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

Pathology: Amyloid vs Tau

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.
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Dr. Agronin:
This is CME on ReachMD, and I'm Dr. Marc Agronin. Today, I'm going to break down the pathology of Alzheimer's disease.

So it's important to keep in mind that this is a disease that we've learned begins years if not decades before people actually present with clinical symptoms. And understanding what's happening leading up to that gives us not only an understanding in terms of what's happening in the brain, but especially where are the points that we need to begin diagnosis and treatment.

So we know that the basis, the pathological basis for Alzheimer's disease comes down to two abnormal toxic proteins. One is a form of amyloid called beta amyloid. This builds up extracellularly, and so it forms what are called senile neuritic plaques outside brain cells, it leads to inflammation, and these plaques as they begin to spread throughout the brain, causes enormous damage to both individual neurons to circuits in the brain, and we begin to see the clinical symptoms over time.

And we know that this buildup of these amyloid plaques is probably the first beginning of the story for Alzheimer's disease, again years if not decades before; we can detect this buildup now. And so this is what we call a presymptomatic stage of Alzheimer disease.

In response, we believe a response of buildup of amyloid, we now begin to see a destabilization of a normal protein inside neurons, something called tau. Tau becomes hyperphosphorylated. It's a normal protein that helps stabilize the microtubules in cells. These form the cytoskeleton; they help with transport. Once tau becomes destabilized, it basically falls off the microtubules. It forms into these – what are called paired helical filaments. These form these hair-like tangles within the cell. And this really begins to destroy the neurons from an intracellular standpoint. And this begins to build up slowly but steadily, and we believe in response to amyloid.

And so in essence, if you're following someone over time, and we can see pathologically what's happening in the brain, there's a pre-symptomatic stage where you're getting already a buildup of amyloid and tau. Then, as individuals begin to have an increasing burden of both proteins, it begins to destroy larger areas of the brain, symptoms begin to emerge.

The problem is that when most people walk into the clinic with enough symptoms to actually get a diagnosis, and historically, the diagnosis was based on the clinical presentation, but now using amyloid and tau as biomarkers, we actually can image them or now have blood tests to identify their presence, or we can do a spinal tap and identify them as cerebral spinal fluid. Already, we're seeing probably peak levels of amyloid and tau by the time someone's already symptomatic. And so the real challenge is it's almost too little too late to get rid of them at that time. The question is, if we can identify them before someone gets symptoms, find ways to get rid of them in the brain at that point, would that make a difference? And this is really where immunotherapy has been so active, trying to intervene, to use monoclonal antibodies to basically target amyloid and tau in the brain, have our brain's immune system using microglial cells to basically eat it up, get rid of it. And what we're beginning to see over time is that a number of agents have the ability to slow down the course of the disease.

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The hope is that we can find the right time, the right medications and doses to really make a meaningful difference, not just slowing this down, but ultimately stopping this in its tracks.

So keep in mind that amyloid and tau is when the story begins; it's not where it ends. Because as these build up and harm the brain, we see loss of metabolism, we see loss of volume, and we can visualize this through FDG PET scans; we can visualize through MRI. So again, when someone comes in with active symptoms of Alzheimer's disease, the pathology has been going on a long time. And this is the great challenge we face.

So this has given you an overview of amyloid and tau, how it fits in the pathology. We're up for today, but thank you for listening.

Announcer:
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