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Beyond Plaques: Current Concepts in Alzheimer's Pathophysiology

ReachMD Announcer:
Welcome to *Neurofrontiers* on ReachMD. This medical industry feature, titled "Beyond Plaques: Current Concepts in Alzheimer's Pathophysiology," is sponsored by Eisai. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is ReachMD, and I'm your host, Dr. Jennifer Caudle. And joining me to discuss the pathophysiology underlying Alzheimer's disease are Drs. Douglas Scharre and Lori Guyton.

Dr. Douglas Scharre is a Professor of Clinical Neurology and Psychiatry as well as the Director for the Division of Cognitive Neurology at the Ohio State University Wexner Medical Center in Columbus. Dr. Scharre, it's great to have you with us today.

Dr. Scharre:
Thanks for having me.

Dr. Caudle:
Of course. And also with us is Dr. Lori Guyton, who is a practicing neurologist with Neurology of Southern Illinois in Herrin. Dr. Guyton, thanks for being here today.

Dr. Guyton:
It's my pleasure.

Dr. Caudle:
Okay, so Dr. Scharre, we're going to start off by discussing how Alzheimer's disease progression impacts cognitive and functional abilities. As the disease advances, what changes can we expect to see in patients?

Dr. Scharre:
Well, we all know Alzheimer's disease is a progressive disease that leads to death. It's neurodegenerative.[1] It makes up 60 to 80% of all dementia cases that we see.[1] And there's several stages of cognitive and functional decline that we break the condition into.[2,3]

One is the preclinical; that's the very earliest stage, is preclinical Alzheimer's disease. And this is where we first start noticing these measurable protein accumulations in the brain, but the patient has no symptoms. It's before any clinical symptoms.[1,2,4,5]

And then you get to the mild cognitive impairment stage. And this is where beginning cognitive symptoms are now appreciated and noticed by family and friends. There's a change in their cognition and their thinking. Sometimes there's a little bit of inefficiency in their day-to-day functioning, but they can still do their daily duties every day without hands-on help.[1,2,4–6]

When you get to the Alzheimer's disease dementia category, here's where we're beginning to be quite noticeable about cognitive issues across a whole variety of domains, plus significant behavioral symptoms start to creep up at this point.[1–3,7]

In mild Alzheimer's disease dementia, symptoms start to interfere with some of these daily activities in that they do need hands-on care from a caregiver for some of them. It could be finances. It could be medication management. [1,4,7] It could be shopping technology.

By the time you get to moderate and severe Alzheimer's disease dementia, the symptoms are much more pronounced. Their symptoms with daily activities require much more help by the caregiver, and in my experience, the behaviors are also much worse in the moderate

to severe stages.[1,4,7]

In fact, at the very end stage, they interfere almost with all daily activities. You almost need to have around-the-clock care.[1,4,7]

So, understanding these stages is really critical for early detection because you can apply the appropriate management at each stage of the disease.

Dr. Caudle:
So, turning to you now, Dr. Guyton, can you discuss the amyloid cascade model as the basis of our current understanding of Alzheimer's disease pathophysiology, and how this model translates to clinical practice?

Dr. Guyton:
Certainly. The underlying neurodegenerative process in Alzheimer's disease is continuous, and it is progressive, and relentless in disease.[8]

The clinical and the pathologic changes underpinning Alzheimer's disease helps guide early diagnosis, and the clinical, meaningful management decisions that we make.[2]

For all along the Alzheimer's disease continuum that Dr. Scharre reviewed, key pathologic changes precede cognitive, behavior, and functional impairments.[9] That is why we want to stress early diagnosis.

These hallmarks which we have known for years include amyloid beta plaques, Tau neurofibrillary tangles, and neurodegeneration.[5]

It is known that research has previously centered around the clearance of amyloid beta plaque formation, but this does not always translate into long term clinical benefit,[10] so we know there's more to the puzzle.

A growing body of evidence does now describe the process of plaque formation as dynamic, and that its toxic to the neurons,[11–13] so it's important that as clinicians, we evaluate our patients and we try to treat before that toxicity builds up, before it takes place.

For the amyloid cascade, it's an ongoing neurotoxic process. It contributes to Alzheimer's disease and begins before and continues after plaque deposition,[11,14] so that is the reason the targeting of our research is not just plaques, but perhaps it's also the toxic species that precede them in the disease process.[11]

Dr. Caudle:
Thank you for that. And you know, getting back to you Dr. Scharre, can you elaborate on some of these mechanisms leading up to and continuing after plaque deposition in Alzheimer's disease?

Dr. Scharre:
Certainly. The amyloid cascade model really gives us a good understanding of how amyloid plaques are formed.[11]

In this pathway, you have the initial release of this amyloid beta peptide. It's sticky and it's soluble at the beginning, but it aggravates.[11,15,16]

So, you start with monomers, and it goes to dimers and oligomers, and they increasingly get larger and larger of these soluble aggregates and eventually become insoluble, and they're stuck in the brain,[11] and these are what eventually become amyloid plaques.

So, the non-toxic forms, the very smallest forms, are the monomers and the dimers, and they can progress and get into this oligomer, which is barely the first toxic stage. Now, oligomers are still soluble, but they begin to be toxic, and they can alter neuronal structure and synaptic function.[11]

As the accumulation and aggregation continues, you get these protofibrils, which are toxic. They're large, they're still soluble, and they're aggregates of these oligomers. And they're directly neurotoxic, increasing the symptoms of neurodegeneration of Alzheimer's disease.[11]

Finally, you get to some of these insoluble forms. These are called fibrils, and then eventually amyloid plaques. And these also cause a lot of neurodegeneration and toxicity to the nervous system and the brain.[11]

We all know that amyloid plaques play a pivotal role in Alzheimer's disease. The accumulation of these plaques are associated with neuronal loss and they contribute to many of the clinical manifestations.[11]

But the amyloid plaques don't always directly correlate with the severity of the symptoms, suggesting that other factors are indeed in

play.[11]

For example, amyloid plaques lead to a series of events downstream, including Tau dysregulation.[17]

We have these hyperphosphorylated Tau proteins that lead to neurofibrillary tangles, and these tangles and these abnormal Tau levels definitely correlate with cognitive symptoms, symptom progression, and neurodegeneration.[18,19]

Dr. Caudle:
Thank you for that. And now, Dr. Guyton, with everything we've discussed in mind, let's dig further into the role of protofibrils in the amyloid cascade model. Can you discuss how they impact the progression of Alzheimer's disease?

Dr. Guyton:
Well, protofibrils are really the most toxic of the soluble chain.[11] They bind to diverse array receptors that triggered downstream pathways.[20]

They have continuous accumulation throughout the process of Alzheimer's disease, eventually leading to death of neurons.[11,13]

Even after the clearance of plaques, highly toxic protofibrils can continue to cause neuronal injury and death.[21]

So, as we can see, based on the normal Alzheimer's disease progression, both the plaques as well as protofibrils could be ideal targets for therapeutic strategies.

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Neurofrontiers* on ReachMD. I'm your host, Dr. Jennifer Caudle, and today I'm speaking with Dr. Douglas Scharre and Dr. Lori Guyton on the evolving understanding of Alzheimer's disease pathophysiology.

Dr. Caudle:
Now, Dr. Scharre, what are some of the other pathophysiologic features, beyond protofibrils and amyloid-beta plaques, implicated in Alzheimer's disease development and progression?

Dr. Scharre:
Well, there are several and many overlapping factors that can contribute to neurodegeneration.

One of the most important ones, and we see it in brains of Alzheimer's autopsy patients, is the Tau protein. They get this hyperphosphorylation of Tau which impacts the microtubules, destabilizes them and causes these neurofibrillary tangles. This contributes heavily to the death of the neuron, neurodegeneration, and cognitive symptoms.[22,23]

There's also this cholinergic hypothesis, that is, disease progression is related to reduction of cholinergic neurons and acetylcholine.[24] Acetylcholine is a neurotransmitter that's heavily involved in the memory circuits.

And then, there's mitochondrial hypothesis. So, you can get impaired mitochondrial function. This impacts the bioenergetic factors in the cell itself and upsets the amyloid beta homeostasis. And so, there's evidence that it leads to increased beta amyloid deposition.[25]

And finally, there's lots of data regarding neuroinflammation. You have pro-inflammatory mediators that directly can activate this neurodegenerative process, impact the neurons and associated cells, and they contribute greatly to cognitive impairment and neuronal death.[26]

Dr. Scharre
So, there are some key factors. That's not all the key factors. There's probably many others. But it just shows how complex the pathophysiology is of Alzheimer's disease.

Dr. Caudle:
And coming back to you now, Dr. Guyton, as a practicing neurologist, why is it important to understand the evolving landscape of Alzheimer's disease pathophysiology?

Dr. Guyton:
Well, it's really important to understand the pathophysiology of Alzheimer's because when we think of the prognosis and the progression that we've made over time, we know that there is a build-up of a-beta. We know that Tau can build up and this process can start 25 years before we make a formal diagnosis of Alzheimer's disease.[9]

We have an evolution of Alzheimer's disease treatment landscape. We need to improve patient awareness. So as a physician, first of all,

I'm thinking about that build-up, but then I'm going to discuss with my patient what's going on with that and why we need to intervene and why we need to treat.[1]

It's not just about recognizing and treating symptoms, but it's about understanding and targeting the nerve degeneration processes that start long before these symptoms occur.[27-29]

Diagnosing is also important, and that can make the difference for patients as well. So, well, if you think about the plaques that formed 25 years beforehand, we think about the patients that we need to educate, then it makes sense that diagnosing allows them to be better off long term. They may have more opportunity for education, more opportunity to plan their future. We may be able to slow the progression of the disease, or maybe they want to enroll in a clinical trial. So, it opens up the window of opportunity in this particular part of the disease process for this continuous nature of underlying neurotoxic processes to be treated and may argue even for a continuous treatment approach.[2,27,30-32]

For neurologists, it's essential to grasp this damaging process of Alzheimer's disease, and that it's ongoing.[11,14] It's important that, as neurologists, we understand pathology because that is how we understand how to treat our patients.

We want to address these issues early on and possibly continuously to manage the disease more effectively and improve the outcome for our patients.[1]

Dr. Caudle:
Those are wonderful insights, Dr. Guyton. And before we come to the end of our program, I'd really like to hear our final thoughts from each of you. And we'll start with you, Dr. Guyton. You know, what are some key takeaways on Alzheimer's disease you'd like to share with our audience?

Dr. Guyton:
Well, I'd like to explain to my fellow clinicians that Alzheimer's disease is changing and is changing quickly, that we really need to focus on the pathophysiology, as we learned today. We want to energetically convey this message to patients and caregivers and providers that there's an increase in awareness of Alzheimer's disease, and we want to make sure that we're diagnosing early. That is of utmost importance. So, the exciting part about Alzheimer's today is that we can do something about it. The exciting part is that when the patients actually understand, they get excited because now they can know that they know that they can do something for themselves. It's critical to understand not only the nature of Alzheimer's pathology, but also the need to recognize the disease at early stages, as that may provide the opportunity to intervene early, change the natural history of disease, and improve the clinical outcomes for the patients that we treat.[1,2]

Dr. Caudle:
Thank you so much for sharing this, Dr. Guyton. And Dr. Scharre, why don't you have the final word today?

Dr. Scharre:
Well, thank you. I think that we've learned a lot about, and we're learning a lot about, in our research, about the pathophysiology of Alzheimer's disease, about these toxic amyloid species, about the amyloid plaque, Tau and several other features that can contribute to Alzheimer's disease. And what we're learning is that, gosh, we can pick these things up at an early stage. And so, if we can translate that to the clinic and be able to identify the early patient when they're just beginning to have symptoms, we can see that there may be many different ways that we can combat this disease, target these different proteins, target these different mechanisms of actions, so that eventually, we'll have better help for patients and caregivers and be able to treat this disease at a much earlier stage.

Dr. Caudle:
Those are great points to think on as we end our discussion today. And I'd like to thank my guests, Dr. Douglas Scharre and Dr. Lori Guyton, for sharing their insights on the current understanding of Alzheimer's disease pathophysiology. Dr. Scharre, Dr. Guyton, it was great speaking with you both today.

Dr. Guyton:
Thanks for having me.

Dr. Scharre:
Yes, thank you for the discussion.

Dr. Caudle:
And for ReachMD, I'm your host, Dr. Jennifer Caudle.

ReachMD Announcer:
This medical industry feature was sponsored by Eisai. If you missed any part of this discussion or to find others in this series, visit *Neurofrontiers* on ReachMD.com, where you can Be Part of the Knowledge.

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