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Mechanisms of Alzheimer's Pathogenesis: How Disease Origins Guide Early Detection Practices

Opening Announcer:

You're listening to ReachMD. Uncover the truth about Alzheimer's in this special series, Alzheimer's Disease: Towards Earlier Detection.

Dr. Birnholz:

Understandings of the origins and mechanisms of disease process for Alzheimer's are evolving constantly, opening doors to improve targets for therapeutic research. But at a time when disease-modifying therapies for late-stage disease aren't yet available, the need for early detection of Alzheimer's becomes critically important. This is ReachMD, and I am Dr. Matt Birnholz. Joining me on this episode of *Alzheimer's Disease: Towards Earlier Detection*, is Dr. Carol Lippa. Dr. Lippa is Professor of Neurology and Director of the Memory Disorders Program at Drexel University College of Medicine. She is also a member of the Alzheimer's Association Board of Directors and Chair of the Delaware Valley chapter's Medical and Scientific Committee. Dr. Lippa, welcome to the program.

Dr. Lippa:

Thank you. Thank you for inviting me today.

Dr. Birnholz:

So, Dr. Lippa, a way of describing Alzheimer's now in clinical practice is often as a "hidden disease." What does that term mean to you when we describe Alzheimer's?

Dr. Lippa:

Well, there are several meanings to it really. One is that we now know that the pathology of Alzheimer's begins in the brain probably a decade, maybe even more before the patient has any symptoms at all. So that things are kind of building up and building up over time and it's quite a ways down the road before the person is symptomatic.

Dr. Birnholz:

And yet it's not simply the clinical manifestations, as we talked about a little bit earlier off-line, we discussed that there are social ramifications to the idea of being a hidden disease. What can you tell me about that?

Dr. Lippa:

Sure, sure, well, there are a few things. One, there isn't that much awareness that Alzheimer's is something you just have to put up with. We have symptomatic treatments for it now and there are a lot of things that you can do if you focus on the behavioral symptoms. A lot of times you can do a lot for a patient with Alzheimer's, but people still sort of keep the person in the house. They don't go out and seek help. So, I think, now we are just starting to get awareness that you don't have to have the person stay hidden. They can come out, get things addressed, try to maximize the memory they have and do a lot of things about the trouble they have sleeping, the appetite, their wandering, their behavior, maybe depression and anxiety, or belligerent behavior. Those kinds of things. There is a lot we can do. The other thing is really the stigma too, is that people don't want to bring it up. A lot of patients kind of withdraw into their homes which is the last thing you want to do when you have Alzheimer's because they are afraid that someone will know, or someone will notice, and they really keep to themselves a lot more. But that is another way that it is sort of a hidden disease and it is counterproductive to the things that people can do to maximize their memory over time.

Dr. Birnholz:

So clearly, a multi-layered term...

Dr. Lippa:

Yes, yes.

Dr. Birnholz:

...when you say that. So earlier I had mentioned, made a thematic focus, the idea of the importance, the value of earlier detection. But there is a common sentiment out there among many people, many

patients, and even some providers, some clinicians, that earlier detection doesn't have much value or meaning, that there is nothing that can be done. How do you respond to that when you encounter that in your practice?

Dr. Lippa:

Well, you can't make the disease go away once it is established but, you know, you can't make hypertension, diabetes or a lot of other things go away once you have them, you just manage them and control them. Now, with Alzheimer's we have symptomatic treatment so that there are pills that you can take that will stabilize memory for a little while and may improve it a little bit, even though we can't make the process go away. So, it's important in making a diagnosis if you want to do what you can do to help the problem. We used to see, everyone came in and they were mild, moderate or severe Alzheimer's, and now, at least a third of the new patients we see don't even fully meet criteria for dementia. They are just starting somewhere down the slippery slope. So, I like to see them early because anything we find whether it's Alzheimer's pathology underlying the symptoms, a mimicker, another sort of a cousin degenerative disease or some kind of a medical problem mimicking it, any of those are more treatable the earlier we see them.

Dr. Birnholz:

Let's talk about that for a second. The mimicker diseases, the medical diseases that manifest similarly to Alzheimer's. What signs and symptoms do you look out for in your practice that really have helped you to hone in on Alzheimer's compared to other mimicker diseases?

Dr. Lippa:

Alzheimer's, the first part of the thinking circuits that get frayed are the links between -- I need to remember this -- in the actual apparatus in the brain that encodes it. So, you remember where you went to school when you were a teenager, who you married, what you served at your wedding, all these things from the past.

Dr. Birnholz:

The last thing, I am not sure...but...

(laughter)

Dr. Lippa:

I won't be too specific there. But, you can't remember a really simple like what you had for lunch or even if you had lunch. And if there is something important you have to remember, it affects the link, like I have to remember this, with just the really easy ability to remember it and that's very specific for Alzheimer's. That's a specific path in the brain and those cells in the circuit are gone first. So, I look

for an Alzheimer's patient, insidious onset when you think about it because it doesn't start (finger snap) just like that. It's sort of progressive loss of the cells, slowly progressive, not that they can't have a good day or bad day, but things seem to be getting worse over time and problems with encoding that new information. A lot of the medical problems will be associated with fatigue; they will be associated with inattention where they can get anything into their memory, they just lose their track. They won't forget to do something like the Alzheimer patient, they will either not want to do it or they will mess it up. It's just organizational. That kind of thing. So, we look for what we call that amnesic pattern. If we give them 3 words -- ball, flag, tree -- and you tell them to repeat them and you tell them you are going to ask them that in a few minutes, they may get everything else correct. All the other mental quizzes or questions you ask them, but when you ask them about the 3 words, they will be like, "3 words?" They just won't, you know, because it's that encoding, and that is a pretty specific pattern. So, you look at the pattern of cognitive losses. You look at the exam, the reflexes are they normal, are they symmetric? Is the strength normal, symmetric? Just the history, did it start quickly, does it get worse and better? Do they have any signs of organ failure and then you get blood work and things like that to check.

Dr. Birnholz:

The idea of the algorithm, the way of thinking through, assessing somebody based on their history when they come in, how they are presenting and how you sort of refine your differential. A number of our audience members who are generalists have this basic idea in mind, but they might not be as exposed to some of the unusual presentations that come in. That we had a chance to speak to some neurologists and one of them talked about an unusual case of a visual organization sort of defect involving trying to organize things on a page and realizing he couldn't do it. Almost like a visual field loss.

Dr. Lippa:

Sure.

Dr. Birnholz:

Have you seen any other unusual presentations that, from your vantage point as a neurologist, don't normally speak up to Alzheimer's but actually turn out to be?

Dr. Lippa:

Well, sometimes, most often those types of patients have these cousin conditions, the different types of conditions, but occasionally someone will have what we call a "posterior variant" and the sense of direction, organization in space kind of presentation. They can have more of a frontal presentation. Occasionally, someone will present with what we call "progressive aphasia" where people can't tag or

they know what they want to say but they lose the fluency, their normal prosody, their sentence length, everything gets truncated to “need water” rather than “gee, I am thirsty, can we get a drink of something?” You know it really gets crunched down, and again, a lot of times that is a mimicker condition. But once in a while there is Alzheimer’s pathology there, so it can present in different ways depending on what parts of the brain are involved. Every single gyrus, every single circuit, every convolution in the brain has a different function. And so, that is why it is so interesting. You know, a dermatologist you get a chunk of skin and you get a biopsy, you get a scratch and it all grows in, and it’s all the same and every cell does this. Every liver cell does basically the same thing, right? You can lose a chunk, you can get a chunk, chunk of lung, well it breathes, you know. But neurons think and every one, depending on their connections, everyone has a little different role and if your Alzheimer’s pathologies, if you have a biological weak point say in the visual spatial, visual organizational area, like the case you are discussing, that’s your weak spot and your Alzheimer’s pathology is hidden. It is possible that you could get that as a manifestation of the disease.

Dr. Birnholz:

So given a strong part of the pathology appears to be this amyloid beta and tau deposition depending on where that is, the symptoms or the signs, what the presentation would be could be very different.

Dr. Lippa:

Right, the amyloid is the component that occurs in the brain like a decade before there are any symptoms, or maybe longer. There are a lot of aged, normal people who die of heart attacks or other things and they never get any symptoms and amyloid all over their brain. And that is there for a long time before you get the tau. So we know amyloid, or most people believe that amyloid, is the trigger for the process. Mutations in the gene that codes for the precursor to amyloid cause Alzheimer’s. Mutations in the tau gene don’t. So, Alzheimer’s is what brings on the disease. That’s what starts it up and it takes a decade before you get the tau in the neurofibrillary tangle. But the tangles are actually what correlates with the severity of the disease more. So, the tangles, your area with tangles, your regional susceptibility to tangles, may reflect the symptoms you show.

Dr. Birnholz:

I also understand that there is budding research that is linking Alzheimer’s to a number of other potential pathophysiological connections: diabetes, infectious disease, autoimmune...

Dr. Lippa:

Oh, yes, yes.

Dr. Birnholz:

...it seems broad.

Dr. Lippa:

There's a lot. There are a lot of potential...well, I think there may be many roads to Alzheimer's. There are certainly genetic forms. There are certain people that if they live to age of onset, they will get the disease, period. You know, fully penetrate, autosomal dominant. So, that's genetic. But there are people that have nothing genetic that we can identify and none of the relatives have anything and in those people some of it is lifestyles. Your cognitive reserve, how smart you are, the packing density of your thoughts, how much you stay engaged in your environment, kind of keeping your brain exercised, if you will, and then there are your medical conditions. Diabetes is terrible for Alzheimer's and the jury is a little bit out, but there are different lines of evidence that it can impact the blood brain barrier and it can predispose you to developing the amyloid and so forth. Vascular risk factors, again, it ruins the vessels bringing blood and nutrients and everything into your brain and there is a lot of overlap between vascular, cerebral vascular, disease and dementia. So, I think that in different people there are probably different environmental triggers that are more involved depending on your particular makeup and your lifestyle what you do.

Dr. Birnholz:

Well, with that I very much want to thank my guest, Dr. Carol Lippa, for joining me today. We have been talking about the drive toward earlier detection for Alzheimer's disease. Dr. Lippa, thanks so much for joining us.

Dr. Lippa:

Thank you for having me.

Dr. Birnholz:

For access to this and other episodes of *Alzheimer's Disease: Towards Earlier Detection*, and to download the ReachMD app, visit us at ReachMD.com. I am Dr. Matt Birnholz, reminding you, as always, to be part of the knowledge. Thank you for joining us.

Closing Announcer:

You've listening to ReachMD. Uncover the truth about Alzheimer's in this special series, *Alzheimer's Disease: Towards Earlier Detection*. To revisit any part of this discussion and to access other episodes visit ReachMD.com/timehidesalzheimers. Thank you for listening.