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Kendal Williams (Host): Welcome everyone to the Penn Primary Care Podcast. I'm your host, Dr. Kendal Williams. Cognitive impairment is one of the most common things we manage in primary care. There are 50 million Americans with dementia. Over 32% of patients over 85 will have cognitive impairment, 10% over 65. So, these are big numbers and we're going to see this a lot. And we have a lot of patients that come in who are concerned that they have cognitive impairment. And so, we have to sort of think through that. I asked an expert to join me to discuss this. Dr. Jason Karlawish is a Professor of Medicine at Penn. He is the Co-Director of the Penn Memory Center, and really a national expert on dementia and ethics around dementia and so forth. Jason, thanks so much for coming.

Jason Karlawish, MD: Oh, my pleasure, Kendal. Thanks so much for having me. Hi, everyone.

Host: Jason, can you tell us a little bit about what you do and your background, just as we jump into this?

Jason Karlawish, MD: Yeah. So, I'm trained in internal medicine and then I did fellowship training in geriatric medicine and additional fellowship training in bioethics as part of my research interest. I came to Penn in 1997 in the Department of Medicine. By about 1998, I was a clinician in the Penn Memory Disorders Clinic, which we renamed the Penn Memory Center. One day a week, I see patients there for diagnosis and treatment and care. And the rest of the time, I devote to research and related scholarship and helping to run the memory center.

Host: So, you're the perfect person to have on to talk about this. I actually want to start with there are obviously different types of presentations of cognitive impairment in primary care. One of the most common things that people come in to me concerned about is memory. So, I want to establish a baseline a little bit. What is normal memory, not impairment, but, you know, normal memory functioning? And then, how do we know if something's abnormal?

Jason Karlawish, MD: Well, First, it's fascinating that for all the behaviors that the brain has, language, the ability to do things, visual recognition and memory, that all cognitive complaints generally are called a memory problem. It's absolutely fascinating. I have patients who come in who clearly have an aphasia, trouble producing words, and the chief complaint is memory. So,

recognize that just because someone says my memory is not good. It may not actually be the ability to encode and remember information, which is what memory is, that is to say short-term memory, but some other aspect of cognitive function. So, that's a key point.

The second is, you know, what's normal memory? Well, formally defined as the ability to encode and then recall information, you know, we have norms for age and education adjusted performance on memory tests. No one knows what those are except a psychologist. But the bottom line is we know our memory is normal because we don't notice it, meaning it does the things we need to do and the people around us also say, "I don't pick up any problems."

and the issue then being, so what's abnormal memory? Abnormal memory, thinking like a clinician, is the person either perceives it's not working as well as it should, "I'm making mistakes, I'm having trouble," or people around them say, "He's making mistakes, he's having trouble," and the problem isn't physical, it's cognitive, and I'll call it memory. So then, the next question is, is it memory or not?

Host: And the thing that usually raises my concern is if I notice it, sometimes you just pick these things up through subtle cues in the interview process. And then, the other thing is that when family members either come in with the patient or call ahead and say, you know, "My husband's coming to see you..." This happened to me a couple times, "My husband's coming to see you. I'm really concerned about this. Can you evaluate it?" And so, let's talk about the evaluation of somebody that you have a little bit greater concern for.

Jason Karlawish, MD: Yeah. Let me just give you one pearl. Under 50, young, complaining of memory, most common causes: anxiety, depression, sleep disorder, substance use, alcohol, et cetera, or combinations thereof. The problems basically are attentional problems, really, is what's going on there. If you can't pay attention, you don't remember, because you didn't even learn it in the first place. Having said that though, once people enter that fifth, sixth, seventh decade of life, a memory complaint may be those things, but it may be a disease of the brain, a neurodegenerative disease. So, you gave me a couple scenarios, what one do you want to start with?

Host: Well, I guess the most common scenario is the patient that's over 50, which I don't know if I've seen a graph on this, I know there are patients in their 40s who present with neurodegenerative disorders, but that's unusual.

Jason Karlawish, MD: Very unusual and if that was the only problem, we wouldn't be having this podcast.

Kendal Williams (Host): So usually, it's 50s, 60s, and so forth that you're starting to cue into this. And let's say, let me give you the scenario that has happened to me recently. The wife called ahead, said, "I'm concerned about my husband. He seems to be having trouble negotiating things like he used to do and doesn't remember things. He hasn't gotten lost, but I'm just concerned that maybe something's going on." Let's just start with that patient.

Jason Karlawish, MD: So, I think when in my world we call that a knowledgeable informant, which is a brutal term. But what we're trying to capture is there are people out there who observe other people's cognition, spouses, adult children, close friends, colleagues at work. And when a knowledgeable informant calls the alert and says, "I'm concerned about memory," that to me warrants an evaluation, because they're perceiving changes in that person's ability to function. And that needs a workup, that needs an assessment. And actually, thank God when they do that, because they're already getting you halfway, well, forget the fraction, but they're getting you some way along in the process, because an essential part of the workup of a cognitive complaint is to gather collateral information, information from a knowledgeable informant. What have you noticed? And that's very valuable information, because it triangulates what the patient tells you.

Sometimes patients don't perceive their problems. I find more and more that's not the case if you really probe. But many patients perceive their problems, but they discount them or otherwise, frankly, because of stigma, embarrassment, and fear, don't admit them or talk about them. In fact, I mean, at the Memory Center, we don't see certain people because they just won't come in because they're so stigmatized. So, if you can get them to come in with the informant, you have got clinical goldmine to find out what's going on because you can interview the patient and you can interview the informant and arrive at a reasonable understanding of whether there's cognitive impairment, and if there is, what might be causing it, and what the next steps are.

Host: So, I assume you start fairly open-ended and just ask basic questions and let them open up about what they're seeing and experiencing, and then you get more specific. What are some of the specific questions you might drill down on?

Jason Karlawish, MD: Well, actually, let's start generally. I'll say, you know, "What's the problem? What have you noticed?" And I just let that chief

complaint-- I don't think we're supposed to call it a chief complaint anymore. But I let that chief complaint unfold and listen to it. And if I've got both in the room, I really have to give each one due time. I like to do it separately. But I have many colleagues who say I do it together with both in the room, but I just make it clear, "Okay, let me hear from you. What have you noticed? All right. Now, let me hear from you." So, I get that chief complaint. And then, if I don't know the patient, I then find out their bio, because what I'm interested in is what was their peak occupation and educational attainment, where has this brain been at, so I get a sense of where we're at. So, I don't even talk about the chief complaint.

And then, I like to ask, "What's a typical day?" I think that question can be saved until later, but I'll just make the pitch that it's a very useful way to get a sense of where the person's at functionally, behaviorally and cognitively in a very non-threatening way because you're just saying, "What do you do all day?" But you get a lot of information because what if you find out, "Yeah, no, he's working at a law firm. Actually just recently, you know, was away for three weeks in France." You know, you've got an idea where the baseline is pretty high. You know what you're dealing with.

So, my appeal would be just get the baseline biographically to get a sense of where the brain was at and in the real world to get a sense of what's up with the brain. This is for a new patient visit with me. So, I'm like a primary care doctor who may know all those things, but never underestimate that those things may have changed since the last time you chatted about them when you were talking about blood pressure or whatnot.

But let's drill down now on what I would ask about in terms of the specifics. In interviewing the informant, I'll ask, "So, have you noticed any changes in Bob's memory? Would you say yes or no?" And if they say, "Yeah, I have." I say, "Okay. Well, does he sometimes, usually or always forget new information?" So, that gives me some sense of the severity. And then, in my brain, I'm trying to go, "Is this a memory, language, or attentional problem?" That's what I'm thinking. And the way I get at that is I say, "Does he ask repetitious questions, meaning ask you a question, you answer it, and then he asks it again, like 20 minutes later?" That's a memory problem. "Does he tell you the same story all over again?" That's also a memory problem. "Yeah, he tells me, 'Like, yeah, yesterday the grandkids were over and they ran after the dog and the dog...' An hour later, 'The grandkids were over and...'" You know, you're like, "Wait a minute, we've heard this story now twice." Also, memory problems, so repetitious questions, repetitious stories; troubles remembering the day of the week, not the date, but the day of the week, Monday, Tuesday, Wednesday,

very concerning, again, for problems with orientation/memory. So, already I'm getting repetitious questions, repetitious stories, more list-making, misplacing objects, and I literally just tick through these. If you listen to my history, this guy's asked the same thing 20 times, okay? That gets me pretty well into the memory area. And then, I want to pivot to other cognitive domains. But do you have any questions about any of that or any sort of thoughts?

Host: No, I just have a comment. You know, it's interesting and I wonder if many people grew up-- I grew up in a household with grandparents and they never went to the doctor. You know, as they got older, you know, I heard the same stories over and over again and we never even considered the fact that they might be developing dementia.

Jason Karlawish, MD: It's new episodic memories. It's not the story about the time I saw FDR or, you know, war stories or stories about stuff that's happened in the recent past. These are changes in what we call episodic memory. And episodic memory is just that, we watch episodes of TV and we remember them when we watch the next episode. We say, "Oh yeah, that's the character in Great, you know, who just did that the last episode, let's see what he's going to do in this episode." It's the episodic memory changes.

Host: Because it's the short-term memory that we're talking about being a problem, and the inability to remember that they already told you that a couple days ago.

Jason Karlawish, MD: That's correct. Because what we're getting at in Alzheimer's disease, one of its four presentations, is damage to the hippocampi and related temporal structures. And those structures encode the ability to learn new temporal and spatial information, things that happened yesterday, where they happened, who they happened with, and when they happened. And as that organ gets damaged or that region gets damaged within the brain, people struggle to remember exactly when things happen. And they may repeat them because they forgot that they told you this in the first place. So, that's drilling in on memory. And again, if any of those things flag, that's to be noted, and let's see what cognitive testing shows.

Language. "Have you noticed any change in your relative's conversational skills, like the way you and I are having a back and forth right now?" And they'll say, "Yeah, you know, he's a little less conversational." That's noted. That's signaling troubles with word-finding, word production. "Well, no, no, no, he's just as conversational." "What about trouble finding words?" And they all say, "Well, we all have trouble finding names." I say, "Well, no, but more like

nouns and stuff, like naming things. Like, do they pick up a pen and go, 'You know, the thingamajob, this thing, you know, this thing, that thing,'" that's suggesting troubles with language. "What about are their sentences organized and grammatical, like the sentence I'm telling you right now? Or are they getting a little more disorganized?" All these things are signals of language problems. If you're picking up a language problem, other than remembering names of proper names of people, that's probably a cause for referral because language problems alone are tough to work up because language is very difficult to assess.

So, we've got memory, we've got language, and then we're going to move into the domain of spatial function. "So, has he gotten lost around the house, trouble finding rooms?" "Nah, nah, he's fine." "Well, What about the neighborhood?" "Nah, neighborhood's good." "Well, what about outside the neighborhood?" "Yeah, actually, a couple times, like in Philly, he's kind of gotten turned around. I'm like, 'Wait a minute. You know, we've done this route five times, you know, 50,000 times.'" That's spatial problems, and that's to be noted. A pearl too, "Are the glasses working, or are we constantly getting new eyeglasses?" That's also a spatial problem, as opposed to an anterior chamber problem oftentimes. People are having difficulty with visual images. And again, if you sat in my exam room, you'd be like, "My god, he asks the same thing all the time."

So now, we've got visuospatial, now we're going to move to executive function. "And have you noticed any change in their decision-making?" "Well, what do you mean?" "Well, is she more differential to you?" "Yeah. Actually, you know, he used to be kind of a take-charge guy, and now he's a guy, 'You take care of it.'" "Been victim of any scams?" "Actually, yeah, I was kind of freaked out that he, you know, couldn't get off the phone. I'm like, 'Honey, hang it up, come on, you know?'" So, changes in decision-making, scams.

And then, I ask about mood? "How's your mood?" Focusing on depression and anxiety, two of the most common symptoms. Pearl, when people bring up what they think is depression, I'll say, "Well, tell me what you notice." Says, "Oh, he just sits there, doesn't do anything." That might be apathy, which is the lack of initiative, another very common symptom in neurodegenerative diseases, lack of initiative. It's basically the teenager won't get off the couch kind of thing, but it's now happening in later life.

And then finally, we've got mood down, I kind of do a run of a review of symptoms for some of the classic physical changes that you see in these diseases. But let me pause and see on all these cognitive questions any sort of questions historically.

Host: So, we have memory, language, spatial awareness, executive function and mood. I want to just ask you about mood because pseudodementia is an issue and you're always trying to figure out how much is it the primary cause or how much is it part of the whole syndrome?

Jason Karlawish, MD: Well, I would never call it pseudodementia. It's real. We do see people who come in where their dominant problem after you do an assessment is either an untreated anxiety or untreated depression. And you'll pick that up because when you start to ask about depression questions, they'll flag positive. "Are you basically satisfied with your life?" "No." "Do you feel hopeless?" "Yeah." You know, I use the geriatric depression scale. I find that a very efficient way to get through this.

For anxiety, it's, "Do you find yourself worrying about the same thing constantly? Do you find yourself waking up from sleep worrying?" That's another common anxiety symptom. Again, a pearl though, if you will, just to use that much overused term in medicine, oftentimes, at least by the time I see folks, these two problems coexist. I often see people who clearly have treatable or, I should say, you know needed-to-treat depression and anxiety and they clearly also have a cognitive problem. Again, if that's a struggle, that's a cause for a referral, but they often coexist. But again that reflects I'm a filter. By the time I'm seeing people, much of the depression anxiety has been identified and treated.

Host: Is the next stage for you to start doing standardized scoring systems like the Mini Mental Status Examination or MoCA, the Montreal Assessment? No?

Jason Karlawish, MD: No. We'll get to that. So with the patient, I also ask the patient, "So, have you noticed any trouble with your memory?" And it's very common, they'll say, "No, no, no." "Well, what about even a little bit, you know, not as sharp as it used to be?" And often, they'll finally break, and the break sounds, it sounds like I'm interrogating, but they'll sort of ease, "Well, yeah, you know, I do struggle, I find." "Okay, well tell me more."

Now, let me give you another pearl. If they say, "Oh, my memory, Dr. Williams, it is horrible." "Tell me about it." "Well, last week I went to the store and I bought seven apples and I put them next to the milk and I was checking out and I realized I didn't have the apples and I went back and I got them." So, they completely remembered this whole story. And so, they don't have a memory problem, they have an attentional problem or some other problem. And so when people tell you a vivid story of their very specific memory loss, they're probably telling you problems with attention. And then when they realize they

forgot something, they'll remember it vividly because they've now emotionally encoded this horrible event. I'm not saying I'm discounting their problem, I'm saying they're not telling you a memory problem.

So, people with true amnestic deficits will often say, "Well, yeah, it's not good, but I can't give you any examples, but it's not good," because they're struggling, it's almost a mind problem, which is, "I know I'm having trouble experiencing the world, but I don't have the ability any more to as clearly remember the experience to tell you about the experience." It's fascinating.

Host: And so, it's partly a language issue as well, because they can't really express what they're feeling in some ways, but they also can't remember the times that they had difficulty, right?

Jason Karlawish, MD: Correct. Exactly. I find the question, "Do you feel that you're not as sharp as you used to be?" is a very revealing one. Many will say, "Well, yeah" and I say, "Tell me more about it." And they'll start to really-- "I mean, the finances is just a nightmare. I cannot stand doing the finances anymore." So, they're exposing executive function, working memory problems, et cetera. "Do you notice trouble getting words out?" Patients who are showing aphasia will tell you, "Yeah. No, I struggle. I really am like, 'What? The thing, the what.' They'll tell you I'm struggling to find words." And also, assess their mood, obviously, which we have already kind of said, but, you know, assess their mood.

So, I'm getting that history from the informant. I'm getting that history from the patient. If you can only get it from the patient, that's okay. But I would ask them, "Is there someone else that we can talk to who knows you well, that you trust, so I can..." Now, granted, if you've identified clear untreated depression, and they're taking a bunch of Ativan that they got from wherever and, you know, you say, "Look, let's focus on that before we bring the family in," although you might want to bring the family in if they're chewing up a lot of Ativan. But if you're still sort of concerned based on what you've heard from the patient, I'd bring the informant in. And so, that's a separate visit. Just come on in and we'll bill that one-- I don't know how you bill anymore, we'll bill that one.

And then, you want to do a review of symptoms for some of the common symptoms that alert you to neurodegenerative diseases. So, seeing things that aren't there. "Do you ever notice like people or animals that might not be there?" And if they're having Lewy body disease, they'll often say like, "Well, yeah, every now and then I'll be like looking out, 'What's that out there?'" They're very vivid, very vivid visual hallucinations that they will admit to if you ask, so

visual hallucinations. "Has your walking gotten slow or unsteady?" Very non-specific, but again, in the neurodegenerative disease world, oftentimes helpful. "Have there been any falls?" Again, very non-specific, but helpful. "Any troubles with bladder control?" Again, very non-specific, but helpful because we do see NPH, normal pressure hydrocephalus, okay? Trouble swallowing, coughing while eating, and then vivid active dreaming. Now, usually I have to ask the bed partner, but they'll say, "Yeah, I mean, they'll be kicking and like, whoa, you know, where's this...?" That is very concerning for Lewy body disease when they have REM-based sleep disorder type problem. And I ask about snoring because sleep apnea can lead to chronic hypoxia and that can cause attentional problems. So, that's a checklist of kind of key things to ask in that list. So, everything we've done so far is history. I haven't done any cognitive testing yet. Do you want to do some?

Host: Let's do some cognitive testing. Yeah, we'll get back to the gait in a bit. Well, let me just say this real quick, you know, our friend and colleague, Josh Uy, who is the Geriatric Fellowship Director and someone I've had the pleasure of getting to know well, did a podcast for Curbsiders, which I'd encourage everybody to listen to. We make no money off this podcast. We have no problems referring to other podcasts. But, you know, Josh was talking about gait and whether people are fast or slow, and we're going to get into the subtypes, but you highlighted that a little bit. He can often tell as people walk in the room, you know, if you've gotten past the point where you know they have a problem, you're starting to subtype in your head based on how they're moving.

Jason Karlawish, MD: So, gait for me, it's the magnetic gait of NPH that I'm looking for, which is the feet kind of notch. They just kind of magnetically move across the floor as though they lift, but they don't quite lift and move forward. That is the classic NPH gait. And then, I'm looking for a Parkinsonian gait, which are some degree of short steps. The other one is the turn. So, it's all very well when you watch them walk. But then, it's, "Okay, go down the hall. Okay, turn around." I don't say like go down ten steps and turn because they're like, "All right, one, two, three," they do it perfect, because they're so primed. I give them, "All right, turn around." And then, I want to see do they do like the, you know, 16 steps go around, very concerning for central Parkinsonism, as well as other causes too, you know, inner ear, et cetera, or just deconditioning particularly in the oldest old. I mean, you know, they're living off of like three little muscles to walk now. So, those are the things I look for on gait.

Host: So, Jason, I want to ask you more about NPH, because we're not going to talk about this much more, but I want to drill down on this because this is a diagnosis that comes up a lot and I want to ask you one specific thing, and

you've alluded to it, and that is it's not referred to in the literature as gait ataxia, it's gait apraxia, and can you make a distinction between those two and what you're seeing again? Can you repeat what you said before, I guess, in terms of what gives you the clue with NPH?

Jason Karlawish, MD: I think we can overthink this. I think the gait of NPH-- first of all, I see NPH patients where the gait is pretty unremarkable, but the cognitive phenotype is pretty compelling. And really, it comes down to the cognitive phenotype really looks like NPH. The imaging is very provocative, and I would not wait for gait disorder to sort of send them off to a neurosurgeon or to a colleague for a large volume tap.

Host: So, it's the cognitive impairment and maybe urinary incontinence symptoms that are cluing you in that something's happening.

Jason Karlawish, MD: At least two of the three of the triad. The cognitive impairment is typically a dysexecutive picture. They're very aware of it. And what they'll describe is, "Yeah, I've got memory trouble." But the more you probe it, it's troubles encoding, paying attention, the spouse will complain, you know, "I have to tell him three things over again, especially if it's multi-step commands." That's a very classic story for NPH.

Host: So, the next step is to do an MMSE or a MOCA. These are scoring systems. They take five or ten minutes to do. They're scored very similarly. What do you prefer, Jason? Which do you use? What are the advantages and disadvantages of each?

Jason Karlawish, MD: I'm a Mini Mental guy because I was raised on it. Having said that, I look at the Mini Mental but I do my another set of testing, which I hope we can talk about as well. I think there's a value though to the Mini Mental or the MOCA, because it gives you a score, bear with me, that you can follow over time and it gives you some hint about the overall severity of a person's problem. So, it does provide a coherent language to talk about cognition.

Having said that though, I think one of the biggest problems is the score, because people will look at the score and say, "Oh, well, he had a 27 and, you know, he's a high school grad and he's 80. So, you know, that's probably normal, right?" And my answer is, "I don't know, because I need to look closer at where those points came from that got him to 27." So, I can take two People who have a Mini Mental of 27 and one of them will be like, "I don't know, I'll need more information," and the other I'll say, "That's concerning." What's the

difference? First person got 27 because they didn't know the county. Who knows the counties? You know, like, I grew up in New Jersey, everyone knows the counties. No one knows counties in Pennsylvania. They don't know the county and then, in the no ifs, ands, or buts, they said no if, and or but. And when they were asked to take the paper with the right hand, they took it with the left hand or whatever. I don't know what that means. But if they got a 27 because they lost all three on the memory item, that's concerning. So, same score, but different causes, if you will, to get to that same score, very different interpretations.

Now, the advantage of the MoCA is it's a harder test. It's got the clock draw. It's got a fluency task, et cetera, whereas the Mini Mental is heavily weighted towards orientation, a little bit of memory, et cetera. The pearl I would give is pick a test, get to know it. But by getting to know it, really look at the score, the sub scores, where did they make their errors, and to what degree do those errors match up with what you've heard in history to say, "Oh yeah, you're right, there it is, they spelled world backwards completely wrong," and there are all these attentional problems. So, that helps to support what's going on.

Having said that, I think one of the problems with the Mini Mental especially is you can do pretty well on it and clearly have cognitive impairment, because it's not a very hard test. The MoCA is a little harder. So, it's a bit more sensitive to pick up impairment. So, I think if I had to pick one, I'd do the MoCA. It does take a bit of time, but it, again, can be worth the effort to really, if you drill down in the subscores, get a sense of what the nature of their impairments is.

Host: Will MoCA pick up patients earlier in the course than the Mini Mental?

Jason Karlawish, MD: Arguably, it will. Again, it's the subscores because it has the clock draw, it has the fluency task, stuff that's just not in the Mini Mental. All these tests are is just a gamish of little subtests put together into a total score. There's no magic or mystery to these tests. They're just, "Give me a 10-item orientation, a 3-item recall, a 5-item attentional task, et cetera. Do all those things and add up the points," whereas the MoCA has different items. Again, I keep on emphasizing the clock draw and the fluency task. It also asks you to remember and recall more words. So, it's just a harder memory test, it has more attention and executive function measures, which again are just going to give you more opportunities to pick up impairment compared to the limited stuff that the Mini Mental measures, which is more oriented around orientation and memory, quite frankly.

Host: So, I guess, you know, based on those scores and your overall assessment, I think of this as staging, I don't think that's the right word, but where are they at in the process?

Jason Karlawish, MD: So, in the end, after you get all this data, history, testing, the question you have to ask yourself is, is there cognitive impairment or not? Meaning the person's performance and cognition suggests that it is no longer "normal", that there are changes in cognition that are causing either inefficiencies or disabilities in daily life. And those two words that I used are really important, inefficiencies or disabilities. And so, let me drill down on them.

When I say someone has inefficiencies in their daily life caused by cognitive impairment, what I'm saying is, they still get things done, they still do their finances, they still shop, they still cook, they still travel from one place to the other, but it takes them longer. They make mistakes and they catch them, they're inefficient. The other term for people with inefficiencies in daily life is mild cognitive impairment. That's what mild cognitive impairment is. Mild cognitive impairment is someone who has cognitive changes that are causing inefficiencies in daily life, just what I described.

Dementia, I gave it away, the disabilities. If someone has cognitive impairment that's causing disabilities, they're describing dementia. In other words, "I am having trouble cooking. You know, I have burned pots on the stove. I have screwed up a recipe. You know, Thanksgiving dinner went from being the much anticipated annual event to being kind of embarrassing story or missteps." That's a classic history we get around the holiday, around by January, the screwed-up Thanksgiving and/or Christmas meal, highly complex executive function activity.

Disability is dementia. So when I say someone has dementia, I'm simply saying they have cognitive impairment that's causing disabilities. I used that phrase, that term disability. I recognize many hear that and go, "Wait a minute, physical disability? Like you can't climb the stairs?" No, it's disability caused by cognitive problem. So, mild cognitive impairment, inefficiencies in daily life, dementia, disability. Now, where one ends and the other begins is a judgment call, how much impairment constitutes disability versus MCI. Again, we could perseverate about it. The bottom line is, "I'm picking up cognitive impairment and it's causing troubles in daily life."

Final point in this discourse is I've been talking about day to day function. And so, one other key point in history to get is to run through the instrumental

activities of daily living, meaning managing money, medications, transportation, technology. And I like that focus, money, meds, transportation, technology, because those are very cognitively intensive activities. And if someone's having inefficiencies or impairments in them, they are essentially telling you, "I'm having cognitive problems." Lost while driving, meals not prepared the way they used to be. Still makes them, but not as sophisticated as they used to be or there's some errors here, et cetera. Checkbooks no longer balanced, bills have been paid twice or not paid at all, medication prescriptions are kind of in disarray, et cetera. Those are pearls that there are cognitive changes going on. With technology, "Yeah, you know, okay on the smartphone, but kind of the texts are getting a little more wacky, et cetera. Got him a new iPad and never mind, we could not learn that iPad. It's just the new iPad was a torture," those are all clues. They're very real world, and I'm on a ramble, but I think this is important. They're also telling you as a clinician the kind of care the person's going to need from their caregiver. So long winded discourse, we started talking about the Mini Mental and the MoCA, but, you know, it led to, "Is there cognitive impairment? If there is, are we talking MCI and inefficiencies or dementia and disability?" And the way you arrive at that is you assess day to day function. You ask about managing money, meds, technology and transportation.

Host: That's very helpful. So, you have a patient with cognitive impairment, you maybe even say that they have dementia because you're seeing some real disability, and then you're now subtyping into the various types. Can we go over for our audience the various subtypes of dementia? We'll just start with Alzheimer's disease because that's the most common. This is going to be 60-70% of patients, I understand.

Jason Karlawish, MD: Maybe. Yeah, the more we know, the more things get complicated. So, once upon a time, but not too long ago, the only way you could be diagnosed with Alzheimer's disease is if you had dementia, because Alzheimer's was a clinical diagnosis. In other words, is there dementia? Yes. Then, what's the cause? The discovery, the description of mild cognitive impairment began to upend that, because mild cognitive impairment was simply describing people with the earliest signs and symptoms of Alzheimer's disease, they just haven't yet progressed to dementia.

Now, amazingly not everyone with MCI has Alzheimer's. That's right. Not everyone with dementia has Alzheimer's. So, we're sort of dancing around the most common question asked whenever you give a talk on this topic, which is what's the difference between Alzheimer's disease and dementia? And the difference is dementia simply describes an individual who has developed, an

adult, who has developed disabling cognitive impairments that are progressive. They've over time changed as opposed to a static picture. That's dementia.

Dementia is caused by many different diseases. The most common, maybe, is Alzheimer's. But other diseases cause dementia. Lewy body disease, that's what Robin Williams had. The comic actor, Robin Williams, had Lewy body disease. Frontotemporal lobar disease, that's what Bruce Willis has. So, very different diseases, but they all are causing dementia. So, Alzheimer's, seen often on autopsy and other studies, but often in coexistence with these other pathologies.

I would be remiss, and we should sort of talk about it and bin it and make sure we focus on it, to not talk about a recently discovered and very common cause of dementia in the 80-plus-year-olds called LATE. In the past, we called them Alzheimer's, but it is a distinct and separate disease. And it is known by this very horrible acronym, LATE, L-A-T-E, which stands for limbic-associated TDP encephalopathy. TDP is a protein that does something with DNA and it misfolds or otherwise gets dysfunctional, forms these pathologic marker granules and leads to this very particular cause of dementia, which once upon a time we said was Alzheimer's. And we should definitely talk more about that.

But I've been on a ramble. Dementia, syndromic description, like heart failure, pneumonia. Alzheimer's, common cause of dementia, like mitral valve disease or pneumococcal pneumonia or COVID, but also Lewy body, et cetera. That's the sort of overview of the distinctions between dementia and these neurodegenerative diseases like Alzheimer's and LATE and Lewy body disease and FTLD.

Host: I wanted to ask you about LATE, because, I had a patient I sent to one of your colleagues who came back, read the note, and he said that he thinks he has LATE. And I said, "I have no idea what that is." So, I looked it up. So, my understanding of these folks is that they have a more benign prognosis, and it manifests much in the memory domain.

Jason Karlawish, MD: Yes and no. Pure LATE, meaning, and I hate these words pure when we describe diseases, but LATE and LATE alone, the dominant regions of the brain affected are hippocampal structures and parahippocampal structures, particularly amygdala and some prefrontal cortex. So, the classic story of a person who only has TDP-43 disease is a notable amnesia and some changes in social cognition, they're more likely to be scammed, make some misjudgments around reading other people's emotions, and have some trouble with decision-making, problem-solving, multitasking, like managing the finances.

The natural history of LATE is one that is quite slow. Families will often say, "This has been going on for a number of years. It's only gotten worse lately." No pun intended. Oftentimes though, LATE coexists with Alzheimer's pathology. And in those patients, it often progresses faster. Just because it progresses slowly is no reason to underestimate the severity of it. In fact, it is a uniquely distinct disease requiring a uniquely distinct approach to its care. The patients have changes in their emotional processing and executive function and oftentimes are victims of scams and make mistakes in finances and other higher level functions. They have well-preserved semantic memory. Semantic memory is a term that describes our knowledge of facts and language distinct from episodic memory.

Episodic memory is learning new information and retaining it, stories, events, things like that. Semantic memory is our ability to learn facts and remember it. Everyone who's listening to this podcast is engaging in both learning some episodic memory. You know, "Kendal and Jason had this fascinating conversation and it was kind of fun. That's an episode in your podcast." Semantic memory is all the facts that we're shoving into people's heads in this cause. People with LATE have well-preserved semantic memory. And so, they'll be able to talk to you and like, "That's dad, you know, talking about his engineering work and, et cetera, helping the grandkids out with their homework. But then when we had dad make dinner, it was a total disaster," or "Dad's fine in his house. But when we have him over, like to the cousin's place, he was kind of confused," because dad knows his house by heart. But when he's in the cousin's place, he has to learn where everything is because it's a new environment. And the dense amnesia and LATE hinders their ability to learn new environments.

We're only beginning to see how this so translates into why these older adults and the typical person with LATE is over 80 years of age. We're beginning to understand how this unique presentation of these cognitive problems really affects their ability to live their daily life. These are the kind of people who, if you move them to a new environment, will oftentimes crash, because they'll be like, "Wait a minute, where is everything?" Because when you walk into a room, you go, "Okay, the table's over there, that's over there. Okay, great." You learn it, you remember it, et cetera. They struggle with that. And so, it's really important to distinguish this disease from Alzheimer's disease, because patients with comparative severities of cognitive impairment otherwise who have Alzheimer's, they still have a relative reasonable preservation of their memory compared to people with LATE. So, it's been a bit of a ramble, but I guess the message to the listeners is get to know LATE because it is probably the most common cause of dementia in the 80-plus-year-olds, which is one of the fastest growing populations.

I will conclude with it has a very signature look on MRI that my colleague David Wolk and others here at Penn have been the leaders in this research. It's a very signature look on MRI, a very profound atrophy of the hippocampi and parahippocampal medial structures with actually a pretty good preservation of cortical architecture. And I've got a couple patients where it's just like textbook to look at that. And in days of old, we call that Alzheimer's. "Oh my gosh, look at that profound medial temporal atrophy. Amnestic disorder, that's Alzheimer's." And we were wrong. We were wrong.

Host: And it doesn't progress in the same way, at least.

Jason Karlawish, MD: You'll see this progressive deficits in memory and more subtle deficits in executive function and emotional processing. But it does progress at a slower rate. It does. But again, if you move that person and disrupt their environment, they go into a cataclysm of-- it's fascinating. I have a couple patients where this happened. Once you can't learn where you are, they get anxious and stressed. And if you get anxious and stressed, you really can't learn where you are. And to put it bluntly, they almost fall apart. I have one patient where the family actually restored the patient back to her original environment. And they said it was a miracle. Within hours, she was back to the way she always was.

Host: So I want to ask you about-- before we get to Alzheimer's, and I really want to dig in on Alzheimer's, but I just want to go through these other dementia diagnoses that we see. You talked about Lewy body disease, mentioned that Robin Williams had that. It has some very specific features. Can you just take us through that?

Jason Karlawish, MD: Yeah. So, good days and bad days, waxing and waning attention, cognitive ability like family says, "Well, you know, some days he's really good." And then, other days it's like, "What's going on here?" Waxing and waning attention, vivid dreams, REM-based sleep disorder type symptoms; talking, thrashing, kicking, particularly the physical motion during dream is a notable symptom. Constipation, autonomic dysfunction, the Lewy bodies that are in the brain, we see them also in the intestinal tract. And we believe that they're affecting function in the intestine as well. So, patients will often have complaints of constipation. Visual hallucinations, they're very aware of them. They often know they're not real or they'll be sort of befuddled, like, "That's not a cat, but God, that looks like a cat over there." Often it's well-formed animals and humans and/or distortions in known physical objects, like, "Wow, the chandelier is melting. Look at that." It's pretty wild actually.

That cluster of symptoms and then, on cognitive testing, notable difficulties with executive function often, less prominent with memory, but memory dysfunction and anxiety. Many of the patients are anxious. Most of them are very aware of their symptoms, very aware to one degree or the other and will be anxious. I'm not saying that's causal, but it's very interesting as I look back on some patients who I saw with very early subtle presentations of dysexecutive problems that didn't really fit the Alzheimer's phenotype of amnesia. They were too young for LATE, they were anxious and, over time, they presented as Lewy body disease. I have several patients started out with inefficiencies in daily life, executive dysfunction, very anxious and, a couple years later, started to show visual hallucinations, REM-based sleep disorder and more obvious cognitive impairments befitting of Lewy body disease.

Host: Is there some overlap with Parkinson's?

Jason Karlawish, MD: Yes. In fact, the Parkinson's and Lewy body fields are in a pitched battle of redefinition. So, the pathology that causes a Lewy body disease was discovered here at Penn. It's syanucleinopathy. Alpha-synuclein is a protein in the brain. It misfolds, that's what the Lewy body is, a misfolded alpha-synuclein. And it's seen in Parkinson's and it's seen in, Lewy body disease. It just presents in different regions of the brain. And the two fields are beginning to say, "If we want to define the diseases biologically, which is where most brain diseases are trying to go, define it biologically, so why don't we just call them alpha-synucleinopathies." And they're debating over what the terms would be. Should we have the subtype of the Parkinsonian versus cortical presentation? This is a very fast-moving area. And actually, this month of October of 2023, there should be some papers released proposing redefinitions of these diseases on the basis of the pathologies. You can detect the pathologies using spinal fluid analyses. There's also a skin biopsy technique. One of the big events in neurodegenerative diseases more generally is the ability to measure the pathologies with either scans or now with blood tests and/or spinal fluid tests. Although spinal fluid has always been available, just never had a business model, but there are blood tests that are emerging.

So, yes, the bottom line is there's an overlap in the pathology between Parkinson's and Lewy body. If you've got a patient who's 65 plus with Parkinson's, there is decent odds that they have cognitive impairment, typically an executive function. The families will tell it to you, oftentimes with great embarrassment. Because the person, it's always kind of a movement thing, "It's just the movement." And then, they start noticing, "Oh, you know, he's kind of having trouble making decisions." They often present with a dysexecutive function. And really, this is the overlap and convergence of the diseases.

Host: I want to get to this later, this issue of diagnosis and how you are starting to get to the point where you're going to be putting people in various subtypes or disease categories, not based on clinical features, but some of these imaging features and what they're showing in LP and so forth. I want to talk about frontotemporal dementia because it is an earlier-in-life disease and has very characteristic features.

Jason Karlawish, MD: The typical story of a patient with FTD that I see, of the behavior variant, has had a history of a misdiagnosed psychiatric illness. The classic story is diagnosed with late-onset bipolar disease. He was fine until he was 61, and then things changed and he was diagnosed with bipolar disease. And oftentimes that is a presentation actually of behavioral variant FTD, notable changes in personality and social cognition.

My general pearl, if you're suspecting behavioral variant FTD, that needs a referral. I would be very reluctant to make that diagnosis without a subsequent workup. Because they do fine on cognitive testing, many of the patients. In fact, they'll memorize the tests. They'll come in and tell you the Mini Mental. Meanwhile, they're, gosh, you know, binge eating, looking at pornography in public settings, hoarding empty Starbucks coffee cups, only eight ounces, "I only collect the eight ounce cups," you know, a variety of changes in behavior, social cognition along lines of obsessions, compulsions, disinhibitions, and oftentimes devastating loss of empathy and emotional recognition. That's the typical behavior variant FTD story. And again, if you're suspecting that, that needs a referral, I think.

There's other variants of the diseases that present with what's called a semantic variant of FTD, where the problem is production of language. And again, this is the kind of patient where the family will say that there's something wrong with his memory, but the more you test memory, it's like, "I'm not picking up memory problems." Again, they're probably suggesting a language problem, which again is the kind of patient for a referral, and a workup on that. The typical ages of onset are in the 60s.

Now, to make things even more wild, FTD is caused by a couple of different pathologies. One of which is TDP-43, which is the same pathology that causes LATE, but it's in different regions of the brain. Now, this has caused a lighter firefight between the FTD community and the LATE community because, you know, given the pathology who owns the disease, it becomes a fascinating issue. So, you've got these 60-year-olds with marked behavioral changes who have TFP-43 disease. And you've got these 83-year-olds with mild behavior changes, dense amnesia, who also have TFP-43. The difference is where in the

brain these problems are happening. You know, literally, the location of the lesions.

Host: Jason, this is great stuff. I can see now that we're going to have to have you back for a second part. Are you okay with that?

Jason Karlawish, MD: Yeah, sure.

Host: That's great. I also want to ask you about vascular dementia, otherwise known as multi-infarct dementia. I think this is usually a little more obvious because you have imaging that's very suggestive, but can you tell us what you think about that?

Jason Karlawish, MD: Yeah. Vascular dementia, it's a bit like trends in, you know, art and culture. Namely, we can see it on MRI. But beyond the subjective assessment of, "Gee, that looks like vascular disease," we really don't have any further way to quantitate it. It's very frustrating in that sense. So, what am I trying to get at?

First of all, the typical story of vascular dementia is amnesia, executive dysfunction. In other words, they just have a hard time learning things and, therefore, remembering. And even if they learned it, they struggle to remember, but they just don't perform like the classic amnestic person who learns it. Like the cognitive testing I do, nevermind Mini Mental, I drill an address into the person's head. They remember this address and I say, "Now, remember that. I'll ask it to you later." A person with Alzheimer's temporal limbic amnestic form will not remember it or remember only a little bit. A vascular dementia person will also struggle, but then get little bits of it. And if you give them clues like, "Was his name John, Joe, or Jim?" They'll go, "Oh, it was Joe." And you're like, "Yeah, it was Joe." So anyway, it's a particular presentation that looks a lot like amnestic Alzheimer's, but then they're not as bad. But anyway, you image them and they're loaded with white matter disease.

Now, you say, "Okay, Jason, how much is loaded?" And that's where I fall apart. Because literally, we look at the MRIs and we go, "Hmm, that looks like a lot of vascular disease." And we're like, "Okay, I guess it does." It does a little bit of a looping effect, like given what you've told me, I'll call that amount of white matter disease vascular disease. But if you said to me, "This guy's totally cognitively normal. Here's his MRI," I'd say, "I guess he's very resilient." And it's kind of the dirty secret in the field. Nonetheless, and I think the issue is it's not just how much white matter disease, it's where it's seen in the brain. And that we're not very good at yet, quantitating how much and the regions within

the brain that is seen. But it is white matter disease, patchy white matter disease seen on the FLAIR images of MRI. By the way, I don't order CAT scans anymore unless the person can't get an MRI. By the way, MRI is the test of choice for evaluating brain architecture and for looking for vascular disease.

Host: You probably have a lot of co-existent vascular disease in all patients just because of how common it is generally in the population.

Jason Karlawish, MD: Yeah, I would say like the most common combination is Lewy body with vascular or Alzheimer's with vascular. That's the most common cause if I had to put the bundle together of thinking through the last hundred patients.

Host: I can't help but ask you this question because it comes up a lot in primary care, and I asked the preventive cardiologists the same question, and they had an answer. But you know, we always talking with patients about statins. So, I give my spiel. I say, you know, the second most common cause of dementia is vascular dementia. And so, statins are going to reduce the risk of that. But do you have any concerns about cognitive impairment with statins?

Jason Karlawish, MD: The answer is no, but I know there are people who are adamant, like "I got on a statin. I never thought clear again." I was part of a cohort, large database case control study of 5,000 people on statins and 50,000 not. And I couldn't make heads or tails of what we found, except I think you just take an empirical approach to them. They complain of cognition, "Well, let's stop it. Let's try it again. Try a different one." I don't find that story holds up much.

What does hold up is untreated hypertension. We have good data that that increases your risk of dementia and we have reasonable data that treating hypertension lowers the risk of dementia. It's not so compelling with statins in terms of the data from randomized trials. Years and years and years ago, we did a clinical trial, NIH did, of statins for people with Alzheimer's. The thing is that was in the days before we had biomarker confirmation, whether they had Alzheimer's, which my guess meant that 30% of the people didn't have Alzheimer's, it wasn't a study powered or designed to look at vascular disease. So, I think it's one of those studies where we don't know what to conclude from it.

So bottom line, I think taking a statin for the purposes of heart health and brain health makes sense. People who complain of the side effects related to cognition, I think that's a very intersubjective issue to be dealt with. You know,

"Let's take it every other day," "Let's switch," et cetera, because the benefits to heart health are so compelling, let alone brain health.

Host: This is a great discussion, very helpful. There's more to go. We really want to understand Alzheimer's and some of the basic science, if you will, that's going on around here, which is obviously leading to new therapies and new imaging techniques and so forth. So, we're going to bring you back for part two, and we'll do that in the next couple weeks. These will come out sequentially.

This is great discussion, Jason. You're really helping us out a lot. So for this part, let's end the podcast now and thank the audience for joining the Penn Primary Care Podcast.

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