the human body that leads to these devastating symptoms. Indeed, many researchers have responded swiftly to this call to arms: a search on PubMed’s database using the keywords “Alzheimer’s disease” indicated that 7,617 articles were published on this topic in 2016 alone. Despite this recently demonstrated scientific interest, the largest questions of influence remain. Two of the major questions that will be explored in this paper involve pathology and genetics.

Questions about the influence of a disease’s
pathology often seem unnecessary, for it is the very study that is pathology seeks to explain the causes of clinical symptoms. But when the nature of the pathology itself is complex, the matter becomes more complicated. Here, the symptoms of AD are caused by the large-scale death of neuronal cells in the brain, causing what often appears to be a shrunken version of the “normal” human brain (National Institute on Aging, 2016). However, what is the cause (i.e. pathogenesis) of this sweeping cell loss? When, how, and why does this pathology result? While there are no definite answers to this question, many experts would bring up two compounds with measurable physical presence in the brains of those with AD: amyloid-beta and tau, often collectively deemed, “plaques and tangles.” Despite their noted association with AD, these proteins have been subject to many questions their specific influence. Amyloid-beta has received the majority of the attention, and will be further described below.

Amyloid-beta (Aβ) is a protein found in the form of extracellular plaques, and is thought to be largely unique to AD (Agamanolis, 2016). Over a century since the disease’s discovery, the detection of Aβ is still used to make a definitive diagnosis upon autopsy because. Barring recent technological advances, there has not existed a means of observing these plaques in living tissue. Despite not offering diagnostic assistance, this method of studying Aβ has allowed scientists to characterize the protein and has resulted in a few important claims frequently made. First, Aβ is a transmembrane protein that is also a segment of a much larger protein called Amyloid Precursor Protein (APP), whose function in the body has yet to be determined (Agamanolis, 2016). When APP is improperly cleaved by a pair of enzymes, the product is Aβ, which is then able to accumulate and form among cells. In addition to simply accumulating in the brain, Aβ is also dangerous to neurons in a few specific ways. First, it disrupts long term potentiation, a process that strengthens connections between communicating neurons (Purves et al., 2001). Second, it harms synapses, the physical spaces that link neurons (Purves et al., 2001). Ultimately, the toxicity of Aβ plaques can result in death of neurons specifically in areas of the brain associated with functions impaired by AD (Agamanolis, 2016). The entire process, beginning with APP and ending with
Perhaps the most surprising is that up to 40% of elderly without dementia have been shown to possess AD pathology. (Morris, Clark, & Vissel, 2014). How is this consistent with the link clearly explained by the amyloid cascade hypothesis? There are several possibilities. One is that there are multiple forms of Aβ, and only one—or some—is responsible for symptoms. Another is that Aβ does not actually cause symptoms at all, but is instead produced by the process that does cause them (Morris, Clark, & Vissel, 2014). Yet another option is that other factors, perhaps external to the brain, counteract the development of symptoms that would normally occur due to Aβ accumulation. This third possibility is heavily implicated with the theory of "cognitive reserve," which suggests that individuals may accrue tolerance for AD pathology over time based on various lifestyle features (Morris, Clark, & Vissel, 2014).

Clearly, this finding indicates a need for resolution among experts. Another finding making a similar demand is the high failure rate of pharmaceutical drug trials that take as their basis the influence of Aβ. A study examining drug trials between 2002 and 2012 determined out of 244 Alzheimer’s drugs tested in 413 trials, only one was eventually approved, resulting in a failure rate of 99.6% (Burke, 2014). Furthermore, these pharmaceuticals often seem to remove the physical traces of Aβ plaques in affected individuals, yet their symptoms remain. To explain this finding, some have essentially argued that removing amyloid after clinical symptoms emerge is too late, and that if these drugs were administered earlier, perhaps they would have more success (Burke, 2014). Using this same reasoning, the finding above—that individuals without dementia can also show pathology—can also be explained: maybe these individuals were on track to develop symptomatic AD had they not died before its onset (Morris, Clark, & Vissel, 2014). This assertion is complicated, and almost every claim or theory in this field, calls for additional refinement.

In a related vein, there are many important questions regarding the influence of genetics on the development of AD symptoms. The role of genetics cannot be adequately explained without first understanding the division between two types of Alzheimer’s disease: early onset (EOAD) and late onset (LOAD). EOAD comprises roughly 5% of all AD cases, and can affect individuals at a much younger age range than LOAD (Agamanolis, 2016). Beyond the time of onset, these subtypes differ primarily in their connections with genetics: EOAD has been found to be caused genetic mutations, whereas no such causal link has been found for LOAD (Hutton, Pérez-Tur, & Hardy, 1998). Specifically, EOAD is caused by mutations in the genes that directly affect Aβ production. One set of mutations is on the gene that codes for APP itself, a gene found on chromosome 21; another, more common variety, involves mutations are on two presenilin genes on chromosome 14, genes that are thought to...
also influence Aβ production (Hutton, Pérez-Tur, & Hardy, 1998). Thus, through direct or indirect impact, these mutations in EOAD are themselves crucial for the maintenance of the amyloid cascade hypothesis. Furthermore, they are inherited in an autosomal dominant pattern, meaning that only one inherited copy is sufficient for an offspring to develop the disease (Hutton, Pérez-Tur, & Hardy, 1998). The complexity emerges, however, when examining the other 95% of AD cases, for this straightforward pattern ceases to hold in LOAD. Thus far, no genetic mutations have found to be definitive causes of LOAD; instead, researchers have been able to identify a susceptibility gene: ApoE.

ApoE controls production of the ApoE protein, which is thought to be involved in repairing the brain after damage (Hutton, Pérez-Tur, & Hardy, 1998). It is found on chromosome 19 and exists in three forms, or alleles: ϵ2, ϵ3, and ϵ4. Of these, the ϵ4 allele has been shown to increase susceptibility of AD, and to do so in a “dose-dependent manner,” meaning that inheriting two copies of this allele increases risk more than inheriting one copy (Ertekin-Taner, 2007). This was demonstrated in a study that found that 55% of subjects with two copies developed AD by age 80, compared with 27% of subjects with an ϵ3/ϵ4 pair, and with 9% of those with two copies of ϵ3 (Ertekin-Taner, 2007).

Conclusion

Although this evidence is quite compelling, there are nevertheless unanswered questions. One concerns the heterogeneity of ApoE’s influence. Specifically, most studies conducted—predominantly rely on Caucasian subjects. Researchers have hypothesized that this observation could be due to genetic and environmental factors and interactions that affect distinct populations differently. Ultimately, it has been estimated that the ApoE ϵ4 allele imparts a risk of 20-70%, a range that evokes the uncertainty characterizing not only this issue but the field in general (Ertekin-Taner, 2007).

The questions that arise in determining the cause(s) of AD are complicated and multifaceted. Those involving pathogenesis and genetics are some of the most studied, but do not exhaust all the avenues of inquiry researchers and clinicians are taking. For example, many have turned towards a closer examination of environmental factors, and others have chosen to focus not on the causality of AD but rather on equally important questions regarding the quality of life of those living with dementia. Each area is critical in understanding this highly complex and common disease, and one can hope that with resources, time, creativity, and persistence, strides can be made in the near future.

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References