

# Nerve Palsy in Infants with Congenital Zika Syndrome

*[Announcer] This program is presented by the Centers for Disease Control and Prevention.*

[Sarah Gregory] Hi. I'm Sarah Gregory and today I'm talking with Dr. Nipunie Rajapakse about the phrenic nerve palsy in infants with congenital Zika syndrome. Dr. Rajapakse is a doctor in pediatric infectious diseases at the Mayo Clinic. Welcome, Dr. Rajapakse.

[Nipunie Rajapakse] Thank you, Sarah. I'm excited to be on the podcast today.

[Sarah Gregory] Well, we're excited to have you here, for sure. Some people might not be aware of what Zika virus is and what causes this. Would you fill us in?

[Nipunie Rajapakse] Sure. So, Zika virus is a virus that was actually first discovered way back in 1947, first discovered in a place called the Zika Forest in Uganda, which is where it gets its name from. And the first time we know that humans were infected with it was way back in 1952. So, it's a virus that we've known about for a while, but we learned a lot more information about it and some of the issues it can cause in the last few years because of the big outbreaks we saw occurring in Brazil and in many areas in Central and South America, which started around May of 2015. So, a few important things to know about the virus is that it is primarily spread through the bite of mosquitoes, but can also be spread through sexual transmission, and also from pregnant women to their babies, which is one of the main things we're going to be focusing on today. We also think that it can likely be transmitted through blood transfusions, but that's not very common.

In terms of types of symptoms it can cause, most people who are infected with Zika actually might not have any symptoms at all or might have very mild symptoms. The most common things that we see are things like rashes, fever, sometimes headaches, joint and muscle pain, or conjunctivitis, or redness of the eyes. These generally can last for several days up to about a week. And most people don't get sick enough that they would need to go to a hospital or sometimes even see a doctor at all. Unfortunately, we don't have any specific antiviral treatment or vaccines for the virus currently, but the symptoms generally tend to resolve on their own without any need for specific treatments.

But, as we have learned about in the last few years, the story seems to be very different when it comes to pregnant women. And even though the moms might not become very sick if they get infected with the virus during pregnancy, it can cause a range of quite serious issues for the developing baby, and this is what has been given the name congenital Zika syndrome. Congenital infections refer to infections that occur either at the time or before birth, and the main issue that most of us have probably heard about is with something called microcephaly, which is when the brain doesn't grow and develop normally, and the baby ends up being born with an abnormally small head. But we're still learning a lot about some of the other effects outside of the brain, as well.

[Sarah Gregory] As you said, the effects of Zika virus on the central nervous system in infants is pretty well documented, but would you give us a little more history on that?

[Nipunie Rajapakse] One of the very first things that doctors in Brazil noticed and reported back in 2015 was a large increase in the number of babies they were seeing that were being born with microcephaly. For a background, it's kind of important to know that there are lots of different causes of microcephaly. Some are related to infections and some are not. But these doctors very astutely realized that something new was going on to cause so many babies to be born with this issue in such a short period of time. And this was kind of what quickly led to further studies and investigations that, over time, confirmed that Zika virus infection was the cause of this increase in microcephaly. Since then, we've learned a lot about kind of the full spectrum of effects that Zika virus can have on the brains of fetuses and newborns who have been exposed. And this seems to range from having actually no effect at all in some babies at birth to having very severe issues with development of the brain, sometimes even resulting in miscarriages or death of the baby shortly after pregnancy...after birth, unfortunately. We have also learned that Zika can affect the eyes, it can cause issues with joints, a finding that we call arthrogryposis, and also issues with muscle tone.

And so, because of these effects that we saw on these babies that were born, a lot of people have been doing research and studies in animals and, as well as during autopsies of some of these babies, who have unfortunately died from the infection, to better understand what types of cells are being attacked or damaged from the virus. And it seems to be a specific type of cell that we call neural progenitor cells in the brain that seem to be the most affected by the virus. But we're still learning more about how the virus interacts with human cells and why it causes these issues. And understanding those types of issues will really get us closer to finding ways to prevent or potentially treat the infection in the future. We're also learning kind of more over time, given that the babies that were born during the outbreaks are still quite young, we are continuing to learn more about other effects the infection has had as they continue to grow and develop over time. The things that might not be noticeable in a young baby at the time that they're born might reveal themselves over time—for example, difficulties with learning or development of their motor skills and language, and things like that. So, we definitely don't know the full story here, but we've come a long way in kind of understanding the effects of this virus.

[Sarah Gregory] Your study did examine infants with congenital Zika syndromes. What were you looking specifically for?

[Nipunie Rajapakse] Yeah, so Sarah, the story of how this article came about is kind of an interesting one. So, I practice at the Mayo Clinic in Rochester, Minnesota, so this is not a place that was within the area of the Zika outbreak. But, we did have a baby that was born here to a mom who had spent some time in a Zika area early on in her pregnancy. And the baby was unfortunately born with very severe signs of congenital Zika syndrome. Many of the issues that the baby had, that we saw, had been previously described with congenital Zika syndrome—so things like the severe microcephaly and some of the joint contractors. But there was one specific finding which was elevation of the diaphragm on one side that we hadn't really heard about before or seen reported in the medical literature that was available at the time. And we didn't really have a clear explanation as to why we might be seeing this. So, one of my colleagues that was also caring for the baby, had seen a presentation at a conference by a neonatologist in Brazil, by the name of Dr. Jucille Meneses, that had mentioned this finding in a small number of babies that they had cared for there. And so we ended up reaching out to her to find out a bit more, and once got to discussing some of our cases, we decided to work together to describe what we were seeing in these babies. So, this article really was a collaborative effort from a lot of people, both

here in the U.S. and in Brazil. And our Brazilian colleagues were very generous in sharing all of their experience and expertise with us, since they'd really been on the front lines managing all of these babies and trying to understand more about this infection.

[Sarah Gregory] What were your findings?

[Nipunie Rajapakse] The unique thing about these four babies that we described in the article, or what we kind of thought to describe, was that they all had this finding of elevation of the right...of their diaphragm on the right side of their chest x-rays. To us, this is a sign that suggests that the diaphragm on that side is paralyzed, or not moving properly. The diaphragm is a large muscle that sits at the base of your chest, and its movement helps with breathing, with expanding and collapsing the lungs. But as we talked to our colleagues in Brazil and kind of collected and compared more information about these patients, we were quite struck by how similar the stories were between all of the babies. And so, we found that all of the moms that were infected were infected relatively early in their pregnancies, and all four of the infants that we described had what we would consider quite severe manifestations of congenital Zika syndrome. So, they had severe microcephaly and also multiple joint contractors. It was also interesting to note that all of these babies had relatively significant breathing difficulties shortly after they were born and, unfortunately, all of them also died shortly after birth because of complications from these breathing issues. And so, we thought this kind of whole description of this group of infants would be kind of helpful for people to be aware of.

[Sarah Gregory] Your article focused on Zika and the peripheral nervous system. How is this different from the effects on the central nervous system?

[Nipunie Rajapakse] Yeah, I think that's a great question. The peripheral nervous system refers to all of the nerves that exist outside of the brain and spinal cord. And so, they do a lot of things like help us move and control our muscles or feel things, like pain or cold, for example. And, so, we know with Zika infection that it is associated with another condition, called Guillain-Barre syndrome, that affects the peripheral nervous system and can lead to paralysis. Thankfully, this is quite uncommon, but it has been described in both children and adults but not in any newborns. We think that Guillain-Barre syndrome is more due to a problem with our immune system response to the virus and not because the virus is attacking or damaging the nerves themselves. So, that's a bit of a different story than what we think might be going on with these babies. The combination of the different findings that we saw in these babies when we examined them was interesting, because they suggest the possibility of involvement of the peripheral nervous system, the spinal cord, or possibly both. But, as we explain in the article, because the babies were so young and quite sick, we weren't able to do some of the additional testing that would have been helpful to confirm exactly which part of the nervous system was involved in them. This is an area that will require some further investigation, as well.

[Sarah Gregory] You talked about how the paralyzing of the, of the diaphragm could be impacted by this. How is it important that the peripheral nervous system does impact the diaphragm?

[Nipunie Rajapakse] Yeah, so the nerve that controls the movement of the diaphragm is called the phrenic nerve. And we have one on either side, so a right and left phrenic nerve, which controls each half of the diaphragm. This nerve starts kind of high up in the spinal cord, so up in the neck, at what we call C3 to C5 level. But from there it travels quite a long distance outside of

the spinal cord, through the chest cavity, all the way down to the diaphragm that sits at the base of the chest. And so, damage anywhere along that entire pathway can lead to the nerve not functioning well and causing paralysis of the diaphragm. And so, that's why we said it was possible that what we were seeing on the x-ray is related to damage kind of anywhere along that pathway, which includes spinal cord, peripheral nerve, or potentially even both areas.

[Sarah Gregory] One of your mothers in your study tested negative for Zika virus, but it appears she did have it at some point in early pregnancy. Why would she have tested negative?

[Nipunie Rajapakse] Diagnosing Zika infection can be quite tricky, especially in parts of the world where there are other similar viruses, like Dengue, that circulate. It's also an area of active research and study as we try and develop kind of the best tests to make a diagnosis. One of the main tests that has been recommended currently is designed to detect a type of antibody that your immune system makes relatively soon after you're infected with the virus. This is called an IGM-type antibody. But the levels of this antibody are quite high near the time of infection, and then can gradually decrease over time. And so, if you are tested many weeks or months after the actual infection occurs, this test can be negative. And we think that's most likely what happened in our case, because the testing was done about 30 weeks after we think that this mom had...had her infection. And so it's not uncommon and we were not terribly surprised that that test was negative.

[Sarah Gregory] Do these results, I mean the results of your study, affect how infants with congenital Zika syndrome might be treated in the future?

[Nipunie Rajapakse] Sure. I think what our study kind of highlights are really some of the things that healthcare providers or people that are caring for these babies can look for to try and determine or understand which babies might have a more difficult course or have a higher chance of dying shortly after birth. I think this is important so that families can be counseled appropriately about what to expect. Obviously, as you can imagine, it's quite a frightening situation for most families, and so it's helpful to be able to give them a bit of warning or better understanding of what might happen. Unfortunately, we don't have any currently available medication or...to treat Zika or vaccines that we can use to prevent it, but these are active areas of research. And so, I think these results are kind of most helpful in kind of putting these findings on the radar of healthcare providers so that they can consider doing studies, like a chest x-ray or other imaging, as part of their workup when they're seeing babies who are at risk for this issue.

[Sarah Gregory] Where will you go from here? Are there any next steps or future studies you're planning or that you suggest doing?

[Nipunie Rajapakse] Yeah, so I think we really need to do more studies to better localize exactly where along the pathway of the nerves that feed the diaphragm this damage has occurred to cause this finding. As I mentioned, we weren't able to do all of the studies that we would have liked to do, just because these babies were quite sick. And so, I think there's still some more work to be done there to better understand exactly why we're seeing this. I think more generally when it comes to congenital Zika syndrome, I think we need to continue to follow all of these children who were exposed and infected quite closely over the coming years to fully understand the effects that it has had on them, in terms of how they grow and develop over time. I think, even though the outbreak itself has ended, there are so many children and families who are going to really live with the impacts of this for the rest of their lives. And I think we have a strong

responsibility to keep studying this infection and find out ways to best support them going forward.

[Sarah Gregory] That brings something else to mind, then, you said the outbreak is over. But isn't this like Dengue or chikungunya or all those other ones? Isn't this something that'll just keep going?

[Nipunie Rajapakse] Yeah, so Zika definitely hasn't completely disappeared. Because there were so many people who were infected and developed some level of immunity in the population during this time that it really spread quite quickly, it's unlikely that we'll see kind of this explosive outbreak situation again, but it certainly will continue to circulate in some of these areas, like some of the other infections that you mentioned.

[Sarah Gregory] So, potentially pregnant women in these areas need to stay alert?

[Nipunie Rajapakse] From our current understanding, we think that, once you have been infected with Zika virus, you likely have some immunity to it. We don't yet understand exactly how long that lasts, but, for sure it is something that pregnant women in these areas need to continue to be alert to do what they can to prevent acquiring the infection during pregnancy and communicate closely with their healthcare providers about...during the course of their pregnancy.

[Sarah Gregory] So, what's your position at the Mayo Clinic and what do you enjoy most about it?

[Nipunie Rajapakse] So, I'm a pediatric infectious disease specialist at the Mayo Clinic in Rochester, Minnesota. In terms of what I enjoy most about my job, I think, aside from the chance to take care of so many wonderful kids and families, which has always been the most enjoyable part for me, one of the things that I really enjoy about the field of infectious diseases is that it's always changing and constantly keeps us on our toes. We have outbreaks, like Zika, that pop up in relatively unexpected ways and we all have to work together quite quickly to try and understand what's going on and how to limit the spread and impact on people. But we also have other issues, like antibiotic resistance, that develop more slowly over time, and are continuing to grow and to challenge us, and will continue to challenge us for many years to come, so I've always kind of enjoyed that aspect of the field. I also love that it kind of extends all the way from understanding and learning about these tiny microscopic organisms all the way up to dealing with large global pandemics and epidemics like this. So, I think it's all quite fascinating and I really love my job and I'm lucky to get to do the work that I do.

[Sarah Gregory] Thank you for taking the time to talk with us today, Dr. Rajapakse. I've been talking to Nipunie Rajapakse about her August 2018 article Unilateral Phrenic Nerve Palsy in Infants with Congenital Zika Syndrome. Listeners can read it online at [cdc.gov/eid](https://www.cdc.gov/eid).

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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