[MUSIC PLAYING]

OSCAR LOPEZ: I'm going to try to give you an overview of what's going on with the treatment. But first, you might have to see some of the slides that-- sort of an introduction slide.

These are my conflict of interest. So this is just a few words about the epidemiology of dementia. And I don't have to tell you that is very prevalent in people 65 and older. And we expect to have a huge population of people with dementia, especially Alzheimer's disease, in the future if we don't find anything that can prevent or cure the disease.

So this is from the Cardiovascular Health Study. And you can see the prevalence of dementia increases with age. And after age 85, practically half of the population that we examined had dementia, more women than men.

But that is an age effect. Women live longer than men. So that explains the increased prevalence in women, I think. But this is just to show you how prevalent is dementia, especially Alzheimer's disease.

So we don't know the cause. We have some risk factors. We have some risk factors that are probable, like age, which I will say is the most important risk factor. The APOE-4 explains about 20% of the cases. Then we have some possible risk factors.

But I will say the most important of a possible risk factor is cerebrovascular disease. There are some studies that found head trauma, family history of dementia, how many kids have Down syndrome. But I will say cerebrovascular disease and cardiovascular disease is a strong predictor of dementia in elderly individuals.

And then we have some factors that protect people, like for example, moderate alcohol intake, Mediterranean diet, physical activity, cognitive activity. All these things are related to a lifestyle and education. So it's not that if you do one thing, you are safe. It's because you have enough time and you're in good health, you can drink alcohol, that you can buy a good diet, and you can do physical activity, and you can share time with your friends. All these things are connected.

And I will say that is a protection. So I will say, I want to put it in other words, it decreases the risk. It's not that you are completely protected.

So the brain goes into this sort of factors that increase vulnerability and factors that compensate. And that's how we are aging. We're aging with increased vulnerabilities and with some factors that can compensate the vulnerabilities.

So describe what you see in red and yellow. This is bad, I will say. This is the relationship between chronological age and gray matter thickness. And you can see on the left that age is associated with decreased volume in supratentorial, infratentorial areas, primary sensory and motor areas, as well as in heteromodal association areas.

On the right, you can see we try to disentangle that. And age has, I will say age is a significant-- has a significant effect on the brain. If we try to disentangle Alzheimer disease, you see the parts that are related to Alzheimer's disease, especially the mesial temporal lobe.

But you also see, in the extreme right, the effects of hypertension. And hypertension has a significant effect on brain volume. And hypertension is extremely prevalent in old age. So we'll say age and the factors that are coming with age are creating this vulnerability state for neurodegeneration.

These are good things here. Great means good. And this is if you exercise, your brain has better volume. This is from the Cardiovascular Health Study. We tested physical activity in 1990, '91, in relationship to gray matter volume in 1998, '99. And we follow these people up to the year 2005.

And you can see the people who walked more than 72 blocks per week had better brain volumes than those who didn't. And especially, the hippocampal volume had some benefits of walking. But in general, physical activity-- and in this case, it's sort of a moderate physical activity, 72 blocks per week. These are the people that they go to the park and they walk a mile or two miles sometimes. They had better brain volumes.

And this is the same thing with diet. And diet had also an effect on the brain. And this is we tested people eating baked or broiled fish on gray matter. And you can see that diet has a positive effect.

But one thing that you need to take into account is that the people having a healthy diet are also the people who are walking in the park and exercising, are the people that are socializing more. So this is difficult to disentangle from what I mentioned before, this lifestyle factor that, in some ways, compensate for the bad things that happen to the brain.

So we know that Alzheimer's disease is a neurodegenerative process. We define neurodegeneration as a term that is used to describe the progressive loss of structure or function of neurons, including death of neurons.

You can see on the left, the neurons in a patient with early stages Alzheimer's disease and on the image labeled as being late stages. And you can see the neurons that are dying, are disappearing. But we don't know exactly what is causing that.

We know that there are they are factors that are related to this process. For example, on the right, you can see an MRI and an FDG-PET. So the MRI is giving us information about brain volume.

And normally, when we order an MRI for our patients, most likely will be reported as normal for age. But if we do an FDG-PET, you can see the patient would have the typical temporal parietal hypoperfusion or hypometabolism, which is an indication of neurodegeneration.

The amyloid plaques, which is the hallmark for the diagnosis of Alzheimer's disease, can be seen by PET. And you can see there, this is a picture compound B. So you can identify the presence of amyloid by PET scans. And these scans are available now to our patients. But unfortunately, insurance companies won't pay for that.

At the bottom, you can see a neurofibrillary tangle that is an internal neuronal deposition of hyperphosphorylated tau proteins. Again, it can be detected now with PET scans. And actually the first tracer was approved recently for commercial use. So now we can order a PET scan for amyloid and a PET scan for tau proteins.

But you can see here, there are many other deletions that happen in the brain of people with Alzheimer's disease. And we don't know exactly what triggers all this pathological cascade. We know the neurofibrillary tangles are there. We know that amyloid plaques play an essential role.

90% of the neurons in the base of forebrain disappear. So that's why cholinesterase inhibitors are useful for the treatment of Alzheimer's disease. There is a synaptic degeneration. Up to 40% of the patients with Alzheimer's disease have TDP-43, which is a pathological marker of frontotemporal dementia.

Up to 60% of the patients with Alzheimer's disease have Lewy bodies, which is the pathological hallmark of Parkinson's disease. And then there are some other pathological lesions that are happening with the neurodegenerative process that practically involve everything that is happening in the brain.

So one thing that is interesting is this is just-- we know that Alzheimer's disease has a long incubation period. And what are the predictors of a person having dementia down the road? And in research studies, we have found-- these are research studies wit-- it's a retrospective analysis.

So we know, for example, that hippocampal volume is a strong predictor of conversion from normal to dementia. Amyloid deposition is a very strong predictor, as well as white matter lesions. So you can see that the whole picture is not very easy to understand. Because you have people that are going from hippocampal volume to dementia, which is a marker of neurodegeneration, people that are going from amyloid deposition to dementia, and people that are going through small vessel disease to dementia.

So sort of three roads, that when they happen together, the risk is very, very high. But you can see people that they go from the vascular area of people going to dementia from neurodegeneration, pure neurodegeneration, and people going to dementia from amyloid deposition.

So this is-- will learn more about this now that we can do all of these studies and we can do prospective analysis. And that will be very important to disentangle how all these factors happen, and how they happen, and can predict dementia down the road.

The other thing that is happening which is a hot topic now is the blood biomarkers. And you can see here, these are people that we followed for about nine years. And you can see those that had low levels of A beta 42 in plasma at an increased risk of having Alzheimer's disease.

So as I mentioned before, this is a long incubation period. The brain and blood biomarkers are present there almost a decade before we start seeing the symptoms.

So how we put together all these pathological events and this complicated pathological process with medication. So on the left, you see how the pathology evolves. And we may have a genetic predisposition. We may. In some cases, there is a genetic predisposition.

Age is the most important risk factor. And there are some comorbid factors like cardiovascular disease and cerebrovascular disease that lead to the presence of tangles and plaques and Lewy bodies. And then neuronal death.

So in the center, we say that when a person-- they're pre-symptomatic Alzheimer's disease should be when we don't have those lesions in the brain. Cognitive problems start happening when those lesions are present. And dementia is when all these lesions are distributed in the whole brain.

So the best treatment would be something that we call primary prevention, which is when the lesions are not there and we intervene. And then, the pathological process will never happen. Secondary prevention is when symptoms are there, the pathology's there, but we don't let this process to progress.

And then what we have now, we got symptomatic treatments that are those that we are using when people are already symptomatic. And we hope that they are some disease modifying treatments. And this is the goal of many of the trials that we have now, which is once you have the disease, the pathology's there, but these treatments will stop progression.

So what are the therapies that we have? So far, more than 190 therapies have been proposed or tested for Alzheimer's disease over the past four decades. And most likely, as I'm speaking now, there are more therapies that are being added to those 190. So we have symptomatic treatments, disease modifying therapies, and cell therapies. That would be, I would say, the way that we can conceptualize the treatments.

So far, we have, I would say, four drugs. Tacrine, nobody's using tacrine anymore. But was approved in 1993. We got donepezil, rivastigmine, galantamine, memantine. And the last medication approved for Alzheimer's disease was in 2003. And after 2003, nothing.

So this is just to give you an idea about cholinesterase inhibitors. These are started [INAUDIBLE] where we tested time to nursing home admission in people with cholinesterase inhibitors or with a combination of cholinesterase inhibitors or memantine.

And what we see here is taking cholinesterase inhibitors alone or the combination, the risk of going to a nursing home decreased. So this, in some ways, the persistent use of cholinesterase inhibitors is doing what it's supposed to do, which is slow down progression. And the combination is shows sort of an abrupt decline is because that group was followed for only 7.5 years.

So far, if you go to drugtrials.gov, there are 233 treatment intervention studies currently funded by the NIH for Alzheimer's disease. And you can see that the majority are non-pharmacological interventions. And then, that is followed by caregiver interventions.

And we have about 39 trials with an early stage drug development. But as you take as a group, all the studies are funded by the NIH. The majority are non-pharmacological interventions.

So this is an example of early clinical drug development and late stage clinical drug development. Those are the Phase II, Phase III clinical trials. Basically everything. But anti-amyloid drugs are the most common trials that we are seeing now. Basically, every aspect of brain metabolism is being targeted by medications that are being tested now.

And you can see oxidative stress, inflammation, multi-target like lithium, other compounds, vitamin D, melatonin. There is a long list of medications that are being tested now. And you can see late stage clinical drug development and the amyloid drugs are the more frequent drugs. And we have added [INAUDIBLE] the LATTICE is a study using lithium in MCI patients.

But people complain that the amyloid-- that all the trials and research is mainly oriented to amyloid. But there are many, many drugs that are being tested now against tau proteins. You can see there, this is a more recent phenomenon. But you have many drugs that are being tested.

Unfortunately, those that were used for progressive supranuclear palsy didn't work. The majority failed. And there is one study on AD, prodromal AD cases, that also failed. But this is a very active field now. We will see more anti-tau drugs coming up in the future.

In terms of non-pharmacological interventions, exercise and cognitive training are the most frequent, then everything else. Everything else, everything that you think that can help a patient is being tested now. You can see there, there is a trial with chocolate. There is a trial with TMS. There are trials with mindfulness, so internet-based conversations. So everything that you think that can work is being tested now, basically.

There is a great deal of activity in the treatment of neuropsychiatric symptoms. Many, many studies are being funded now. There are pharmacological and non-pharmacological studies. There is even one study with ECT for agitation in Alzheimer's disease.

The LiBBY trial has been recently funded. This is a THC and CBD in people in late stage dementia in nursing homes. But basically, there is a great deal of activity in terms of neuropsychiatric symptoms. We are doing here the S-CitAD study, which is escitalopram in patients with agitation.

So other interesting compounds that are being tested in terms of neuropsychiatric symptoms are the dextromethorphan with quinidine for agitation. It's a drug that was approved for mood lability, people who cry or laugh for no reason at all, very common in MS or ALS.

And they did some trials in people with Alzheimer's disease. We can go over trial design later. But basically it's a trial that, after the first phase, they exclude people who were not responding to the drug.

This is the pimavanserin. It's a drug that was approved in Parkinson's disease with psychotic features. There are some studies in dementia in general that also show that worked. This is a study that was done in people residing in nursing homes. And you can see there, it was not very successful in this group.

So this is just going back to some good things that we can do to prevent cognitive problems. This is a typical study. It's called the FINGER study. It was done in Finland.

This is a study where a group of people were brought to a clinic to exercise, to do cognitive stimulation, to manage cardiovascular disease, to improve diet. So you have a group where you, basically, are-- who's coming to the clinic almost every day.

And then you have another group who came to the clinic only three times over a period of 24 months. So when you compare the two groups, there is a difference in terms of cognition, in executive functions, in a summary of neuropsychological measures processing speed, but not in memory.

So these studies, they have this problem with the control group. Because the control group basically goes into an area where [INAUDIBLE] has no connection with the investigators or with any type of treatment where you have this other group where you are basically giving them everything.

So there are some other studies that were done in some ways tested this. One was the life study that was done in people with-- these were 730 older adults that we brought them to the clinic. And they had very intensive physical stimulation.

But this was a group that was able to walk 400 meters. And in this study, motor function improved. But there was no effect on incident cognitive symptoms. The SPRINT MIND study was done in people where they tested intensive versus standard blood pressure control.

And the study was stopped because it was positive in the sense it reduced mortality, decreased the risk of cardiovascular disease, lowered the risk for mild cognitive impairment, but had no effect on incident dementia. So that's, I will say, these are the two most important studies. Because they were done in a large group of individuals.

So just going back to the therapy segment just to review very briefly what I said, these are examples of symptomatic, disease modifying, and cell therapy interventions. I don't think that we are now in a position to talk more about stem cells or gene therapy. So I'm not going to talk about cell therapy.

So in terms of symptomatic medications, the typical symptomatic medications are the cholinesterase inhibitors and memantine. Many studies with valproic acid with antihypertensives with ibuprofen and celecoxib, all those studies were negative.

Diet, you can buy Axona and you can buy Souvenaid. And the internet is where you can access those diets using Amazon. But the studies, the trials, were-- the trials that showed efficacy were funded by the companies that manufacture those diets. So we don't have a sort of a more rigorous assessment of the outcomes or the intervention with a diet.

Disease modifying treatments, there are many. The most common now is a passive and active immunization. But we have a large number of interventions that we thought that were disease modifying.

In terms of administration, we have oral/nasal. The typical oral is the cholinesterase inhibitor. The nasal is the insulin nasal spray. I'm going to talk about this in a few minutes.

The subcutaneous and intravenous, typical was the IV/Ig trial and all the other anti-amyloid drugs. And in terms of devices and surgeries, practically everything has been tested from the nerve growth factors inserted into the fornix or the nucleus basalis of Meynert to ventricular peritoneal shunt and plasma exchange, which I'm going to talk about this later.

So these are the large scale prevention trials. I'm not going to describe this in detail. But you can see on the right, the column on the right, they were all negative.

These are current prevention trials. They haven't finished. So the A4 is still ongoing. The AHEAD trial, A3A45 study just started. Actually, we are going to do it here in Pittsburgh.

The DIAN-TU, when they did the futility analysis, it was negative. But because they found a positive effect on the biomarkers, they decided to continue with this trial.

There is another large study that is being done in Colombia. There is a small cohort here in the US. But this is mainly done in a population with a PS1 mutation. In this group, they developed Alzheimer's disease around age 45. There is another study, the Generation trial, that is being done in people with APOE4 carriers. But all the studies are ongoing.

So these are the results of the majority of large scale studies done recently. You can see they are the solanezumab. The three studies were negative. The bapineuzumab trial was negative. The verubecestat study was negative. That was in patients with Alzheimer's disease. There was another study in pre-Alzheimer's disease patients. And the p-value was 0.01 in favor of the placebo group.

Aducanumab is a drug that is being now considered by the FDA. And it could be approved. They have one trial was negative and one trial that was positive. And you can see there the p-values. And the way that people present now, the effect sizes is in percent of less decline after one year of treatment.

And you can see that in terms of the CVR, there was 22% less decline. ADAS-cog, 27% less decline. And with the ADCS for activities of daily living, it was 40% less decline. So stay tuned. Because this drug may be approved by the FDA very soon.

Other therapies, the intranasal insulin was negative. The idalopirdine was negative. It was a serotonergic medication. And the plasma exchange, the paper was published about two months ago. The ADAS-cog, I will say, 0.06, the p-value in terms of ADAS-cog. And we consider that positive because if you see the effect size, which is 66% less decline over one year. The ADCS for activities of daily living is 52%. And the CDR sum of boxes is 71%. And the CGIC, which is the impression of the physician on improvement of the patient, was 100%. So it was no less decline. It was about the baseline.

So I'm doing this with the iMac. It looks very nice. Just to give you an idea about all these studies, when we talk about a negative study, you can see that the lines, they overlap, basically. The placebo and the treated groups are very similar. And you can see how this-- you can see the outcomes of these studies. And these were, I can tell you, very expensive studies, huge effort to do it all over the world, and with, unfortunately, negative results.

So one thing that we know is that these anti-amyloid drugs can reduce the A beta plaques in the brain. And you can see on the left, that's the aducanumab trial. And you can see that using an amyloid tracer, how the placebo-- there are big changes in terms of amyloid deposition. So they have an effect on the biomarker. The biomarker is amyloid deposition.

On the right is this coming from the bapineuzumab. And in the bapineuzumab, clinically the trial was negative. But in terms of the biomarker, it was positive. But what you see there, there are examples of some patients where there was a decrease of amyloid positivity. You can see that the Patient B, there is basically a significant decrease of amyloid deposition.

And you have other cases like Patient C where amyloid continued to be deposited in the brain. Same thing with Patient D. But in some cases, there is a decrease of amyloid deposition. And when you analyze this as a group, it's statistically significant.

One of the concerns with these drugs, with the anti-amyloid drugs, is the presence of amyloid-related imaging abnormalities. These are the bapineuzumab was 16%. The aducanumab is between 35% to 55%. Practically half of the people treated develop amyloid-related imaging abnormalities. And they are mostly present in people carrying the APOE4 allele.

So I'm going to talk a little bit about plasma exchange. You know that total or therapeutic plasma exchange is very common. It's a very common methodology used in all the hospitals. It separates plasma from blood cells, remove a volume of plasma that contains a toxic pathological substance, and returns the cells to the subject, and replace the plasma by an albumin solution.

So it's been use for many neurological disorders. It's very common in myasthenia gravis, in acute disseminated encephalomyelitis, paraneoplastic syndrome, in many neurological disorders. And the plasmapheresis is also used in many non-neurological disorders. So it is widely used in medicine in general.

So this is really nice. You can see here, I'm going to describe the AMBAR study, the Alzheimer Management By Albumin Replacement. So these patients were treated with plasmapheresis. And the plasma was removed. It was a mechanical removal of toxic proteins, although you see there, amyloid proteins, the plasma exchange remove practically many proteins.

It was replaced by an albumin solution. It is very safe and effective in terms of many neurological disorders. The idea, we focus on Alzheimer disease, the idea was just remove A beta from the periphery. And that will suck up beta amyloid from the brain.

So this is sort of a very simplified description of a trial. 347 patients entering the study. They have one therapeutic plasma exchange per week for six weeks. And then they have a low volume plasma exchange for about 12 months. So the total treatment lasted about 14 months.

And everybody had the albumin at 20%, the replacement was used albumin at 20%. There was a group that received IgG, 20 grams. And the other group, 10 grams. The idea of using immunoglobulins was just to protect the patients. Because when you do plasma exchange, you're also removing immunoglobulins. So the idea was just to use IgG as a protection, not as a cognitive enhancer.

So these are the cognitive results. You can see there on the left, the treatment in all the patients, the p-value is 0.06 with 66% less decline. And in terms of the ADCS, activities of daily living, there was a statistically significant with 52% less decline.

But the effect is mainly seen in those patients that have moderate Alzheimer's disease, with a mini-mental between 18 and 22, and was less evident or basically we don't see any difference with the placebo in those with mild. But in those with moderate, the difference was statistically significant with 61% less decline.

So these are when you examine all the arms, the three arms, of the trial. And you can see that, basically, it doesn't matter how you administer the plasma with albumin, the results are very similar. So it's not that, I will say, there is no difference among the three arms that were used. It's basically how you replace the [INAUDIBLE] the administration of plasma with albumin.

These are the CDR sum of boxes, which is another measure of efficacy. And if that was positive in all patients and in minor, moderate. The ADCS, the CGIC, which is the impression of a physician of improvement, it was statistically significant in all patients regardless of the severity of the dementia.

And again, this is just showing the three arms in their CDR-Sum of boxes. All the arms were different from the placebo. Same thing with CGIC. It was statistically significant, all the arms compared to the placebo.

So in terms of biomarkers, I'm showing only the CSF, A Beta 42. And you can see that after the first, on the left, after the first period of about two months, there is a statistical difference between baseline and two months. But the difference was not significant after 14 months.

You see that the placebo is getting worse. There's less beta amyloid in CSF compared to the treated group. But it's not reaching a statistical significance. In the mild cases, very similar. You see the strength of the placebo getting worse, but it's not statistically significant. And in the moderate cases, you see that the difference is statistically significant. So we'll say the biomarker is positive in the moderate cases.

So where are we going from here? I think that we are entering a new era of Alzheimer's disease treatment. These treatments are difficult to administer. They are not simple. Although it looks like you do an infusion of the anti-amyloid drug or you send a patient for a plasmapheresis would be enough, these treatments require very, very close follow up of the patients.

We are going to see an increased role of blood and imaging biomarkers. For example, the aducanumab trial for the infusion, the patients need to be amyloid positive. So you need to show that the patient has no A Beta 42 in CSF or a positive biomarker.

For the plasma exchange, it doesn't matter. It's not required for that. But for the anti-amyloid drug, all these patients are going to have a biomarker at the beginning of the treatment. So that's why I'm saying, this is not easy in terms of management.

It's possible that there will be a combination of treatments in the future. I wouldn't be surprised if we start seeing these anti-amyloid drugs with anti-tau. It's going to happen, I hope. This is the way that the field is going.

And the traditional treatments, the cholinesterase inhibitors and memantine would remain as symptomatic treatments for Alzheimer's disease. And the treatment of risk factors as prevention for AD still needs more-- we still need to know more about this. This remains elusive.

Thank you very much.