Transcript Details
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The Time Is Now: Early Diagnosis and Intervention in Alzheimer's Disease

ReachMD Announcer:
Welcome to *Neurofrontiers* on ReachMD. This medical industry feature, titled "The Time Is Now: Early Diagnosis and Intervention in Alzheimer's Disease," is sponsored by Eisai. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Alzheimer's disease is a fatal disease. It not only accounts for 60 to 80 percent of dementia cases, but was also the seventh leading cause of death in the U.S. in 2020 and 2021.[1]

This is ReachMD, and I'm your host, Dr. Jennifer Caudle. And today we'll be speaking with experts to share their insights on the critical need for early-stage diagnosis in Alzheimer's disease based on our evolving understanding of disease progression.

Joining me for this discussion 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's a practicing neurologist with Neurology of Southern Illinois in Herrin. Dr. Guyton, thank you for being here.

Dr. Guyton:
It's my pleasure.

Dr. Caudle:
Alrighty. So, we're going to start off with you, Dr. Scharre. Can you walk us through the clinical stages within the Alzheimer's disease continuum?

Dr. Scharre:
Certainly. Yeah. Alzheimer's disease, as everyone knows, is a progressive neurodegenerative, irreversible condition that impacts cognition and impacts function.[2] It impacts behaviors, quality of life, eventually causes death. And the disease management and treatment options will vary depending on where someone is in the course of the condition.

So, there are different stages of Alzheimer's disease.[1] The very earliest one we call preclinical Alzheimer's disease. This is usually maybe stage 1 or stage 2, and this is where the pathology in the brain first starts to develop, but the patient has no symptoms. They're completely normal thinking, no one could tell any difference between them. At Stage 2, maybe there's some very subtle neuropsychological tests that you could tease out, but for the most part, no problems.[3]

When you get to mild cognitive impairment, also called, due to Alzheimer's disease, it's also called stage 3. This is where you're starting to see significant cognitive issues that are noticed by family and friends, and this is a change from their previous situation. They also have maybe reduced efficiency with their ADLs, that is active as daily living, their daily function, but they don't require any hands on

assistance to do things that they used to be able to do and maybe there's a little bit of depression or irritability.[1]

When we get to stage 4, that's mild Alzheimer's disease dementia. And this is where it's quite obvious that they have cognitive issues. It affects their daily life, it can be seen every day. And typically, they may require at times hands on assistance with their day-to-day activities, could be in finances, technology, medication management, things of that nature. And at times they may still have issues with depression and anxiety.[1]

The next stage typically we talk about is moderate Alzheimer's disease dementia, sometimes called stage 5, and here, the symptoms are very pronounced. They interfere with daily activities, quite noticeable.[1]

Behavior changes are quite noticeable typically in this stage. In terms of cognition, the individual may not even recognize their loved one. Functionally, they may have difficulties just doing basic activities of daily living.[1]

Finally, a severe Alzheimer's disease dementia, sometimes referred to as stage 6. Here, they're very impaired. They need help with almost all daily activities. In fact, they may have physical ability issues such as walking or swallowing or incontinence are not uncommon.[1]

Dr. Caudle:
Turning to you now, Dr. Guyton, how do these stages of disease progression in Alzheimer’s disease impact patients, families or caregivers, and healthcare providers?

Dr. Guyton:
In my experience, development of the signs, particularly the early symptoms, creates a worry and anxiety in the patients and their families. Often, my patients have had a mom or a dad, or maybe a brother or sister with Alzheimer's disease. They've seen it. They've lived through it. Maybe were the caregivers for those patients. And they're afraid now, because they have a symptom, that they're getting the same thing.

I have some patients that have absolutely no insight when I ask them how they're doing and they'll say, well, I have some memory problems – and they know they have memory problems, but they say, so do all my friends. So, they think it's normal. They think it's fine. And so, they say, so, I guess I'm just fine. I'm OK. And so, what happens is they start to think that because it's common, it's normal.

So as a physician, what I need to do is really educate. Educate why the common is not normal. I need to push back that curtain and really look at their day-to-day activities. What do they struggle with? What do they have difficulty with? Because although we've had significant advancements in the field of Alzheimer's disease, there remains some unmet need.

We have a considerable number of individuals who meet diagnostic criteria for dementia, but they're undiagnosed or they're misdiagnosed, and then we have treatment delays.[4]

Other types of dementias can clinically mimic Alzheimer's disease and contribute to that misdiagnosis. Sometimes, plaque deposition can occur as a co-pathology, so it can be seen in other disease states, not just Alzheimer's disease.[5]

Dr. Caudle:
Thank you. And getting back to you, Dr. Scharre, now that we’ve looked at the clinical features in Alzheimer’s disease progression, can you tell us about the pathophysiological features?

Dr. Scharre:
Certainly. Yeah, Alzheimer's disease involves a neurotoxic process that starts along the whole course of the build-up of these toxic amyloid species.[6]

So, in 25 years before you start having cognitive issues, oftentimes we're seeing these changes in the brain. Maybe the first changes are the amyloid beta peptide, that's a protein, and then maybe after that, the Tau protein, we start seeing that's coming into the brain that could cause issues with thinking.[6]

In terms of the amyloid cascade, it starts releasing this amyloid beta protein and they keep getting more and more and more and they build up eventually to these insoluble amyloid plaques that everyone knows and we can see that on the pathology of people that have died of Alzheimer's disease. But it's very important to know that in between those stages, there’s soluble forms before it gets to this insoluble plaque. There are soluble forms that also have neurotoxicity. There is evidence that these soluble forms, particularly the oligomers, the protofibrils, are forms that can impact the neuron, cause increasing cell death and basically enhanced neurodegeneration.[6]

And so, in the Alzheimer's treatment paradigm, it's going to be important to not only provide help to get rid of the big plaque amyloid pathology, but also probably these other neurotoxic soluble species.

And our understanding of mechanisms underlying Alzheimer's disease is growing, and these advances are going to help inform us in terms of management and treatment options. So, obviously targeting amyloid beta has been sort of the hallmark.[7] But there are several other ways that we can somehow look at to impact the impairment seen in Alzheimer's disease.

These additional mechanisms include the cholinergic hypothesis, include mitochondria, include Tau pathology, include neuroinflammation, include systemic inflammation.[8] And unfortunately, many people with Alzheimer's disease come in and are diagnosed only significantly after symptoms have started.[2] And it's important to know, though, that changes in some of these Alzheimer's disease biomarkers can be occurring before you even have clinical symptoms.[2]

Right now, we're using PET and spinal fluid to try to test to find the earliest symptoms, sometimes in the preclinical and sometimes in the very early clinical stages where they begin to have thinking problems. Right now, we're in this transition where we have this integration of blood-based biomarkers and these could really make significant help in terms of us diagnosing people that are in the earliest stages, both in a research standpoint and the clinical standpoint.[9]

In fact, the Alzheimer's Association Work Group currently recommends using blood-based biomarkers in the context of a thorough clinical evaluation for, like, the biological diagnosis of individuals with the very early symptoms of Alzheimer's disease.[9]

Dr. Caudle:
Now, Dr. Guyton, how do these developments in understanding the underlying science impact your clinical practice?

Dr. Guyton:
Historically, we've only had treatments that address symptoms without targeting disease pathology, so there may not have been an urgency to diagnose before or to add interventions for early-stage disease.[10]

And so, because of that, there is a misperception, a widespread misperception that really, we can't do anything, we can't treat, so therefore, patients don't come to the doctor, or families don't understand the reason for that.[11] So, I believe these developments in understanding have the potential to take us from a watch and wait position to a diagnose and treat early strategy.

So, early Alzheimer's disease stages can be really in the optimal therapeutic window.[12] There is a point in time where it's the best to treat these patients. So, we need to be looking at it as clinicians.

As Dr. Scharre said, it can predate the clinical symptoms of pathology can predate their symptoms by years, so it's important to try and intervene before the irreversible damage or loss of neurons occur. So, sometimes in my practice, patients will come in and there have maybe a different reason for coming, and it may be a foot pain, or it may be a headache, but when I'm talking to them, I realize that they have some cognitive impairment and so we get on that pathway. So, intervening early can delay disease progression.[12]

Diagnosing patients as early as possible is important because it gives patients and families a chance to benefit from education on the effects, the prognosis of disease, the opportunity for quality of care, time to build a plan for the future, and to assess treatments that may delay progression and slow cognitive and functional decline.[2]

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 impact and benefit of early diagnosis of Alzheimer's disease.

Thank you for that. And now, Dr. Scharre, I'd like to hear more about the potential benefits of diagnosing Alzheimer's dementia at an early symptomatic stage of disease. Can you share your thoughts on this?

Dr. Scharre:
Certainly. The impact of an early diagnosis is critical.[13] It could not be more stressed.

Early diagnosis will allow a better understanding of symptoms, behaviors that you can share with the patients who have the cognition to be able to understand it. Early diagnosis gives patients the opportunity to be in clinical trials, to participate in research that is critical in finding the new treatments for Alzheimer's. And early diagnosis is incredibly important for support services, community resources, starting available treatments when you're in the window that these treatments would be most effective. They can address safety concerns of these individuals. And so, it's a very important, as Dr. Guyton was mentioning, this sort of active shared decision-making role.[13]

Potential benefits if you diagnose early, is that you can start treatments earlier and the earlier diagnosed, the more treatment options that could be available, and typically the better the outcomes. And so, we want to have early diagnosis in almost any condition that we have, and hopefully all of this will help slow down the progression of the disease.[13]

Unfortunately, we get to a lot of times where we're not diagnosing early. There's a delay in the diagnosis. And what does this do? This delay is referral to the cognitive experts. They have limited treatment eligibility because they've missed this window of opportunity. You're not getting the benefits of early treatment. The patient has decreased autonomy, you know, they can't participate as much in this decision making. And of course, the disease burden is much further down the road, that you've lost this time that you could have been doing something about it.[1]

Dr. Caudle:
And coming back to you now, Dr. Guyton, what should clinicians in the community be aware of regarding potential challenges in diagnosing early Alzheimer's disease?

Dr. Guyton:
Well, there's really an urgency to diagnose and treat early, and it's been challenging in the past.[11]

We have several common barriers to early detection and the first one, as I referenced earlier, are patient-related barriers. Patients not disclosing their symptoms. They don't think it's important. Maybe they think it's just part of normal aging.[11]

And then the stigma. The stigma that it has among their family, among themselves, so they're unwilling to undergo further testing.[11]

The second barrier is the resource-related barriers, so limited referral options. Getting them into a cognitive center or neurologists, maybe inadequate time to assess patients and long wait lists. And the other barrier with resource that I've seen in my community is really treatment option in terms of getting them in for certain testing that we need, maybe MRI centers, maybe any type of testing that we need if it's backed up or it's a delay, that's another delay in treatment.[11]

Physician-related barriers is they struggle to identify cognitive impairment that isn't due to normal aging. So as a result, we really need to educate ourselves to learn what it is to diagnose early, to learn about the new developments in Alzheimer's disease care.[11]

Dr. Caudle:
And as we come to the end of our program, Dr. Guyton, what are some insights from clinical practice that you'd like to share with our audience today?

Dr. Guyton:
One of the most important things, I think, is the fact that we need to diagnose this condition early. There's a window of opportunity for the treatment where the treatment would be most successful. So, in my clinical practice, we're facing a paradigm shift and diagnosis in management. I believe a key part to this is educating ourselves, our patients, to overcome potential barriers to early Alzheimer's disease detection.

So, certain strategies that we can do to educate patients and caregivers are several things. The first thing is memory health discussion. In all of our discussions with health care providers and patients, we need to make sure we're talking about memory. We need to make sure we're educating patients and care partners about this condition and about the early state of it. We need to increase awareness about cognitive health, including the normal aging versus that with the abnormal. We need to normalize our cognitive health discussion, so we have really kind of a template of what we need to be asking and what we need to do. We need to educate on common symptoms of MCI due to Alzheimer's disease and early Alzheimer's disease dementia. And lastly, we need to explain the impact of delayed diagnosis on treatment options and outcomes.[11]

So, in my own clinic, I found that patients come in now, and they come in saying I want the test for Alzheimer's. I want to be evaluated for Alzheimer's. I'm concerned, I have some symptoms, I'm afraid. And so earlier testing and evaluation is really there for those that desire it.

And I'd like to say to my fellow clinicians treating Alzheimer's disease that in the current treatment landscape, the option of taking a backseat in action is no longer viable. We need to be in the forefront, we need to be looking for it, we need to be conscious about what's going on with our patient behind the curtain. By delaying intervention, patients are at the risk of becoming ineligible for certain treatments as disease progresses, so I urge my fellow neurologists and doctors to really consider these strategies to diagnose and treat Alzheimer's disease in its early stages.

Patients are at risk of becoming ineligible for certain treatments if we wait too long. So, I urge my colleagues to consider these

strategies, to diagnose, and to treat Alzheimer's disease in its early stages.

Dr. Caudle:
Thank you very much for sharing, Dr. Guyton. And how about you, Dr. Scharre? What key takeaways would you like to leave with our audience today?

Dr. Scharre:
Well, as Dr. Guyton mentioned, we must have regular and routine conversations about cognitive health so that patients who are developing Alzheimer's disease at the earliest stages can get the help that they need. Earlier diagnosis provides us opportunity to initiate treatment at the earliest stage and of course, we believe that we're going to have better outcomes the earlier we try to treat something.[2]

And then, the earlier intervention, of course, will allow people to preserve their cognition and function for a longer time.[2]

You know, we don't have a cure right now, but I agree that …we've made considerable progress in understanding the disease and expanding the therapeutic landscape. So, although treatment decision-making can be quite difficult, I believe that not acting has even more severe consequences.

Dr. Caudle:
Thank you so much for that, and thank you both. Those are great points to consider as we end our discussion today. I'd like to thank my guests, Dr. Douglas Scharre and Dr. Lori Guyton, for sharing their insights on the urgency, benefits and impact of diagnosing and managing early Alzheimer's disease.

Dr. Scharre and Dr. Guyton, it was great to have you here today.

Dr. Guyton:
Thanks for having me.

Dr. Scharre:
It's been a great pleasure.

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

ReachMD Announcer:
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