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TTR Levels and Associated Disease Risk: Insights from 2025 PNS Conference

Announcer:
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Dr. Masri:
Baseline, or naturally occurring low TTR, or transthyretin protein level, is associated with comorbidities and different diseases. Let's review these insights from the UK Biobank database, which was recently presented at the annual meeting of the Peripheral Nerve Society in Edinburgh, Scotland. This is ReachMD, and I'm Dr. Ahmad Masri.

Recently, the interest in TTR protein and transthyretin itself has really been revitalized by the discovery that transthyretin amyloidosis is a lot more common of a disease than we used to think or know about. And this was prompted by the improvement in the diagnosis and diagnostic methods we use as well as the availability of evidence-based therapies that actually do work in this disease space.

So the research that was presented at the Peripheral Nerve Society focused on studying the association between low transthyretin level and different diseases that are found in the UK Biobank. And in the UK Biobank, as you're aware, it's a large biobank of patients in the UK. In this study, about half a million patients were included, and there were a few patients, about 234, with TTR amyloidosis that were looked at or studied in a separate cohort.

Now, as a subcohort of the UK Biobank, there are about also 50,000 patients or so who had proteomics that were measured using the OLINK platform.

And so the findings from this research investigation is that patients who have spontaneously or naturally occurring low TTR levels had an association with elevated NT-proBNP in the TTR population, as you would expect, and had an association with low ApoA1, which we really don't understand why exactly this happens.

In terms of different comorbidities, patients with ATTR, when they had lower TTR levels, as you would expect, they had more comorbidities.

And so that includes vascular disease, such as peripheral arterial disease, as well as stroke, TIA (transient ischemic attacks), and also hemorrhagic stroke. They also had diseases related to cognition, such as cognitive impairment, dementia, and Alzheimer's disease.

Now, outside of TTR amyloidosis, patients having a low TTR level were associated with having other diseases and comorbidities, such as osteoporosis, peripheral arterial disease, stroke, TIA, which we mentioned already, as well as cognitive impairment, dementia, and Alzheimer's disease.

And these things are important to put into context. And the context is that when you have a spontaneously occurring low TTR level, you actually don't necessarily know what led to that low TTR level. There are a lot of reasons why TTR levels can go down. And that's, in my opinion, very distinct from what happens when you are trying to treat patients with transthyretin amyloidosis, and you're trying to manipulate TTR one way or another, either increasing TTR by using a stabilizer or decreasing TTR by using a knockdown agent or a

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silencer.

But, ultimately, the idea here is that TTR level does correlate with diseases when it's on the lower side and that TTR level, I think, needs to be put into context in the future of studying what happens to our patients as we continue to manipulate TTR either up or down. And we really need to think about these associations since, in clinical trials, we typically look at a range of 3 to 5 years of follow-up, and our patients are being diagnosed earlier, are living longer, and we need to be able to follow them over more of an extended period of time.

Finally, one needs really to know what happened first. Did you get a low TTR level and then you got a disease developed over X number of years of follow-up? Are these associations observed associations that one is leading to the other? There could be also sometimes reverse association there.

The bottom line is that the take-home message from all of this is that it's important to continue to evaluate serum TTR levels and their association with different outcomes and different diseases in patients as well as in the general population. Also, the fact that TTR is associated with these different conditions that we talked about. And then, finally, is that we really have to produce data and produce evidence that can direct us to how these TTR levels are playing a role in patients' health and in patients' diseases as well.

And so that's all the time we have today. I want to thank you, the audience, for listening in and keeping up with new evidence in transthyretin protein and transthyretin amyloidosis.

Announcer:
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