[MUSIC PLAYING]

GAURAV PRAKASH: So we're talking about shingles today. We're talking about the problems it causes to the eye. And then once I'm done with the clinical aspects, Paul will start and we'll discuss about the research we are doing at University of Pittsburgh regarding this. So let's talk about what shingles is. Shingles Is basically a painful rash which is caused by reactivation of the varicella zoster virus.

Now this is the same virus which causes chickenpox. So we all know chickenpox. We know shingles. They are basically caused by the same virus. Now this can be potentially blinding. It can make the patient lose their vision forever, and even if you recover fully, it can have a long-term neurological and healing problems, and that's why it becomes a public health crisis.

One of three people will develop shingles. If you have three friends, look at the pictures in your mind. Most probably one of them in their lifetime is going to develop shingles. It's that common. The risk increases in seniors, and the CDC has recently noted the risk increase is actually exponential. That means as you grow older, the risk does not grow straight forward. You are at a higher risk when you are more than 50 years of age.

And this has been the traditional teaching that if you are older than 50, you have higher chance of shingles. Unfortunately, now this scenario is changing. You have got younger population in clinics who are coming up with shingles. People in their 30s, 35s, even sometimes younger people have shingles. And this is a worrisome trend. Shingles does not differentiate. It hits all demographic subgroups.

And the risk increases with conditions which can cause your immunity to go down. It could be stress, but mostly immunosuppression is caused by conditions such as IV, cancer, diabetes, or when you're undergoing chemotherapy. However, as I talked about younger people and shingles. Similarly, people with normal immune system can also get shingles. So it is a problem. So I'll also look at the development of shingles. When do you develop shingles and what happens?

So chickenpox is the first part of this disease spectrum. When you're younger in your earlier life, or sometimes really when you are even old and you've never had chickenpox before. You develop the basic chickenpox. It heals, but the virus never goes away. So think of this as a cross section of your skin. Virus goes down inside the nerves over here. Somewhere over here it tends to hide inside the nerves.

Virus keeps on staying in those nerves, and whenever you have a situation when you have reduced immunity, the virus tends to react to it. So look at this as the nerve endings. The virus is staying over there dormant, nicely. You have even forgot that have had chickenpox before. And induced immunity makes the virus come up to the surface and reactivate, which presents as shingles.

So the cycle is like this. You pick up chickenpox first. The surface heals, but the virus stays inside the body, inside the nerves. Under episodes of reduced immunity, diabetes, stress, HIV, immunosuppression with chemotherapy, the virus reactivates and causes shingles. When you have shingles, there are certain stages through which the body undergoes.

The first phase or the early phases when you have no rash, but you just have the clinical features of malaise, fatigue, fever, and you have got itching and burning on one side of the face of the body or the trunk, depending on what type of shingles in one what you're having. This develops into the next stage in which you develop the classical rash, which is typically 24 to 48 hours after developing shingles.

This rash is typically one-sided. Shingles does not involve bilaterally until very, very rare. It is involving only one side of the body. And this is the time when you double the pain and the complications. Now the reason why this is important is, many times patients who have mild malaise or fever or fatigue who are in the early phase, will actually be missed. That means we'll not come to know that they have shingles until they develop the rash.

You might come to the ER or go to your PCP, and we might just think that you have early virus four rooms and you might have to go back home. This is a very common situation. The next step is the ulceration phase. The ulceration phase happens around three to four days from the zero phase, in which these blisters open up and start ulcerating. And the pain and the complications continue at this point in time. This is a really painful period for the patient.

By the 7th to 10th day, depending on your immune system, if it's healthy or not, the ulcers heal by scarring. And by this time, most patients are not infectious. So you can go back to work at this time. You don't pass on the risk of passing the virus to anybody else by the time develop scarring. Long-term sequelae persist, but around 30 days is when your rash starts to disappear. And sometimes you can have a rash sticking around for a very long period of time. The discoloration reacts, I'm sorry. Not the rash.

It's also OK to vaccinate somebody 30 days or longer. It's debatable, and we'll talk more about the immunity after the first episode. But many times it has been asked that, when it's OK to vaccinate. So beyond 30 days when you don't have the classical infection, you are OK to vaccinate back again for shingles, if needed.

Let's talk about the eye complications. And the eye complications have a blanket term called as herpes zoster ophthalmicus. Fortunately, the eye is spared in around 98% cases of shingles. That means the area which involves the eye, nerves [INAUDIBLE] in all the eye are not affected. Only 2% cases develop that. But there's more to this problem. Of this 2% cases, who will get shingles? Most of them who get the ophthalmic symptoms are actually at risk of losing their sight.

So these are potentially sight threatening. There are a lot of complications which can happen, and we'll cover them slightly over here to get an idea. The next slides. But shingles can actually involve, or rather, herpes zoster ophthalmicus can actually involve any part of the eye. The most common involvement is infection on the cornea, which is painful. You have difficulty in blinking. You have foreign body sensation. And that's the initial presentation mostly.

This can lead to something called as corneal scarring. My cornea is the front part of the eye. It should be absolutely clear for light to travel inside the eye and for you to see well. But if you develop a scar in front of your cornea, light cannot pass in the eye that's the way it's supposed to go. And then you get halos and glare and sometimes even loss of vision because of this.

Now in a normal corneal scar, if you try to do lasers or we try to do cornea transplants to make them feel better, the problem with shingles is, as we talked about, that the virus never grows back again. And the virus actually takes away the healing potential of the eye. So even if you do a corneal transplant, there's a very high rate of corneal transplant failure in patients where unfortunately, they have shingles.

So we are looking at a double whammy over here. First the virus causes problems and scars. And then once again, when you do an intervention, the healing is very, very poor because of the damage to the nerves. We develop something that is called the neurotrophic cornea. That means the cornea does not have any nerve endings which are active, and it takes away the incentive to heal.

It can also cause inflammation in the middle part of the eye called the uvea at the back of the eye, which is called as retinal. Again, these are sight [INAUDIBLE] complications. So all in all, herpes zoster ophthalmicus, or the eye involvement in zoster or shingles, even though it's seen in maybe 2% patients who develop zoster, 100% of these patients are at risk of sight loss and therefore, it becomes a ocular urgent situation and it needs to be tackled immediately.

Now before we go to treatment, I want to answer one question which has been asked many times in the clinic setting for us. Is shingles contagious? So the simple answer is that shingles is basically a reactivation of the virus which you already host from before. You had chickenpox and then you are having shingles. So technically, shingles is not contagious, but you can get chickenpox from somebody who had been infected from shingles. Let me explain this once more.

Let's say somebody was never vaccinated and never had chickenpox and now you come in contact with somebody who is having early shingles and they have ulcers which are infected, right? In that situation, if you get the virus from them through direct contact to the skin of a shingles blister, or rarely, and that's rare, don't get scared about that. It's rare. By breathing the zoster virus through the air, you can actually pick up chickenpox from these people.

So if you never had chickenpox in your life or you were not vaccinated, you are at risk of catching the virus, which can manifest as chickenpox in that first episode. And fortunately, not shingles.

Treatment. So the silver lining in the story is that we have a straightforward and fairly effective treatment for shingles. We need to start a full dose of oral antivirals as soon as the diagnosis is made. Treatment of choice is a medicine by the name of valacyclovir, which is known by the brand name, Valtrex. It specifically acts on cells which have been infected with the virus. And therefore, it does not cause damage to the normal human tissue. Which is a great fact, because it can be given to a lot of patients on a very long period of time.

In fact, patients who undergo ocular surgery after shingles, probably cataract surgery, sometimes even a transplant, we have to give them even lifelong support with Valtrex in some cases. Other supportive treatment includes steroids, lubricants and antiviral ointments based on the clinical features, but as a patient or as somebody who's going to take care of somebody who will have signature shingles and feature, as a care provider, you should know that antiviral pills are safe. They can even be given the long-term and they are the treatment of choice in patients who develop shingles.

Let's start with role of vaccines. I will cover this briefly, because Kip is going to cover in much more detail regarding this. Shingrix is the recombinant zoster vaccine we give as a vaccine of choice in the United States right now. Two doses, two to six months apart, and it's typically for immunocompetent patients who are more than 50 years of age as of now. You should take it even if you had a prior episode of zoster as it talked about in the slide sometime back.

But you should wait for the current episode to resolve. You should not take it on day 7 or day 10. Probably take it after a month. If you had a prior dose of the previous vaccine Zostavax, which is not available in the US anymore, you should again take Shingrix. It's more effective compared to the previous vaccine. You can take it when you have chronic medical conditions unless there is a specific contraindication or precaution when it should be there.

In case if you have immunocompromised, does it rule out the shingles vaccine totally? No. There are certain situations in which you can give it in immunocompromised adults also. One of them is if you are taking a low dose immunosuppressive therapy like mild steroids. If you anticipating immunosuppression, that means you're going to be started on medication which can reduce the immunity, you can take shingles vaccine. That's absolutely fine. Or if you have recovered from immunocompromising illness and you don't have immunocompromised, you are fit to take a shingles vaccine again.

At this point, I'd like to stop my presentation and to thank my clinical team at the Cornea, Refractive and External Diseases services. And I'll pass it on to Kip to continue with the rest of the presentation.

PAUL (KIP) KINCHINGTON: And I'm also going to just reiterate a couple of points that Dr. Prakash brought up so that you have a good memory of this. So just as a disclosure, I am a paid consultant for Merck & Co. So as Dr. Prakash pointed out, shingles is a disease that happens as we age or we get sick from elderly diseases. And it rises rapidly after 50 or 60 years old. And about half of people get it by the time they're 80. So it really rises quickly. And it's estimated that about 10% of 80-year-olds have had it twice.

So as we put it out. This is because your immunity declines naturally with age or it drops with diseases such as cancer, transplants, particularly bone marrow transplants, or if you're infected with HIV and AIDS. So while we know this is an elderly disease, this is a graph that shows you the rates of shingles that is happening. While at 70-year-olders, at 60 to 70-year-olds, it's flattened out over the years. Notice there's a increase in 50 to 60-year-olds and 40 to 50-year-olds. It is rising.

And one of the things we're trying to do is to understand what might be the predisposing factor for this age increase. So it does affect people we know. Tony LaRussa, the manager of the St Louis Cardinals, had it at the age of 66. It stopped his games for many weeks. He had facial pain light sensitivity and was in bad shape. A temporary loss of vision. And it's not just the older folks. Lin Manuel Miranda who wrote *Hamilton* got facial shingles recently, just last year.

He tweeted he wanted a lefty Phantom mask, which didn't quite fit, but it points out that shingles can affect you at young ages as well. The one that I know well is David, or that know about, is David Letterman who had facial shingles in 2003. He was only 55. He had vision problems and he did get a pretty bad eye infection. He got pain, long-lasting itch. And it was only this, and his heart bypass, were the only things that stopped his appearance on *The Late Show.*

And he did a top 10 good things about having shingles, which involved many swear words, and also top things to stop you from scratching. So (CHUCKLES) it's not such a funny thing anymore. And I just want to bring this up. So chickenpox is a skin disease, but it eventually has to travel down these nerves, your sensory nerves, and it hides in the dorsal root ganglia. And in the case of the eye, this is the trigeminal ganglia, which is near the brain.

And that is where the virus resides for decades. And then something triggers it and it has to come back down these nerves, and then appear at the skin. Now because the nerves were involved, it very often damages the nerves. And so that's one of the big problems with shingles, is the nerve damage. So you end up with a nerve. It could either leave it normal, or it does two things.

One of them is it makes it what is known as neurotrophic, where you lose sensation. There is no sensation at all. And this happens in the cornea, as I'll mention next. The other one is neuropathic, and this leads to pain. And what we're trying to understand is what defines whether the virus is going to do a neuropathic pain or neurotrophic lack of sensation.

So here's a case of neurotrophic where it stops nerves from functioning, which is shingles-induced anesthesia of the cornea. Dr. Prakash mentioned this. So your cornea has lots of nerves in it. When shingles affects your eye, all these nerves retract, or they become non-functional, so that you actually lose sensation in your eye. The effect is it makes your cornea go numb and you don't know when you've damaged it, such as putting eye drops in, which we all do when we're a little older.

Then you can scratch it and get a bacterial infection. At the other end of the spectrum is pain. 90% of shingles people want some kind of pain relief. And about a third of patients develop this chronic, long-lasting pain, which can last for years. And for reasons unknown, that in the face and the ocular region is often more severe. And it's difficult to treat. Many patients get no benefits from any kind of treatment. As I said, you hate your life. We're trying to understand why acute pain becomes chronic pain.

So, and I'm just going to reiterate this. So one of the worst types of shingles pain is known as allodynia. And this is where something like a feather or hair or clothing or a wind gust even, makes it really, really painful. And then if you take this away, it still echoes on pain. So allodynia makes life very difficult because you can't wear clothes, you can't deal with, you don't want your hair in your face because it drives you such pain. This could be really difficult to treat. It could last for years.

So just two people that have had shingles, bad shingles pain, is Rosanne Barr, who said it was the worst pain that she'd ever had, and Richard Nixon, who was really badly incapacitated by the long-term effects of having shingles. So what could be done about shingles? As Dr. Prakash mentioned, get vaccinated. Vaccines do work for most people. So this shows you the kind of vaccines there are. So for chickenpox, we've had a vaccine since 1996. This is a live attenuated virus, which means it's a weakened form of the virus that normally causes chickenpox. And it's give it to young children.

It worked really well, and still most children in the US are getting this vaccine. It has very rare side effects, but for the most part, this is a vaccine that almost everyone gets. And the age is about 30 of people that have this. Most people under the age of 30 have been vaccinated. The shingles vaccine was very similar to Varivax's. Based on the same virus, but it's 10, 12 times more powerful. And it was given for 10 years or more to adults over the age of 50. And it cut down shingles by about half, and it reduced the pain or the burden of disease by about two-thirds.

Now this was a pretty good vaccine for 10 years, although the immunity did not last a long time. And it was recognized that it's not a good vaccine for the immunocompromised, because it is a weakened live virus. And it didn't work so well at higher ages, but it was very, it was the best thing that we had. The new vaccine, which just came out a few years ago, is Shingrix. It's a sub-unit vaccine. There is no live virus. It's just one of the proteins that the virus makes. It's given to adults and it's given as two injections two months apart. It can have some painful side effects and this we have to be careful of, because people don't get their second dose.

But the protection seems to be long-lasting, longer-lasting, and it could be given if you've had the Zostavax already. But there is a little bit of a problem. It's that most shingles patients are elderly, and they're not keen on generally getting a new optional vaccine. Many people don't know how bad shingles and the pain can get. So I'm going to bring up our research then as a transition to research.

So we have this journey that goes down nerves and it hides here, and then it transports back. My lab group study how the virus resides in this ganglion and how it goes up and down these human neurons. Now half the problem is that we've had is that we've had to work with human neurons. You can't use animal models to study some of these latency and reactivation mechanisms. So to do that, we make human neurons from human stem cells. This is a picture of a human stem cell, ball of human stem cells growing.

And we can direct that down a pathway so that it forms these axon projections that are coming out. And then we eventually end up with these balls of neurons, of which many of them are sensory, and they project all these axons out. This allows us to, in a dish, to be able to study VZV latency and ask the question what the virus makes in neurons? What are the triggers that cause the virus to reactivate from its latent state or quiet state? And how it moves along these tracks to get from the nerve cell body to the skin, the periphery?

This is a particularly interesting area. We're starting to actually come up with a shingles in a dish, if you were. So we have these little chambers which I'm showing here. They're about a centimeter across. And in this region right here, we have little channels. And this is an enlargement of those channels. What we could do is we could seat those precursor neurons on one side, get them to grow their axons through the channels, and that we can say, this is like the periphery, the skin, and we could infect the virus, watch the virus go up to the neuron body and go latent. And then we can also watch it come back down and infect skin, or as we've been using, corneal cells, which represent the eye surface.

So this is a picture, for example, of looking at one of these channels right here. And this is the channel. You can see these axons. And these little green dots are viruses that we can label so that they're green. Now this picture here shows a picture of one of those viruses actually moving in an axon towards the neurons in the ganglia, or the model of the ganglia. We can actually get pictures and films of the virus coming back down as well.

So we're using this cultured neuron. So we're asking these questions. How does the virus travel? It's got to go in two different directions, because when it sets up latency for chickenpox, it has to get to the ganglia. And yet to cause shingles it has to go from the ganglia back to the skin, or the eye. So we're looking at how the virus does this and what proteins are involved and can these be targeted?

The second question is what is the virus doing now during that long, latent state that lasts for decades? What do they do? I mean, can we stop them from allowing the reactivation and shingles to develop? Then what are the triggers of VZV to renew its growth and cause shingles? Can we prevent those? Finally we're trying to remove the latent virus from the ganglia using new methods. Some of you may have heard of the CRISPR methods that are used for gene altering. We're trying to apply CRISPR to be able to remove the latent virus from neurons using this culture system.

So the second part of our research was pain. How does VZV cause chronic pain and this long-term pain of postherpetic neuralgia? So we have a new animal model of shingles face, skin and eye pain which uses rats. What we could do is we could put virus into the regions around the eye, and it goes to the trigeminal ganglia, and it signals pain to the brain. So VZV is put at a rat whisker pad and the virus gets to the trigeminal ganglia.

Humans have the most virus in their trigeminal ganglia. So how do you get a rat to tell you its pain? Well, this is how we do it. So we put the rats in an enclosure like this. And half of it is dark and half of it is clear. And what we do is we put virus on one side of the face. And then because rats are nocturnal, they will like to stay in the dark side. They hang around here. But what we do is we give them a stimulus. We touch the side with the virus in them if their head is in this side, and we touch the other side as the control if their head is in this clear side.

And I'll show you one little bit of data. These are the controls. And you see that, over time, the animals stay in the dark side. This is the time spent in the dark side. They stay there. They don't move out from the dark side. Whereas if they've got virus and we're touching them on the side with the virus, they move to here, because they want to avoid being touched. And so the animals are feeling hypersensitivity.

So basically rats with pain, they move to the clear side to avoid touch. And this is against their natural behaviors. And the lab has a little joke that these are what we call Star Wars rats, because they avoid the dark side. (CHUCKLES) So we're using this model to understand how VZV alters the nerves to signal pain, and then also block nerve sensation in the cornea. We're looking to see if these pathways could be targeted to prevent pain from developing, and we're using the model to test new treatments that might more effectively block shingles' chronic pain.

One of these approaches is to actually test gene therapy systems to block the pain, which we think have the potential to be used in humans. So I'll finish up there. This is the lab. This is my group in the lab a year or so ago. We have current and former members. All this work was done in collaboration with Ron Goldstein at Bar Ilan University, who is an expert on converting human, developing human neurons from stem cells.

And the face model was developed with Phil Kramer and Bill Goins. And our support. I just want to mention our support was from the National Institutes of Health. We've also got research from Research to Prevent Blindness and The Virginia Kaufman Fund. But The Eye and Ear Foundation has been key to developing these kind of tools. So I'll end there. Thank you for listening. And if there's any questions, you have my information.