Macrophage Activation Associated with Ebola

[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. Anita McElroy, a pediatric infectious disease physician and a scientist at the University of Pittsburg. She's also a guest researcher at CDC. We'll be discussing her article about macrophages, an infection-fighting cell, and their connection with Ebola. Welcome, Dr. McElroy.

[Anita McElroy] Hi Sarah, it's great to be here.

[Sarah Gregory] So, what are macrophages and T-cells?

[Anita McElroy] So, macrophages and T-cells are both different types of immune cells that we have in our body. And they work to recognize infections and to fight them off.

[Sarah Gregory] So tell us about your study.

[Anita McElroy] So, this study was actually born out of an observation that we had, thinking about patients who had severe or fatal Ebola virus disease. And those patients tend to have a lot of inflammation, and it's very similar to patients who have a severe inflammatory disorder that has a really long and complicated name called hemophagocytic lymphohistiocytosis. We just call that HLH for short. And HLH is sort of inflammation gone wild.

But inflammation is really an important part of the body's function. It's how your body recognizes infections. It tells you you've been infected, and that inflammation is immune cells and other immune factors that get sent to a site of infection. That's why when you have a cold, you might have swollen lymph nodes or a runny nose or nasal congestion. These are just symptoms that you experience as your body's fighting off infection. And that's good, right? That's a natural inflammatory process.

But sometimes, the inflammation is a lot more than it should be, and that's when your body overreacts to an infection, or maybe your immune system just isn't working correctly. And this can trigger a really dangerous type of inflammation that can be excessive. And we noticed that patients who have severe or fatal Ebola virus disease have some kind of clinical and laboratory similarities to patients with a severe inflammatory disease, like HLH. So, the whole reason to do the study was to try and understand if Ebola was triggering an inflammatory disease, and which types of inflammation were active during the Ebola infection.

[Sarah Gregory] Let me stop you for a second here. So, what is HLH?

[Anita McElroy] So, HLH stands for hemophagocytic lymphohistiocytosis. It's a big, long word, but it's an inflammatory disorder that can happen when your immune system is overreacting to something. Classically, we see this in patients who have had a virus called Epstein-Barr virus. That's the virus that people think of as causing the disease known as "mono."

[Sarah Gregory] Okay, alright—so, you were saying…

[Anita McElroy] We were thinking that patients who have Ebola virus disease had a lot of features that were similar to HLH. And so, the point of the study was to try and understand what types of inflammation were ongoing in patients with Ebola virus.

[Sarah Gregory] Well, Dr. McElroy, what did you find?

[Anita McElroy] So, we found evidence of macrophage activation in the patients who had very severe and fatal Ebola virus disease.

[Sarah Gregory] And why was this study important?

[Anita McElroy] This study really suggests to us that patients who have severe and fatal Ebola virus disease have excessive inflammation. And there are drugs that are available that could decrease inflammation, specifically the macrophage activation that we saw in the patients who had severe and fatal Ebola virus disease. So, the thought is that these drugs could improve outcomes in patients with EVD.

[Sarah Gregory] What other kinds of studies on this topic would you like to see done?

[Anita McElroy] There's actually quite a few very important studies that have already been done and published in the literature by other investigators. So, Dr. Mühlberger's lab at Boston University demonstrated that pathogenic Ebola viruses activate macrophages in a tissue culture dish. And they do that by interacting with a protein on the surface of macrophages that is known as TLR4. There was a second group of investigators out of UTMB, from Dr. Bukreyev's lab, and they demonstrated that, if you block that interaction between Ebola and TLR4 on macrophages, you improved survival in a mouse model of Ebola virus. So, this suggests that we could improve survival by blocking this interaction, potentially, in people. But the really important and absolutely critical experiment that needs to be done now is to repeat these experiments using a TLR4-Ebola blocker in a nonhuman primate model of Ebola virus disease.

[Sarah Gregory] How long did this study take and what were your first steps?

[Anita McElroy] Well, that really depends on how you think about it. So, the Viral Special Pathogens group at CDC, they're involved with Ebola outbreaks that have occurred over decades. And our study encompasses samples from an outbreak that occurred in 2000–2001—so almost 20 years ago—as well as one that occurred in 2014, and historical samples from human autopsies that date back as far as 1995. So, we started putting together the data for the study in mid-2017 and we were looking at soluble laboratory markers of inflammation in the serum and plasma samples from the patients from previous outbreaks. And as we moved along in the study, we realized that we would benefit significantly by involving some of our colleagues from the Infectious Disease Pathology branch. And Rose Martines and Luciana Flannery, in Sherif Zaki's group, provided the data showing macrophage activity in the tissues of fatal cases. And that really helped to bring the whole story together.

[Sarah Gregory] So, what was your initial hypothesis? Did you have any expectations when you began?

[Anita McElroy] Well, as you mentioned, I'm a pediatric infectious disease physician, and as…in that role, I've been involved in the clinical care of patients with this inflammatory disorder known as HLH. And, having seen those patients and having done studies on patients with Ebola virus disease, I was really expecting to find laboratory features of HLH in patients with severe Ebola virus disease. However, we found that patients with Ebola virus disease look a lot more like a related inflammatory disorder that is known as MAS, or macrophage activation syndrome. In HLH, it's T-cells and macrophages that both, together, drive the disease pathology.

But in macrophage activation syndrome, it's largely just the macrophages. And our data from this study showed that severe and fatal Ebola virus disease is more associated with macrophage activation than with T-cells, and this was somewhat of a surprise to me.

[Sarah Gregory] So, what was the most challenging aspect of this research?

[Anita McElroy] I think any time you're doing any kind of work in BSL4 containment, that lends itself to being the most challenging aspect. So, all of the work that we do with Ebola virus has to be done in a biosafety level 4 containment lab. So, we wear a really heavy suit that's made of very thick plastic material and the air that you breathe when you're in that suit is provided by a hose that hooks into the suit. So, any time you move around the lab, to go from one place to the next, you have to unhook your air and hook your air back up. You also have to wear two pairs of gloves and this really can alter your dexterity. So, it turns out that everything you do in the BSL4 lab takes you probably two to three times the amount of time it would take you to do it in a regular laboratory. And that can really bring a lot of challenge to studying Ebola virus.

[Sarah Gregory] I can see how that would actually be quite daunting. But I do have to say that I think many people, when they think of us here at CDC, they kind of think that's what we're all doing, all the time.

[Anita McElroy] (Chuckles)

[Sarah Gregory] So, there's an outbreak going on in the DRC right now. Will this research help clinicians there?

[Anita McElroy] You know, this research has the potential to help clinicians who are caring for patients with EVD in the future. And that is only the case if the hypothesis that we've generated proved correct in nonhuman primate models. So, as we've talked about, our data suggests that using specific inhibitors of the immune system could improve clinical outcomes. But we would never suggest that these be evaluated in humans before they've been tested and proven in the best animal models, and that is in fact the nonhuman primates. So, if these types of therapies do prove to be effective in nonhuman primates, then yes, they could be helpful to clinicians in the field. But we have to keep in mind the real challenge to field care of patients with Ebola is the logistics and resources that are needed to get the effective care to the places where these infections are happening. So, getting effective immunotherapeutic drugs to patients in affected countries could still prove to be challenging.

[Sarah Gregory] People were so terrified of Ebola when we first had the big outbreak that began in 2014. Do you think people are getting sort of complacent about it now and is this good or bad?

[Anita McElroy] Yeah, it's a really unfortunate reality. I think we are getting complacent because there hasn't been any spread outside of DRC related to travel from the infected areas. But this outbreak continues to smolder. Just recently, the latest case updates were over a thousand cases of Ebola virus disease in the DRC, and as long as this outbreak is ongoing, there's always going to be a risk of spread outside of the region. And complacency, I think, is always bad, right? It isn't good that people have become complacent. But we're fortunate that there's some new tools that are available that did not exist in previous outbreaks. So, we have both experimental therapeutics, as well as experimental vaccines, that are being evaluated in ongoing clinical trials in the field. And this is a huge advance, but it doesn't replace the very

important and the most difficult work, which is identifying contacts and tracing them. And that's where the real challenge still lies.

[Sarah Gregory] So, I know this is hard, probably impossible, but what do you think the future of Ebola viruses will be?

[Anita McElroy] Yeah, I wish I could say that we're going to beat this thing and we'll be able to eliminate the virus. But that's just not a reality, because this virus has a natural reservoir. I feel like the best-case scenario is we can achieve enhanced surveillance and action, so we can make early detections of infections and get those individuals into appropriate care. And we could potentially have a vaccine, if this trial works out quite well, that can be used broadly, right, in high-risk areas and high-risk populations. So, we're talking about healthcare workers in West Africa and in sub-Saharan Africa. But the reality is, probably the worst-case scenario, is we keep on doing what we're doing now, and we just have this reactive process that on…that goes on, and we're using insufficient resources to deal with the problem in the developing world.

[Sarah Gregory] Can you remind us what the natural reservoirs are?

[Anita McElroy] So, it's thought that the bat is the natural reservoir; there is certainly data to support that, but it hasn't been proven definitely. No one has yet isolated live virus from a bat, only viral sequences from bats.

[Sarah Gregory] Okay. If you could fix just one problem, science- or health-related, what would you choose?

[Anita McElroy] This is a little off-topic from a virology perspective, 'cause I'm a pediatric infectious disease doc, so I think I'd focus on maternal and child health. So, I'm always alarmed by the global under-five mortality rates that are published by WHO every year. In 2017, that number was 5.4 million children died from mostly preventable diseases. In fact, neonatal mortality accounts for almost half of those deaths in children under five. But, in addition to the neonatal mortality, infectious diseases really lead the charge in childhood mortality. Diarrheal diseases and pneumonia make up the other big pieces of that pie chart that makes up all of under-five childhood mortality. And I think we could do a really good job of improving childhood survival if we had universal access to clean water, which would help with diarrheal diseases, and universal access to pneumococcal and Hib vaccination, which would help against the childhood pneumonia deaths.

[Sarah Gregory] And people would use them?

[Anita McElroy] Yes.

[Sarah Gregory] What is the number one best thing that people can do to protect themselves in a world of global diseases?

[Anita McElroy] So, I'm gonna kinda cheat here and give you two, 'cause they're really related. The first one is one you alluded to in our last question, which is get vaccinated, right? We have many readily available vaccines that protect against a lot of different infectious diseases. These vaccines are safe and effective and we need to use them. And the second thing is to wash your hands, right? Handwashing after using the restroom, handwashing before and after food

preparation, handwashing after caring for people who are ill. Those two things really could protect people from our global infectious disease issues.

[Sarah Gregory] Okay. And so, finally, I know you've said you were a pediatric infectious disease physician, so why were you studying this and why is it important to you? And tell us a little bit about what you do at CDC.

[Anita McElroy] Sure. I think the only way that we can really develop ways to fight against highly pathogenic viruses, like Ebola, is to understand how they work. How exactly do these viruses make people so sick? So, our goal from these studies is to use what we learn to come up with new ideas on how to treat patients with Ebola virus disease. And this is, in fact, a goal of any physician or scientist, right? We all want to make a difference in the world around us. Right? We want our work to have a positive impact on others. I'm no different in that regard. I just happen to be fascinating by emerging viruses, so that's where I focus my effort.

My job at CDC is that of a guest researcher. Now, I've been there since 2007 and I work in the Viral Special Pathogens Branch, and this is led by Stuart Nichol. And the section that I'm in is the Molecular Pathogenesis and Therapeutics Group, which is led by Kristina Spiropoulou. And the scientists at VSPB are a really unique group of folks. They study highly pathogenic viruses, like Ebola, and the work is quite broad. So, the branch provides diagnostic and epidemiologic support all over the world. We do basic laboratory science to understand how viruses work. We also study viral pathogenesis in animal models, and we develop new drugs to fight against these viruses. So, VSPB scientists really work together to combat highly pathogenic viruses, and they provide a special and unique skill set that supports CDC missions. So, it's been a real privilege and honor for me to participate in that work over the last 12 years.

[Sarah Gregory] Well, thank you so much for taking the time to talk with us today, Dr. McElroy.

[Anita McElroy] Thank you, Sarah.

[Sarah Gregory] You, our listeners, can read the February 2019 article, Macrophage Activation Marker Soluble CD163 Associated with Fatal and Severe Ebola Virus Disease in Humans, online at cdc.gov/eid.

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

[Announcer] For the most accurate health information, visit cdc.gov or call 1-800-CDC-INFO.