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The Era of Early Detection and Treatment of Brain Amyloid Deposition in Asymptomatic Individuals?

Article:
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Guests: Dr. Danni Li and Dr. Will Mantyh from the University of Minnesota in Minneapolis, Minnesota.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett.

In 2024, an estimated 11% of Americans 65 or older were affected by Alzheimer disease, experiencing some degree of dementia and memory loss. While Alzheimer disease [AD] has historically been considered a clinical diagnosis made largely on the basis of patient symptoms, recent years have seen a transition to a biological definition that requires evidence of abnormal protein accumulation. Improved understanding of Alzheimer disease pathophysiology has led to the development of new medications that target these abnormal proteins, but it is still unclear what causes production and accumulation of abnormal proteins in the first place. To truly prevent Alzheimer disease, the initial pathological steps must be fully characterized, which would allow early intervention before signs of cognitive dysfunction become apparent.

A new perspective article appearing in the September 2024 issue of *Clinical Chemistry* highlights a recent publication studying patients 20 years before Alzheimer disease diagnosis, and characterizing the early changes that may lead to fundamental breakthroughs in prevention and treatment. In this podcast, we're pleased to welcome the article's authors. Dr. Danni Li is a clinical chemist with research expertise in the development of blood biomarkers for neurodegenerative diseases, including Alzheimer disease. Dr. Will Mantyh is a behavioral neurologist specializing in the diagnosis and care for patients with neurodegenerative disease. Both are at the University of Minnesota in Minneapolis.

And Dr. Mantyh, let's start with you. Let's just get the basics out of the way. What do you mean by biologically defined Alzheimer disease, and how is this different from older uses of the term Alzheimer disease? How has the diagnosis of Alzheimer evolved, and how should a doctor diagnose Alzheimer disease in 2024?

Will Mantyh: Alzheimer disease used to be purely a conversation with the doctor, having a face to face visit and having a brain scan. And if the doctor heard a story about progressive decline in cognition, such as a patient forgetting where their car was, asking the same question over and over again, getting lost in a familiar neighborhood, and that this decline happened slowly over years, and that their brain scan showed atrophy of the brain, maybe the medial temporal lobes were the most prominently affected. That would constitute a diagnosis of Alzheimer disease. But what we found is that 20% of those "Alzheimer disease cases" were actually not Alzheimer disease, and that was even for subspecialists who were experts in the diagnosis of Alzheimer disease. Some of those other diseases may have been dementia of Lewy bodies, or hippocampal sclerosis of aging, among other neurodegenerative diseases.

And so new biomarkers entered the scene a decade or more ago in the form of cerebrospinal fluid biomarkers. And they allowed physicians to detect the abnormal proteins associated with Alzheimer disease, such as amyloid beta and hyperphosphorylated tau. And those cerebral spinal fluid tests are now commonplace in clinical practice and have really ushered in what's called the biomarker era of Alzheimer disease. We not only have cerebral spinal fluid testing, we have neuroimaging, such as pet or positron emission tomography, where we can look at amyloid beta and hyperphosphorylated tau using PET radioligands. And now, of course, blood-based biomarkers that are really revolutionizing our ability to test for biomarkers in an accessible, cost effective, and scalable way.

And so now the diagnosis of Alzheimer's is no longer just a doctor's face to face visit and an MRI scan. A visit may now constitute serial spinal fluid testing, PET testing, and some clinics are now incorporating blood based biomarker testing as well. And so that really helps to confirm the diagnosis of Alzheimer disease, which is especially important for anyone considering a new Alzheimer disease drug where we're targeting a particular protein. And so we want to make sure that we are confirming the presence of amyloid beta and hyperphosphorylated tau before enrolling a patient in a monoclonal antibody therapy that is designed to take off one of those proteins, in particular the amyloid beta pneumococcal antibodies that are hitting the market.

Bob Barrett: What is the significance of the *New England Journal* article, and how do the author's findings help us understand the pathophysiology of Alzheimer disease?

Danni Li: So, as we kind of wrote in our *Clinical Chemistry* perspective, before this *New England Journal* article that our understanding of Alzheimer disease pathology has actually

progressed significantly. But those prior studies are based on cross sectional findings and short-term longitudinal data from literature. But we were able to came up with a hypothetical progression of those biomarker of AD. And that was first actually proposed by Cliff Jack and colleagues that kind of conceptualized AD as this pathophysiological cascade involving a long presymptomatic stage.

So the first abnormal, as Will mentioned, is abnormal CSF, a beta and amyloid PET, and followed by phosphorylated tau, and then followed by neuroimaging abnormalities such as PDG PETs, as well as atrophy on structural MRI. And then also other scientists, such as Randall Bateman and colleagues that from WashU also confirmed those models of the progression of AD biomarkers that using autosomal dominant AD. But those work that based on Cliff Jack and Randall Bateman are based on cross sectional data as well as short-term longitudinal follow up without long-term follow up. So the significance of *New England Journal of Medicine* paper is that they use long-term follow up data in the China Cognition and Aging Study, and they follow those people over 20 years. They really use the best study design we have available to confirm those data that we have from previous study of how AD progress. That's the significance of this paper.

Will Mantyh: You know, just to drive the point home, I think we're seeing cerebral spinal fluid measures of amyloid beta 42 becoming abnormal 18 years prior to a diagnosis of symptomatic Alzheimer disease. This is something that I think everyone more or less suspected. But to confirm that there's such a long prodromal phase is very impressive and that we're seeing a study be able to longitudinally follow people over 20 years, it's a huge accomplishment and really confirms that this is a disease that takes decades to evolve over time. Something that will very much help with clinical trial design and predictive medicine.

Bob Barrett: Doctor, what is the current landscape of Alzheimer disease biomarkers?

Danni Li: As Will mentioned, that now Alzheimer disease biomarker involve including not only neuroimaging biomarker such as amyloid PET and tau PET, but also CSF biomarkers such as a beta 42 to 40 ratio, phosphorylated tau, and also, very excitingly, that we now have blood biomarkers for diagnosis of Alzheimer disease. We have a lot of tools available to help, from blood to CSF to neuroimaging approach.

Will Mantyh: I totally agree with that. And I'll highlight that the field has exponentially grown and now we have an armamentarium as Dr. Li mentioned, of different tests, whether it's cerebrospinal fluid tests, whether it's positron emission tomography, or new

blood tests that are really giving neurologists and other dementia experts the ability to detect this disease in vivo.

Bob Barrett: Let's talk about Alzheimer treatment. Why is the detection of brain amyloid deposition important for treatment? And how should a doctor treat Alzheimer disease in 2024? And, well, how has that evolved over time?

Will Mantyh: Yeah, so maybe I'll start with the treatment and then talk about the importance of amyloid detection afterwards. The treatment of Alzheimer disease, up until very recently, was what I call symptomatic, meaning that we had no ability to actually treat the disease itself. We could treat just the symptoms. So we could treat, let's say, depression, we could treat anxiety, we could treat agitation. We could treat to a very, very small degree, cognition. But those medications to treat those symptoms really were a little bit like a drop in the bucket. You know, we more or less had very limited ability to treat Alzheimer disease in general. And it didn't really matter if someone had, let's say, Alzheimer disease or an alternative form of dementia that mimicked Alzheimer disease. So, let's say we misdiagnosed someone with Alzheimer disease and they really had dementia of Lewy bodies, or maybe they really had hippocampal sclerosis of aging, which is a mimic of Alzheimer disease. Those medications more or less could be used equally across those three different neurodegenerative diseases.

Now, with the advent of drugs that try to take off those abnormal proteins associated with neurodegenerative disease, you definitely need to make sure that that patient has the protein that you think they have. So, in the case of Alzheimer disease, we now have two treatments that can pull off the amyloid beta protein from the brain. And so we need to be extra special sure that the patient actually has the associated amyloid beta protein present. And that's where CSF, PET, or blood-based biomarkers come in. As we look forward, there are a lot more treatments coming down the pipeline, which maybe we can talk about in our next question. But it will be increasingly important to verify and confirm that someone has the associated protein that you're targeting.

Bob Barrett: Well, we know early detection and diagnosis of almost everything is very important, but why is it very important in Alzheimer disease detection? And looking ahead, what future developments do you anticipate in the realm of Alzheimer disease treatment?

Will Mantyh: Yes. I'll divide that in two different categories. The first category is just preparing for the future. As you're aware, I think everyone's aware, most of us have an affected relative with Alzheimer or another type of dementia. It's a disaster in terms of if you're unprepared, you can't deal with

unanticipated financial issues. I had a friend of mine whose father recently spent $50,000 being taken advantage of by a phone scam and giving away prepaid gift cards. That's because the family really didn't know that this patient had Alzheimer disease, and he had full access to his bank account. Patients with Alzheimer disease, of course, face potential catastrophic healthcare costs. Alzheimer disease is associated with a whole host of comorbidities, not least of which is falls. And so preparing patients ahead of time for safety-proofing the house, making sure that someone's advanced directives are in place. So that's end of life care. What would you want to have happen at the end of your life? Would you want aggressive medical care or would you want less aggressive medical care? Those very difficult questions to ask are important to ask when the patient is still fully cognizant of their health status and their healthcare needs. And so if you are diagnosing the disease late, when someone's already demented, it becomes very difficult to have a well delineated plan of action.

And then the second category, beyond what I call the social and family elements of the Alzheimer disease diagnosis, is that newer treatments are now targeting the pre-symptomatic phase. And some of the new drugs that have just hit the market are showing greater benefit when a patient is in the earlier phases of the disease. In fact, there's a huge difference if a patient is being given the drug in a very early symptomatic stage, when the tau tangles have not yet spread throughout their brain, versus patients who are in a more advanced stage and whose tau tangles have spread significantly. So those earlier stage patients stand to benefit up to quadruple compared to the late stage patients. I shouldn't say late stage, but the patients who are still in the early stage, but who have more significant tau tangle spread. And so being able to diagnose someone early does have significant clinical benefit.

And furthermore, we're seeing the field evolve towards the pre-symptomatic phase of Alzheimer. So before someone has symptoms but those Alzheimer proteins are present, we're seeing drug companies now targeting that phase of disease and there's a strong theoretical rationale for why that phase may provide the strongest benefit. So, can we give someone these medications and take away those proteins before the brain is actually damaged? So that's one thing these drugs can't do. They can't take away damaged parts of the brain. They can't resurrect dead neurons, but they can take away those proteins. And so if we can take them away before the damage is done, theoretically we should see much greater benefit.

And we are seeing some signal for that in, for instance, the autosomal dominant form Alzheimer disease, where you have

a very good idea of when a patient will develop their symptoms. And if you can target those autosomal dominant forms of Alzheimer disease in patients that yet have symptoms, we're seeing half the risk of developing Alzheimer disease as you normally would expect. So, again, there's some early data showing that maybe the pre-symptomatic stage will be the best time to target Alzheimer. And maybe Alzheimer disease will be sort of like a colonoscopy, where everyone who turns 50, and I believe that actually maybe changed to an earlier age, although I haven't kept up to date on that. But basically, at a certain age, someone would automatically get a, let's say, blood test for Alzheimer. And if it's positive, they would be referred for more confirmatory testing and potentially enrollment in a disease modifying therapy. So earlier is better, time is brain, is an increasingly supported way of treating Alzheimer disease and probably other forms of dementia as well.

Danni Li: You know, maybe the future would be that it's kind of like treating cardiovascular disease. So if you kind of reduce people's risk early by detecting them, then you can actually really prevent the future, in this case, development of dementia and making sure people lead a better and healthy life. So I think this concept applies to other aspects of medicine and as well as in the realm of Alzheimer disease. That's the goal, and we're hopefully getting there through all those exciting developments of therapy and diagnostic tests.

Will Mantyh: I'll just add one other point, that Dr. Li brought up this idea of exercise and changing your diet or other lifestyle risk factors, and we're seeing that cerebrospinal fluid amyloid beta 42 level drop almost 20 years before symptom onset. That means that there's a long time that someone can enact changes to their lifestyle to potentially further delay the onset of dementia. So there's some data showing that exercise can slow down the course of dementia by up to 50%, some case studies even more than that.

So if someone, let's say, gets a cerebrospinal fluid amyloid beta 42 test 20 years before they are set to develop symptoms of Alzheimer disease, that's a ton of time where someone can start to change their lifestyle and maybe prolong the onset to 40 years. Yeah, it's not just drugs, but it's also the lifestyle approach that could be important here for early detection of Alzheimer disease proteins. I really think a lot about how future Alzheimer treatment's going to work and whether there'll be specialized clinics for people in their 30s and 40s even, and then getting them enrolled in a fitness program, a diet program, and hopefully by that time, we'll have medicines with less side effects that we can start at a pre-symptomatic stage.

I'll say this much, too. There's an idea that these new anti-amyloid drugs cause side effects because they're activating the immune system when those anti-amyloid proteins attach to amyloid beta in the brain. And so if there's less amyloid beta in the brain to begin with, there's a thought, again, this is not proven at all yet. There's a thought that if we're treating someone just when the amyloid protein is starting to be deposited in the brain, there might be such a low amount there that the risk for side effects is negligible. Again, we don't know if that's true, but that's another potential reason why earlier is better.

Bob Barrett: That was Dr. Will Mantyh and Dr. Danni Li from the University of Minnesota. They wrote a perspective article on the early detection and treatment of Alzheimer disease in the September 2024 issue of *Clinical Chemistry*, and they've been our guests in this podcast on that topic. I'm Bob Barrett. Thanks for listening.