Research Blog for April

- **Blood Pressure Treatment May Aid Cognition in Very Early Alzheimer's**

A new analysis of data from a Phase 3 clinical trial testing the blood pressure medication Nilvadipine supports evidence that its use helps to slow cognitive decline in Alzheimer's patients with very mild, very early stage disease.

Nilvadipine is a dihydropyridine calcium channel blocker approved to treat hypertension (high blood pressure) in several European countries and Japan, but not in the U.S.

A Phase 3 randomized controlled 72-weeks clinical trial, called NILVAD (NCT02017340), involving 497 patients with mild to moderate AD, took place across Europe to test Nilvadipine as a potential treatment for AD.

A review of the data by a team from Roskamp Institute in Florida, segregating patient data based on the disease stage, showed that, compared to very mild Alzheimer's given a placebo, those at the same very early stage but treated with Nilvadipine (0.8 mg tablet) had lesser cognitive decline at 52 and 78 weeks. This included a slower decline in memory and loss of language skills.

However, those with moderate Alzheimer's disease treated with Nilvadipine experienced a greater cognitive decline compared to those given a placebo.

"**The possibility that Nilvadipine may impact the three main pathologies of Alzheimer's disease (amyloid, tau and neuroinflammation) makes it potentially very useful among current therapies,"** said Rudolph Tanzi, a neurology professor at Harvard Medical School. While more trials are needed, the hope is this drug may ultimately be effective for both presymptomatic prevention and treating early-stage patients.

Source:
https://alzheimersnewstoday.com/2020/03/30/blood-pressure-treatment-may-aid-cognition-in-very-early-alzheimers/

- **Body mass index, diet, physical inactivity, and the incidence of dementia in 1 million UK women**

The objective of the study was to help determine whether midlife obesity is a cause of dementia, and whether low body mass index (BMI), low caloric intake, and physical inactivity are causes or merely consequences of the gradual onset of dementia. The

study involved recording these factors early in a large 20-year prospective study and relating them to dementia detection rates separately during follow-up periods of <5, 5 to 9, 10 to 14, and 15+ years.

A total of 1,136,846 UK women, mean age 56 (SD 5) years, were recruited in 1996 to 2001 and asked about height, weight, caloric intake, and inactivity. They were followed up until 2017 by electronic linkage to National Health Service records, detecting hospital admissions with mention of dementia.

Dementia detection during years 15+ was associated with baseline obesity, but not clearly with low BMI, low caloric intake, or inactivity at baseline. The latter 3 factors were associated with increased dementia rates during the first decade, but these associations weakened substantially over time, approaching null after 15 years.

Conclusions Midlife obesity may well be a cause of dementia. In contrast, behavioral changes due to preclinical disease could largely or wholly account for associations of low BMI, low caloric intake, and inactivity with dementia detection during the first decade of follow-up.

Source: **https://n.neurology.org/content/94/2/e123**

- **Decline in cognitive resources Influences physical activity after midlife.**

The objective of this study was to test whether the level of cognitive resources explains engagement in physical activity across aging and whether the age-related decline of cognitive resources precede the decline in physical activity.

Data from 105,206 adults aged 50 to 90 years from the Survey of Health, Ageing, and Retirement in Europe (SHARE) were used to examine whether the engagement in moderate physical activity and its evolution across aging were dependent on cognitive resources.

Cognitive resources and physical activity were measured 5 times over a 12-year period. Delayed recall, verbal fluency, and the level of education were used as indicators of cognitive resources. The frequency of engagement in moderate physical activity was self-reported.

Results: Lower cognitive resources were associated with lower levels and steeper decreases in moderate physical activity across aging. Results further revealed a

time-ordered effect with a stronger influence of cognitive resources (delayed recall and verbal fluency) on subsequent changes in moderate physical activity than the opposite.

Conclusion: These findings suggest that, after age 50, the level of engagement in moderate physical activity and its trajectory depend on the availability of cognitive resources. (PsycInfo Database Record (c) 2020 APA, all rights reserved)

Source: Health Psychology. Advance online publication. https://doi.org/10.1037/hea0000857

- **A perfect storm brewing for individuals and families impacted by dementia**

People with neurodegenerative disease are among those most vulnerable to COVID-19. Though having Alzheimer's or a related disease does not by itself render a person susceptible to COVID-19, co-existing health conditions such as cardiovascular disease pose a higher risk of complications related to COVID-19.

Behavior symptoms stemming from cognitive impairment or dementia increase the possibility of infection. While people with Alzheimer's Disease need consistent reminders, or help, to wash their hands, people with frontotemporal dementia struggle with social distancing, and those with communication challenges have trouble understanding the pandemic or communicating their concerns to caregivers.

Social-distancing measures mean that caregivers are taking on even more work themselves. In-home healthcare aide staff are unavailable due to health issues, childcare responsibilities at home etc. Even when available, home-health aides pose a risk of transmitting infection.

Loss of in-home health aids, adult day programs, and residential care spots (admissions paused due to Covid-19) imposes additional stress on caregivers, already stressed by COVID-19 uncertainties.

Mounting caregiver stress, sensed by people with dementia, tends to create a vicious cycle triggering behaviour changes —anger, agitation, anxiety, confusion, reduced appetite, sleep issues, resisting care, refusing medications, overwhelming caregivers further.

Under-staffed care homes relying on visits from family and volunteers have to rely on support staff without dementia care training, causing anxieties for residents with dementia, and consequent behaviour changes.

Source:
https://www.alzforum.org/news/community-news/perfect-storm-families-grappling-dementia

- **Individual Differences in the Effects of Physical Activity on Cognitive Function in People with Mild to Moderate Dementia**

The aim of this study was to investigate whether the effect of physical activity on cognitive function in persons with dementia is moderated by patient characteristics as Apolipoprotein E and dementia type.

The study included 101 individuals with dementia and calculated the reliable change index to determine the change in global cognition, executive function, episodic memory, working memory, and processing speed before and after a 12-week exercise training.

The researchers found that only a minority of individuals with mild to moderate dementia showed significant and reliable improvements on global cognition (4.5%) or on any of the cognitive domains after a 12-week physical exercise intervention. Moreover, they found a smaller decline in episodic memory after the intervention in persons with non-Alzheimer disease compared to persons with Alzheimer's disease.

The researchers did not find significant associations between *APOE ε*4 status and global cognitive change or change in any of the domains. They observed a positive relation between baseline MMSE score and post-treatment change in executive function, while they found a negative relation between baseline MMSE score and post-treatment change in processing speed.

These findings indicate that persons with less severe cognitive impairment at baseline show less cognitive decline in executive function after the intervention, while in contrast (and counter-intuitively), persons with more severe cognitive impairment at baseline show less decline in processing speed after the intervention.

These findings stress the need for a personalized approach when designing and analyzing interventions for persons with mild to moderate dementia to target those who benefit most from physical activity intervention

Source: Journal of Alzheimer's Disease, vol. 74, no. 2, pp. 435-439, 2020

- **Active Tau Vaccine: Hints of Slowing Neurodegeneration**

At the second biannual Advances in Alzheimer's and Parkinson's Therapies Focus Meeting (AAT-AD/PD), speakers gave updates on two active tau vaccines currently in clinical trials.

One of them, AADvac1, reportedly slowed neurodegeneration biomarkers in Phase 2. The other, ACI-35, elicited a weak immune response in people, and needed to be redesigned to boost immunogenicity.

The primary outcome of safety was met; the vaccine was well-tolerated, with no difference in adverse events between the vaccine and placebo groups except for more injection-site reactions in the former. A secondary outcome, immunogenicity, was also positive.

AADvac1 showed a highly significant impact on neurodegeneration, as measured by plasma NfL and supported by an effect on CSF tau, p-tau, and DTI. The researchers believe the data indicate a disease-modifying effect, particularly in younger AD patients. Axon Neuroscience is planning a Phase 3 trial that will run for 24 to 30 months.

The second vaccine, AC Immune's liposomal supra-antigen vaccine was well-tolerated but elicited a weak immune response, and booster shots had little effect. The second-generation vaccine, ACI-35.030, produced a stronger immune response.

Source:
https://www.alzforum.org/news/conference-coverage/active-tau-vaccine-hints-slowing-neurodegeneration

- **The Best Phospho-Tau Marker for Alzheimer's Disease?**

A flood of recent data seems to leave little doubt that phospho-tau217 is the better of the soluble tau markers for studying Alzheimer's disease thus far. At this year's virtual AAT-AD/PD meeting, **Oskar Hansson**, Lund University, Sweden, reported that p-tau217 in the CSF correlates more strongly with neurofibrillary tangles and amyloid plaques than does p-tau181 or total tau. CSF p-tau217 climbs higher, and better distinguishes AD from controls and non-AD forms of dementia, as well, said Hansson.

- CSF P-tau217 strongly correlates with plaques and tangles in AD.
- It distinguishes Alzheimer's from other dementias better than does p-tau181.
- P-tau217 best predicts accumulation of neurofibrillary tangles.

"This is a very nice way, with an intervention study, to address the cascade we are suggesting," said Hanson. "The next step would be to see if the treatment reduces the accumulation of tangles."

Source:
https://www.alzforum.org/news/conference-coverage/217-best-phospho-tau-marker-alzheimers

- **In DIAN-TU, Gantenerumab Brings Down Tau. By a Lot. Open Extension Planned**

At the AAT-AD/PD meeting, researchers unveiled the story of how Gantenerumab gained a second wind in the Dominantly Inherited Alzheimer's Network trials unit (DIAN-TU).

According to topline results reported by researchers, Gantenerumab, a monoclonal antibody targeting aggregated forms of Aβ is still very much in the limelight. Besides removing amyloid plaques from the brain and normalizing CSF Aβ 42, this antibody reversed toward normal the elevated levels of CSF total tau and p-tau181, an AD-specific, pathological form of this neuronal protein. Gantenerumab further stemmed the rise of the general neurodegeneration marker CSF neurofilament light.

The effect sizes of this biomarker response were so large that they prompted the DIAN investigators and Roche to invite DIAN participants—who have devoted four to seven years of their lives to this trial, depending on when they enrolled—to join an open-label extension. It will explore high-dose Gantenerumab therapy for several additional years, to see if sustained Gantenerumab therapy near the highest tolerated dose removes both plaques and tangles all the way down to a hypothesized, yet-to-be-defined threshold at which cognition and function might start to benefit. The researchers also want to learn if a longer time on such a high dose gives the brain time to adjust to life without plaques and tangles—that is, to heal.

Source:
https://www.alzforum.org/news/conference-coverage/dian-tu-gantenerumab-brings-down-tau-lot-open-extension-planned

- **Aβ in Lewy Body Disease: Two Diseases at Once, or Another Beast Entirely?**

Many people with Lewy body diseases (LBDs) such as Parkinson's ultimately develop dementia, and many have Aβ plaques and tau tangles. Do they have two diseases at the same time, or is this combination of scourges a unique entity unto itself?

At the virtual AAT-AD/PD meeting, held early April, researchers reported that **people with PD who carry genetic risk variants for Alzheimer's disease were more likely to become cognitively impaired.** Similarly, AD variants predicted which PD patients harbored Aβ and tau proteopathies in their brains.

In people with dementia with Lewy bodies (DLB), Aβ plaques seemed to worsen cognitive decline more than tau tangles did, suggesting an etiology distinct from AD.

Together, the studies suggest that Aβ could exacerbate both tau and α-synuclein aggregation in LBD. **This is why Aβ-targeted therapies could benefit people with synucleinopathies.** Second, while Aβ plays the role of instigator in AD, it appears to drive progression throughout the disease process in LBD. Therefore, while ridding the brain of Aβ may be too little, too late, for people with symptomatic AD, it could slow the disease in people with LBD, according to researchers.

Source:
https://www.alzforum.org/news/community-news/av-lewy-body-disease-two-diseases-once-or-another-beast-entirely