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

What to Know About the Pathophysiology of Alzheimer's Disease

Announcer:
You're listening to *Alzheimer's Disease: Towards Early Detection* on ReachMD, and this episode is sponsored by Lilly. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Alzheimer's Disease: Towards Early Detection* on ReachMD. I'm Dr. Charles Turck, and joining me to help break down the pathophysiology of Alzheimer's disease is Dr. Marc Agronin. Dr Agronin is the Senior Vice President for Behavioral Health and the Chief Medical Officer for MIND Institute and President of the American Association for Geriatric Psychiatry. Dr. Agronin, welcome to the program.

Dr. Agronin:
Thank you, Dr. Turck. It's great to be here.

Dr. Turck:
To get us started, Dr. Agronin, would you give us an overview of the clinical stages of Alzheimer's disease?

Dr. Agronin:
Sure. So Alzheimer's disease, which I should add, is really at epidemic proportions now in this country as 5 to 6 million Americans have it currently. The numbers are predicted to double in the next several decades. But this is a progressive neurocognitive disorder. It usually begins with short-term memory deficits. And this is largely because the first area of the brain that's affected is the hippocampus and entorhinal cortex, which has everything to do with short-term memory processing.

And so in very early stages, at least clinically, we know that individuals begin to experience these short-term memory changes. Slowly but steadily over time, we begin to see other cognitive domains affected, things such as visual-spatial abilities, language function orientation, executive function, and social cognition. And so what we see over time is this slow unfolding in decline within these different areas. Once somebody begins to have clinical symptoms in earnest we do, for example, neuropsychological testing. We see this whole spectrum of changes. And that's one thing that is distinct about Alzheimer disease compared to other forms of neurocognitive disorders.

Now even though this is a clinical stage, and we see that it begins to progress and involve more functional changes in addition to changes in mood and behavior over time, we need to keep in mind in our era now that we're able to actually identify biomarkers that can allow us to make detection of Alzheimer's disease even before people were symptomatic. So for instance, the main biomarkers we look at include things such as cerebral atrophy loss of metabolism, especially in the temporal and parietal regions of the brain on both sides. And then we see, and we can detect this now by specialized PET scans, the buildup of amyloid protein-based plaques in the brain on an extracellular level. And these what are called neurofibrillary tangles composed of an abnormal form of tau protein, intracellularly in the brain. And so we can actually identify all these biomarkers beginning to change years before clinical symptoms appear. So it's essentially a preclinical stage of Alzheimer's disease before individuals begin to show symptoms.

Once they show symptoms, as I mentioned, we have the slow unfolding, which can take place on average over 8 to 10 years. Many individuals have courses of 12 to 15 or more years to the point where their cognition and their function is so degraded that individuals essentially become bed bound. They have difficulty walking, even swallowing, and that usually leads to their demise over time.

So it's a very long process. Courses vary depending on many different factors. But it's important to understand that this is a marathon, not a race. We're working with someone with Alzheimer's disease.

Dr. Turck:
Now zeroing in on the pathophysiology of Alzheimer's disease, what do we need to know about the roles of amyloid beta peptide and the tau protein?

Dr. Agronin:
Well, one of the current theories is what's called the amyloid cascade hypothesis. And the belief is that the really essential pathophysiology of Alzheimer's disease is the buildup of two abnormal proteins. One is a form of amyloid protein, which is a normal transmembrane protein, but in Alzheimer's disease, due to the effects of certain enzymes, it's cleaved into an insoluble form of amyloid called beta amyloid. Because it's insoluble, it clumps together into oligomers, and these clump together further into the core of these, what are called neuritic plaques, which begin to develop throughout the brain. And the plaques, because they can't be well mobilized by the brain, essentially cause inflammation and this leads to damage over time.

At the same time, if you look inside brain cells, what you see is these tangle-like formations of what we know as hyperphosphorylated tau protein. Again, a tau is a normal protein inside neurons; it's used to support the microtubules in it. So it has an essential role, but when it becomes hyperphosphorylated, it forms these tangles, which basically destroys the neurons. The theory is that amyloid and tau kind of work in concert; one triggers the other. And tau is believed to be the more damaging of the two proteins.

The real challenge today is that as we've developed therapies, specifically immunotherapies, to mobilize and get rid of amyloid in the brain and now to get rid of tau in the brain, what we have not seen is basically a reversal of the symptomatic picture. In fact, immunotherapy that's even able to achieve pretty much removal of amyloid plaques from the brain significantly may slow the course of disease a little bit, but it does not restore function; it doesn't reverse it. And even the slowing of it is quite modest. And so this has really led many people to call into question the role of amyloid and tau. Clearly, we need to better understand how they work, how they work in concert, and to develop therapies that are going to make a difference.

And so there have been so many clinical trials out looking at amyloid and tau. Many other trials are trying to look at other potential mechanisms that are involved in Alzheimer's disease and to put a less of an emphasis on amyloid and tau. So it's still a quandary now. There's still tremendous amount of research going on.

And I would say the only good news is that our understanding of the disease has deepened. And the amount of funding which is going into research has increased significantly over the past couple of years. And that should help in general the research community to gain more ground here.

Dr. Turck:
For those just tuning in, you're listening to *Alzheimer's Disease: Towards Early Detection* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Marc Agronin about the pathophysiology of Alzheimer's disease.

Dr. Turck:
Now if we continue focusing on the pathology of Alzheimer's disease, what could you tell us about neuronal death and brain atrophy?

Dr. Agronin:
If you look at any aging brain, we see that atrophy is the rule over time. We lose brain cells. It's possible to grow new brain cells in late life, but that's the exception rather than the rule. The process that happens more often is synaptogenesis. So brain cells are making new connections, which really emphasizes the importance of ongoing learning as we get older. Now in Alzheimer's disease, neuronal death has accelerated. As a result, atrophy is accelerated.

So if you follow an aging brain over time with Alzheimer's disease, you're going to see this tremendous loss of neurons and tremendous atrophy. In fact, in a comprehensive workup, we often like to look specifically at the volumetrics of the hippocampus because you often see disproportionate atrophy within the hippocampus, or the memory processing center, early in the course of the disease, which is often a clue that this is likely Alzheimer's disease.

We don't have any way to reverse this process. It begins in, as I mentioned before, a hippocampus entorhinal cortex, but the entire brain is affected. And so if you track these brains over time, you see this tremendous atrophy taking place. This corresponds to metabolic changes that you can also see in functional PET scans at the same time.

Dr. Turck:
And we've certainly covered a lot of ground today, Dr. Agronin, but before we close, is there any other information you would like to leave with our audience?

Dr. Agronin:
I want to emphasize the fact that the numbers of individuals with Alzheimer's disease has grown tremendously, mainly because aging is

a main risk factor, and we're living longer, healthier lives. We need more research. We need to make sure that people get comprehensive evaluations to make certain that we know if it's Alzheimer's disease or not. Regardless of the type of neurocognitive disorder, it's so important for us to really provide comprehensive treatment over the long run.

Dr. Turck:
Well this has been a fascinating look at the pathophysiology of Alzheimer's disease. And I want to thank my guest, Dr. Marc Agronin, for joining me to provide his insights. Dr. Agronin, it was great having you on the program.

Dr. Agronin:
My pleasure, thank you so much.

Announcer:
This episode of *Alzheimer's Disease: Towards Early Detection* was sponsored by Lilly. To access other episodes in this series, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!