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Markers of Memory: Pathological Biomarkers of Clinical MCI Due to AD

Announcer:
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Dr. Sabbagh:
This is CME on ReachMD and I'm Dr. Marwan Noel Sabbagh. Today we're going to discuss pathological biomarkers of clinical mild cognitive impairment due to Alzheimer's disease.

Historically, we've always taken an approach of a diagnosis of exclusion, meaning excluding other pathology, but we're now moving toward the trend of focusing on biomarkers for inclusivity. And why is that? Because we know that the pathological changes that lead to an Alzheimer's disease dementia occur prior to the onset of symptoms, as you see in the Alzheimer's disease continuum.

So, the left-hand side could be up to 20 years before onset of symptoms, and that correlates with accumulation of plaques and tangles. So, by the time they come in the door, they have probably had accumulation for up to two decades. And so, it's important to recognize this.

There is a new framework called the ATN, amyloid, tau, and nerve degeneration, which is a pathological framework, meaning it's constructed out of biology. We know that you have to be A-positive to be ATN significant. So, you could have another neurodegenerative disease without amyloid, it might just not be Alzheimer's disease. So, A has to be positive, and you would expect to be T-, or an N-positive as well. And that's the research framework that is now being moved slowly into clinical applicability. The reason it's important is that A-positivity can be determined in a variety of different ways. One of the ways you can determine amyloid positivity is with amyloid PET, and we expect if you're a binary – positive or negative.

So, if you look at the left-hand side of the slide, a negative scan, the gray matter and white matter are clearly differentiated. A positive scan means the gray matter and white matter are blurred. There are three approved. The tracers include florbetapir, florbetaben, and flutemetamol, and they are now reimbursed by Medicare. So, we are now using them more than we have in the past in clinical practice. As I said before, the accumulation pathology occurs well before the onset of symptoms. So, amyloid CSF markers are changing, and then amyloid PET are changing well before the onset of symptoms, and then you see the accumulation of Tau, and then you see the accumulation of CSF tau, and then you see the changes of neurodegeneration, and then you see the cognitive impairment. So what I'm saying is the pathological markers precede the onset of clinical symptoms.

One of the things we also can look at is CSF biomarkers, and people say to me, Gee, that's awfully invasive, and I say to you, of course, if you have meningitis and encephalitis and a variety of other neurological conditions, you're going to get a lumbar puncture. So, there's no reason to not add Alzheimer's to the list of things you can do. What we expect to see is in CSF is the amyloid goes down, Tau goes up, phosphorylated Tau goes up, and that it's very, very accurate with an accuracy of greater than 96%, studied in over 200 studies and 20,000 patients. What we expect also to see is that amyloid CSF correlates very, very well with amyloid PET, with a Kappa of 0.9 seen,

meaning a 90% correlation between CSF and amyloid PET. And that is very diagnostic as you see. So, low amyloid/high Tau, highly diagnostic as you see on the left-hand side of the slide, and it's highly predictive. So, if your amyloid is low and your Tau is high, the probability of progression is somewhere about 90% in 5 years, so it's both highly diagnostic and highly predictive.

What about plasma biomarkers? Well, they're slowly starting to make their way into clinical practice, and it's a very exciting development. What we see, though, is that plasma amyloid goes down, and it's a ratio of 42 to 40. There are different platforms, you can use mass spec and Samoa and other things, but the point is, is that it correlates well with CSF and with PET, and so your amyloid 42 to 40 ratio would go down as you're moving toward an Alzheimer's process. Your p-Tau would go up, p-Tau 181, as you see in the middle, correlates, goes up as you dement, and you're Alzheimer's disease pathology, amyloid-positive. And on the right-hand side of the slide, you see that if you're p-Tau is elevated, the probability of progression is very, very high.

Another measure we're looking at is p-Tau 217. We know that p-Tau 217, up beyond a certain cut-point has an area on the curve of 0.96, so 96% likelihood that if your p-Tau levels are elevated, you have probably both Tau pathology and amyloid pathology, and people think that we could coalesce a diagnosis into a single blood test. That is to be determined.

Thank you for listening.

Announcer:
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