



**YOPD Council: Dementia
with Guest Speaker Dr. Rodolfo Savica, MD, PhD
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Davis Phinney Foundation**

Melani Dizon (Director of Education and Research, Davis Phinney Foundation):
I am here today with Dr. Rodolfo Savica. How are you doing? Thanks so much for joining us.

Dr. Rodolfo Savica, MD, PhD (Doctor and Faculty at the Mayo Clinic, Rochester, MN):
I'm doing very well. Thanks, what about yourself?

Melani Dizon:
Pretty good. This is going to be a little bit different than our normal panel. We usually have about seven or eight of us on and we pick a topic and talk about it. Today, we have brought on Dr. Savica so we can get a real deep dive into YOPD Dementia and right now if you guys can just let us know that you're here and you can hear me, you can click the little chat icon at the bottom and just say hello and let us know where you're calling in from. Hi, Athens, Georgia. Love it, love always the first person that goes in there. Hi from Detroit. Palmetto, Florida, Wyoming. Hi, Polly so glad you're here. Columbus, Ohio, Rochester, New York. Great, thank you everybody.

I'm going to do a little intro first. So, Dr. Savica is a medical doctor and PhD and is a faculty at the Mayo Clinic in Rochester, Minnesota. He focuses on Parkinson's, Lewy Body Dementia, and early life risk factors. In addition, he's interested in YOPD, Dementia, and the role of the late life consequences of head trauma. Thank you so much for being with us today.

Then Tom Palizzi is going to be my co-interviewer. Many of you know Tom, you've seen him for many many months in a row if you've been joining us for our Council. Tom is a regular YOPD Council member, he's one of our Davis Phinney Foundation Ambassadors, and we're going to be tag-teaming this interview, so thanks for coming here, Tom.

Tom Palizzi (Davis Phinney Foundation Ambassador and YOPD Council Leader):
No problem, glad to be here.

Melani Dizon:
So, real quickly, I'm going to enable the live transcript. If you like to see the words on the screen, then you can just leave it as it is, or if you don't like it, you can just click the little arrow that's by the CC and say hide subtitles, so you don't have to see that. You can feel free to chat in the little chat box like we're doing right now. And if you want everyone to see your question or comment, feel free to click the little blue button that says, all panelists and attendees. If you

just want to talk to panelists and attendees, make sure you just select that, so not the whole group will be able to see your comments, it's up to you how you want to do it.

Let's see. I will be giving a recording to everybody; you'll see the video, the audio, and the transcripts when we're done. And you can drop your questions in if it makes sense to hold them till the end, we'll do that. Otherwise, we will just kind of go and pop in as we're talking about a specific topic.

So, I'm excited to get started. Dr. Savica, what is YOPD, and do you consider it, is it considered a separate, a different disease, is it different enough than Parkinson's for people who get it later onset?

Rodolfo Savica:

Wow. That is a very, very articulated and complex question, and there are many questions within the same question. I would say that first thing first, is let's go and step back. You were saying YOPD, which is totally fine, I'm not going to argue against different nomenclature.

But as we all know, you may read young onset Parkinson's disease, early onset Parkinson's disease. I don't know, any other adjective that you might interact with and find. That is a major problem. In the US, not so much. But if you think about it, the way you call a condition, the way you call a disease, changes the way, regrettably agencies, the way the disease is defined.

I give you an example. If I ask around in these 112 people, participants around here, I ask you guys here in the panel here, and say, Okay, what is young onset Parkinson's disease, when do we consider young onset Parkinson's disease, at what age? I would have 114 different answers to the same question, which is a major problem. Clearly, what we can say is that I will use the term early onset Parkinson's disease because I want to time it earlier than the usual onset of Parkinson's disease. So, it's before the usual onset of Parkinson's disease, of the motor symptoms of Parkinson's disease, that are usually occurring around 65, 70 years of age.

So, everything, paradoxically, which is before that, can be considered early onset Parkinson's disease. In the literature, if you want to use the term young, you can consider somebody 60 and below, in terms of onset. In some literature, you got 55 and below. To be more conservative, in some of the literature you go 40 and below, but you realize that there's a huge difference between 40 and 65.

I'll give an example, in some countries, and I mean countries these because we are trying to define the nomenclature. We're trying to harmonize the word to call this condition in one way. It's a disaster. Trust me, a disaster, I'm losing my mind how around that.

For example, in Australia, they talk about young onset Parkinson's disease, before the age of 65, because 65 is the age of retirement in Australia. I don't know whether it's the right choice,

you know, but every country is different, we have to consider it something different for every country.

Biologically it's different. If we move from mere nomenclature, that we have to do for research, or to harmonize the regulatory agency, or for funding purposes, because funding is important, research is important, and advocacy is important.

But if we move to the biology. Clearly, late onset Parkinson's disease, so something that happens around 65 and 70, well, the motor onset happens there, compared to what happens in 50s, 40s is likely a complete different disease. A complete different biology underlies the two different aspects. The outcome is the same. The outcome is damage of the substantia nigra, damage to the basal ganglia, the area where the dopamine is contained, but what brings this damage in is different.

Are different conditions, different diseases, different biology, and different tissues, different organelles, and I use the term organelles on purpose, organelles not organs, little or more functional unit of the cell that are involved.

I'll give you an example. That is very important. Everybody knows, in this call I guess that the presence of the Lewy bodies, is the hallmark of Parkinson's disease, right? If you look at the brain of patients that have Parkinson's disease, we see Lewy bodies in different areas of the brain. Well, if you open up the brain of younger patients, you may not see any Lewy bodies, at all.

This is telling us that it is different. You heard also another thing that I say, motor onset, in other words, tremor, rigidity, falls, but we know that the late onset Parkinson's disease, there's a number of symptoms that can precede the motor onset for many years, and talk about anosmia, so lack of sense of smell, not acuity, like in coat of arms but more prolonged, constipation, dream enactment behavior disorder, so the tendency to live out the dreams, and many others, depression, anxiety, many others.

In early onset Parkinson's disease, in young onset Parkinson's disease, these symptoms are not very common. So, patients do not have this long latency of what, 10, 20 years before the motor symptoms start. Sometimes, even the presentation of symptoms is different, and maybe many, many people in this webinar may have that, may see that, for example, the typical motor onset of Parkinson's disease later in life is presence of tremor, a feeling of stiffness, maybe a frozen shoulder, people slow down, people tend to fall, probably balance issues, so forth. Let's go back.

If you look in the younger people, one of the most common symptoms is that when people are exercising, they're having contractions, cramps, what we call dystonia, but initially they look like cramps.

And so, patients are going to the orthopedic doctor and saying you know I'm running a marathon and around my third hour of run I have a cramp that is very odd. And every time, every time I run, I have the same problem. So, you're thinking you have what, an orthopedic problem, and most of the time, it is indeed, it can be the onset of Parkinson's disease that behaves in a completely different way, at the beginning, in younger patients, compared to later patients.

So, clearly, we have epidemiological data, that supports the difference between younger onset, early onset and late onset. We have biological data, that supports early onset versus late onset.

We have some genetic data. However, I don't want to get there but it's important to say, not every young onset patient has a strong genetic familiar background. That was the original sin, quote, quote, of the literature thinking, oh early onset Parkinson's, young onset Parkinson's, is a genetic disease, it's only present in the family if you have a strong familial background, not always the case.

Actually, it is the opposite. Familial cases are a little bit less common in terms of genetic frequency compared to the sporadic one. Many, many people here may have Parkinson's, and they may not have anyone in the family with Parkinson's disease. So, you see, but you say, oh my god, but so, what do I have? You have early onset Parkinson's, but it's not a strong genetic background we can pinpoint and argue there.

When we say, epidemiological, biological, genetic, clinical symptoms are different, and when we talk about clinical symptoms, we talk in terms of treatment, management. The management is slightly different, the progression is slightly different, the prognosis is different and depends, among many factors. The life expectancy is completely different. And most importantly, and then we can talk more about it, and maybe some other panelists can talk about it, the social aspect, the societal aspect, the needs of our patients in their 40s, 50s, even early 60s, are completely different than the needs of our patients in their 70s and 80s and 90s.

You have responsibility on your work, on your family, on your kids, on your life, even if you don't have any of these, but you just want to live your life, you have 40 years ahead of you at least, and it's different than adding a condition, that is still serious, still to be considered, in late 70s or early 80s. So, it's a very different, there are two different conditions, named the same way. But we have to strongly think and talk about the fact that there are different needs, different understanding, different biology, different data, and different everything basically. They only have the name in common.

Melani Dizon:

That's a lot. So, basically then, you know one of the things we've heard, once you're YOPD, you're always YOPD, because if you were early onset diagnosed, you're gonna have, even if

you're 70, like you were diagnosed when you're 40, you're going to have a different trajectory than...

Rodolfo Savica:

Absolutely. Absolutely This is an important... Mel, if you don't mind, this is an important thing. Very important. Now we see, now, we are seeing patients that have 70s, or even 80s and have had the disease for 30, 40 years, they're still a young onset Parkinson's. It doesn't really matter. Aging is something that we don't control. We age every day, right, unfortunately. And so, it doesn't matter. The age when we see the patient, when I see the patient in the clinic, it doesn't matter. I'm interested to know when the motor symptoms started, and please mark my words, when the motor symptoms started. If we are pinpointing the non-motor symptoms we go way back when and it's more complex.

Melani Dizon:

So, YOPD and dementia are not frequently discussed together. So, what does it look like, well, first of all, I guess, let's do a relative comparison, what does dementia tend to look like in people with later onset Parkinson's? And then what does it look like for people that were diagnosed YOPD?

Rodolfo Savica:

So, memory loss and dementia is a very complex phenomenon, in the general population, but especially in people with Parkinson's.

We have three things that are ongoing in people that have Parkinson's disease. We have three processes, aging, and that is an increased risk for all of us in this room to have plaques and tangles of the Alzheimer disease type. We get older, the plaques build up. We know that. There's little to say.

We have in later onset Parkinson's disease the presence of Lewy bodies that are causing a different way of cellular damage that can indeed cause memory loss. And we have vascular changes that are occurring at the same time and causing additional damage. So, when we get older, there are three things that are interplaying that we have to consider every time.

If we talk only about one, in this case, just the damage caused by the Lewy bodies, so not about Alzheimer disease tangles, not about the vascular changes, I can totally say, without further risk, that the memory loss that we see in Parkinson's disease is completely different than what we see in Alzheimer disease.

Dementia is a memory loss, that is interfering with our activities of daily living when patients may or may not have insight about the problem. And the memory loss that we see in Parkinson's disease in terms of testing, is a completely different one. It's not necessarily memory, oh I forget the name, or I'm forgetting where I place things. It's mostly having to do

with psycho motor slowing, especially in Parkinson's disease, we're already slower in movement, but also in thinking at times, in planning ahead, in doing multitasking. And sometimes people say, you know, something that was taking me, a task or doing two tasks at the same time, it takes me so much longer than before.

That is one. The other aspect of the memory that is affected is usually what we call the visual spatial memory. So having a good depth perception, seeing our body in the space, and understanding our space awareness. This is very different from what we see in Alzheimer's disease, where usually working memory, the short-term memory is the first, generally speaking, domain to be affected.

So, we already have a different number of memory problems. And some of these memory problems, especially the planning, that will be called the executive function, may respond to the appropriate treatment. May respond to dopamine. They may respond to carbidopa/levodopa, the gold standard of medication. So even when I see somebody in their 70s or 80s that have Parkinson's disease. They have Parkinson's disease and they come and say you know my memory is not good. I say, hold on. Let's optimize the treatment with carbidopa/levodopa, with dopamine and see after the optimization if you still have memory loss.

If you still have memory loss, we have to go a different route, but it's possible that your memory loss will improve, the brain foggy will improve, the feeling of, I don't feel that I'm able to get to that speed may improve with the replacement of the treatment of carbidopa/levodopa.

But I told you, we're talking about Lewy bodies here. If we adopt this knowledge, and we bring it to the young onset group, we are doing a mistake, because, as usual we cannot use the knowledge that we have in the later onset Parkinson's disease, to the younger onset. It is simply wrong. The later onset Parkinson's disease, I can tell you that some memory loss, ranging from mild, very mild to very severe is present, at about 39% of the people, but again, wide range, from massive dementia to some minor problems.

Young onset is not this way. Young onset are usually people, patients, I tend to say people, because I don't care about the idea of patients... So, people that are working, are functioning, are still an integral part of the society. So, their mental needs are higher. They require way more ability in terms of functioning in every day, especially in an everyday life when we are constantly bombed, bombarded by 20 million stimuli at the same time. The most common symptom of early onset Parkinson's disease is what they call brain fog, are the words. They feel...

Melani Dizon:

You got a big smile there. Tom.

Tom Palizzi:
Yeah...

Rodolfo Savica:

It's like you have cloud, like yeah, like it's hard to describe. We don't have words to describe it, but brain fog is the most common one, say, you know, I'm able to do stuff.

I do stuff, but it's taking me longer to go there. And if you ask me how frequent is a full-blown dementia in early onset Parkinson's disease? I tell you, it's not very common, not very common.

If you ask me, oh, but about 20 years later? Well 20 years later, you might have Alzheimer, you know, because you're aging, or 30 years later, you might have, if you're 80 now, and you had Parkinson's for 40 years, and you're 80, you may have Alzheimer on top of your Parkinsonism or your early onset Parkinson's. So, we have to consider this difference, that the more we get close to a later age, the more, there is a risk of Alzheimer disease plaques and tangles and vascular changes that have a major role, because we age, all of us. In terms of are there forms of early onset Parkinson's that can cause dementia per se?

Yeah. There are some. When talking about familiarity. If somebody has some genes that are producing too much Lewy bodies, then for sure, you may have an earlier onset of memory loss, but if you don't have this gene, if you don't have this cascade of events leading to the accumulation in the brain. We don't see that very much. We don't see atrophy; we don't see shrinkage of the brain. The brain doesn't shrink that much.

I mean, it shrinks because we get older, again, after the age of 25, it's going down. There's nothing we can do about that. You're just going downhill. If you ask me what about dementia Lewy Bodies? What about the same condition, you know dementia Lewy Bodies, but Parkinsonism, with more memory loss, with more hallucinations, is there a condition called early onset dementia Lewy Bodies?

Yes, but it's incredibly rare.

To be honest, we are publishing a paper on early onset dementia Lewy Bodies, and there's nothing out there. We are among the first that ever published on that, why? Because it's a condition that has not been very well described, we're talking about a handful of cases, people in their 40s and their 50s, again, likely they have some genetic predisposition and some environmental effect on the genes, causing an acceleration of these processes, because it's a very unusual presentation of this particular condition.

Melani Dizon:

That's super helpful. Tom, can you tell us a little bit about, you smiled when he said the brain fog, can you tell us a little bit about that experience for you and then you can ask your question?

Tom Palizzi:

It's a common thing, right, I think all of us with Parkinson's experience that at some time or another maybe sooner than others, whatever, but we're all kind of different. But the brain fog, it really it just that. I feel like my head's a puzzle, and all the pieces are pulled apart. So, it's just really kind of, like the doctor was saying it's hard to describe it. I mean it's unique and I hear Davis talk about the brain fog and that so...

Melani Dizon:

Is that something that you felt, I mean, I remember your diagnosis was fairly quick. I mean, you went to the doctor, you know, you got your diagnosis, but was that brain fog, was that something you felt for a while before you got diagnosed?

Tom Palizzi:

You know early on, there was very little brain fog, the brain fog developed as time went on, so lately, you know, it's getting to be more, shall I say visible if you will, but more there. Early on, I functioned basically normally. I think that the non-motor symptoms developed just like the motor symptoms, kind of slowly over time they get worse and worse as things go on.

And I think what I suffer from mostly now is memory loss or my wife will say I told you we were doing this, and I said, when did you tell me that? And the ongoing argument ensues, and I usually lose. But that makes sense. I mean, I faced, and I understand that. I hear that from my kids too, my son will say dad, we talked about this the other day, so it's like, yeah, I really need to pay close attention, so part of a brain fog, part of the memory thing, it's all, it all comes to play.

Rodolfo Savica:

One thing is you use a term that I think is crucial, attention. Focusing, attention, this is something... the attention network, which is called the attention network, it's a network that we have to keep us aware about things during a day. And it's relevant for our, you know memory, it's a network that goes in the frontal lobes, it's really in the frontal lobes, and we know that this network, this part of the network requires dopamine to function.

So, sometimes, and I don't say this is your case, Mr. Palizzi, but I say sometimes, some patients are reporting that they have a constant memory loss, but when the medication drops, the memory loss is worse.

And then when the medication comes back in, you know, I mean some of the non-motor fluctuations, the memory loss is better. This is for other symptoms such as anxiety, sometimes depression. Some patients are reporting, not everyone, but reporting that as the medication fluctuates their mood responds to the fluctuations of the medication, which has to do with their pathway that goes from the center of the brain to the frontal lobes, and it's responsible

for the mood and for the memory and for the attention. It can respond to changes in medication, it can.

I don't say it will necessarily respond, but it can respond. One thing that I want to tell that to me is very, very, very important.

So, there are some medications that are known to worsen things like memory. For example, dopamine agonists, Requip, Ropinirole, a Rotigotine patch, if taken at a high dose, can cause memory problems. It's important to know, but also, and again, it's not in everybody, but it's something to consider, something that, again, is a really relevant point is that people who are using carbidopa/levodopa, Sinemet, sometimes if they aren't functioning very well, the brain doesn't work, doesn't matter the age, at this point it's any age. It's hypotension, so low blood pressure caused by low perfusion in the brain, and hypotension that you don't need to, if you measure the blood pressure maybe is around 100, 110, so not necessarily too low, for me too low is below 90, that's the systolic, that's the top number. But if I, or Mel, or whoever, is having a blood pressure, constantly, of 100, 105, our brain when we have more in demand, or more brain activity, will be profuse less, and the lack of perfusion can make us in a brain fog.

So, again, I don't say this is always the case but those are the things that can be manageable, low blood pressure, adjusting the medication, and minimize anything else that can interfere with memory loss.

Melani Dizon:

Great. Somebody said my wife was diagnosed at age 37 and passed away five months ago at age 66. For the last one and a half years she had paranoia. The real problem was paranoia, as a result she refused to eat. Is this unusual?

Rodolfo Savica:

Well, we are talking about 30 years later. You know, clearly the damage, unfortunately, has been built up through the years. I wouldn't be very surprised. However, it's possible but unusual, if you told me that the paranoia was present for 25 years. If it were present for 25 years, maybe the diagnosis should be revised. But the last year, I mean, last year and a half, when the damage accumulation of proteins, the biochemical damage is being built up, some of the areas of the brain that are responsible hallucinations, for psychosis, can be indeed affected.

And that is not uncommon, the paranoia that is being described is, she doesn't want to eat, she doesn't want to eat, and people may have different ones.

People may have problems with thinking that their husband or their wife is an imposter, people may think, what is called reduplicative paramnesia when they're seeing multiple houses, thinking that there are multiple houses that is still the same house but multiple ones. People

may have what is called the Othello syndrome. In other words, if you know Shakespeare, it's paranoid jealousy, so excessive jealousy toward a partner.

But again, in early onset Parkinson's disease, I'm not expecting these earlier. It can happen, but I'm expecting these later on in life. One thing I want to tell you.

One of our recent studies shows that the life expectancy, the medial survival time from early onset Parkinson's disease, so diagnosis to death, it is 38 years. And that's exactly what this person commented, 35 years later, you know, if somebody's diagnosed at 45, their life expectancy is 38 years later, so 86, 84, I don't know the calculation. I'm not good at math, never been. But, you know, that is an important point that is different than late onset Parkinson's disease.

Melani Dizon:

Right. Somebody said, can you say more about optimizing medication to work with memory loss? Is it a matter of working with the doctor and doses via trial and error to determine the appropriate dose of medication? And somebody also said around this, is executive function a form of dementia?

Rodolfo Savica:

Well yes, so there are, let me start with the last one. In memory, there are four main domains in neuropsychology to explore memory. The four domains are, executive function, language, visual spatial, and working memory.

So, language is clearly the ability to understand and talk, visuospatial memory as I mentioned before are space awareness, knowing where you are and understanding the space around you, executive function is planning, and working memory is the ability to recall one thing once you learn.

If one of these domains, doesn't matter which one, one of these domains, is down, completely down, you can have a diagnosis of dementia based on the fact that one domain is down. There are some conditions for example, the primary language disorder, aphasia. People are not able to speak because their language center has been shrinking down, that they are considered to have a form of dementia, in spite of the fact that the other three domains are basically intact.

So, it is a matter on how much, to have a diagnosis of dementia, to how much this deterioration of the domain involved, is interfering with our activities of daily living. If it's just, and just quote quote, a mild interference, we can call it a mild cognitive impairment.

What is the problem, that usually the working memory is the first one that goes off when people are having Alzheimer disease. So, since it's very common, the translation is that, oh, if I don't remember the name of my family members, I have Alzheimer disease, which it's true, it's

maybe the most common form of dementia. Yeah, but there are other forms that are equally present, obviously less common, but that are equally present, and you can have a diagnosis just with one domain less.

The other question was the optimization, that is very important. This is something that you have to work with your doctor. One thing that we are trying, I'm trying, we are trying at Mayo, but I'm trying personally, is to customize, individualize very specific treatment for my patients.

In other words, I need to know how long the medication lasts, how long does it take to kick in, what kind of diet is being used, what kind of dose seems to be having an effect, what kind of duration of effectiveness, if there are some peak moments or phenomenon, like for example dyskinesia or dystonia. Once you tell your doctor all this information, he or she should be able to find the best that work for you.

On the other hand, sometimes it's not easy. Sometimes, it's an art that requires some time and if your doctor doesn't spend too much time with you, it's very difficult to individualize this part, especially, let me touch base again with early onset. If somebody's having a high-profile job. And even if it's not high profile, somebody is working at an office, and he or she's doing multiple things at the same time, or somebody's an athlete and needs to run or needs to bike, their requirement of the medication is different according to what it is needed in the time.

If, I have a patient who runs marathons. I had to give more, but it's something that we have to discuss okay, you know, let's anticipate the crash, let's give you half more or one tablet more of Sinemet and so forth.

Likewise, if somebody has, and we know for example, it depends on the jobs clearly, but sometimes it's, you know my mornings are always difficult, my mornings I have plenty of things coming. In the afternoon, not so much. Or maybe I'm good, but next week I'm incredibly stressed because I have a presentation to give. And I want to be doing a good job and so forth. Maybe the week prior, we have to find a way, talking to your doctor, to adjust the medication because maybe your body requires more. And then once that stress, or the sport activity, the event, you can go back to a more regular dose, but the entire question is that your doctor in yourself, should not be afraid to optimize, to individualize the treatment, according to your needs.

I want to say something and then I'll stop. It's like diabetes. Right. I don't have diabetes, but somebody has diabetes right. And then, high glucose level, the glucose comes up. Now, we have ways to measure, in real time, the level of glucose in the bloodstream. And then there are ways to give different amount of insulin according to the requirement of the time. We have to do the same, more or less in Parkinson's disease. When there's more need, we can give more. Otherwise, we can give less.

Melani Dizon:

Okay, so is there a similar thing that you can do depending upon maybe a certain diet that someone has? Like let's say they're a vegan or they're, I don't know, just something, do you do that?

Tom Palizzi:

That's something we can do, we can look to do to, if we start to notice signs like this right?

Rodolfo Savica:

So that is a great point, and diet, it's something that's getting more and more important. And to be honest, it doesn't matter whether people are gluten free, vegan, vegetarian, pescatarian, you name it. The list is endless. Or like me you eat everything. I mean, I'm Italian, it's tough to be vegan and Italian, trust me.

Melani Dizon:

I'm Italian, I hear you.

Rodolfo Savica:

It's kind of tough, but anyway, forget about the joke. One thing I try to do, there are a couple of things I recommend to my patients. Number one, when we are forced to take medication very often, obviously we want to make sure, the gold standard is carbidopa/levodopa, right? We want to make sure that carbidopa/levodopa is given on an empty stomach. I cannot say this enough. Empty stomach means one hour before meals or two hours after meals. It's not possible at times, if you take your medication every three hours. It's going to be tough.

So, what I recommend. I recommend a high protein diet. I recommend having a meal at breakfast, maybe coffee, no milk, or maybe delayed an hour to get milk. Having minimal lunch with maybe some carbohydrates no more than that. And having the larger protein meal at night. However, however, especially in early onset Parkinson's disease, there is a mounting amount of evidence, mostly in animals that intermittent fasting seems to be working better. Intermittent fasting, you can see online there's plenty of ways to do it. People are going 24 hours without eating, I do it personally, I always did it, it's basically I eat one big meal at night. And then I don't do breakfast. I maybe eat an apple at lunch. And that's it, That's intermittent fasting.

Interesting. Without getting too you know philosophical. Even the major religions. You know, were talking about fasting, all of them. Major religion, I mean, I don't want to say, minor religion or other but Christian, Jews, Muslims, everybody's having a moment of fasting, which is good for your body.

So, we're not inventing anything new, but what we know is that in mice, intermittent fasting seems to be delaying the damage caused by the mitochondria, hyperactivity.

And in early onset Parkinson's disease the mitochondria, these organelles I was talking about before, are maybe the most likely target of our disease. In other words, are the ones that are driving more than in late onset. That energetic crisis, leading to cell damage. So, intermittent fasting is something that can impact this particular pathway, and it's something that can help, can help quite a lot.

Melani Dizon:

Tom, do you have any questions you want to ask? He's covered so much of what we were going to ask.

Tom Palizzi:

Yeah exactly. I've loved the questions you've already answered which has been great. I've learned so much already. I'm just amazed at how deep this has gone so quickly. So, I really, really appreciate that.

Rodolfo Savica:

Pleasure.

Tom Palizzi:

I think really what I think most, most people like me are going to want to know is, I was diagnosed with early onset or young onset, whatever you want to call it. And does that impact my life worse in the future? I think you answered it earlier that there's no real evidence to support that.

Rodolfo Savica:

Let me say this, and this is very important. So, I am talking about big numbers, I'm not talking about individual patients, so clearly everybody's different, and there are exceptions in the big numbers, but if you look at a population, so, we are looking, we have been looking in the population living in southeast Minnesota. So, the entire population, working, that lives in Olmsted county, we're able to follow them from the moment that they were born, or they moved here, to the moment they died.

So, we have 30, 40 years of observation of medical records that we review. So, we have a very good snapshot, on a population. The population is clearly white, Caucasian, Northern European heritage, so it may not apply to everyone, but it can give us a snapshot.

What we know is that a diagnosis of early onset Parkinson's disease, usually is more benign. It means that it does not progress as fast as late onset Parkinson's. The survival time I told you is 38 years from diagnosis, which if you're diagnosed at 35, 40, it's still 78, 80, which is more or less the life of our humans in the Western world.

The important thing, say okay, you're talking about my life expectancy but what about my quality of life? If I tell you that this is a little bit more benign, means that generally speaking, we don't see the same kind of decline that we see in a later onset patient. Obviously, they're older, there's the aging process, there's major comorbidities that can put people down.

One thing is important also, that it seems that the patient at early onset Parkinson's disease, always responds to the medications, it's just a matter of adjusting them. And the complication, the very feared complications such as dyskinesia, for example, that are very feared, and these are a problem right, you are concerned about that, they are present, only in 12% of our patients, which is a small number. Again, it can happen, but it's more of what we see later on. And we are adjusting for the medication, in other words, we're using the same amount that we are changing. So, what you will see in the future, I'm thinking that clearly, it's better not to have any disease in life, right.

Don't pick any disease, but early onset Parkinson's disease, overall, given this big number trajectory and again there are exceptions to the rules. Okay, it's a disease that is way more benign than later onset, especially in some characteristics. I'm sorry, sir. If you're a woman, you have a better prognosis. Generally speaking, if you started with tremor, if tremor is present from the beginning, seems to be a better prognostic sign. In other words, people are having a better prognosis with tremor than patients that don't have tremor at all. And there are some mounting biological evidence to support, why this is happening, it's not just random, there's a good reason why diseases can happen.

So, in addition, the third thing is that response carbidopa/levodopa, what I mean with that. There are some genetic forms, I'm sorry my voice is getting down, there are some genetic forms that even a smidge of L-dopa will cause major side effects, dystonia, dyskinesia and so forth, unless we do the genes, we don't know whether somebody is having this mutation. But if you or any patients do not have this mutation levodopa will always work.

Okay, so I gave you a couple of things. One other thing that I want to mention, and I know the Davis Phinney Foundation is strong in that, and I am super strong in that, is exercise. Working out. All my patients, any age but especially young, are working out. And the young, to me, the young, I don't want them to work out, like the elderly. I want the young to work out like the young. What I mean is that I want the young to work to go, okay, I like biking, well, excellent. You don't bike with people in their 80s, you bike people in their 30s or 40s or your age, and they say, but I'm not there. Ok, yes, okay you're not there. You will make it there.

And if you need more carbidopa/levodopa you will take it and you will be able to pick up. That is an important thing. Like boxing, I love the Parkinson boxing clubs. They're fantastic. Somebody in their 30s, 40s, you want to do box, you do the regular boxing.

You go to the regular Boxing Club, not to the Parkinson's Boxing Club. You like to martial arts go to Grapple, I'm not kidding Grapple, Brazilian Jiu Jitsu, those are fantastic activities, because they allow proprioception to be constantly stimulated, prevent falls and falls are my biggest fear.

But doing the regular one, tell the trainer, hey I have Parkinson's disease. So, I mean maybe I'm not the fastest, but still, you want to measure yourself with people at your age, not people in their 80s, when you're not related to them. You're not related at all so that is something that I always say to my patients.

Melani Dizon:

That's really interesting. Also, so along those lines. Somebody said, often when they exercise, really hard like right after they have increased brain fog. And then, after they recover, they actually feel better with their non-motor symptoms and their motor symptoms. Is that common?

Rodolfo Savica:

Very common.

Melani Dizon:

And the brain fog, what's happening to make the brain fog, is it just that you've kind of gone through your medicine, you've metabolized everything?

Rodolfo Savica:

Likely there's a requirement that is higher. And so immediately there's a lack of dopamine, or any other chemicals, but then the exercise has the surge back on these particular chemicals. It's very common to say you know right after, I'm exhausted, I'm fatigued, and wiped out. But I rest a few minutes and I feel great. That's exactly what happens many times and I'm not surprised to hear that indeed.

Tom Palizzi:

You know, that's definitely the case and I think, I do a lot of cycling, I run a Pedaling for Parkinson's three days a week and again, I think the idea there is to push it, not just pedal, so there's...

Rodolfo Savica:

Correct. Correct.

Tom Palizzi:

Somebody posted a really interesting question here just a minute ago about plasticity and the possibility of creating new pathways.

Rodolfo Savica:

Absolutely. Absolutely. So, it's kind of complex, I will try to cram it in a little amount, so, we have some systems. Our system is the basal ganglia, the basal ganglia is a system that we have had ever since we were born, that is relevant to regulate and to clean out the noise around a movement, around an action. And it's something that we've developed ever since we were young. So, in other words, if I do this movement, I am very precise in doing it. I'm not doing everything else. My basal ganglia is removing everything else while allowing these movements very precisely.

And ever since I was a little kid, I was born, I developed the system. But it's interesting because there's a big cortex, and the basal ganglia are little, tiny nuclei, that did not evolve as much as the cortex. So, everything goes in this little narrow path, which is very difficult to manage. What we want to do when we are getting older at any age. We want to make sure that this noise surrounding the basal ganglia that is trying to do that, is removed, and we want to make sure that the basal ganglia are getting more information about the noise from somewhere else.

So, that is why it's crucial to build new pathways. This is crucial using what, the plasticity of the brain is something that happens anytime. Clearly as we get older is different. But there are some movements, some activities, including movements that can help dramatically increasing the plasticity, increasing the basal ganglia activity. And there are some chemicals that are produced during exercise. The famous BDNF, brain-derived neurotrophic factor that increase dramatically, and help restore new cells and sprouting new connections.

Clearly, let's say Grapple, just because it's what I do for fun. It's my side job. So, I teach martial arts as side job. So, let's say you do martial arts, and you never do martial arts, but you like to do it. That is a great opportunity, because then your body would use completely different motor pathways, motor areas that you've never used before. So, that would improve the quality of your movement to regularly. Just because you're giving more information coming from different sources. So, it is very important, and the plasticity is something that I am really keen to do, that's why I say my patients are always told to exercise.

However, evolutionarily we have a problem. The evolution of the basal ganglia I mentioned is being delayed. We are about half a million years behind, compared to the rest of the cortex. I'm not kidding.

So, there's a fish called lamprey. That is the one that diverged from us, but all the animals and monkeys and all the vertebrates are having the same basal ganglia structure, it's very small.

Finally, some monkeys now they seem to have something called hyper direct pathway that goes from the basal ganglia straight to the frontal lobe, without getting different additional stations. And it seems that humans have that. But the idea is that these are newer yet young, yet to be developed pathways that can help compensate, some of the problems that we are having with movements later in life like Parkinson's disease. So, it's very complex but it's fascinating to be honest.

Melani Dizon:

Um, let's see. So, a couple of people are asking, just the relationship, is there any, does DBS do, can do anything around dementia, symptoms, executive function, anything like that?

Rodolfo Savica:

Well, historically, historically the selection of the patients, the patients that have memory loss, were excluded for deep brain stimulation. So, for example, if somebody was having in the testing, for DBS you have to go into a center for testing including a full hour of memory testing. If in the memory test patients are not doing that well, there's always a risk that the Deep Brain Stimulation can make things worse a little bit in terms of memory. So, the short answer is that deep brain stimulators should not have any effect on executive function, if anything they can make things a little bit worse.

There were some studies, years ago, down from some of the pioneers on the DBS field, coming from Canada, Lozano and his team from Toronto. They were studying Deep Brain Stimulation in Alzheimer. They had a number of cases of Alzheimer, and they were stimulating some areas of the brain that were allegedly probing memory. And they did not see any particular improvement, but there's a good reason why because memory is everywhere, and the anagram of memory are stored everywhere.

And there's different kinds of memory, so stimulating one area doesn't necessarily mean that you will improve. Again, there are some patients that report some improvement, because of the dopaminergic requirement that is changed. But remember, there are some patients with deep brain stimulation that even though, from a motor standpoint, from a tremor, rigidity, standpoint, they do not require carbidopa/levodopa, they do require it because they have fluctuations of their non-motor symptoms like anxiety depression and memory loss. So, just to tell you that DBS is really focusing so far on the motor aspect of the problem, not necessarily the non-motor one.

Tom Palizzi:

I was gonna say I had another question for you, but I forgot. Nah, I'm just kidding.

When I was diagnosed years ago, 13 years ago, shortly after that, maybe 10 years ago, I said to my doctor something along the lines of that I'm mostly worried about losing my mentality, my cognitive capability than I am the mobility capability. And she jumped on that, she goes well let's get you tested for, let's have a psych test to see how you perform. That scared me to

death, but what I did notice from that is it really helped me establish a benchmark, of where I was, so I had something to compare my cognitive ability to later in life and so what are your feelings on that?

Rodolfo Savica:

I think it's good, having a baseline you say having a two-to-four-hour memory test would be good, but also having the paper and pencil test done, 10 minutes in the office of your physician, can be very important even earlier on. And if, as you say, I'm worried that with time, things can be worse, having a baseline, a few years prior can help see if you have a decline. There are only two things that we have to consider. Obviously as you get older, you're missing some of these points. As you get older, 20, 30 years later, your memory test has to be adjusted for the age that you have and usually they are because the tests are standardized.

One of the things I do, and this is when the behavioral neurologist comes in. I'm also a behavioral neurologist so that's the point. Sometimes, as you know, you say I was scared to death, clearly, I'm pretty sure that when you did the test you didn't feel the best. At the end you say oh my god, I flunked it, oh my god. I'm so anxious, it's going to be a problem, which is true. That makes a world of a difference. Anxiety, depression, the mood the state of mood, maybe that morning you fought with your friend or your wife, you know, something that can interact and interface with our performance. Sometimes I'm ordering, when I'm worried about memory test, a PET scan of the brain. The brain PET scan, not CAT scan, PET scan, is an objective measure of how the brain is using glucose, and it's heavily used in behavioral neurology, to see the different patterns of memory disorders.

So that would be something that even if you're upset, or if you're anxious, or if you have a panic attack in that moment it should not be affected. So, I say, I agree with you, getting a baseline is important, either a paper and pencil test, and if the paper and pencil test is done by your physician is down, a big test, two to four hours, but if even if there are some issues because patients are anxious, upset or they don't like it, PET scan can be a very good alternative, I would say.

Tom Palizzi:

That's exactly what happened to me I walked in the room to get my test and beads of sweat were coming up my forehead. The doctor says, are you okay are you having a heart attack or something? He said look, I'll give you half hour to settle down then we'll get to your test and fortunately I was able to get through it okay so.

Rodolfo Savica:

That is a real problem, that is a real problem indeed.

Melani Dizon:



Well, I know I could talk to you for three hours and I know a lot of people on here have said this is the best YOPD discussion we've ever had. So, we're really happy because Dr. Savica is actually going to be joining us for our YOPD Victory Summit Event. That will be happening at the end of June, so look out for that. And so, we'll have more opportunities to ask you lots of questions. Dr. Savica thank you so so much for being here today. Thank you, Tom for tag teaming with me and we will get everyone the recordings and everything you need, and I'm just so so grateful for you to be here.

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