The Downtown Review

Volume 1 | Issue 2 Article 3

March 2015

Novel Advances in Alzheimer's Disease

Jacob P. Naumann
Cleveland State University

Dementia is an umbrella term used to describe conditions characterized by a decline in mental ability due to neuron damage that is severe enough to hinder daily activities. [3,12] Following the model of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), mild neurocognitive disorder is diagnosed if an individual with dementia presents cognitive decline that is not severe enough to impede daily activities. Major neurocognitive disorder is diagnosed if an individual with dementia presents with significant cognitive decline that interferes with daily life. [2]

Whether the diagnosis is a major or mild neurocognitive disorder, though, the DSM-V model recommends physicians to specify the type present: Alzheimer's disease, fronto-temporal lobar degeneration, Lewy body disease, or mixed conditions. [2,4] Furthermore, the DSM-V model advocates that physicians specify the form of cognitive impairment instead of using the overhead term "dementia" as the diagnosis: long-standing observational studies are supporting the notion that, more often than not, individuals apparently suffering from dementia are suffering from multiple neurological pathologies, colloquially called mixed dementia. [3,16] The most common form of these dementias, accounting for 60-80% of cases, is Alzheimer's disease (AD). [1,3]

AD is a neurodegenerative disease that exacerbates with progression. An estimated total of 5.2 million Americans are currently living with AD, with 5 million of those individuals being 65 years or older. The average duration of Alzheimer's is six to eight years from diagnosis until the ultimate death of the patient. [3] At the moment, once diagnosed with AD, there have been no signs of remission in patients. While the disease has been discovered for over a century, it is only within the past couple decades that the underlying mechanisms of the pathology are becoming better understood.

The main neuropathological feature in AD, like many other neuro-degenerative disorders, is an atypical accumulation of protein deposits. There are two hallmark pathological mechanisms that create these deposit accumulations, and both can be seen on the microscopic level throughout the neocortex. The first mechanism is the formation of senile plaques, also known as neuritic plaque or amyloid plaque: these are contained in

the extracellular space surrounding neurons.[7] Found in the neuropil, amyloid plaques have dense inner cores made up of amyloid filaments. These filaments are monomers arranged in β-sheet conformation that chemically adhere to one another.[7] Once these sheets are in a large enough concentration, a conformational change takes place that changes the soluble protein into insoluble β-amyloids. These amyloids aggregate into amyloid fibrils and eventually form extracellular neuritic plaque. These neuritic plaques are surrounded by dystrophic neurons and microglia.[7,15] Dystrophic neurites are thickened and tortuous neuronal processes, while microglia are cells derived from bone marrow that function as phagocytes in the central nervous system that cause an inflammation response. Similar proteinaceous deposits can also present in the walls of cerebral vasculature in a process known as congophilic or amyloid angiopathy.

The main components of the protein deposits contain amyloid-beta protein (Aβ). Aβ protein is formed from atypical proteolytic cleavage of the gene amyloid precursor protein (APP).[7,13] The primary function of APP is not fully understood, but APP itself is a transmembrane protein that is concentrated in the synapses of neurons. The two enzymes that sequentially cleave the APP gene are the beta amyloid converting enzyme (BACE), also known as beta (β) secretase, and delta (γ) secretase.[9] It is important to note that the APP gene can be cleaved with no consequential Aβ peptides as well. These two enzymes, alpha (α) secretase and γ-secretase, can cleave APP but liberate different peptides that are considered non-pathogenic.[9] The α-secretase cleavage prevents the amyloid beta formation and is seen as a non-amyloidogenic pathway in the processing of APP.

As noted earlier, the issue arises when a harmless soluble peptide, cleaved by α- and γ-secretase, becomes insoluble when cleaved by BACE. Once BACE releases the Aβ peptides, the monomers clump to form oligomers and ultimately the pathogenic aggregates of neuritic plaques.[9] The main role of Aβ protein in the pathogenesis of AD is its largely toxic nature found in vitro and in vivo.[15] While the toxicity mechanism is uncertain, it has been suggested to introduce apoptosis, activate aberrant microglial, and produce hydrogen peroxide. It is also believed to interrupt intracellular calcium

homeostasis due to the activation of ion channels.[13,15] In normal amounts, calcium helps play a role in synaptic transmission, but in excess amounts neurotoxicity is seen. Disrupting the homeostasis inside a neuron leads to synaptic dysfunction, which is a major symptom of AD.

The second hallmark pathological mechanism of AD that is shown to affect normal neuronal function is the presence of another type of deposit found inside the neuron itself. Seen throughout the neocortex, these intracellular inclusions are deposits known as neurofibrillary tangles (NFT). [13] NFT's contain an atypically phosphorylated type of tau (τ) protein. Tau protein is regulated by phosphorylation but individuals with AD show hyper-phosohorylated neuronal microtubule binding of τ protein, which accrue as paired helical filaments. [8] These paired filaments aggregate into the intracellular NFTs found in patients with AD. Once the τ protein is defective and the formation of NFTs occur, the protein can no longer carry out its normal function of stabilizing microtubules in the neurons cytoskeleton. The neurofibrillary tangles also block the transport of essential molecules and nutrients to the neuron, which is believed to play a role in apoptosis. [12,13] In patients with AD, neuron loss disproportionately affects cholinergic neurons, which are the neurons that use acetylcholine as their neurotransmitter for cell signaling. It is suggested that cholinergic neurodegeneration is due to abnormal functioning of acetyl-cholinesterase (AChE) and cholinergic muscarinic acetylcholine receptors (mAChR).[15] This may be combated via AChE inhibitors or mAChR agonists that have been shown in studies to slow the progression of AD by improving the cholinergic deficit in the early stages of the disease.[15] In either case, the increased phosphorylation causes the τ protein to reallocate from axons into dendrites and cell bodies where the tangles cause neuron dysfunction and apoptosis.

These two pathognomonic alterations combined are accompanied by brain atrophy, with the damage being especially profound in the hippocampus and prefrontal cortex. [12] These areas of the brain are heavily involved in memory and cognition. These neuropathological mechanisms, respectively the formation of Aβ proteins and τ tangles,

are the reason AD is identified as a misfolding protein disease and also classified as a taupathy. As noted throughout the literature, AD shares many underlying characteristics with prion diseases but AD is a non-communicable form of proteopathy. [12] It is worth noting that through postmortem, these plaques and tangles have been found in patients who were never clinically diagnosed with AD – which is most likely due to the notion that senile plaque deposits are also a byproduct of senescence. The cholinergic hypothesis of memory dysfunction in senescence and AD is one proposed theory, in which cholinergic hypofunction is present and cognitive deficits manifest. [15] Furthermore, even though plaques and tangles are seen with biological aging, patients suffering from AD have much greater concentrations of amyloid plaques and tau tangles, which also present in different anatomical locations of the brain. Subsequently the relationship between the pathological mechanisms of AD is complex and is also not entirely understood.

Presently, there are two known genetic mutations that increase the risk of AD. It is well understood that the genes on chromosome 21 encode for APP, and is the reason the same polypeptides are found deposited in the brains of patients with trisomy 21.[15] The risk of AD is higher in patients with Down Syndrome because of the extra chromosome and subsequently an extra copy of the APP gene itself. It is key to note that patients with Down syndrome almost always manifest AD like cognitive disorders. In less than 1% of diagnosed AD cases, gene mutations for the genes of APP, or the components of γ-secretase (Presenilin-1 and Presenilin-2) are found. These mutations to APP or γ-secretase cause an increase in Aβ peptide generation and ultimately lead to familial AD.[9] Inheriting any of these gene mutations guarantee that the individual will develop AD. [3] The second genetic mutation that is a major risk factor for AD is a variant of the apolipoprotein E (ApoE4 or ε4) allele. Having a copy of the ApoE4 allele is not a determinant of the disease, but it is shown in up to 65% of cases.[5] It is suggested that each present ApoE4 allele increases an individual's risk of developing AD fourfold, and also increases the risk of them developing the disease at a younger age.[9] The role of ApoE4 and the consequential Aβ formation is unknown, but some researchers propose

that it increases Aβ aggregation and deposition while decreasing Aβ clearance. [9] Whichever the case, large deposits of Aβ that form neuritic plaque can produce local inflammatory response microglial and further lead to apoptosis.

Since the underlying pathological mechanisms of AD are multifaceted, the National Institute on Aging (NIAA) and the Alzheimer's Association (AA) have published new criteria and revised diagnostic guideline for AD. Their aim in doing so is to help healthcare providers better diagnose the disease as well as model AD on a continuum, a continuum that has been proposed because longitudinal findings of age-related neurological and cognitive changes have shown a clear temporal delay between the beginning of neuropathologic characteristics and clinical symptom manifestations in patients. [3] Before continuing, too, it is important to note that the NIA-AA suggests further research is required before the proposed diagnostic criteria is used in clinical practice by physicians.

Nonetheless, the main difference between the 1984 diagnostic criteria and the 2011 criteria is based on two major implications. The first is that before the revisions, a diagnosis was solely based on a physician's clinical judgment concerning the root or cause of an AD patient's symptoms. Physicians would take into account the reports of the patient, family, and friends, as well as neurological assessments and cognitive examinations. However, the new criteria identify three stages of AD, with the first stage occurring before any noticeable symptoms occur. In contrast to the original criteria, memory loss and a regression in cognitive abilities must have already been present to be diagnosed with AD. [3]

Secondly, the new criteria features biomarker tests in which biological factors that can be observed and measured are present. Once a biomarker is found, it can give information on the presence of the disease or the potential risk for developing AD. Levels of the proteins discussed earlier, that is in fluid beta-amyloid and tau, in the cerebrospinal fluid (CSF) and blood plasma are two possible biomarker tests that are being studied for AD. [4]

The latest research indicates that the biochemical changes in the brains of AD patients may begin twenty or more years before any clinical manifestations appear. [3,15] With new evidence supporting this notion, the 2011 criteria revisions suggest that in some cases mild cognitive impairment (MCI) and certain dementias are actually early stages of AD. Due to this, the three stages of AD, as defined from the revised criteria narrative, are preclinical AD, mild cognitive impairment (MCI) due to AD, and dementia due to AD. Preclinical AD is defined as the first stage in AD in which patients have measurable changes in the brain, CSF, or blood. These biomarkers indicate early signs of the disease but no noticeable symptoms such as loss of short-term memory. This stage is pre-symptomatic in nature and needs more supportive research before diagnosing preclinical AD to a patient. Mild cognitive impairment due to AD is the second stage on the continuum of Alzheimer's. This stage is characterized by mild and measurable changes in cognitive abilities, which are noticeable to the individual, family members, and friends but have no affect on their daily activities. A recent study shows that this symptomatic and pre-dementia phase of MCI affects as many as 20% of individuals who are sixty-five years and older. [11] Additionally, further cognitive decline is expected in individuals with MCI. Scientist are now suggesting that when individuals progress from MCI on to dementia, the MCI was actually an early stage of the particular dementia, not a separate condition in and of itself. [11] This biomarker correlates with the progression of AD because studies indicate the pathogenic nature of even small aggregates of Aβ interfering with synaptic transmission, and the toxicity to neurons and the synaptic cleft. [8] The last and final stage on the continuum is the dementia due to AD phase. This phase is characterized by clinical symptoms that affect memory, cognition, and behavioral changes. Unlike the second stage of MCI, the dementia phase does impede the individual's ability to accomplish daily living functions.

As stated earlier, biomarker tests are being examined for efficacy in diagnosing AD. The newest revision offers two biomarkers to help aid the future clinical diagnosis of dementia by offering greater precision and better projection of when the dementia is

going to interfere with the individual's everyday lifestyle. The first biomarker displays the level of beta-amyloid protein accumulation. It is proposed that beta amyloid protein deposition reaches a peak before any clinical symptom onset occurs. Once the beta amyloid protein peak is present, synaptic degeneration through the tau protein pathological mechanism ensues and ultimately causes neuronal death. Once this pathological point is reached, the onset of explicit symptoms is present and neuronal tissue loss is widespread throughout the patient's brain. The second biomarker is a clear indication of the neurons in the brain being damaged or degenerating through brain scan imaging. Further research is being conducted to look at the efficacy of MRI, FDG-PET, and amyloid beta protein imaging to diagnose specifically preclinical and mild cognitive impairment due to AD. [3]

These two biomarkers are important in the combat against AD because many scientist believe that to preserve the brain function of the individual, treatment will be most successful when given during the newly proposed preclinical or mild cognitive impairment due to AD stages of the disease. [15] It is currently unclear whether these two biomarkers should be used separately, in conjunction with one another, or if there are other accurate biomarkers available. It is probable that certain biomarkers will be more effective at different stages of AD's continuum. Having biomarkers to distinguish the stage of dementia is important when combating the symptoms of AD. Since AD is fatal, the goal of healthcare providers is to slow the progression of the disease. Biomarkers can be used to help aid in this combative task by encouraging new treatment methods with advancements in research as well as the potentiality to decrease symptoms of AD.

Symptomatology of AD can be studied and evaluated through medical diagnoses such as mental status testing, blood testing, physical and neurological exams, as well as brain imaging. It is important to know that trans-cultural studies have shown that while most symptoms of AD are similar in nature, different symptoms of AD can present due to demographic, socioeconomic status, and cultural influences. [6] The commonality of symptoms included early onset of short-term memory loss, difficulties in planning and

problem solving, misperception with the time or location of oneself, and alterations in the mood personality of the individual. [2] The most manifested of these symptoms is short-term memory. It is suggested that neurofibrillary plaques and tau tangles first appear in the hippocampal region of the brain. This region is found in the medial temporal lobe of the brain and is part of the limbic system. It is known to play a large role in spatial memory, short-term, and long-term memory.

Atrophy of the hippocampus especially effects episodic memory, or the memory of autobiographical events that is suggested to be the first type of memory to be lost. [6] The second type of memory lost is semantic memory, or that in which the comprehension and denotation of words becomes disrupted. Common symptoms of semantic memory loss are when patients lose the capacity to differentiate fine categories and eventually lead to a broader range of categories. Patients may be able to distinguish their children's name but eventually just call them by terms such as son or daughter. The last memory system to be effected by AD is procedural memory, the memory in which the ability to perform tasks and skills become lost. Eventually, due to degeneration of the hippocampal region, all sense of reason, attention, and focus is lost while aphasia sets in. [6] Brain tissue ultimately shrinks widespread throughout the brain affecting the frontal cortex and cingulate gyrus. Damage to cingulate gyrus cuts off the thalamic nuclei input and manifests through improper emotion formation, memory, and learning.

With new technological advances and the growing knowledge on the pathology of dementia it is a promising time for patients battling AD and healthcare providers trying to give those individuals the best quality of life possible. The new diagnostic guidelines proposed by the NIAA and the AA may provide healthcare providers and those working directly with patients afflicted by AD new therapeutic and preventative techniques to assist patients with AD, and their families, through the transitional periods of dementia. Since the discovery of Alzheimer's in 1906, there has continued to be advancements in the etiology, symptomology, and treatment of AD, and the recent diagnostic changes

recommended by the NIAA and the AA continues to offer hope to those who have been touched by Alzheimer's.

References

1. Alzheimer, A. *Allg. Z. Psychiat.* 64, 146–148 (1907).

2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th edition). Arlington, Va.: American Psychiatric Publishing; 2013.

3. Gaugler, J., James, B., Johnson, T., Scholz, K., & Weuve, J. (2014). *2014 Alzheimer's Disease Facts and Figures* (2nd ed., pp. 2-80). Chicago: Alzheimer's Association. Retrieved from http://www.alz.org/downloads/Facts_Figures_2014.pdf

4. Jack, C. J., Knopman, D. S., Weigand, S. D., Wiste, H. J., Vemuri, P., Lowe, V., & Petersen, R. C. (2012). An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. *Annals Of Neurology*, *71*(6), 765-775. doi:10.1002/ana.22628

5. Jack, C., Lowe, V., Weigand, S., Wiste, H., Senjem, M., Knopman, D., & Petersen, R. (n.d). Serial PIB and MRI in normal, mild cognitive impairment and Alzheimers disease: implications for sequence of pathological events in Alzheimers disease. *Brain*, *132*1355-1365.

6. Karim, S., Minhas, H. M., Bhattacharya, S., Sein, K., Nayar, B., Morris, J., & Burns, A. (2011). The symptomatology of Alzheimer's disease: a cross-cultural study. *International Journal Of Geriatric Psychiatry*, *26*(4), 415-422.

7. Kerr, M. L., & Small, D. H. (2005). Cytoplasmic domain of the beta-amyloid protein precursor of Alzheimer's disease: function, regulation of proteolysis, and implications for drug development. *Journal Of Neuroscience Research*, *80*(2), 151-159.

8. Ksiezak-Reding, H., Morgan, K., Mattiace, L. A., Davies, P., Liu, W. K., Yen, S. H., & Dickson, D. W. (1994). Ultrastructure and biochemical composition of paired helical filaments in corticobasal degeneration. *The American Journal Of Pathology*, *145*(6), 1496-1508.

9. Kumar, V. (2003). Central Nervous System. In *Robbins basic pathology* (9th ed., pp. 835-838). Philadelphia, PA: Saunders.

10. Lazarczyk, M. J., Hof, P. R., Bouras, C., & Giannakopoulos, P. (2012). Preclinical Alzheimer disease: identification of cases at risk among cognitively intact older individuals. *BMC Medicine*, *10*127. doi:10.1186/1741-7015-10-127

11. Lopez OL, Jagust WJ, DeKosky ST, Becker JT, Fitzpatrick A, Dulberg C, et al. Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study. *Arch. Neurol.* 2003;60:1385- 9

12. Martone, R. L., & Piotrowski, N. P. (2014). Alzheimer's disease. *Magill's Medical Guide (Online Edition).*

13. Masters, C. L., Multhaup, G., Simms, G., Pottgiesser, J., Martins, R. N., & Beyreuther, K. (1985). Neuronal origin of a cerebral amyloid: neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaque cores and blood vessels. *The EMBO Journal*,*4* (11), 2757-2763.

14. Schliebs, R., & Arendt, T. (2011). The cholinergic system in aging and neuronal degeneration. *Behavioural Brain Research*, *221*(2), 555-563. doi:10.1016/j.bbr.2010.11.058

15. Villemagne, V. L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K. A., Salvado, O., & Masters, C. L. (2013). Amyloid β deposition, neuro-degeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *The Lancet. Neurology*, *12*(4), 357-367. doi:10.1016/S1474-4422(13)70044-9

16. Wang, B. W., Lu, E., Mackenzie, I. A., Assaly, M., Jacova, C., Lee, P. E., & Hsiung, G. R. (2012). Multiple pathologies are common in Alzheimer patients in clinical trials. *The Canadian Journal Of Neurological Sciences/Le Journal Canadien Des Sciences Neurologiques*, *39*(5), 592-599.