Aging: What to Expect?

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[00:00:04] **Dr. Carlos A. Pardo:** I would introduce the topic of aging in rare neuroimmune disorders, but we are going to make this as an interactive session because, in clinic, I frequently get questions about aging, and, particularly, questions related with: What is going on with my body? Is my disease coming back? And this is a frequent concern.

[00:00:32] Patients that had myelitis when they were 40s, they reach age 60 and experience some type of regression of motor, sensory, or gait disturbance. And that, obviously, generates a lot of concerns and a lot of anxiety about what is going on. So, what I'd like to do is a brief introduction about: what is the biology of aging?

[00:01:00] So, it's extremely important because, in the past 15 years, we have been learning more and more about what is the meaning of aging, and the life expectancy in many developed countries has gone from 65 to 80, and there are even some patients that are a little bit higher than 80, while there are some countries in which the life expectancy is only 50s or 60s.

[00:01:26] One thing that we have learned is that there are a lot of determinants of the process of aging, not only biological, but also environmental factors. Let's touch a little bit about that. I'm going to show you a couple of slides.

[00:01:43] The first thing is, aging, in many ways, is determined by genetic factors. Genetic factors are basically the imprint that we have in our DNA. And the key of aging is because all our cells in our body actually are dividing almost constantly -- some are very fast speed, some are very slow speed.

[00:02:06] The process of aging is actually determined in our chromosomes and determined in our DNA. As the cells keep dividing, there is a structure, basically in the cell, that is called telomere that is going to be checking on you and say, “Okay. I'm getting older and older.” So, a telomere that is long means that it's a young cell.

[00:02:30] A telomere that is short means that that cell has been divided for several times. And at some point, basically, the receptor is gone, and the cell is stopped dividing. Okay? So, telomere is one of the ways that we use in biology to check the aging process in a cell.

[00:02:48] But the other problem that we are dealing with is, the DNA, our basically, genetic code, keep reproducing, and keep dividing, and keep basically duplicating, generating misinformation. So, in other words, as DNA replicates, it may add errors, and that is actually something that is called genetic instability.

[00:03:18] And that's actually one of the reasons patients get cancer, because cells keep dividing. And at some point, it generates signals that are wrong for proliferation, and you can get cancer and other problems. But the second thing that is important from biological point of view is cellular senescence. In other words, our cells are designed to stop dividing and getting, basically, a cycle -- a biological cycle.

[00:03:43] There are other biological factors. Oxidative stress is a very important factor. I always call oxidative stress is the rustiness of the cell. In other words, when the metabolical function of the cell generates toxic material, that is going to damage cells and is going to damage the process of reproduction and duplication of different cells.

[00:04:06] And that actually is going to produce a significant impact in one portion of the cell, that is mitochondria. Mitochondria are small batteries inside our cells. So, mitochondria are critical for the cell to keep active and keep energetic.

[00:04:23] And that mitochondria frequently gets exposed to a lot of factors that produce what we call mitochondrial decay and produce damage of the small battery. If the small battery runs out of energy, the cell is going to die.

[00:04:38] But the other thing that we have is epigenetic factors. So, what are epigenetic factors? 'Epi' means things that are outside of the genetic context. So, epigenetic factors are the environmental influences that our DNA is exposed to. So, we have many environmental factors that damage the DNA.

[00:05:03] We have toxins in the environment. We have other effects of temperature, climate change, and disease that may affect the signal from the DNA. And that is basically specified in the DNA because the DNA keep adding some molecular elements that are called methylation and histone modification that eventually are going to derail the normal cycle of a cell.

[00:05:34] Now, the next thing is other factors that are extremely important. When we run a process of maintaining a normal body, we need to produce proteins. When we are getting all that, actually, one of the key factors that we deal with is disturbance in protein processing, meaning that our proteins are going to be damaged.

[00:06:06] Number one, because some areas of the body, particularly the brain, start accumulating proteins in a very abnormal way. For example, Alzheimer's disease is a disease that is produced by accumulation of proteins that are normally produced but, for some reason, accumulate and produce damage of the neurons. Those proteins are called tau proteins or neurofilament. And eventually, other material, like amyloid, basically gets deposited in the brain and produces neurological degeneration.

[00:06:41] In the same way, there are areas of our body, like our muscles, in which the process of production of protein decrease. Then, we start having a decrease in the muscle bulk, something that we call sarcopenia. So, when patients with neurological diseases, myelitis, neuromyelitis optica are getting older, one of the key elements of the process of rehabilitation is avoiding sarcopenia, because after we reach the age 60, 65, 70, we start that process of losing muscle fibers, and that is detrimental, obviously, for the body function.

[00:07:23] So, it's important that, even if you are in the limit of age 60, 65, you keep going and you get the guidance from your physical therapy, your rehabilitation doctor, to avoid the process of sarcopenia, because that is basically a very important part of our aging that is going to produce significant damage.

[00:07:44] The insulin and the nutrition are very critical, and you have been exposed to all of these new concepts of insulin resistance and the diet to modify insulin resistance. That's actually very important because all our cells depend on the sugar, depend on the glucose. And, for that, they need insulin and the signalling from the insulin to maintain the normal energetics.

[00:08:11] So, it's extremely important to keep an eye because this sensitivity to insulin is modified when we are getting older. And that's the reason we have more tendency to develop diabetes when we are getting older, particularly with diabetes Type 2.

[00:08:25] But the last factor that I'm going to make emphasis is inflammation, and this is probably a critical factor for many of us. Number one, when the immune system is getting older, there are processes that are going to be accelerated, and there are other processes that are going to be slower. So, in other words, aging affects the immune system to the point that some pathways in the immune system are going to be more susceptible to be disrupted.

[00:09:01] So, we know very well that after age 50 and 60, some of the vaccinations that we received when we were infants or during childhood, that vaccination, that immunity start basically decaying. So, it's going away. And that basically reflect the aging of the immune system, and that's a factor that is important to pay attention.

[00:09:25] And that the reason many times we encourage patients to get vaccinated for shingles, because after age 50, patients basically don't have too much immunity against shingles, and they get shingles. Obviously, that's going to be detrimental.

[00:09:39] But the other thing that happened from aging is a concept, basically, that was introduced a few years ago. The aging of the immune system also implies that we are in a mode of low-grade inflammation all the time.

[00:09:54] So, as we get older, actually, we have at this degree of chronic low-grade inflammation that, unfortunately, is going to damage all organs. It's going to damage the structure of blood vessel endothelium , and that is obviously going to contribute to the process of aging.

[00:10:12] So in summary, we have many different factors that influence aging in neurological disorders, and the main goal is to try to control that. And as I always say, it's extremely important to understand that our body is very different.

[00:10:28] So, let's take a look at this complex picture. This is the spectrum of myelitis and myelopathies in 2024. So, the process of aging is going to be very, very accelerated in some patient that have chronic immunological disorders.

[00:10:47] So, patients with multiple sclerosis, patients that have ongoing autoimmune disorders, the process of aging may be somewhat influenced by the immune system. The autoimmunity that they have as part of the disease is going to be impacted by that.

[00:11:02] Now, if you take a look of AFM, the aging probably is not going to be affected dramatically, but in some circumstances, the fact that there was a one-time event that produced damage in the spinal cord and the reserve of the spinal cord, that may be influencing later the function of the motor system.

[00:11:21] But in many ways, monophasic events like monophasic myelitis or an infection that produce myelitis are not going to produce the magnitude of impact as patients with autoimmune disorders may have for the future process of aging. And the same happens with vascular injuries of the spinal cord or mechanical injuries of the spinal cord, like spondylosis or even some of the toxic metabolic disturbance.

[00:11:48] So, in other words, aging is a process of budget. Okay? Our body is our ATM, and we are always getting money from the ATM. So, we need to keep in mind that we need to keep a good reserve and that we need to keep, basically, a good amount of rehabilitation and support for our body to avoid that the process of aging producing a significant impact in the overall neurological function. After that, the money is on Dr. Levy.

[00:12:23] **Dr. Michael Levy:** I don't know, I just feel a sense of doom right now. Feel like my telomeres are shrunken, and my ATM reserve is about empty, but we're happy to take some questions on aging in TM, in NMO, and in all neurological diseases.

[00:12:49] **Dr. Carlos A. Pardo:** Jacinta has a question.

[00:12:51] **Audience Member 1:** Hello. Can you hear me?

[00:12:53] **Dr. Michael Levy:** There's a mic behind you.

[00:12:59] **Audience Member 1:** Someone asked me not long ago. Her mother has had NMO for over 20 years. She's reaching her 70s, which is still young. Let's not forget that. Her question for me is, “As my mother grows in age, should her care need to change? Are there any changes that neurologists that are working hard to help them overcome some of the symptoms of NMO, especially with the new therapeutics, will the therapeutics still work? Will her body respond the way it has?” I don't know the answer. I'd love to hear your thoughts.

[00:13:49] **Dr. Michael Levy:** Do you wanna go first?

[00:13:50] **Dr. Carlos A. Pardo:** Go ahead.

[00:13:51] **Dr. Michael Levy:** I would say that there's two parts of that. The first is on the immune system. I tend to be gentler with people who are older. The definition of older is 10 years older than me. So, I'm 49, it means 59 and above.

[00:14:08] No, seriously, I do try to use medications that aren't maybe as immune-suppressive, if I can, for people who are older. The other part of that is on the symptom management. Those issues get compounded with age, if it's weakness, or pain, or things like that.

[00:14:29] People who have transverse myelitis and have been stable for 20 years are going to have new things come up. They get worried. We MRI them, everything is the same. So, what's going on? We think it's the aging process overlapping with the damage that was done a long time ago. The management is, as Doctor Pardo said, maintaining good physical health, diet, sleep, hygiene, all of those things. So, I do think that issues do come up, and I try not to overreact. I try to be gentle on the immune system, and I try to push on physical therapy, and diet, and things like that.

[00:15:10] **Dr. Carlos A. Pardo:** Leah.

[00:15:15] **Audience Member 2:** Okay. All right. So, concerning the Shingrix vaccine and the CDC recommending it being over 50, if we're already immunosuppressed and our immune system is weaker because of NMO or MOG, then should we go ahead and take it? And if we took it, because of being on Rituxan, and we're switching to an FDA-approved treatment and might have B cells one day, should we get it again?

[00:15:41] **Dr. Carlos A. Pardo:** It's a very good question, and it's very frequent question. And my advice is always to get Shingrix. And if you are in a very focused therapy plan for depletion of B cells -- actually, I always check antibodies against the virus that produce shingles -- and if the person is young and the antibody level is very low, I always recommend vaccination.

[00:16:09] But after age 50, if you have an immunological problem, I definitely recommend to be vaccinated because the shingles virus actually may produce meningitis, and that is a very devastating disease when it shows up in patients that are immunosuppressed.

[00:16:30] **Dr. Michael Levy:** And there's another reason. For those of you who saw the news articles this summer, two big studies using Shingrix reducing the risk of Alzheimer's disease and dementia later in life by 20-25%. That's a huge number. So, all of you caregivers and all your family members should take the Shingrix vaccine.

[00:16:52] Even if you were vaccinated as a child for VZV -- that's actually the inactivated virus -- it still lives within you. You still want the Shingrix vaccine to prevent [latency]. We don't know why it prevents dementia in the future. That's something that's an active area of research, but it's something that looked very real in epidemiologic studies.

[00:17:14] **Dr. Carlos A. Pardo:** Greg?

[00:17:15] **Audience Member 3:** Hi. Couple of quick questions regarding insulin resistance and inflammation. Curious, your thoughts on GLP-1 agonists. I know that some folks with MS are experimenting with that, and could it help stave off issues associated with aging? I know that they're doing some work around it, speaking of dementia. That's one.

[00:17:40] And then, the second is, on the topic of this anti-aging or reversing-aging movement, folks like the Dr. Sinclairs of the world talking about NMN, or NAD+, or metformin. In the context of us here -- I know it's very early on in that research -- but could therapies and things like that help in our world?

[00:18:12] **Dr. Michael Levy:** I'm a big fan of GLP-1 drugs. For people who are overweight and obese, it does --

[00:18:19] **Dr. Carlos A. Pardo:** Do you mind translating what is the meaning of that?

[00:18:21] **Dr. Michael Levy:** GLP-1 drugs, yeah. These are the injectables that you've heard of: Ozempic, Wegovy, Zepbound. These are weight loss drugs. They're injected -- and I think there's a pill form now -- and they have a really good outcome for weight loss.

[00:18:39] And it looks like, even in mouse models of MS, these EAE models, at least at Johns Hopkins with these studies that were done, they may be beneficial even in just calming inflammation a little bit. Not a huge amount, but added to the benefit of the weight loss, it looks like something that should be studied.

[00:18:59] For MS and probably for other diseases, we need to study this. If you can reduce your body weight at least from an obese BMI (over 30) to under 30, in MS, your risk of a relapse drops 30% just from weight loss.

[00:19:15] And it's probably a good idea for vascular health and long-term health in all diseases. So, weight loss without GLP-1 drugs -- great, that's awesome too. But with the medication, some people need help for weight loss. I think it's a good thing.

[00:19:31] **Dr. Carlos A. Pardo:** The other thing is very interesting, and actually, early this year, there were a couple of papers in Nature -- that is the one of the most important science journals -- on the anti-inflammatory effect of these medications. And I think that this set of medications has opened the door to a lot of research in different directions, because I think that controlling that pathway appears to be some way approach to manage inflammation to manage neurodegeneration.
[00:20:07] Michael mentioned the work that was done at Hopkins with some animal models of Parkinson's disease. They were using that model; they were not using the model for evaluating, basically, obesity in mice. They were trying to control Parkinson's disease.

[00:20:22] And, actually, the results are extremely encouraging. So, I think that these new set of drugs actually is opening a different window that probably we are going to learn in the next five years a lot.

[00:20:39] To tell you a truth is that the reason I wanted to show that there were 10 different factors, and perhaps 20, so I don't think that we are going to have a magic pill to control those 10 or 20 factors. I think that the most important part is you need to accept that your genome has an expiration date. All right.

[00:21:03] So, that means that your body has an expiration date. I don't believe that you are able to modify that. You can modify that with some of the factors that we mentioned, but in general, I think that I don't believe that it's going to be a common strategy to deal with aging.

[00:21:23] **Audience Member 4:** My question is in regards to MOG antibody disease, but I suppose it could be part of any of these disorders. As we age, I have been told by physicians that maybe my immune system might get weaker over time. Is there any thought that has been put behind this for those people who are on preventative medications? That maybe, after a while, as somebody has been on there for a long time and aged through, that they could maybe go off of them for a little bit or work towards getting off of them ever? Have you thought about that?

[00:22:05] **Dr. Carlos A. Pardo:** Go ahead.

[00:22:06] **Dr. Michael Levy:** I think it depends on the disease, to be honest. With multiple sclerosis, people over age 55, 60, 65, there is an attempt to take them off of medications. But, as we saw in Copenhagen last month at a major meeting, even people in their 60s and 70s, when they come off of medications, there's some disease activity in MS.

[00:22:30] With NMO, I don't take people off of medications. I've hospitalized people in their 90s -- it's not pretty. But I do try to be gentle when we immune-suppress them because there is a balance that we have to reach.

[00:22:45] And with MOG, I think that there's a lot of potential for MOG people. As you know, about half of MOG people eventually will get over the disease. The antibody goes away, and a lot of people don't need medication long term, and some do.

[00:23:01] But it's hard to predict who does and who doesn't. It's a little bit of a risk. Some people come off, and then we just observe closely. So, I think it does depend on the disease, but it is something that we've thought about.

[00:23:18] **Audience Member 5:** Hi. So, there's a lot of evidence that non-biological factors can induce epigenetic changes on -- okay, so you know where I'm going -- epigenetic changes on DNA. I'm wondering if you have thought about the implications of non-biological factors, such as psychological stress, and how those could influence aging in people with rare neuroimmune diseases?

[00:23:44] **Dr. Carlos A. Pardo:** It's a very good question, and the answer is yes. Stress actually produces a lot of biological effects. Stress affects hormonal pathways. Stress affects the insulin pathways. So, stress is a determinant of not only problems in rare neuroimmunological disorders, everywhere in health of our body is going to be affected.

[00:24:11] So, stress has different versions. Stress has the version of difficulties on daily living and difficulties that are maybe just episodic, but some of them are chronic. There is one stress factor that is very critical and important: malnutrition. We have malnutrition in many areas of the world and that is a very important determinant epigenetic factor for aging. So, yes, going back to the original question, stress is a major determinant of how our cells age.