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Dementia on a Spectrum: Preclinical Stages of MCI in AD

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Dr. Hardy:
Hello, this is CME on ReachMD and I'm John Hardy. Today, we're going to discuss the preclinical stages of MCI in Alzheimer's disease. So, I think we'll start by looking at the final pathology of Alzheimer's disease, which is shown here. Here in this Silverstein section, you can see the plaques of Alzheimer's disease. They're about a 10th of a millimeter across, and they are stained. They consist largely, not entirely, but largely, of amyloid, and you can see many neuropil threads. And they largely contain the tau protein. And, so this is the gross pathology of – the histopathology of Alzheimer's disease.

Now, when you see this histopathology, what you don't know is the order in which these pathologies, develop. So, you can see this if you're like car crash, but you can't tell what came first. You can't tell whether it was the plaques that came first, or whether it was the tangle pathology, or whether it was, the cell loss that also accompanies the disease. So, you can see the end result, but you can't tell which came first. And what attracted me to genetics was that it would enable us to find how the disease started. And what was important to us was a particular family with the disease, and this is that family with disease, which we published on, now, quite a while ago. And there you can see 10 children, 5 of whom black, triangles have the disease, and double cousin, one of whom, has the disease. And you're looking at the top half of chromosome 21, and what you can see is that all the affected members, share that chromosome segment, but 2 unaffected members, #9 and then, #11, share the top of the chromosome and the bottom, but they're not affected. And that tells us that the disease gene is likely to be between those two parts of the chromosome and the APP, the amyloid gene, is in the middle of that gap.

And so, this is telling us that in this family, amyloid is where the disease started. And that allowed us to say, in our paper is bottom right. Dennis Zelko wrote a similar paper at the same time, saying that amyloid in this family is where the disease starts, and so the simplest explanation is that amyloid is always where the disease starts. So, this is the amyloid hypothesis for the disease.

Now, when we did this, when we wrote this paper, we had the idea that the time that Alzheimer's disease pathogenesis took was very short. But we now know from work done by many pathologists over, and clinicians, over many years, that the disease takes is a long time, and that's shown in this famous, slide from, Cliff Jack and David Holtzman showing that, if you look at the vertical red arrow, if the disease starts at, the clinical features of the disease start there where the vertical red arrow is, if that is at 70 years, you can see that there are biochemical changes which we can pick up, either by PET scan or by blood marker, analysis much, much earlier. Along to the left of that, maybe starting at 50 years old with the changes in CSF A-beta. So, this is a process which takes a very long time. But of great importance here is where the position of MCI. If MCI, as you can see in that rising segment at about 60 years old in this particular instance, this is when you have the mildest clinical features before you reach clinical dementia. And so, MCI is something you find right at the beginning of the disease process.

So, thanks for listening to this episode.

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