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New Data on the Pathophysiology of MCI and Dementia

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Isaacson:
My name is Richard Isaacson. I'm a Preventive Neurologist at the Institute for Neurodegenerative Diseases of Florida. And that's in Boca Raton, Florida. We're going to talk about today New Data on the Pathophysiology of MCI, or Mild Cognitive Impairment, and Dementia.

It's really exciting that there's an emerging science on the novel pathological drivers of MCI in the early stages of Alzheimer's disease. And I think understanding these mechanisms and understanding the pathologic proteins and the cascade of events that happens throughout the early course of this dementing illness is really our best way forward to identify, diagnose, and then treat in those earliest stages.

So when it comes to Alzheimer's disease, there are truly many therapeutic targets. And we try to direct these new therapies, whether it's drug therapies or lifestyle interventions, we try to direct these at the underlying Alzheimer's pathophysiology. And we're studying this in an ongoing way. I really believe that understanding these various pathways for Alzheimer's allows us for the exploration of multiple interventions that may potentially be used in combination to treat Alzheimer's. Just like any chronic disease of aging, we just don't have that one magic pill or one magic infusion or one magic anything. But when it comes to Alzheimer's and diabetes and other chronic diseases, I think it's going to be a little bit of this and a little bit of that; lifestyle changes, different drugs to treat different pathophysiologic mechanisms, as well as really assessing and then treating the risk factors to hopefully slow and reduce risk for future cognitive decline.

Our field has studied a variety of mechanisms from anti-amyloid antibodies and vaccines, working on clearance mechanisms, and looking at targeted therapies for apoE, which is a genetic variant that increases risk, focus on tau aggregation, especially looking at neuroinflammation, focusing on the tau pathology itself as well as neuronal loss or brain cell atrophy. As of course, looking at synaptic loss and neuronal loss as a whole. BACE inhibitors have been studied, gamma secretase inhibitors. And I think really, the saying that goes sometimes is we need multiple shots on goal. We need to fight neuroinflammation, we need to fight amyloid, we need to fight tau, and we need to fight the underlying biology of the disease, glucose hypometabolism. There's just so many different pathways, and I think that's really where our field will go when we have these multiple tools in our toolbox to fight Alzheimer's pathology.

In terms of an example of the therapeutic targets, beta amyloid-related disease-modifying strategies really is where we've come a very, very, very long way. And this cascade tries to explain a little bit about the various, really, levels in the cascade that we can intervene. And if we can intervene in these ways, and maybe even in different ways using different anti-amyloid strategies, maybe that's how we can have the most benefit.

When it comes to disease-modifying therapies directed against tau, these have been designed in various ways, for example, to inhibit tau phosphorylation, to inhibit tau aggregation, to compensate for tau loss of function, or even inhibit the seeding or the spread of

pathologic tau. And while we don't have a, you know, FDA-approved anti-tau drug at this time, I'm excited for the future of the field and to follow up on this neuropathologic target.

Now, I think some things that people don't exactly consider in Alzheimer's pathology is that, well, peripheral and central cholesterol metabolism is altered in Alzheimer's disease. As I mentioned earlier, people with the apoE4 variant of the apoE gene increases risk, especially if person has two copies of that apoE4 variant. And those people also have higher levels of oxidative stress and lipid peroxidation. Neurons and astrocytes can eliminate excess lipids, but we really need a functional apoE-HDL particle for this to occur. So we think that some of the effects of apoE4 on Alzheimer's risk is likely mediated through elevated serum cholesterol. And what we do in our program, and I think what physicians do all over is when we, you know, manage vascular risk factors, like managing cholesterol, This is really hopefully an exciting way forward to try to prevent some of the morbidity that we have and try to minimize cognitive decline.

Now there are a lot of systemic treatments and targeted treatments that are not just pharmaceutical based. We have sleep, diet, and nutrition, stress management and exercise, as well as targeted therapies like hormone replacement, supplements, and drugs. Each of these interventions attacks different areas in the Alzheimer's pathophysiologic progress from oxidative stress, insulin resistance, to calcium toxicity and amyloid burden and tau, and this is really where our field needs to go, multimodal therapies. The management of mild cognitive impairment due to Alzheimer's disease includes pharmacologic therapies, including several now FDA approved drugs, but we can also do other things like physical exercise, cognition-based interventions, cognitive training, and of course, multidomain interventions. In our group, we've really taken an individualized clinical management approach and shown that people with mild cognitive impairment can have better outcomes in our Comparative Effectiveness Study.

So with that, thank you for your time. I hope you learned something today.

Announcer:
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