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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

How Alzheimer's and Lewy Body Pathology Impact CAA Risk Factors

Dr. Turck:
Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and Dr. Jagan Pillai is here with me today to discuss his research on how the presence of Lewy body pathology alongside Alzheimer's disease changes the risk factors for cerebral amyloid angiopathy. Dr. Pillai is a behavioral neurologist at Cleveland Clinic Lou Ruvo Center for Brain Health and is an Associate Professor at the Cleveland Clinic Lerner College of Medicine.

Dr. Pillai, it's great to have you with us today.

Dr. Pillai:
Well, thank you, and thank you for inviting me to the program.

Dr. Turck:
So if we start with some background, Dr. Pillai, would you tell us about your study and how cerebral amyloid angiopathy is associated with dementia-associated pathologies, particularly Alzheimer's disease and Lewy body pathology?

Dr. Pillai:
So cerebral amyloid angiopathy is a common neuropathological change seen sometimes by itself but sometimes along with other pathologies like Alzheimer's disease, and CAA is characterized by deposition of the amyloid beta protein, the same protein that accumulates in Alzheimer's disease. Here it accumulates in the blood vessels of the brain, and so it's a independent risk factor for things like strokes and intracerebral hemorrhages. And in the context of these new medications for Alzheimer's disease, they also increase the risk of having side effects, and they're an exclusion criteria for use of some of these medications if they are severe.

Dr. Turck:
And could you tell us a little bit about the methods you employed when conducting your study?

Dr. Pillai:
Sure. The primary question we wanted to answer was the cerebral amyloid angiopathy is well known to be associated with Alzheimer's disease pathology, but oftentimes Alzheimer's disease pathology is not seen in a pure way. Oftentimes, it's mixed with other pathologies, common ones being things like Lewy body pathology that's seen in Lewy body dementia. About 50 percent of Lewy body dementia often has mixed pathology, and we want to know what is the prevalence of CAA pathology in the context of Lewy body pathology and what are the risk factors for the severity of this pathology when it's presented with comorbid pathologies like Lewy body pathology. So we conducted a retrospective study of over 2,000 participants who were part of the National Alzheimer's Coordinating Center cohort. This is a cohort that includes subjects across the United States who were followed longitudinally in the Alzheimer's disease research centers across the country and who went on to have autopsy and their brains examined to evaluate the degree of the pathology to address these questions.

Dr. Turck:
So with that background in mind, let's zero in on the results. What were the major findings of your study?

Dr. Pillai:
I think there were three key findings that I wanted to include. The first one was CAA was seen in both people with Lewy body pathology alone and people with both Alzheimer's disease and Lewy body pathology, so this pathology was not limited to just the Alzheimer's disease group alone.

The second thing that we noticed was that older age is definitely a risk factor for the cerebral amyloid angiopathy in these groups. However, there were slight differences between other risk factors for this pathology of CAA. APOE4 gene carrier status, which is already been described to be a risk factor for CAA, was seen to be a risk factor in Lewy body pathology and Alzheimer's; but interestingly, someone who has homozygous status, that means they carry both copies of the E4 gene, had a much higher risk of having CAA when they had Lewy body pathology than with Alzheimer's disease or with Alzheimer's disease and Lewy body pathology combination, so the odds were about 25 times higher in the Lewy body pathology group compared to just the Alzheimer's group, which is just 3 times higher. So that was surprising for us given the fact that CAA has been more often related to Alzheimer's disease pathology in the literature than Lewy body pathology.

We also noticed that factors like lower educational status tend to increase the chances of having CAA in the mixed pathology group, and so did male sex.

Dr. Turck:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Jagan Pillai about his study on how the presence of both Alzheimer's disease and Lewy body pathology impacts risk factor considerations for cerebral amyloid angiopathy.

Now, Dr. Pillai, what precautions or strategies would you recommend for clinicians when considering the use of anti-amyloid immunotherapy?

Dr. Pillai:
So CAA severity is screened for and before starting the new anti-amyloid therapies by having an MRI scan and looking for microhemorrhages, more than five or more in number. One of the factors that is not looked for is the presence of copathologies before starting these new anti-amyloid medications.

So currently, we have strong biomarkers for amyloid and phospho-Tau pathology that help us make a diagnosis of Alzheimer's disease in the clinic. But what our study suggests is that in addition to the Alzheimer's pathology of amyloid and Tau, the presence of Lewy body pathology can modify the risk of CAA in the background and potentially the risk of side effects using these medications.

There are new biomarkers for alpha-synuclein that are currently available that can be measured in the CSF and skin, so I think it's an exciting time to see if a better characterization of these additional alpha-synuclein biomarkers would be helpful in counseling patients before they make a judgment on being on new anti-amyloid therapies regarding their risk of side effects like brain edema and cerebral bleeds.

Dr. Turck:
So bringing the discussion back to your research a bit, how do you think it could impact clinical practice in terms of evaluating and managing patients?

Dr. Pillai:
I think our study sheds light on the fact that looking at Alzheimer's disease patients using Alzheimer's biomarkers alone may be incomplete given that there might be copathologies in many of these patients that may impact clinical outcomes related to CAA for them, especially when they are on the new anti-amyloid medications for a year or more. So even though this study does not suggest clinicians change their practice immediately, this study does shed light on the fact that clinicians need to be aware that copathologies might impact risks related to anti-amyloid therapy in the context of CAA in the background.

Dr. Turck:
And before we close, Dr. Pillai, are there any other key takeaways you'd like to leave with our audience?

Dr. Pillai:
I think what this study definitely shows is that characterizing patients using biomarkers and understanding their underlying pathology before having targeted anti amyloid therapies for one or more co-existing neurodegenerative pathologies is going to be crucial and key to better patient care in the coming years, and we are likely to see a lot more advances and impactful ways we can help our patients in the next few years.

Dr. Turck:
Well, with those final comments in mind, I want to thank my guest, Dr. Jagan Pillai, for joining me to discuss his research on how the presence of Lewy body pathology alongside Alzheimer's disease impacts the risk of cerebral amyloid angiopathy.

Dr. Pillai, it was a pleasure having you on the program.

Dr. Pillai:
Thank you. Thank you for having me.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.