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Endogenous Lithium Levels and Alzheimer Disease.
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Guests: Dr. Imir Metushi is an Assistant Professor at UCLA and Director of the Pathology Research Portal. Dr. Ray Suhandynata is an Associate Professor at UC San Diego, Co-Director of the Clinical Toxicology Laboratory, and Associate Director of the Clinical Chemistry Laboratory.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Alzheimer's disease is the leading cause of dementia in American adults 65 years and older, and estimates predict 14 million affected individuals by 2060, with an associated cost of care of $1 trillion.

Although substantial efforts aimed at understanding the mechanism of disease have identified several contributors like age, genetics, and lifestyle factors, we still don't really understand how Alzheimer's works. As a result, most new drugs fail clinical trials and those that are approved show less than ideal benefit to risk ratio.

Is there a better way? What if we shifted our focus from treating affected individuals to preventing disease in the first place? A recent study in *Nature* identified lithium as a potential protective agent in mouse models of Alzheimer's disease. Could this be used safely in humans to slow disease progression or prevent Alzheimer's disease from developing at all?

A News & Views article in the March 2026 issue of *Clinical Chemistry* summarizes the *Nature* article, describes its importance in the larger field of Alzheimer's disease research, and predicts what the findings might mean for the clinical laboratory. Today we welcome two of the article's authors. Dr. Imir Metushi is an assistant professor at UCLA and Director of the Pathology Research Portal. Dr. Ray Suhandynata is an associate professor at UC San Diego, Co-director of the Clinical Toxicology Laboratory, and Associate Director of the Clinical Chemistry Laboratory.

Dr. Metushi, let's start with you. Can you remind us where we stand with Alzheimer's diagnosis and treatment today and then explain what's new about thinking of lithium as an endogenous factor in Alzheimer's disease, rather than just a psychiatric drug?

Imir Metushi: So, in this article, we start by reminding readers just how large the Alzheimer's problem already is. Alzheimer's disease

is the leading cause of dementia and a major cause of death in adults, with tens of millions affected globally and cost projected to approach a trillion dollars over the coming decade. We've made some real progress on the diagnostics with tests such as CSF tau, amyloid beta, PET imaging, and now the FDA approved plasma phospho-tau assays.

So, we're much better at establishing the diagnosis and tracking pathology, but from a therapeutic standpoint, we still only have modest effective symptomatic drugs with monoclonal antibodies that slow early disease, but cause significant toxicity and come at a high expense.

Lithium enters this story from a different angle. Traditionally, we think of lithium as a high dose mood stabilizer for bipolar disorders, which has a narrow therapeutic window and associated with renal and thyroid toxicity. What's new in the Aron *Nature* paper, and what we highlight in the News & Views, is the idea that lithium is also a naturally occurring brain trace element and that the brain may become relatively lithium deficient in Alzheimer's disease.

This is a conceptual shift. Instead of asking, "Can we push more a drug onto an already diseased brain?" we're asking whether a loss of physiologic micronutrient, in this case lithium, might be one of the upstream sparks for the beta-amyloid and tau pathology. If this is true, then carefully restoring low physiologic lithium levels could be more like correcting a deficiency rather than adding to a classic pharmacological burden.

And this has a very different implications for both safety and the prevention strategies.

Bob Barrett: So, doctor, what are the key mechanistic findings from the recent *Nature* study that really underpin this endogenous lithium concept?

Imir Metushi: Aron and colleagues used the inductive coupled plasma mass spectrometry to quantify 27 different metals in the postmortem human brain from individuals with no cognitive impairment, mild cognitive impairment, and Alzheimer's disease. And then they did additional studies in mouse models of Alzheimer's disease. Lithium turned out to be the outlier. It was significantly reduced in the prefrontal cortex of people with mild cognitive impairment and Alzheimer's, while the other measure metals were not consistently altered.

Then they asked where the lithium was going. When they compared amyloid plaque to plaque-free regions, lithium was highly concentrated within the amyloid plaques, and the amount of lithium trapped in plaques increased from the mild cognitive impairment to Alzheimer's disease. So, while lithium

in plaque-free tissues also fell. This suggests that amyloid acts as a sink and sequestered lithium, effectively depleting bioavailable lithium in the surrounding brain.

So, they did a number of things and then they moved on to the mouse models, where they could manipulate lithium more directly. When they fed Alzheimer's disease on mice models, a lithium-low diet, pathology accelerated. There was more amyloid plaques, more tau tangles, microglial activation, loss of synapses and myelin, and overall worse learning and memory.

Now, conversely, when they replace lithium with lithium orotate, which is an organic lithium salt, that binds less avidly to amyloid than lithium carbonate, which we're more familiar with, and by the way, this was done at a very low dose, they could reverse memory deficit, reducing amyloid and tau pathology without obvious toxicity.

So, overall, mechanistically, a big part of the story is the GSK3β pathway, which is a kinase that promotes tau hyper phosphorylation. So, lithium is a well described inhibitor of GSK3β and can favor pro-survival, pro-synaptic pathways, and reduce neuroinflammation at low doses. Taken together, you end up with a coherent model.

You know, you get amyloid plaques that sequester lithium, lithium deficiency. It relates to putting a break on the GSK3β and related pathways, and that drives a vicious cycle of amyloid tau inflammation and synaptic failure.

Bob Barrett: Okay, well, Dr. Suhandynata, let's bring you into this because those mechanistic data are very striking, but won't clinicians naturally ask, where's the human evidence?

Ray Suhandynata: Yeah, that's exactly the right question. And at this stage I describe the clinical evidence as associative, but not yet quite definitive. I would say that the first link stems from ecological and population-based studies evaluating the association between Alzheimer's disease and trace lithium concentrations in drinking water. A 2024 systematic review summarized five population-based studies from Denmark, Japan, Scotland, Texas, and across the United States.

Across these studies, trace lithium concentrations in the range of 2 to about 15 micrograms per liter in drinking water were often associated with lower dementia incidents or mortality. Although the dose response appeared to be non-linear and not every study found robust association. One of the most frequently cited studies is the one from Denmark, which was a nested case-controlled analysis involving more than 73,000 dementia cases and 733,000 controls. This was a really compelling study where people living in municipalities

with higher long-term lithium exposure above 15 micrograms per liter in drinking water had around a 17% lower incidence of dementia compared with those in the lowest exposure band.

Again, it's important to remember that the relationship observed was not always predictive and is critical for everyone to keep in mind. These findings are further supported by a 2022 retrospective cohort performed in the UK, which evaluated nearly 30,000 older adults undergoing secondary mental healthcare, of which around 550 had been exposed to lithium.

After extensive adjustments for demographics, comorbidities, and other medications, lithium exposure was associated with about a 45% lower risk of Alzheimer's disease, along with similar reductions for overall dementia and vascular dementia. This was particularly interesting as many of these patients have bipolar disorder, which itself is associated with increased dementia risk.

The observation of a protective association despite the background risk is especially compelling. Furthermore, there have been several small, randomized clinical trials that have attempted to investigate the effects of lithium in the setting of Alzheimer's disease. One study used a 300 microgram per day dose of lithium, which appeared to stabilize common decline of Alzheimer's patients compared with placebo across 15 months. Although the sample size was small.

It's important to keep in mind that initial trials were promising are still relatively underpowered. So I think the fairest way to look at it is that the evidence is encouraging and generally lines up with the mechanistic story but we still need well-controlled high-powered clinical trials investigating the effect of lithium on Alzheimer's risk and progression before drawing strong conclusions.

Bob Barrett: So, just quickly following up on that, if we think about translating research findings in mice to humans, what are the key issues?

Ray Suhandynata: That's a great point. The lithium orotate formulation that was looked at in the Aron paper is attractive as the studies performed and might suggest that the lithium delivered in this formulation avoids being trapped by amyloid plaque and is effective at very low doses.

However, this may not directly translate to humans and must be done with caution. At therapeutic doses for bipolar disorder, we aim to maintain serum lithium levels between a narrow range of around half to one millimole per liter, to manage the well-known risk associated with toxic

concentration such as chronic kidney disease, thyroid dysfunction, tremors, and weight gain.

The epidemiological studies and low dose trials, however, suggest that much lower exposure, often with serum levels less than half a milli mole per liter, or even micro doses may be sufficiently effective, with a much more favorable safety profile.

For lithium orotate specifically, we don't yet have high quality pharmacokinetic and safety data profiles in older adults with comorbidities. However, it's sold over the counter in some markets and hasn't gone through the rigorous evaluation we require for a drug that might be taken chronically by people at risk for dementia. So, I think it's really important to emphasize that lithium supplementation is not something I would recommend people start on their own. Rather, it needs to be studied in controlled trials with appropriate monitoring by qualified healthcare providers.

Bob Barrett: Well, finally, doctors, I'd like you to both chime in on this. We'll finish with the clinical laboratory side. From a lab perspective, how might this evolving story about endogenous lithium change what we do in the lab over the next decade? Should we be thinking about lithium as a biomarker or even a micronutrient that we routinely measure?

Imir Metushi: So right now, most clinical laboratories only measure lithium in the context of therapeutic drug monitoring. Typically using method optimized for relatively high concentration that are seen in bipolar treatments. Those assays are not designed for trace physiologic level we're thinking about in Alzheimer's, for example.

In the near term, I don't think we're at the point of adding lithium levels to routine dementia workup. But I could see a clear role for clinical laboratories as partners in building the evidence base, developing and validating sensitive assays, helping to define reference intervals, and integrating lithium into multianalyte panels for research.

If future trials show that correcting lithium deficiency is beneficial, then I do think that clinical chemists will be central to implementing safe and standardized monitoring practices for lithium measurements.

Ray Suhandynata: Yeah, those are great points, Dr. Metushi. To add on a little bit more, one of the important takeaways from the study is that inductively coupled plasma mass spectrometry can robustly quantify lithium at sub-ppm levels in brain tissue and blood.

So, a logical next step is to bring assays with that level of sensitivity into clinical research protocols. That said, this requires careful attention to detail to both the pre-analytical and analytical variables. On the pre-analytical side, we would need to avoid lithium heparin tubes, which are commonly used for plasma collection and would completely confound trace lithium measurements.

Additionally, we would also need to consider incorporating trace-free metal collection tubes into clinical research protocols and standardizing specimen type, whether it be serum, plasma, or even whole blood. On the analytical side, methods would need very low limits of detection and robust precision at the lower end of the measurement range, ideally with standardization against meteorologically traceable reference materials, so results can be compared reliably across studies and across platforms.

Bob Barrett: That was Dr. Ray Suhandynata from the University of California, San Diego, and Dr. Imir Metushi from the University of California, Los Angeles. They wrote a News & Views article in the March 2026 issue of *Clinical Chemistry,* describing a potential role for lithium in the prevention of Alzheimer's disease, and they've been our guests in this podcast on that topic. I'm Bob Barrett. Thanks for listening.