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**ReachMD**
www.reachmd.com
info@reachmd.com
(866) 423-7849

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Amyloid and Tau in Alzheimer's Disease: Insights into Disease Progression

**ReachMD Announcer:**
Welcome to ReachMD. This program, titled "Amyloid and Tau in Alzheimer's Disease: Insights into Disease Progression," has been organized and funded by Biogen. It was hosted by AD/PD and was previously recorded, so the Q&A functionality is not available. Dr Mattson-Carlgren has been compensated by Biogen for his participation, and this program is intended for US healthcare professionals only. And now, here's Holly Brothers.

**Holly Brothers:**
Good morning, good afternoon and good evening.

I'd like to welcome you to this live webinar titled Amyloid and Tau in Alzheimer's Disease: Insights into Disease Progression, hosted by ADPD and sponsored by Biogen.

I'm your moderator, Holly Brothers from Biogen, and I'd like to introduce you to our esteemed speaker, Doctor Niklas Mattsson-Carlgren.

Dr Mattsson Carlgren is an associate professor at Lund University.

The primary focus of his research is Alzheimer's disease and other neurodegenerative diseases, and his investigations range from the molecular mechanisms of disease to clinical characteristics along a continuum from preclinical disease to advanced dementia.

He's also part of the executive group of the Biofinder study.

Dr Mattsson-Carlgren is a prolific contributor to Alzheimer's field with over 180 publications that populate top tier journals.

Major themes of his work include the evolution of biomarkers to improve diagnosis and prognosis of disease, and investigations into amyloid and tau, as well as other proteinopathies and biomarkers.

Thus, you'll see why Dr Mattsson-Carlgren is uniquely suited to present the topics of the webinar today.

Next slide, please.

These topics will include: an exploration of the pathology of the Alzheimer's continuum, a deep dive into tau clinical pathological correlation, how we will move or maybe moving toward a biological definition of Alzheimer's disease and future directions in Alzheimer's disease.

I'd like to encourage you to submit questions using the question-and-answer function here.

And we will have a question-and-answer period with Dr Mattson-Carlgren after the presentation.

All together, we think that this webinar will be about 45 minutes.

Next slide, please.

If you're interested in these topics, I'd like to invite you to join or to view the Know Tau educational platform developed by Biogen.

This webinar will be filmed or recorded and join other video recordings as well as modular chapter content on this platform that we hope that you will find interesting, informative and engaging.

Now I'd like to pass it over to Dr Mattsson-Carlgren to begin.

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**Dr Mattsson-Carlgren:**
Thank you so much for the introduction.

And hello, everyone.

So my name is Niklas Mattsson-Carlgren.

I'm a specialist physician at the Memory Clinic in Malmö, Sweden, and a researcher and associate professor at Lund University in Lund, Sweden.

And today, we'll be discussing the latest insights into the roles of amyloid and tau in Alzheimer's disease progression.

These are my disclosures, and this is a content specific disclaimer that at this time there are no approved products that target tau and the efficacy and safety profile of tau targeting drugs has not been established.

We'll start by exploring the pathology of the Alzheimer's disease continuum.

Alzheimer's disease is the most common cause of dementia.

It accounts for about 60 to 70% of all cases of dementia.

The lifetime risk for Alzheimer's disease is about 20% for women and about 10% for men.

Now the prevalence of the disease is increasing.

It is projected to almost double every 20 years from now, making early diagnosis and intervention increasingly important.

The neuropathological hallmarks of Alzheimer's disease include both amyloid plaques, neurofibrillary tangles of tau, but also downstream responses such as glial responses and synaptic and neuronal loss.

The symptom disease include memory loss that disrupts daily life, confusion with time and place, challenges with planning or solving problems, difficulty completing familiar tasks, problems with communication, and decreased judgement.

Importantly, the pathology of Alzheimer's disease begins years or even decades, in some cases, before clinical symptoms appear.

The disease is therefore now considered a continuum where aggregation of brain pathology with amyloid and tau are early pathological changes.

But the level of tau aggregation over time and neurodegeneration that comes with it correlates strongly with clinical symptoms of the disease.

Let's look at how biomarkers evolved over the disease course.

Alzheimer's disease biomarkers manifest at different times.

β-amyloid pathology can be detected early before symptoms, either using measures in cerebrospinal fluid or with amyloid PET imaging.

Tau pathology usually starts in the medial temporal lobe, the MTL, and it can be detected there years before dementia onset in Alzheimer's disease.

Now, the initial tau changes can occasionally be seen prior to a rise in amyloid biomarkers, but the substantial increases happen only once amyloid aggregation has started.

The widespread neocortical spread of tau happens later and is often linked to accelerated neurodegeneration and cognitive impairment. So note that the prominent changes in tau biomarkers happen after signs of amyloid aggregation, but can still occur several years before dementia due to Alzheimer's disease.

In healthy neurons, tau is found throughout the neuron, with a variety of functions being described.

The protein is, for example, involved in microtubule stability, axonal transport, synaptic function and also DNA maintenance.

Now, in Alzheimer's disease, the tau protein undergoes changes.

It becomes hyperphosphorylated.

It misfolds and aggregates first into smaller oligomers and then subsequently into larger and larger structures, including neurofibrillary tangles and other large structures.

Besides the phosphorylation, other modifications of tau can also occur such as truncations and these may also promote aggregation of the protein.

In Alzheimer's disease brains, besides the neurofibrillary tangles, which are found in cell bodies, tau also aggregates in so-called neuropil threads, in neural dendrites, and in tau positive neurites found in amyloid plaques.

Different variants of tau deposits have been visualised and described.

For example, as shown here, the spectrum of neurofibrillary tangles, from diffuse to pre-tangle to mature tangles and finally ghost tangles, are thought to resemble the development of pathology that really starts with early, potentially even reversible changes, and finally manifest in late and irreversible pathology.

The aggregation of tau appears to be toxic to neurons and there are several potential mechanisms that can mediate this toxicity.

For example, toxic tau may potentially impair axonal transport, but also cause mitochondrial dysfunction, DNA damage, and dysfunction to the synapses.

All of these changes may be central to the loss of neurons and ultimately the cognitive decline as seen in Alzheimer's disease.

Alzheimer's disease is considered to be an amyloid-driven tauopathy.

The spread of beta amyloid occurs early in the disease and it engages large areas of the brain already quite early actually and it's mainly the isocortex or the new cortex that is involved in amyloid deposition.

Other more basal evolutionary older parts of the brain have actually much less or later involvement of amyloid pathology.

Note that the spread of amyloid is quite diffuse over the brain as seen in these images here, as we go from left to right in more and more severe stages of the disease.

And there is less of stereotypical predictability in the deposition of amyloid compared to deposition of tau.

The main paradigm that links amyloid, tau and other aspects of Alzheimer's disease is called the amyloid cascade hypothesis.

It's visualised here in this figure.

Now according to this hypothesis, amyloid levels rise in the brain either through increased production of pathological substrates, especially forms of amyloid peptides that are prone to aggregation.

And this appears to happen in most individuals with dominantly inherited forms of Alzheimer's disease as seen in sort of the left pathway here in this slide.

Most patients with the disease do not have dominant forms or dominant inherited forms, but rather sporadic forms, non-dominantly manifested forms of Alzheimer's disease.

In these individuals, it is thought rather that amyloid levels rise due to failure of clearance mechanisms of amyloid in the brain.

Either way, through mechanisms that still remain debated, the increase in the pathological amyloid leads to changes in tau metabolism, which ultimately controls the downstream clinical aspects of the disease.

More specifically, according to the amyloid cascade hypothesis, toxic amyloid species promote pathological tau via increased tendency to phosphorylation and misfolding of tau protein.

Now, importantly, the abnormal metabolism of β-amyloid proceeds the spread of tau beyond the medial temporal lobe.

It's also known that β-amyloid pathology may trigger neuronal hyperactivity.

This has been suggested as a potential mechanism linking amyloid to tau, since tau may spread across connected neurons in an activity dependent manner over networks in the brain.

Tau in turn mediates the synaptic dysfunction and neuronal death more closely than amyloid.

This interaction really remains complex, but there is accumulating evidence supporting that amyloid comes early and drives tau pathology, which then drives neurodegeneration and clinical symptoms.

Soluble tau biomarkers such as cerebrospinal fluid and plasma levels of phosphorylated tau, p-tau, correlate with amyloid PET imaging, and such correlations are seen even before the tau PET signal starts to increase.

This means that the relationship between amyloid deposition and changes in soluble tau probably comes very early in the disease.

In later disease stages, tau biomarkers may correlate with both amyloid and Tau PET.

This is congruent with the hypothesis that soluble p-tau is somehow involved in the amyloid dependent formation of neocortical tau tangles.

The strong correlation with the PET measures has made these fluid p-tau measures critical for early diagnosis and monitoring of disease progression, as we will discuss soon.

The soluble tau biomarkers may also be used to study disease mechanisms in vivo directly in humans.

For example, soluble levels of the p-tau217, a variant of phosphorylated tau largely mediated the statistical effect of aggregated amyloid on aggregated tau and this mediation effect was even stronger when only considering tau depositions outside of the medial temporal lobe, so the neocortical engagement of aggregated tau. This may support directly in humans a link between amyloid induced changes in tau metabolism and downstream tau deposition spreading over the brain.

We'll now continue with a deep dive into the clinical pathological correlations of tau.

Despite traditionally being a histopathological construct and part of the gold standard diagnostic workup for Alzheimer's disease at autopsy, Braak staging has now also been applied in vivo using tau PET to target and track neurofibrillary tangles.

A stereotypical pattern of tau progression is visualised here.

We start to the left where you can see the early Braak stages that describe mainly the preclinical accumulation or the very early accumulation of neurofibrillary tangles within the medial temporal lobe in the transentorhinal cortex in stage 1 and entorhinal cortex in stage 2.

The subsequent Braak stages really describe the spread and accumulation of neurofibrillary tangles, first as it spreads to inferior temporal neocortex in stage 3 and then further to association cortices in stage IV and V, and finally reaching primary sensory and association cortices in stage VI.

However, note that this is the stereotypical pattern of tau spread and it has been described different variants of tau progression that also correlate to some degree with the different clinical presentation and different atrophy patterns in Alzheimer's disease.

The tau PET Braak stages have been used to show associations in vivo between multiple domain specific and global cognitive outcomes with tau accumulation.

So for example, these slides here show how different cognitive tests or cognitive outcomes are associated with the presence of different Braak stages as determined with tau PET.

So for example, early Braak stages I to II, they were mainly associated with memory impairment, but not other aspects of cognition, and they were fully compatible with absence of dementia.

Stage II was associated with memory dysfunction, but also not too much other cognitive domains.

So this is sort of compatible with a perseverance of neurofibrillary tangle accumulation restricted to the medial temporal regions, but not engaging too much other parts of the brain instead.

Most individuals at Braak stages by PET III to IV really had signs of mild dementia and stages V to VI were essentially incompatible with normal cognition.

We'll now move towards the biological definition of Alzheimer's disease and discuss how biomarkers actually impact the diagnostic criteria of the disease.

First, we'll look at the 2024 Alzheimer's Association criteria and how they structure the diagnosis of Alzheimer's disease.

This is a framework which is built around biomarker categories and the biomarkers are divided into Core 1 and Core 2 biomarkers.

Core 1 biomarkers, they become abnormal early in the disease process, and these include amyloid PET as well as both cerebrospinal fluid and plasma biomarkers that are closely related to amyloid and phosphorylated tau, especially p-tau217 and p-tau181.

According to these criteria, an abnormal Core 1 biomarker result should be sufficient to establish a diagnosis of Alzheimer's disease even in individuals who are still cognitively unimpaired.

So it's really biological definition of the disease.

Instead, Core 2 biomarkers, they reflect the later changes in the disease that accumulate over time, especially deposits of aggregated tau in the brain that can be measured using tau PET or, very recently, also with certain biofluid markers such as MTBR-tau243, which we'll talk more about later.

Although these biomarkers, the Core 2 biomarkers are not required for diagnosis, they provide important prognostic information, and they also importantly increase the confidence that a patient with Alzheimer's, that the patient with symptoms, have these symptoms due to Alzheimer's disease, and rather than Alzheimer's disease being present in a sort of pre symptomatic stage, while symptoms can be caused by another factor.

Staging is also critical part of these new criteria.

So the 2024 research framework proposes a biological staging system that can be applied using either imaging or fluid measures.

This goes from stage A to D, where stage A is the initial stage, so this is characterised by abnormal core 1 biomarkers, either with amyloid PET or with reliable p-tau measures, but there's still no significant tau aggregation, so the Core 2 biomarkers remain negative.

Stage B is called an early stage, and here still the core 1 biomarkers are positive, and there is also now some tau PET positivity, but it's restricted to early regions, restricted to the medial temporal lobe.

Stage C is an intermediate stage and here the tau PET signal engages more larger parts of the brain with moderate neocortical uptake. And finally in stage D is an advanced stage where there is a high or prominent neocortical tau PET uptake over wide regions of the brain.

This staging system is intended to be integrated with clinical information because this it's important to recognise that there is a lot of individual variability such as presence of co-pathologies and also differences in cognitive reserve and brain, brain reserve and resilience, and this can influence how symptoms manifest at each biological stage of the disease.

It's therefore really important to note that biomarkers should be considered in conjunction with clinical information because there is this considerable variability in the population.

For example, the table shown here in this slide, it shows the combinations of clinical stage versus biomarker stage.

Now individuals who lie on the diagonal, the green diagonal, their clinical stage are sort of synchronised with their biological stage.

But there may also be individuals who lie above the diagonal.

These have a worse clinical stage than you would expect for their Alzheimer's disease biological stage.

They often have greater than average comorbid pathology which can contribute to these more worse symptoms.

Instead, individuals who lie below the diagonal, they have a better clinical stage than expected for their biological stage.

Here we may expect to see exceptional cognitive reserve or resilience that delay or reduce symptoms.

These are not the only set of novel criteria.

There is another set of criteria by the International Working Group, which has also proposed biomarker-based definitions of Alzheimer's disease, where Alzheimer's is also defined based on the presence of biomarkers and specific clinical phenotypes.

These different sets of criteria are largely aligned the Alzheimer's Association and International Working Group criteria, but they differ in some aspects.

For example, in the classification of cognitively unimpaired individuals with positive Alzheimer's disease biomarkers, they according to the Alzheimer's Association framework, these are considered to be in the very early stages of Alzheimer's disease, and according to the International Working Group, they are rather considered to be at risk for Alzheimer's disease.

Let's now focus a little bit on the critical relationship between pathological tau and neurodegeneration in Alzheimer's disease.

It's well established that p-tau, hyperphosphorylated tau, is closely related to disease progression.

High levels of p-tau, both in cerebral spinal fluid and in plasma are robustly associated with worsening cognition and brain atrophy.

For example, plasma p-tau181 tends to increase as individuals progress along the Alzheimer's disease continuum from cognitively unimpaired to mild cognitive impairment and finally Alzheimer's dementia.

Even more interesting, recent research shows that CSF p-tau217 not only increases longitudinally but also correlates more strongly with both amyloid and tau PET measures than p-tau181.

So these different p-tau measures contribute different information.

Another variant that has been proposed is p-tau205, which increases even in later disease stages and has been linked to reduced white matter integrity, perhaps suggesting that the different forms of p-tau may reflect distinct aspects of Alzheimer's disease and neurodegeneration.

In summary, the different p-tau measures appear to be central players in this cascade that leads to cognitive decline and brain shrinkage in Alzheimer's disease.

The predictive power of tau biomarkers is now a major research focus.

Studies have shown that baseline tau PET imaging is superior to both amyloid PET and MRI to predict the cognitive decline in individuals in early stages of Alzheimer's disease.

For example, there was a large international study which demonstrated that baseline tau PET signal was associated with more rapid cognitive decline as measured by MMSE, and shown here, compared to MRI and amyloid PET.

Notably, plasma p-tau217 and tau PET, they have comparable associations with cognitive decline, especially among cognitively unimpaired individuals.

It's also important to consider age here, individuals over 70 years old tend to experience more rapid cognitive decline at similar levels of tau pathology compared to those under 70.

This highlights the importance of age as a modifier in disease progression.

Let's turn to a newer and highly promising biomarker, MTBR-tau243.

This marker specifically tracks the microtubule binding region of tau and this is a major component of the insoluble tau aggregates in the brain.

Recent research have shown that CSF levels of this tau variant, MTBR-tau243 has a significantly higher correlation with cognitive measures than traditional p-tau measures such as p-tau217 and p-tau181.

And moreover, the longitudinal rate of increase in MTBR-tau243 was greater in individuals who were positive for both amyloid and tau PET compared to those who were negative for both or only amyloid positive.

And this suggests that MTBR-tau243 may be especially useful to monitor disease progression in later stages of the disease, even when tau pathology is present.

There are now some very exciting pilot studies which have also shown results for plasma levels of an MTBR-tau243 variant, which shows strong correlation both tau PET and with brain atrophy and cognitive performance of this plasma measure.

And of course, this availability of a measuring plasma opens for new possibilities for minimally or non-invasive monitoring of disease progression.

And finally, we'll talk a little bit about some future directions in Alzheimer's disease research.

Let's just briefly revisit the role of amyloid, because a better understanding of the neurotoxicity of different amyloid species and how these interact with tau may be crucial for developing effective therapies.

Amyloid beta is produced as a soluble monomer, but it can aggregate into various forms.

Importantly, soluble amyloid oligomers are believed actually to be more toxic than the insoluble plaques and made directly damaged neurons and cause cognitive impairment.

Now overall, the exact links between amyloid pathology, inflammatory response and engagement of tau.

These links are thought to be key to the development and progression of Alzheimer's disease, and it really remains an important focus of Alzheimer's disease research to understand these links in detail.

Beyond the basic disease mechanisms, there are also several exciting directions for Alzheimer's disease clinical research.

First, we need to continue developing predictive and monitoring biomarkers, especially those that can detect disease at the earliest

possible stage.

Second, given the substantial heterogeneity and variability of disease progression, there's a growing need for individualised management approaches and this includes the identification of subtypes of pathology which may be linked to specific clinical phenotypes and presentations and rates of progression.

Third, we must really identify the optimal time to try to intervene in the spatial and temporal spread of tau pathology.

This may of course differ hypothetically for different types of treatment.

Fouth it is really important to understand if reducing tau, even in the presence of amyloid can have an impact on clinical decline.

This would be crucial.

Fifth, we must determine which tau species or forms that are the most promising therapeutic targets.

And sixth, we may determine more specifically how tau PET burden affects the efficacy of new interventions.

For example, if some interventions are more helpful than others at a certain level of tau PET burden, this can be critical for designing clinical trials and personalised treatments.

And seventh, we should explore the relationship between tau PET and other imaging techniques such as glucose PET or MRI to gain a more comprehensive understanding of disease mechanisms and exactly what tau is doing to the brain.

And eighth, we need to understand the potential for interventions very early, even in cognitively unimpaired individuals, to really prevent the development of symptoms overall.

And ninth, we can identify other drivers of tau pathology besides amyloid and understand their role in disease progression, although they may be smaller than amyloid.

Now all of these are ambitious goals, but they are really essential for advancing our understanding and treatment of Alzheimer's disease.

So in summary, Alzheimer's disease is an amyloid driven tauopathy with biomarker changes occurring years before clinical symptoms and early diagnosis and intervention are crucial and new biomarkers, especially related to tau, are revolutionising our approach to Alzheimer's disease.

And with that, I would like to thank you so much for joining.

**ReachMD Announcer:**
This program was organized and funded by Biogen. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge. Biogen-272453 | Date of preparation December 2025

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