Zoom in on **Dementia & Alzheimer's**

When Dementia Strikes in Middle Age: The Challenges of Early-Onset Alzheimer's Disease
Thursday, April 18, 2024 | 1 p.m. EDT
Transcript of Zoom with Gil Rabinovici, MD, Distinguished Professor and Director, UCSF Alzheimer's Disease Research Center

NANCY LYNN: Good morning, good afternoon, and welcome to Zoom in on Dementia and Alzheimer's, which is being brought to you by the Alzheimer's Disease Research program at BrightFocus Foundation and is supported in part by educational funding from Biogen, Lilly, and Genentech. And we're delighted to welcome you this morning to learn a little bit more about the challenges of early onset Alzheimer's disease. We received a lot of questions, nearly 100 questions today on this, and so I'm going to try to get to everybody's questions.

Also, a lot of the questions we received, and we receive each week, are not on the week's topic. So I just want to remind everybody, we've done 10 episodes previously on different aspects of medications, treatments, information about Alzheimer's and dementias, from basic science through behavior. So if we aren't answering a question today on the topic that you asked about, remember, you can access these for free on all of these topics. You can just visit brightfocus.org/zoomin. And also, if you have topics that we haven't covered that you're extremely interested in, please put that in the chat box as well.

And now I'm going to introduce our expert speaker for today. Dr. Gil Rabinovici is the Edward Fein and Pearl Landreth Distinguished Professor in Memory and Aging at the University of California San Francisco. And you can tell who that speaker is because he has a San Francisco background on his screen. Dr. Rabinovici is a neurologist who cares for patients with memory problems and other brain issues. And in research, Dr. Rabinovici investigates how to use advanced brain imaging techniques to improve the accuracy of dementia diagnoses, and to better understand the biology of neurodegenerative diseases, with the overarching goal of accelerating drug development. He serves as director of the UCSF Alzheimer's Disease Research Center. And as study chair for two large multicenter studies, examining how PET amyloid scanning, a brain imaging technique, can improve the diagnosis and treatment of cognitive disorders causing memory changes. He is also a principal investigator on several national projects to learn more about Alzheimer's disease and related disorders, including a study that is currently active called the Longitudinal Early Onset Alzheimer's Disease Study, that's known as LEADS. Welcome, Dr. Rabinovici, thrilled to have you here to talk about early onset Alzheimer's disease.

I'm going to jump right in. And I'm sorry, I forgot to introduce myself. I'm Nancy Lynn, Senior Vice President of Strategic Partnerships at BrightFocus. Welcome, doctor.

DR. GIL RABINOVICI: Thank you so much for the opportunity and the very kind introduction, Nancy.

NANCY LYNN: My pleasure. Let's start with a question from Amy in Stevenson Ranch, California. What are the main differences between early onset Alzheimer's disease and Alzheimer's after age 65? And several people asked, how do you define middle age. So let me let you start with the differences.

DR. GIL RABINOVICI: Great. Thanks for the question. So there's kind of an arbitrary cutoff that's used a lot in the scientific literature, which is that if people develop symptoms of Alzheimer's disease before age 65, that is considered early onset. And if people develop them after age 65, that is considered, quote, unquote, late onset Alzheimer's. The rationale for that

threshold is not scientific. It's actually based on the mandatory retirement age in Germany in the 1980s, when the scientific research started. And so some of the initial studies out of Germany kind of arbitrarily said, if people develop symptoms before their age of retirement, that's early onset. After, that's late onset. So that's the history. There's no biology or science, it's completely arbitrary.

That said, there are some differences in how the disease presents when people develop it at a younger age. And so when people develop symptoms of Alzheimer's later in life, in their '70s, '80s, '90s, most commonly people develop memory problems early on. Forgetting conversations, having difficulty driving to familiar places, misplacing objects. Those are the common symptoms early on in people who develop the disease later in life.

Now, many people who develop early onset Alzheimer's, also present with memory problems. However, in addition to, or even more than memory, some patients have difficulty with other aspects of brain function. Some patients have difficulty with their language functioning. They have difficulty thinking of words, understanding what they're reading. This presents not with memory problems, but really with difficulty communicating and speaking. Other patients present with vision problems. They have trouble judging spatial distances, spatial relationships, locating objects, driving at night. And a lot of times, people initially think this is a problem with the eye, not the brain. They go and get their vision tested by an ophthalmologist or an optometrist. But eventually, someone figures out that this is actually a brain problem and it is often due to Alzheimer's disease. These syndromes are called posterior cortical atrophy, or PCA, is the visual presentation of Alzheimer's. And progressive aphasia means a language disorder is the language presentation. And then sometimes people have trouble not with their memory, but with what we call their executive function. So planning, concentrating, multitasking, making difficult decisions, some changes in their judgment. And that can be an early manifestation of Alzheimer's.

And so there's a lot more diversity in the types of symptoms that people experience early on when they develop the disease at a young age. And

the reason is, that Alzheimer's can affect different parts of the brain in different people. And that seems to be particularly true when people develop symptoms at a young age of onset.

NANCY LYNN: It's interesting. Several people did ask about PCA, so I'm glad you mentioned it. And we may be able to talk a little bit more about that as we go on. So Phil, from Copley, Ohio, had asked, what are the very early behaviors that would be noticed? And you mentioned several of them. But it seems like there's a wider array of symptoms. And so one of the real issues is about how to get a diagnosis. And I imagine it sounds like it's even a little more complex when you are dealing with early onset. And these were two questions that really hit me Elaine from Stockton, California: How do you get a doctor to take you seriously when you say you have memory problems, and you're only 59? Susan from Huntsville, Alabama said, it took me five years to finally get the diagnosis of early onset diagnosis, Alzheimer's disease, for my husband at age 55. Why does it take so long to get a diagnosis when all the research says to get diagnosed early?

DR. GIL RABINOVICI: Yeah, it's an excellent question. If I could, I wanted to take a step back and talk about the behaviors, and then I can talk a little bit about the diagnostic odyssey, I call it, that faces a lot of patients and families, especially when they present at a young age. So when people develop cognitive decline at a young age, one early question as a doctor is, it Alzheimer's or is it a different disease? And the two most common causes of early onset dementia are either Alzheimer's or a disease called frontotemporal dementia, or FTD. And I saw that you had a previous guest talk about this in the setting of Bruce Willis and his public struggle with FTD. FTD presents with changes in behavior and personality. People start to become disinhibited, they make inappropriate comments, they behave sometimes inappropriately in social situations. They lose their drive. They become apathetic and kind of indifferent about things they used to care a lot about. There can be loss of empathy or caring for other people. There can be changes in eating behaviors. And so when people present at a young age with changes in behavior and personality, it's usually not Alzheimer's. It usually is a different disease called FTD. And the treatment is very different for FTD than for Alzheimer's. And so one

of the earliest questions when I, as a neurologist, am evaluating a patient who's presenting with an early onset dementia, is it Alzheimer's, that typically presents, as we discussed, with cognitive changes, memory, language, spatial abilities, or is it FTD, typically with changes in behavior and personality? And so that's a very important distinction. Alzheimer's tends to affect the back of the brain, parts of the brain that affect vision, memory, certain elements of language. FTD tends to affect the front of the brain, parts of the brain that are very important for behavior, emotional function. Both really can present with language problems. So just wanted to make that distinction between FTD and Alzheimer's.

In terms of diagnosis, this is incredibly challenging for a lot of reasons. First of all, when people are developing memory loss in their 50s, doctors usually don't think about Alzheimer's disease. The stereotypical vision of Alzheimer's is that it presents in older people. And so a lot of times, doctors are considering other things that are very common for people in their 50s, like depression, sleep disorder, anxiety, just a general burnout and being overwhelmed. I'm in my early 50s, so I'm speaking here from personal experience. But people don't actually often think about Alzheimer's in that context.

The other challenge is these unusual symptoms. So if it's not memory loss, but if people are describing that they have difficulty seeing, a lot of times, doctors are not going to think about a brain problem. They're going to think about an eye problem. Sometimes if people have difficulty with their language or communication, people think more about strokes than they do about Alzheimer's. And so it's both the young onset and the atypical symptoms that are a real challenge to I think getting the right diagnosis.

And then the other aspect to all of this is, that it takes a lot of time to really get an accurate diagnosis. I know that you've had previous panelists speak about how we make a diagnosis. A lot of it is focused on getting a very detailed history from the patient, and often from a spouse or some other family member who interacts with them closely, doing a careful medical history, sometimes doing some really formal memory testing or cognitive testing. When people are coming to their primary care providers, these are usually very busy practices. And doctors don't necessarily have the

time to take that history and do all the assessments that are necessary to be confident in coming up with this diagnosis. And so one of the really important directions in research, is how to come up with efficient ways of getting all of that information and coming up with a diagnosis in a less time-intensive process. And I know you're going to have a future panelist talk about AI, or artificial intelligence, and the idea that maybe we can utilize a lot of data streams to help people reach a diagnosis early on.

A major breakthrough is the development of what we call biological markers or biomarkers, tests that doctors can order that can confidently tell us if they have Alzheimer's changes in the brain. Alzheimer's is defined by the accumulation of two toxic brain proteins called plaques and tangles, amyloid plaques and tau tangles. And we have advanced brain imaging tests, spinal fluid tests, and now blood tests, that can actually tell us with very high accuracy whether people have those changes. And I think that will really help doctors in screening for and making an accurate diagnosis of Alzheimer's, to give them the diagnostic tools that they really need to confidently determine if someone's memory loss is due to Alzheimer's or whether it's due to some other factors, like a sleep disorder, a mood disorder, or something else.

NANCY LYNN: So there's a screening when you go into the doctor and say I have, and then there's a diagnosis, which is further down the line. Can you go talk a little bit about the different tests that are done, or should be done, let's say, along the progression? And are there different tests for people with early onset than late onset?

DR. GIL RABINOVICI: Yeah, really important question. So first of all, the most important thing is, actually taking a careful history. Understanding what were the earliest symptoms that the patient experienced. And it's really important to talk to the patient and to talk to another care partner, a spouse, an adult child, or someone else who interacts with the patient frequently. And the reason is, that sometimes when people are experiencing memory loss, they're less aware of it than their spouse might be or the family. They're forgetting that they're forgetting, if you will. And so getting that history both from the patient and from someone else, is really the key often to a diagnosis.

And when we hear this constellation of symptoms, you know, I started

having trouble driving at night. And then I was trying to read, and I couldn't really keep my eyes focused on the right line in the book. And we recognize these constellations of symptoms and say, aha, these sound like weird symptoms, but we recognize them as a constellation that suggests, for example, PCA, this visual variant of Alzheimer's. It is helpful to do some formal testing. And so if you only test someone's memory, you could entirely miss early onset Alzheimer's, if their flavor of Alzheimer's is more around visual symptoms or language symptoms. And so what we do in our clinic, we do a brief battery. It takes about an hour, but we test these different, what we call, domains of cognition. Episodic memory, the ability to learn and retain new information. Executive function. So, the ability to process information quickly, think flexibly, multitask. Visuospatial function. So, the ability to appreciate spatial relationships, copy designs, recognize things that you see visually. Language testing, the ability to name different objects, produce correct language, grammar, comprehend language. We do a battery of tests. It's pretty brief, but we're testing all of these domains, to make sure that we can detect early changes in any of them that could signify early changes of Alzheimer's disease.

NANCY LYNN: Two quick questions, one from 321Go on YouTube. What procedures determine the presence of plaques and tangles? So first you're saying, get the history. That will give you the indication of what further testing you do. And now we want to do the biomarker testing.

DR. GIL RABINOVICI: Right. So in addition to getting the history and doing the memory testing, it's really important to do a general medical history. Understand what other medical conditions patients have that can affect the brain, what medications they might have. A lot of medications, even ones that you wouldn't think of, can affect memory. For example, if people have an overactive bladder, there's a medicine that you get, and it helps relax your bladder, but it also might impair your memory. A lot of sleep aids. Sleep difficulties and insomnia are very common in people in their 50s and 60s. A lot of those medications can impact memory. So we look at all of that.

And then in terms of laboratory testing, we usually start just with a panel to look at basic medical conditions. How is the liver functioning? How

are the kidneys functioning? What are the electrolyte levels? The blood counts. We look at thyroid function. Having low thyroid is very common as people enter middle age, and that can affect memory. Looking at vitamin B12 levels. Vitamin B12 deficiency can affect memory. So we test for things, medical things, that are correctable, and can contribute to memory loss. And we recommend doing a brain scan, typically a CT scan or an MRI scan, just to get a general sense of the structure of the brain, to see if there is any evidence of strokes or masses, tumors, or anything else that could explain memory loss. And we also look for atrophy or loss of tissue in particular brain areas. So for early onset Alzheimer's, we look at the amount of tissue in the back of the brain, which is the part of the brain that is more susceptible to Alzheimer's. How does that compare to the front of the brain? So those are the basic tests that we do.

And actually, until about 20 years ago, that's all we could do to evaluate someone for Alzheimer's. And beginning about 20 years ago, there was a huge advance in that we began to develop tests that could tell us if people have these bad proteins, the amyloid plaques and the tau tangles, which actually, Alzheimer himself described in his initial report in 1906. And to this day, these two bad proteins the plaques and the tangles, define the disease. Until 20 years ago, the only way we could know for sure if someone had plaques and tangles in the brain, is to look at the brain under a microscope after they passed away at an autopsy. So we could suspect Alzheimer's. We could say that someone probably has Alzheimer's, but we didn't know for sure. And even the best, this is very humbling, but the study suggests that even the best and most experienced clinicians, when they diagnosed Alzheimer's just based on these clinical criteria, they were correct about 70% to 80% of the time. So somewhere between 20% to 30% of the time when an expert clinician thought someone had Alzheimer's, they actually had a different cause for their memory loss. What changed about 20 years ago, was the development of tests that could directly detect the plaques and tangles not after someone died, but during life, and actually very early on.

And so there have been a number of tests that were developed. One, is to measure the levels of the proteins, the amyloid protein and the tau protein, in the spinal fluid. So this is done through a procedure called a lumbar puncture, or colloquially known as a spinal tap, where we

put a small needle in the lower back, we extract some of the fluid that surrounds the brain and spinal cord. And by measuring the concentrations of these proteins, we knew with pretty good accuracy whether people had plaques and tangles. About 20 years ago, scientists in Pittsburgh developed an imaging technology that allows us to inject a dye that binds to amyloid plaques in the brain and lights them up if they're there. This is called an amyloid PET scan. And this can tell us whether people have plaques, where the plaques are, and how much plaques are in the brain. This has turned out to be incredibly important in developing new therapies. And then about 10 years later, so in around 2014, people developed a new technology that allows us to image tau tangles. Again, using a dye that we inject through an IV, lights up the tangles. And that is called a tau PET scan. So a PET scan is just a type of brain scan. And the type of dye that you inject can detect plaques and amyloid PET scan or tangles, a tau PET scan. And so this really revolutionized how we do clinical trials and research in early onset Alzheimer's disease. We could directly detect these core elements of the disease. We knew with high certainty that people's symptoms were or were not caused by Alzheimer's disease, depending on the results of these tests. But the problem was, that the tests weren't widely available. It's not so easy to get an amyloid PET scan covered, or even have access to it for most people.

NANCY LYNN: Still not easy.

DR. GIL RABINOVICI: A spinal tap is also a safe procedure, but it's not the most pleasant. And wasn't so widely available. So what's really exciting, is that in the last four or five years, there are now blood tests that can detect these proteins, the amyloid proteins and the tau proteins, and with very high accuracy, as good as spinal fluid or PET scans, tell us whether people have Alzheimer's. And think that will really help with getting the correct diagnosis early on. We, as doctors, even the experts, let alone the busy primary care provider, really need that objective biological evidence of Alzheimer's to make the diagnosis with high confidence, especially in younger people, where the symptoms can be atypical, unusual.

NANCY LYNN: Thank you. That was really comprehensive, and I appreciate it. And BrightFocus Foundation was one of the early funders of

C2N, who developed the blood tests.

DR. GIL RABINOVICI: Oh, wonderful, yeah.

NANCY LYNN: So, extremely exciting time for us to watch that developing.

DR. GIL RABINOVICI: Yeah.

NANCY LYNN: And I just want to say, it is still difficult for a lot of the country to find places where they can get these PET scans and blood tests and so on. And if someone wants to participate in a research study or in trying to get those tests and isn't sure how to proceed locally, they can look for an Alzheimer's Disease Research Center near them. You can just actually Google, if you have the search engine, for Alzheimer's Disease Research Center, and find the nearest academic center to you.

DR. GIL RABINOVICI: Yeah.

NANCY LYNN: They're obviously not convenient for everybody.

DR. GIL RABINOVICI: Yeah. It's getting better, so I think there are about 35 centers that are funded by the NIH to do research work in Alzheimer's disease, and are called Alzheimer's Disease Research Centers. And those centers have access to these most advanced technologies, the blood tests, the spinal fluid tests, the PET scans. And actually, there's more and more funding for all the centers to do that as part of their evaluation. So that's a really excellent point, a very good resource.

NANCY LYNN: I'm going to get to Donna, your question about risk factors, I think, what would bring it on. But before we do that, there were a lot of questions about what are the stages, and roughly the timeline of progression. I was really fascinated that several people, I'm looking at a question from Carolyn in Berkeley Springs, West Virginia, but several people asked about life expectancy and the stages of progression. It seemed so they can determine when they might need to put someone in memory care or when they need help in the house with caregiving. Can you talk about the stages, the progression, and the life expectancy?

DR. GIL RABINOVICI: Yeah, so this is a very long and protracted disease. It takes place over decades. And so actually, stage one is a stage where people have no symptoms at all. But they are starting to develop the plaques and tangles in the brain. And so we know that the plaques and tangles, these bad proteins, may start to accumulate in the brain 15, 20 years before people have even the earliest signs of memory loss. And that's really important, because it means that there's a very long time window for us to intervene, potentially, with medications to try to prevent, delay, or even prevent the occurrence of memory loss in the first place. And detecting Alzheimer's at that stage relies on these biomarkers, the blood tests, PET scans, or spinal fluid tests. So more and more, we're talking about early, early diagnosis. So there's a stage called subjective cognitive decline. And that's a stage where people are noticing their memory changing. But when we test them, they actually score normally on the memory tests. And so they're not yet showing impairment by our measures, but they know something's going on. They know that there's something going on. And more and more, we're going to try I think to make the diagnosis at those very early stages.

And then there's a transition from people being cognitively normal to impaired, called mild cognitive impairment, or MCI. And this is a term that means that people have a decline in their memory or other functions that's more than would be explained for age, that they scored low on some of the cognitive tests that we do, the memory tests that we do, but they're still independent with their daily function. They're still able to go about paying their bills, making their appointments, managing their finances independently. So that's kind of a transition zone between being cognitively normal and being impaired.

And then there is dementia. And the definition of dementia is, that people have a decline in their memory or other cognitive abilities that is more than can be expected for age, and now starts to interfere with their daily life. They're not able to manage things independently, take their medications independently, manage their calendar, make appointments. And in that dementia stage, early on in mild dementia, it's really those more complicated activities of daily living, like managing finances,

managing calendars, managing medications. And what we call the moderate stage of dementia, it's difficulty doing some basic self-care activities. So, dressing, preparing food, hygiene, toilets.

And then in severe dementia, really people are dependent on someone else to help them with all of these activities. So those are some of the definitions that we use in trying to stage the disease. And people might call that stage 1 to 6. There's different scales that we use, but conceptually, that's what those stages mean. The average sort of timeline from diagnosis to death is really variable across patients. On average, it's about eight to 12 years from diagnosis until someone passes away. But there can be patients who can live with Alzheimer's for 20 years, because even though their memory and cognitive abilities are impaired, their basic ability to walk, to swallow, breathing, all of those things can be unaffected until very late.

And then some people, for reasons that we don't fully understand, develop a more accelerated version, and they actually can go through those stages much more quickly than eight to 12 years, until they pass. And so one of the big mysteries is why the disease can present as kind of slow and insidious in some people and more aggressive and rapidly progressive in others. It is true, as a general principle, that the younger the diagnosis, the disease does tend to be more aggressive in its rate of progression. So that's true on average. People with early onset Alzheimer's on average, do progress more quickly than people who develop the disease later in life.

That said, I've had many patients with early onset who have had a much slower course. And we don't fully understand, Nancy, the biology behind that. And what's really frustrating to patients and families and to us, as doctors, is we don't have a good way when we're meeting a patient of actually looking in a crystal ball and predicting what their Alzheimer's will look like, how fast will it progress. And that's obviously, one of the first questions after diagnosis is, what can we expect? And unfortunately, we don't have the tools yet to tell people what we can predict that the single patient level. We can cite a lot of statistics based on thousands of patients, but it's very hard to predict for the individual what this will look like.

NANCY LYNN: And that's why it's really important for anyone who can to

participate in research studies like the one that you're doing, so that we're getting more information. And we can talk about the trial a little later. And I know there someone put about finding a trial into the chats, and that the association does, at BrightFocus, also has a pretty navigable link to find a trial. clinicaltrials.gov is a place you can find trials, but it's really kind of hard to navigate. So there's also a lot of groups trying to make it easier to find and participate in clinical research.

And I'll just quickly mention that in June, we are going to start our first episode where we feature every other month, one clinical trial with a person that has started it and is running it, even if they're global trials, where you can walk through what the process is and how to participate and ask any questions that you want. So for anyone who's interested in the study, we're starting that series in June.

I want to go in so many directions, but let me go in one direction and then another first, and the second one is going to be on the risk factors and what can you do to prevent. But to what extent is this genetic versus environmental? And I think that would also lead us to the question that there isn't just one type of early onset. People have heard about the families in Colombia. And so can you talk a little bit about genetics and genetic testing, we had some questions on that, and then we can move into modifiable risk factors.

DR. GIL RABINOVICI: Yeah. So about 1% of all cases of Alzheimer's, and about 5% of all cases of early onset Alzheimer's, are due to a mutation in a single gene. And it's one of three genes. They're called APP, Presenilin 1, and Presenilin 2. Those are three genes. And if you have a mutation in that gene, you're going to get Alzheimer's at a young age. And this is what we call 100% penetrance, which means that basically if you have the mutation, you're destined to get the disease, and there's a 50% chance that you transmit the disease to any one of your children. So everyone has two copies of every gene. And if we have one of these mutations in one of your copies, that causes Alzheimer's. Usually, the presence of those mutations is pretty clear from the family history. So people tend to have a family history of others developing the disease at a young age over multiple generations. And that is the case in Antioquia, Colombia, for

example. And so that accounts for about 5% of early onset Alzheimer's. And you can test for those mutations. So as a doctor, if I see someone and they talk to me about a family history, their mom developed Alzheimer's disease in her 40s, and their aunt and uncle did, and their grandfather on that side and so on, then we test for that gene. We do genetic counseling. And then we know the cause of their Alzheimer's. About 95% of people who develop Alzheimer's at a young age don't have a mutation in any of those three genes. About half of them have one or more copies of a gene called APOE4. APOE4 is the most common genetic risk factor for Alzheimer's disease.

So let me do a little basic genetics for APOE. APOE is actually a gene that helps our body metabolize cholesterol. And we all have two copies, and there are three possible types of APOE. So most people have APOE3. APOE2 is pretty rare, but actually helps protect people against Alzheimer's disease. And APOE4 is a risk gene. About 20% of us have at least one copy of APOE4. And if you have one copy, your risk is about three times higher compared to the general population of getting Alzheimer's at some time in your life. If you have two copies of APOE4, your risk is about 10 to 12 times higher than the general population. So this is a risk gene. Many people get Alzheimer's without APOE4, and people can have APOE4 and never develop Alzheimer's, but it's a pretty significant risk gene. So that 50% of the people with early onset Alzheimer's carry one or more of these risk genes in APOE4. The other 50% are a mystery. We don't understand why they're getting Alzheimer's in the absence of the two major risk factors, which are older age and APOE4 gene. And that is why we are trying to do large international studies to really collect DNA from hundreds or thousands of patients to try to identify whether there are other genes that increase their risk that we haven't yet identified.

And why that's important, is because those genes might give us clues about Alzheimer's that could translate into new treatments. And so that is a very intense area of research right now, is trying to understand additional genetic risk factors. Now, there are environmental risk factors, as you mentioned. And many of them are actually modifiable. So some of them have to do with lifestyle. The diet that we eat, getting good sleep, getting regular physical exercise. And when I say exercise, I mean aerobic

exercise, cardio, but also, muscle stretching and resistance exercise, that balanced exercise program. Being social. Actually, recreation and engaging with other people, that exercises parts of our brain and help can help protect us against developing dementia. And then cognitive activity, starting with the level of education that we get, but continuing throughout life. How do we exercise and stimulate our brain? All of those lifestyle choices can be helpful in trying to protect us, our brains, and help us develop healthy brain aging. And then there are other modifiable risk factors. So we talked a little bit about sleep disorders. We talked about mood disorders, social isolation, alcohol abuse, hearing impairments. A lot of diverse different things that we can actually do something about throughout our lifespan that can help protect us against developing dementia and Alzheimer's.

And so I think it's really important for people to understand that there's a lot we can do throughout our lifespan. And this is true of people who might be at higher risk, because they do have a family history or not. There's a lot of things that we can do to try to protect our brain. And in fact, the amount of cognitive, physical, and social activity that we do throughout our lifespan, can help protect us against Alzheimer's in later life. All these risk factors seem to be important for early onset Alzheimer's, as well as late onset. And one category, sorry that I haven't mentioned that's really important, are vascular risk factors. So things that we think about as risk factors for heart disease, like high blood pressure, high cholesterol, being overweight, diabetes. These are things that are really important for us to screen for and treat, because all these vascular risk factors can actually contribute to our risk of developing both early and late onset Alzheimer's.

NANCY LYNN: That's fantastic. And we did an episode with Dr. Richard Isaacson earlier just about modifiable risk factors, and another. And we'll keep doing these as the field learns more. Let's see, I wanted to get to Anne's question, because a lot of people are asking this. Is this happening more? And what percentage of people with Alzheimer's have early onset?

DR. GIL RABINOVICI: Yeah, great question. I'll start with the second part, because that's easier. So we estimate that about six million Americans,

sorry to be so US-centric, we probably have an international audience. But just to focus on the US for a minute, there are about six million Americans living with Alzheimer's disease. About 5% of them have early onset Alzheimer's. So that would be about 300,000 people just in the US living with early onset Alzheimer's.

Is it increasing? That's very hard to say for early onset Alzheimer's. In general, we know that the prevalence of dementia is increasing. But that's really due to people living longer. So most of that increase in the overall number of people living with dementia worldwide, is actually driven by people who develop dementia at a much older age, in their 80s or 90s. So people just live longer. And the longer you live, the higher the risk for dementia. So that seems to be driven by older people. The young onset is hard to know, because we don't have good epidemiologic studies about it. We talked about how hard it is to get a diagnosis, even for people who are seeing experts. And so we just don't have a very good handle, Nancy, on how common early onset Alzheimer's is in the general population.

Another major limitation of a lot of the research, is that it has really had sort of poor representation of more diverse groups. And so a lot of the research that's being done in the Alzheimer's research centers or in clinical trials, enrolls typically high socioeconomic status, highly educated people, often non-Hispanic whites, and there's been poor representation. We, as a field, have done a poor job of engaging other communities, Latino, African-American, Asian-American, Pacific Islander, and we know that these different racial and ethnic groups may have different social determinants of health, or different predictors that can affect their risk of dementia. And so one of the major goals in general research, and in particular, in early onset Alzheimer's, is to engage more diverse populations, so that we can really understand how the disease affects people in a globally representative way.

NANCY LYNN: Here, here. BrightFocus is doing several programs in support of increasing diversity in research and clinical trial participation, because it's critical. So we talked a little bit about living better, healthier, let's say, to reduce your risk factors. I want to jump to treatments, because people have asked about very specific things that are interesting. And a

YouTube question came in about how do you manage heat sensitivity. We also had questions about, are there treatments for anxiety and depression? Are there treatments for insomnia? And are there disease-modifying treatments? So what about the drug world or the herbal world?

DR. GIL RABINOVICI: Yeah. So we have a variety of treatments in our armamentarium to treat different symptoms. So if people develop depression and anxiety, we treat them with antidepressants, SSRI or SNRI types of drugs. And they can be very effective and helpful in managing mood symptoms. Insomnia is a tough one, because a lot of the drugs that we use to treat insomnia kind of knock people out. They're what we call benzodiazepines. So they're like having a few drinks. They really slow the brain down, and that gets people to sleep. Drugs like Ambien, those are really not good for patients with Alzheimer's disease, because they do slow the brain down, and they can actually exacerbate symptoms. And so there are a number of different approaches that we try, beginning with just sleep hygiene. Regular behaviors around sleep, limiting caffeine intake, limiting alcohol intake at night, getting to bed at a certain time, trying a drug like melatonin, that's very gentle and doesn't affect memory and thinking. And I would just say, people should be very cautious about drugs to treat insomnia, and ask, could these affect my memory or my loved one's memory.

Now in terms of treating Alzheimer's itself, there are a couple of drugs that have been around, or categories of drugs that have been around for many years. One category are called cholinesterase inhibitors. Sorry, that's a mouthful, but these are drugs, I'm sure people have heard of them, like Aricept, and there's two others that are very similar. Razadyne, Exelon is their brand names. These drugs enhance a brain chemical called acetylcholine, which is a brain chemical that helps the brain cells communicate with each other and send electrical signals. And in Alzheimer's, the level of that chemical goes down. And what Aricept or its cousins do, are they boost the levels up. And so they help the communication be better. Those drugs are what we call symptomatic drugs. They don't change the course of the disease in terms of plaques and tangles, but they help with the symptoms. Most people don't feel like their memory is better on those drugs, but over time, we know that

the memory goes down less quickly in people who are taking these drugs compared to people who don't. And so that's kind of our front line therapy.

When people enter the moderate stage of dementia, so when they're starting to have some difficulty with their basic activities of daily living, we often add a different category of drug called memantine or Namenda. That's a drug that acts on a different brain chemical called glutamate. But it really does the same thing. It doesn't prevent progression, but it slows that process down a bit. Those drugs have been around for over 20 years. They're safe. There's some benefit. And so those are kind of our first line. In the last two or three years, we have had some breakthroughs in Alzheimer's drug developments. In particular, in a new class of drugs that are antibodies that are infused through an IV, and remove plaques from the brain. And the one that is fully approved by the FDA and now covered by Medicare, is called lecanemab or Leqembi. I know you've had a specific panel specifically focused on that new drug. That drug removes plaques from the brain. It doesn't, again, stop the disease progression, but it slows it by about 27% in the clinical trial. And there is evidence that drug can reduce, for example, the chance of someone at the mild cognitive impairment stage from progressing to the dementia stage of the disease over a year and a half. It reduces the likelihood of that happening by about 30%.

So these drugs are not for everyone. They are really intended for people at the early clinical stage at the mild cognitive impairment MCI stage, or very early dementia stage. There are a number of factors that would exclude people from treatment, and there are some significant side effects that we could go into if you'd like. So they're not for everyone, but they are the beginning of a new era, I think, in Alzheimer's disease care, where we actually are modifying the core biology of the disease in a way that could be very meaningful and very impactful. So think these drugs are just the beginning of a new era of treatment. And certainly, we offer these drugs to patients with early onset Alzheimer's disease. There's less data, to be very transparent, about how they respond to the drugs, because in most of the trials, the average age was 73, 74. So there were some people in that under 65 category that were included, but not very many. Most

people had late onset Alzheimer's. And so it's going to be very important as we start to implement these new therapies, to understand whether people with early onset Alzheimer's respond as well, better, or not as well as people with more typical late onset Alzheimer's. But certainly if they're otherwise good candidates, we are offering this drug to people with early onset.

NANCY LYNN: And so Leqembi can be tried with early onset. You've said that. And you talked about it slowing disease progression. And Lisa asked about it slows disease progression, but does it also improve, I'm going to use my own words here, activities of daily living? Because I know that there was a data on that from the Leqembi study.

DR. GIL RABINOVICI: Yeah. It doesn't improve, but it slows the decline. And so the primary measure they looked at in that clinical trial was a scale that looks at both cognition and function, called the CDR Sum of Boxes. And there was an effect on both cognition and daily function. And in secondary endpoints in those trials, they also looked at specific scales that measure activities of daily living, and showed again, not an improvement, OK, no one should expect that they're going to be better with the drug, but a slowing of decline. So people were able to do more independently for longer if they took the drug than if they took placebo. And so, yes, there is a benefit in those very meaningful outcomes. It's a modest benefit, to be honest. It's not a cure. But it is really the beginning of foothold, we think, of modifying the biology of the disease. And it offers, I think, great hope for what's to come in the coming years.

NANCY LYNN: I like that, getting towards hope at the end here. And I do want to end, we only have about eight minutes, and I hope you'll come back to talk about the study you're doing and maybe studies in general on early onset, but a couple of things I just wanted to try to cover before we leave. Is also about how to interact if your loved one has been diagnosed or you think they're-- So there were two questions that came in that really struck me. One from Tammy in South Carolina. She wrote, I am beginning the newness of strange. Family and friends are having a difficult time with my Alzheimer's. How do I explain to them that each day I feel different? And then the second one, Jamie from Alabama. What's the best approach

for discussing or not this condition when he doesn't acknowledge it? He talks about his family members who have symptoms, but doesn't acknowledge his own. Should we discuss or leave it alone?

So I know that brings up a world of things that you could say about agnosia and so on, but if you have early onset and people are noticing, how do you discuss? And how do you, if you should discuss with somebody who doesn't acknowledge that they're having this?

DR. GIL RABINOVICI: So, first of all, my heart goes out to both of you. These are really challenging to navigate. So for patients, so the first is coming think from someone who's experiencing Alzheimer's, and how to talk about it with other people. Obviously, it's a very individual choice. I think I kind of am a believer in being direct and talking about it. I think my patients who have been forthcoming with others about their Alzheimer's in general, have not regretted doing that. Have been happy that they were able-- instead of trying to hide it, because I know there's a lot of anxiety about trying to hide your symptoms and you don't want to be around other people, because you don't want them to notice. And I do think there's a benefit to having that elephant in the room out in the open and talking about it. It's a very individual decision, obviously. But I think as a society, we really need to destigmatize the whole concept of Alzheimer's. There's huge stigma. Some people talk about it as the A word. It's the disease that's most feared by older adults. I think a lot of people still in their minds, think about Alzheimer's disease as someone who's in a nursing home, unable to dress themselves, feed themselves, talk, or communicate. I've told you that people can have Alzheimer's disease and have very mild, if not no symptoms at all. And so I think we really need to change our mindset about what the diagnosis means. It means people have plaques and tangles in their brain. People can be extremely articulate, highly functional, have a ton to contribute to society, to their family and friends when they're living with Alzheimer's. So I think as a society, it's very important that we change our entire thinking about this. And we talked earlier about diagnosis. Doctors are really scared of giving this diagnosis, because it sounds like a death sentence. It isn't. There's a lot of hope. There's a lot of things we can do. And people who are coming to the doctor seeking an explanation for their memory loss, they really

want answers, even if they're tough answers. Even if they're difficult diagnoses. People who are coming to the doctor are looking for that. And so we really owe it to our patients to be honest.

How to interact with a loved one who has Alzheimer's and doesn't kind of recognize their own symptoms, it's a really tough situation. In general, I would not recommend confronting them or trying to explain or convince them that they have memory loss. You really need to realize that their experience is very different than yours. They're not noticing that they're asking you the same question they asked you five minutes ago. And so when you tell them that, it really conflicts with how they're experiencing the world. And I don't think there's much accomplished by continuously bringing it up. So I do think you have to be a little agile. And it's not helpful, I think, to talk about it constantly. It's just a new reality of life, and you deal with it. But trying to convince people that they're having symptoms that they don't recognize, is usually just a cause for distress for your loved one. It's not going to help them see things differently. Their experience is just very different.

NANCY LYNN: Yeah. And one of the things about getting an early diagnosis and trying to recognize the disease and destigmatize it when it's early, is also that your loved one can make decisions earlier about what they want in their future. And also, potentially participate in a research study, where not only is it a benefit obviously for the field to have greater knowledge for the future, but you often get better care if you are in a trial than you do left off on your own.

DR. GIL RABINOVICI: Yeah, no, those are really important points. And so research isn't for everyone, but I would encourage people to learn more about it and see if there is a study that is right for them in terms of the level of engagement. I'll just bring up one study with your permission, Nancy, which is funded by the NIH. You mentioned it in the introduction. It's called the LEADS Study. And this is a study that's particularly focused on early onset Alzheimer's. So we have about 20 centers around the US that are recruiting patients who develop symptoms before age 65, and following them over time. We are doing all the advanced testing, the blood tests, the PET scans, and we actually disclose the PET scan results

to patients and families, so they can be certain about their diagnosis. We're studying the genetics of early onset Alzheimer's. We're trying to understand what are the best measures to determine if different drugs are working in this particular population, where memory loss might not be the primary symptom. And we are actually opening international centers for your international audience. The first few international centers will be opening in London, Amsterdam, Buenos Aires, Sweden. And so this is really an international network, and we are hoping to have that network be a focus of drug trials in this future iteration, so we can really focus on patients who have early onset and atypical Alzheimer's and offer them the opportunity not just to be involved in research, but actually to have access to these new, potentially very impactful therapies through clinical trials.

NANCY LYNN: Thank you for that. And Donna's asking how can we get in touch with Dr. Rabinovici? How can people either get in touch with you or pursue participating in this study?

DR. GIL RABINOVICI: Yeah. So the principal investigator of the study is Liana Apostolova. She's at Indiana University. The co-principal investigators are myself at UCSF, Brad Dickerson, who's at Mass General, and Maria Carrillo, who's in the Alzheimer's Association. There's a website both through the Alzheimer's Association and through Indiana University. I just saw something flash in the chat that we're not taking new patients. This is about to change. So we actually were so successful in this trial, that we fully enrolled all 400 patients that we told the NIH that we would enroll. And so we've recently modified the protocol to allow us to recruit more patients. And that should be approved in the next one or two months. So if people are looking to get into the study, it's true, right now, we have a little lull as we need to get IRB approval to increase our sample size. But that's coming imminently. And so our plan is to be able to continuously take new patients. So be patient and stay tuned, and there will be an opportunity to participate.

NANCY LYNN: We have somebody on the call who's written that she's tried Phoenix, LA, and San Francisco. So, what's the timeline for Sarah?

DR. GIL RABINOVICI: Yeah. Give us like a month or two months. I'm hoping in May that we'll have approval.

NANCY LYNN: Another two months.

DR. GIL RABINOVICI: Yeah. And then it will be all the sites. So it's not like any one site is closed. All the sites right now are temporarily fully enrolled. But that should change, I think even as soon as May.

NANCY LYNN: Yeah. And Leanne Krillenberger says, can we get a list of the study sites. I think what we can do, unfortunately, we're going to have to wrap today, but in about a week or so, we'll have a recording of this program and send it out with resources. And I think with the resources, I know Amanda is on here, we could potentially include a list of sites. I think, according to what Dr. Rabinovici just said, we won't know at this moment which ones are active and which ones are not, but keep checking back over the next few months, as it sounds like the study will start recruiting again in sites that are not currently recruiting. And somebody just asked, are there sites in the UK.

DR. GIL RABINOVICI: UCL, the University College London, Dementia Research Center is a LEADS site. I don't think they're quite open, but again, they're imminently ready to start recruiting.

NANCY LYNN: What I would love to do, since there's so much interest, is have you come back, Dr. Rabinovici, for when we start the clinical trial series, and literally walk people through how they can participate, where they can participate. And so I want to thank you so much for your time today. We could easily have done another hour here. And I apologize to folks that if we didn't answer your question, you can write to us at reply@brightfocus.org and we will try to answer the question that we didn't get to today.

I'll go on to the next slide, if you need some resources. And again, we will have resources specific to early onset and to the LEADS trial that will be emailed to you if you are participating today. But we also have a wide array of resources at brightfocus.org that you can ask for.

And next month, we have a friend of Dr. Rabinovici's coming on to talk about a critical topic that so many people are writing about and talking about, artificial intelligence and Alzheimer's, and how AI is revolutionizing dementia detection and treatment. I hope everyone will join us.

And again, thank you Dr. Rabinovici. It's always really special for us to have on somebody who sees patients and conducts research. A lot of time there's a big disconnect. But what it means for us, is that you can speak to people in normal English in ways that they can understand, and even ask questions directly. So, please share the episode, folks, with your friends when it gets emailed to you, if you know people who would like some of this information. Or write to us if there's a particular angle or questions that remain.

Thank you, Dr. Rabinovici. Dr. Rossi, thank you. And M Squared, and my team, Amanda and Beth, who are on, thanks. Thanks for your help. And I hope we'll see you all next month.

DR. GIL RABINOVICI: Thank you very much. It's been a pleasure.

Useful Resources

BrightFocus Foundation: (800) 437-2423 or visit us at BrightFocus.org. Available resources include—

- Longitudinal Early-onset AD Study (LEADS)
  - To learn more and sign up, call toll free 877.38.LEADS (877-385-3237)
- Early-Onset Alzheimer's Disease
- Genetic Testing for Alzheimer's Disease
- When Alzheimer's Disease Begins with Vision Problems