December 2020

Alzheimer's disease

somewhat different

The US version of hr | Ascent provides guidance on how to underwrite cognitive issues

A challenging and devastating dementia

Alzheimer's disease is the most common form of dementia, with affected persons experiencing loss of memory, personality, independence and ultimately death from this neurodegenerative illness. It places an immense burden on healthcare systems and families of individuals with Alzheimer's and due to its increasing prevalence – a result of aging populations globally - it represents a looming healthcare catastrophe.

Multiple disease-causing mechanisms at play

A number of disease-causing mechanisms for Alzheimer's have been identified since modern research into this form of dementia started in the 1980s. Two such key disease-causing mechanisms are the respective accumulations of two types of toxic proteins in brain tissue, known as:

1. Amyloid-Beta protein, and
2. Hyper-phosphorylated Tau protein.

Amyloid-ß deposition

Toxic amyloid accumulation results in so-called neuritic plaques and extracellular neuronal deposits. These two changes are essential neuropathologic changes of Alzheimer's - yet there is still so much not known about these pathological findings.

In particular, it is still not clear whether amyloid deposition causes Alzheimer's or whether the disease results in amyloid deposition. What is known is that amyloid accumulation in the brain results from the overproduction of this protein (seen in younger patients with Alzheimer's) and/or decreased clearance thereof, which is the mechanism more likely evident in older-onset Alzheimer's.

There are many objective data points in support of neurotoxicity from amyloid deposition. Some of the most compelling of these data points are:

- Increased amyloid deposition seen in Down syndrome with its characteristic neurological disease.
- Genetic mutations, found in familial early-onset Alzheimer's, encode the protein that generates amyloid and cause the most aggressive forms of Alzheimer's disease.
- The APOEε4 allele, which is the most common genetic risk factor associated with non-familial Alzheimer's, is credibly associated with decreased clearance of amyloid of the brain.

A number of so-called acquired mid-life risk factors have been shown to increase the risk of amyloid deposition later in life and include:

- Hypertension and dyslipidemia
- Cerebrovascular disease and peripheral atherosclerosis
- Sedentary lifestyles, obesity and type 2 diabetes
- Head injuries with a history of loss of consciousness
- Medications including anticholinergics, benzodiazepines and proton pump inhibitors (PPIs)

Another challenging characteristic of Alzheimer's is that it has a very prolonged incubation period with amyloid

accumulation within the brain occurring as early as 15 to 20 years before the onset of Alzheimer's symptoms.

Is the amyloid accumulation theory flawed?

Researchers have been reluctant to abandon amyloid deposition as a central pathophysiologic mechanism behind Alzheimer's disease despite the litany of failed anti-amyloid drug trials with small molecule and monoclonal antibody agents.

Between 1998 and 2017 there have been 146 failed therapeutic drug trials for Alzheimer's disease, which has many experts in the field wondering if the amyloid accumulation theory as a key cause of Alzheimer's is flawed. Critical appraisals of these trials have suggested some reasons for the lack of therapeutic drug success in this field and include:

1. Optimal dosages of some anti-amyloid drugs needed to achieve adequate reductions in brain amyloid are not clinically tolerable.
2. Levels and durations of biochemical effect from anti-amyloid drugs required to achieve desired clinical effects, are challenging to define.
3. Selection criteria of appropriate Alzheimer's disease populations, for example early, mild Alzheimer's disease patients, to target in drug trials are not yet clearly established, especially when considering the prolonged incubation period of Alzheimer's.
4. The dichotomous designs of large clinical trials (i.e. the so-called focus on "all or nothing" clinical outcomes) are scientifically inappropriate for a complex disease like Alzheimer's.
5. Disease modification in Alzheimer's may only be possible with combination drug therapy - for example in addition to the anti-amyloid therapy look to use an anti-tau protein drug therapy for a dual-prong treatment strategy.

Innovations in cognitive testing and non-pharmacological dementia treatment

In the absence of therapeutic drug success, optimism in the fight against Alzheimer's disease is emerging from innovations in cognitive testing and non-pharmacologic Alzheimer's interventions, such as the eye-tracking technology and cognitive health program on offer through Neurotrack. One of the several eye-tracking tests for cognition performed by Neurotrack is a 12-minute visual paired comparison test, which is a robust memory test and may be ideally suited for cognitive screening in an automated underwriting environment for life and long-term care insurance. For more information on the Neurotrack solution see this article.

Underwriting cognitive impairment

The US version of hr | Ascent, Hannover Re's underwriting manual provides up to date guidance on how to underwrite cognitive issues including:

- Age associated memory impairment
- Mild cognitive impairment
- Alzheimer and other forms of dementia

Contact Hannover Re to learn more.

Nico van Zyl
VP, Chief Medical Director
Hannover Re

nico.van-zyl@hannover-re.com

References

Kuller LH, Lopez OL. Dementia and Alzheimer‘s disease: A new direction. The 2010 Jay L. Foster Memorial Lecture. Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association; 9/2011, Vol 7(5), pp. 540 – 550

Duce JA et al. Therapeutics for dementia and Alzheimer’s disease: New directions for precision medicine. The British Journal of Pharmacology; 8/29/2019, Vol 176 (18), pp 3409-3412

Selkoe DJ. Alzheimer Disease and aducanumab: adjusting our approach. Nature Publishing Group UK; 5/28/2019

Schneider L. A ressurection of aducanumab for Alzheimer’s disease. Lancet Neurology; 2/2020, Vol 19 (2), pp. 111-112

Toyn J. What lessons can be learned from failed Alzheimer’s disease trials? Expert Review of Clinical Pharmacology, 5/2015, Vol 8 (3), pp. 267-269

Arvanitakis Z et al. Relation of cerebral vessel disease to Alzheimer’s disease dementia and cognitive function in elderly people: a cross-sectional study. Lancet Neurology; 8/2016, Vol 15 (9), pp. 934-943

Abbott A et al. Failed Alzheimer’s trila does not kill leading theory of disease. Nature; 11/23/2016, Vol 540 (7631), pp. 15-16

Smith AD. Why are drug trials in Alzheimer’s disease failing? The Lancet; 10/30/2010, Vol 376 (9751), p. 1466

PhRMA. Researching Alzheimer’s Medicines: Setbacks and stepping stones; Fall 2018