

Mark Masselli (00:04)

Researchers tell us that 10 to 35% of people suffer from long covid following an acute covid infection. That means millions are still struggling with long covid, even five years after the pandemic started.

Dr. Gabriel de Erausquin (00:19)

The parts of the brain that are affected by covid overlap significantly with those that are affected early in the course of Alzheimer's disease. They're not identical, but they overlap significantly.

Margaret Flinter (00:32)

Our guest is a leading long covid researcher, Dr. Gabriel de Erausquin, a neurologist at the University of Texas Health San Antonio. He's the first guest in our two-part series about the latest long covid research.

Dr. de Erausquin (00:45)

I do agree with the overall gist of the, of the publication. This is that I think that it's not nearly as common as we thought usually it would be, and that the overwhelming majority of the cases that are reported as long covid adding indeed, perhaps an extension of, anxiety and depression in people who already had significant impairment prior to being infected.

Margaret (01:13)

This is Conversations on Healthcare.

Mark (01:27)

Well welcome Dr. de Erausquin, to conversations on healthcare.

Dr. de Erausquin (01:31)

It's a pleasure to be here.

Mark (01:33)

That's great. You know, you've studied the effect of long covid on cognitive impairment among more than 3,500 adults from eight countries. You recently published study found that older adults with long covid had double the risk of moderate to severe cognitive impairment compared to younger patients. I wonder if you could tell our listeners about the importance of this finding and the implications.

Dr. de Erausquin (01:59)

That's an interesting way to, place to start. The importance will depend on whether what we have, found generalizes and what they mean by that is, remains true, over the long term. The data we have now, overwhelmingly are from one or one and a half years after the original infection. And, we're now long past that. The, the timeline, and what we need to figure out, and we're doing studies currently to address that question, is whether what we found, in that initial sample set of samples is stable, meaning it remains, the same has gotten worse or the, or the, the impairment has become progressive or has recovered to some extent. Mm-hmm. And that is really the crucial question. Most of the indications we have from, follow up data are that it is either the same or progressive. We don't see recovery in older adults. We do see significant recovery in folks under the age of 60, but not in, people over the age of 60. So what this implies is that if assuming it remains true, the, it implies that, the, the likelihood of developing significant cognitive impairment, which is already a public health problem. As you might know, the rates of dementia in the adult popul- older adult population in the United States and worldwide because of the aging of the population itself, have increasingly become a public health concern and are only likely to increase over the next 10 or 15 years. This would imply if it remain true, as I suggested, that, the, the magnitude of that crisis is at least two times greater, if not more.

Margaret (04:19)

Well, I'm sure this, caused you to, look at the data and ask whether there were predictors, that you could find of, who was likely to have this dementia like impairment, in older adults, whether there was a genetic connection or comorbidities. Can you tell us a little bit about that?

Dr. de Erausquin (04:39)

Yes, we know a little bit about what predictors are related to the acute function and, the, the best predictor is, appears to be persisting in impairing refractory function, and that seems to correlate quite, closely with the ongoing presence of cognitive impairment. Other predictors such as, for instance, the severity of the acute disease itself, whether the person required oxygen management or, or even admission to an intensive care unit are less robust. They do predict a little bit of the risk, but not, not as clearly.

Margaret (05:28)

And I wanna make sure I heard you clearly. Did you say olfactory difficulty with smelling was the primary predictor?

Dr. de Erausquin (05:35)

That is what I said. Yeah.

Margaret (05:36)

I see. Okay. Thank you. Just wanted to make sure I heard that right.

Dr. de Erausquin (05:40)

The other predictors that you mentioned, genetics are precisely what we're looking into now. We are covering out a, longitudinal study that will be completed in three and a half years from now or so in samples in, three countries in the United States at five different sites, in Argentina and in Nigeria. Addressing precisely that question and focusing on those populations or the segments of the population that were most severely affected by the, disease itself. I call itself both in terms of morbidity and in terms of mortality. The, in, in the United States that you might as, as you will remember, the locations that where the hot spots of the pandemic, where the, the two coasts, so, Seattle and New York particularly. And, the populations that were most affected were, native Americans and Hispanics, followed somewhat, behind by African Americans and the least affected population were, Caucasians or whites. The study focuses on those populations, so we'll focus on both. We have a sample in Seattle, sample in New York, two samples at the border, San Antonio and Laredo, and then as I mentioned, Nigeria. And inside in northern northwestern Argentina, it's also a Indian, overwhelming the population because those are the populations most effective. Hmm. The rationale is that, as you were suggesting earlier, there may be a genetic predisposition, for the long-term cognitive impairment that follows the disease. And the, the early data suggested indeed, we are on the right track. Mm-hmm. We found that about 50%, depending on, you know, the, the margins of the estimates between 40 and 60% of the risk of developing cognitive impairment after Covid was indeed inherited. What genes are affected is the part of the study that remains to be done. We are looking at very detailed genetic descriptions, so what's called whole genome sequencing to, to address that question.

Mark (08:19)

You know, you reported that for long covid patients over the age of 57, the symptoms associated with cognitive difficulties look much like earlier, early dementia. I'm wondering if you could share more, with us about that finding?

Dr. de Erausquin (08:33)

Sure. Actually, the, the term dementia, like was coined, earlier than us, by a publication in early late 21 or early 22. I can't recall right now exactly the date. Looking at the UK Biobank sample, this is a, population sample, population-based sample of the United Kingdom that, has fairly detailed data including, brain imaging on an ongoing basis. When they looked at the consequences of covid in that sample, they found a segment of folks that had what they call dementia like symptoms. We use the same, turn of phrase to describe the findings in, in our international samples, for simplicity's sake. But what that means is that these people have primarily difficulties with recall of very recent information, what people tend to call short-term memory, meaning, you know, conversations that we had in the past 24 hours or, or very recent events, what's we call episodic memory. So the substance of what, may have happened when, when I went to dinner, last week, that type of memory loss is the earliest affected in Alzheimer's disease, and it also seems to be the earliest and most prominently affected in long-term covid. The second type of impairment is also common frequent, you know, frequent problem that we all have after the age of 50, but becomes much more prominent in early Alzheimer's disease. And that is we tend not to recall, a word that we want to use in conversation or the, you know, the normal case. We typically recall the word a few moments later, after had its tip of the tongue for a little while. In the case of Alzheimer's disease, the word tends not to come back. Mm-hmm. And, in the case of these folks with long-term covid, the, the loss looks more like it does in Alzheimer's. This extends to names of, acquaintances or, or friends or in, in more severe cases, family. Mm-hmm. This naming impairment is actually quite common, and that is seen as well. Mm-hmm. The third type of, cognitive difficulty that this folks experience is, with what's typically called, executive function, meaning the common ability to sequence and prioritize and, do hierarchical organization of tasks. For instance, covering out the recipe or making a small repair or using the, remote control of the, of the television set and things of that sort that require a little bit of organization and, correct sequencing in order for, for them to, to be effective. That tends to be low, lost early in Alzheimer's disease, although usually after the loss of memory, function. And the same happens in, in this group of people. Now, what we have called, or what

has been called by the UK Biobank people, dementia-like symptoms is the presence of all three of those types of deficit simultaneously in the same person to a significant degree, significant, statistically speaking. So more than one and a half standard deviations away from the average for that sample.

Margaret (12:31)

Maybe I could ask you, because I think some of this is probably new to our listeners, to differentiate since you're noting that this is more likely in older persons than younger persons. Younger persons with on covid seem to recover the cognitive function, but older people are at risk for the, dementia, symptoms or conditions, just by virtue of age. How do you sort the two out? And of course, what people would wanna hear is what's the best advice for treatment?

Dr. de Erausquin (13:05)

We didn't sort it out. It was empirical. What we did is we looked at the population as a whole, and in statistical terms, we look at what's called the distribution of a particular phenomenon, meaning the frequency with which that particular phenomenon occurs in a sample or a particular population, on everybody's familiar with the notion of the bell curve. The bell curve is the typical, what's called normal distribution of a phenomenon in a population sample, meaning that you have an average that is the most common value for that particular feature. Say height one, five feet 11 or five feet 10, and then you have tails both ways, a tail that moves towards lower heights and a tail that moves towards taller heights. And, and you have extremes of that distribution, that are typically what's called two standard deviations, or three standard deviations away from that mean the value in the center. Now, when we looked at the, distribution of these data, we looked, it looked not like a single bell, but rather like a camel back, meaning that it had two separate pigs at different ages. And that is characteristic of, what's called a bimodal distribution sometimes, but it's characteristic of a phenomenon that splits, a population, into different groups that, that tend to be statistically distinct. Now, when we looked at the distribution of the cognitive impairment in this, in these large samples, or these 3000 people or so from throughout the world, we found that indeed the distribution of the, the cognitive impairment was very different from different age groups. I see. And that's, that's where the, the conclusion comes from. So it was an empirical finding. It was not something that we were looking for necessarily, although we had some hints from, from previous data that that may be the case.

Mark (15:26)

Well, you know, you conduct The...

Dr. de Erausquin (15:27)

Sure. Go ahead, sir.

Mark (15:28)

Well, you conducted some earlier studies that found that covid infection led to elevated neurodegenerative biomarkers in inflammation in the brain. And this occurred even among people without a history of neurodegenerative disease. Tell us what you think that suggests.

Dr. de Erausquin (15:47)

That actually is the, the strongest bit of data. We, I was focusing mostly on the international study, but because that's the one you, pointed me to in the beginning. But as you point out, we have in some of these samples, some and some other samples from other groups. For instance, the sample in, in, in New York City from Langone School of Medicine. Mm-hmm. That, the group has been led by Dr. Ky, that that group and ours have found very similar, things. And as I mentioned, the via the UK Biobank has also similar data. Let me walk you through what are those findings? The first thing is that these folks that have more, severe cognitive impairment or difficulties tend to have changes in, brain structure, meaning the volume of particular parts of the brain that correlate with that memory, language impairment. The parts of the brain that are affected by covid overlap significantly with those that are affected early in the course of Alzheimer's disease. They're not identical, but they overlap significantly. Similarly, you pointed out to, biomarkers folks refer to, biomarkers when they're talking about the presence of abnormal proteins in, bodily fluid. Typically, there are other ways to look at it, but usually what we look at is abnormal amounts of proteins, either in the spinal fluid, which as you know, is the, the liquid abates the brain or in the blood, in the blood. When, either the group in New York or or group in Greece looked at this, they have found consistently that, after covid, particularly in the immediate acute phase after covid, the biomarkers of neurodegeneration that are commonly Alzheimer's disease were also abnormal in this population. We have not looked at that in our sample yet. We have the data, but we were pending the results. But overall, the conclusion is that there is a significant overlap in the clinical manifestations, in the brain changes, and in the body fluid biomarkers between the changes that we see in a older adult population after

Covid. And the changes that you see, or actually I should generalize a bit more in the cognitive impaired population after covid, because the, the, the New York sample didn't distinguish by age and that what you see in early Alzheimer's disease, there are more than one is the possible explanation for this.

Margaret (18:51)

You know, I wonder if you could, again, for our audience, as a whole, can you just back up a little bit and, maybe talk about the, what is the pathway connection about loss or change in smell and taste, that we see with early dementia and that you're seeing, with long covid? Maybe just for our, our audience.

Dr. de Erausquin (19:12)

Of course. Loss of smell is actually a very early manifestation of a number of diseases, not just Alzheimer's. It is very common in Parkinson's disease. It's rather common in frontotemporal dementia. And, it is actually seemingly common in Alzheimer's disease. The reason this occurs in Alzheimer's disease anyway is that, eh, early memory or, or, short term memory related structures overlap with what is called the extended olfactory network. This is actually the part of the brain that processes olfactory or smell related information after the initial sensation of smell is detected. Much like, when you look at, the parts of the brain that compute, visual information, the light, and the, that that is shown in the eyes, initially affects the activity of the so-called primary visual cortex in, in the occipital lobe. But then from there, it bounds, if you will, or, or goes to other parts of the brain that are responsible for more complex processing of that light signal. The same happens with the smell. You have an initial, detection of the sensation of smell, and a discrimination of what that smell might be, that in the temporal lobe then goes to other places. And so that those other places, the extended of factory network in the brain are affected early by Alzheimer's disease and also by long-term consequence of covid.

Mark (21:03)

You know, doctor, you have a follow-up study involving about 4,000 people in five locations around the world. These are patients who contracted COVID when they were over 60 years of old age. I wonder what the preliminary data showing. Also wondering, are these, individuals who were treated with Paxlovid or how, how are you separating out that, that group, or do you care, or does that matter in your, in your study?

Dr. de Erausquin (21:30)

So these are folks that were, affected by the first wave of the pandemic, meaning, they were contracting the infection between 2 20 20 and 2021. We are interested in particular in the variants of the virus up to Omicron because those are the ones that appear to have had the, the strongest impact on the central nervous system function. So that is the preliminary study I was pointing to when I was referring to our data in Seattle, New York, Texas, and, and the, Nigerian and Argentina regarding the question of treatment. We are agnostic to the treatment that they may have received because during the first year of the pandemic, no treatments were available. Vaccines were available for the first seven, six or seven months. So we're collecting that data, but we have not looked at it yet. We don't know, with any detail if the, for instance, if the variants of the virus, have a definitive impact on, on how likely you are to develop any of these symptoms. The initial impression is that up to omicron, all of the initial variants had roughly equal likelihood causing this cognitive impairment. But, but we need to look at that in more detail. Like vaccines had an interesting impact, though, in the preliminary, in the early analysis, we did an, a preliminary analysis, 500 cases or so, And, a bit against my expectations. I have to admit, I thought vaccines were not going to be relevant for this particular long-term sequela, but it turns out that they are people who acquired the infection before being vaccinated. And this is regardless of vaccine type, we, we had too much variability in the types of vaccines that people were receiving to be able to make any sense out of it. But it seems like people who were vaccinated before, before, being exposed to covid had a lower risk of developing cognitive impairment than those that were vaccinated after having covid. Mm-hmm. That is very preliminary data from only about 500 patients, but if that were to be true, that would be perhaps one of the first, positive, definitive, positive effects that the vaccines have had. Mm-hmm. Because otherwise, as you probably know, they did not reduce the risk of infection, and it's very unclear whether they reduced the risk of severe this severe disease. Yeah. But they appear, they, they appear to have reduced the risk of long-term sequela, and that would be a really good thing.

Margaret (24:25)

That would be very important to know, especially, we live in such a time of science skepticism. Mm-hmm. There are still those who doubt, I think everything about covid, the, the treatment, the severity, and whether long covid is real. And I think a British medical journal, analysis reported that major flaws in the current body of published research on long covid, have likely grad, have greatly exaggerated the true risks of developing the

condition. That's a very global, kind of statement. When we look across the age range being from children to our, our elders. What were, what was your reaction, to that piece of work?

Dr. de Erausquin (25:04)

I have to admit that I'm, somewhat sympathetic for, to the finding and in the sense that, what we know about the long covid and younger adults strongly suggests that, at least a number of those cases were people who had significant impairment before having covid. The biggest predictors of, younger, the younger adult version of co of long covid are a preexisting anxiety and depression, symptoms of, chronic pain such as fibromyalgia diagnosis or, or, or chronic fatigue syndrome. And in fact, the clinical manifestations of, long covid are seem to overlap with chronic fatigue or, or fibromyalgia to a significant extent. That doesn't mean that in my mind, long covid does not occur in those patients. In fact, I, I treat a, a significant number of those patients. Mm-hmm. And I am convinced that, when you look, carefully enough at the biomarkers of inflammation, they're pre and they're present. The disease is, distinct. In other words, it's not just fibromyalgia or just chronic fatigue. There are, specific changes in their blood biomarkers. And they tend to have two particularly notable symptoms. One of them is, physical, impairment, meaning fat ability, which is similar to chronic fatigue, but, but it's manifested more apparently with, the presence of, for instance, the incapacity or the inability to walk or any length of distance without, having to rest. And, significant respiratory impairment, that often forces them to wear oxygen when they walk about. So these two manifestations are actually, might want, say, unique, but, rather specific to, to young adult long covid. I do agree with the overall gist of the, of the publication in the sense that I think that it's not nearly as common as we thought initially it would be, and that they were holding majority of the cases that are reported as long covid adding indeed, perhaps an extension of, anxiety and depression in people who already had significant department prior to being infected. I see a fair number of dose as well,

Mark (27:57)

Doctor, I think, mm-hmm. Let me, I can just get in one last question here. I know, so many...

Dr. de Erausquin (28:02)

Before, before you do, let me just say that that doesn't apply to the dimension like symptoms. The dimension like symptoms are absolutely solid, in their presence when they are present and, and they are not accounted for by preexisting disease. We made a point of excluding those very carefully. What we don't know and that this is hugely important, is whether what the disease did was to accelerate a pathological process that was going to happen anyway. Mm-hmm. In other words, these are folks that were going to develop Alzheimer's later point in life. And what Covid did was to

Mark (28:38)

Accelerate it.

Dr. de Erausquin (28:39)

Precipitate it, make it happen sooner. And that we don't know. Mm-hmm.

Mark (28:43)

You know, the work that you're doing, the work you're doing is so important and you mentioned NYU Langone, and, while so many people would like, this to be in the rear view mirror, there's important research work that needs to be done. If you look at the lay of the land, how is the support and funding out there for this type of research? What are the obstacles you're facing? I think this is an important, issue because, it's such a complex and perplexing problem, that obviously needs, science, to take a hard look at it.

Dr. de Erausquin (29:22)

You would think that would be an easy target for the NIH review. Thank God, and I have not, an inside information that may allow me to tell you why we have not been affected by any of those reviews, so far.

Margaret (29:41)

We're glad to hear that.

Dr. de Erausquin (29:43)

Yeah. There are two, as you probably know, two lines of, investigations or research that have been primarily targeted by the review. The first one was, what they, they consider the government considered to be, related to DEI, other was the minority targeted research or, underserved populations, research and such in that round, for

reasons that escape me, because we are targeting, the population that was most affected by covid, that is by definition minoritized. We were not affected, in other words, we were not, told that we're our, we're, at risk of being, reduced or canceled the second round of, which is very risk. It actually happened last Friday, reviews. And, and, the second pause in funding is for international funding, which again, should affect us quite dramatically because, the large part of what we do is international. But my reading of the, the decision, the note, is that it will not affect us, at least for this year. I have not heard definitively from our program officer at the National Institute of Aging, whether that's the case or not. But, the reading, just reading the note, it seems that we are not under the categories of, research that they are going to, pause.

Mark (31:27)  
Wonderful.

Margaret (31:27)  
Wonderful. I can tell you we're happy for you, on that. It's important work. And we wanna thank you Dr. de Erausquin, for joining us today for this important conversation. For those who want to learn more, look for part two of our long covid series. And thank you to our audience for being here. Just a reminder, be sure to subscribe to our videos on YouTube, find us on Facebook and x, and please share your thoughts and your comments about this program. Take care, and be well.

(31:58)  
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