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Investigating HLH: Our Current Understanding of a Rare Disease

**Announcer:**
A rare, deadly disease that leaves patients in critical condition and doctors searching for answers, knowing the signs can save a life. This is Investigating HLH, a podcast about hemophagocytic lymphohistiocytosis, brought to you by Sobi, Inc.

**Dr. Narloch:**
Hello, everyone. My name is Adam Narloch, and I'm excited to kick off Episode 1 of Investigating HLH, a podcast sponsored by Sobi, Inc. I currently work as a thought leader liaison for Sobi. It's a biopharmaceutical company dedicated to developing and delivering innovative treatments for people with rare diseases. Throughout this series, we'll be talking to experts in the field of hematology/oncology, rheumatology, and immunology about hemophagocytic lymphohistiocytosis, also known as HLH. Our discussions will cover multiple topics, including the pathology of HLH to how it's diagnosed and managed.

For this episode, we'll begin with a general introduction to HLH, a brief overview of the history behind the disease, and then talk more in depth about our current understanding of HLH. Joining us for this discussion is Dr. Michelle Hermiston, a pediatric hematologist/oncologist and bone marrow transplant specialist and the Director of the Pediatric Immunotherapy Program at University of California San Francisco Benioff Children's Hospital. So welcome to the podcast, Dr. Hermiston, and thank you for joining us. If you'd like, please tell us a bit more about yourself and your experience with treating HLH in your practice.

**Dr. Hermiston:**
Thank you so much, Adam, for this opportunity to speak with you about HLH today. As you noted, I'm a pediatric hematologist/oncologist and bone marrow transplant specialist. I also direct our Pediatric Immunotherapy Program at the University of California, San Francisco. HLH is one of my favorite diseases. It's fascinating. It's complicated. It requires a large team of people to care appropriately for these children and, um, adults afflicted with this disease. And so, the opportunity to share our current understanding of this disease with listeners is very exciting to me.

**Dr. Narloch:**
Thank you, Dr. Hermiston. Now to dive deeper into some of the background about HLH, I've read that the first case for this disease was published way back in 1939 as histiocytic medullary reticulosis. Years later, in 1952, there was another case that reported this condition in two infant siblings and proposed the name familial hemophagocytic reticulosis. Clearly, there have been major advances in our understanding of HLH since then. So to help us better understand the recent history, we would love to get your impression of how the research has evolved during the time that you've been in practice.

**Dr. Hermiston:**
Thank you, Adam, that's a great question. I think it's fascinating, but this is such a young disease relative to things that were described much earlier in the literature. And I think that reflects the complexity of actually recognizing these patients. There are sprinkles through the literature of case reports until the early 90s. And I think HLH is one of the perfect examples of how research collaborations are essential to improve outcomes for rare diseases.

The Histiocyte Society is an international organization that is collaborative efforts globally of physicians throughout the world who are interested in caring for children and adults with histiocytic disorders. And it is really through this organization that I think outcomes have improved. The society back before I was a physician, in 1994 initiated its first international collaborative trial called HLH-94. Members of the organization recognized that HLH was an excessive and damaging to the host hyperinflammatory disorder and proposed uh, a set of

guidelines or diagnostic criteria for inclusion into the study, and then evaluated whether immune suppression helped the outcomes of these patients who had a specific subtype of HLH called primary or familial HLH. The outcomes of that showed that with immunosuppressive care, we could cure about 60% of patients provided you got their inflammation under control and then took them to definitive therapy with a bone marrow transplant.

A second international trial, uh, occurred in, uh, 2004 which looked at, um, randomized patients to addition of a medication called cyclosporine, which, um, ultimately was found not to, um, make a difference. But I think it was really these two efforts at an international level that really improved outcomes for this disease.

It is interesting that at that time, I think many physicians didn't recognize HLH, and one of the key goals of the Histiocyte Society at that time was to improve awareness of this disease. I think the pendulum during my career has kind of shifted to the other side and now many people think everything with a little bit of inflammation is HLH. And our goal now is to help educate people on how to think about and how to approach patients with this disease. And I think that's one of the really exciting things about this podcast series, is an opportunity to share our current information and knowledge about this disease.

So in terms of my own involvement in this field we are part of the North American Consortium for Histiocytoses which was initially organized by 12 – content experts from 12 centers with interest in this disease and we've been organizing and leading clinical trials in that space. I've also contributed some animal studies within my own laboratory looking at mechanisms of cytokine-mediated glucocorticoid resistance and potential ways to try to circumvent that from a therapeutic standpoint.

And then I think some of the other exciting advances in the field have been improved recognition, understanding on a molecular level of kind of the cytokine differences in the genetic contributions to this disease that I think are really going to be changing how we treat these patients in the future, and hopefully towards much more personalized and tailored type of approach as more information becomes available about these patients.

**Dr. Narloch:**
Sounds like we've come a long way, which is encouraging to hear when talking about such a rare and dangerous disease. But as we know, when it comes to medicine, there's always more to unravel and learn. I'd like to dive a little bit deeper into our current understanding of HLH and the mechanisms behind it. It's been established that this is a disease of immune dysregulation at its core. Could you tell me a little bit more about this immune dysregulation and the systems that it affects?

**Dr. Hermiston:**
Yes, certainly. One of my favorite topics, so I could talk for hours on this. So I think in answering how immune dysregulation leads to this phenotype of HLH, an excessive immune activation, it's important to remember how our immune system is designed to work. Our immune system really has two purposes. The first is to eliminate infected cells or infections that we encounter in our environment. And the second is to recognize and eliminate malignant cells. In individuals with HLH, the immune system response is initiated appropriately, but there's an inability to terminate that response. So if you take as an example, you are infected with a virus that leads to activation of your T cells when they recognize that this virus is not supposed to be in my body, those activated T cells release cytokines. There's a variety of those. One of the key players, we know, is interferon gamma, and that leads to activation of other immune cells in the microenvironment around that virus, and particularly macrophages and neutrophils. The purpose of macrophages is to essentially phagocytose or eliminate that infectious agent. Or if it's malignancy, the malignant cell. And the T cells help in this process by a process called cytolytic granule release, where they release granules into the target cell and those granules are toxic to the cell and cause it to die. Normally, once you eliminate the antigen, the infection, or in this case, you know, for in our example, the virus that's the end of the immune response. You have a few cells that remain around as memory for the next time you encounter that virus, and you get better.

In individuals who have HLH, that process starts appropriately, but there's often an inability to terminate the immune response, and so you end up getting more and more and more cytokine activation and production initially from the T cells and then from the target cells, the macrophages in particular, and it's really those cytokines that lead to all the sequelae we see of hyperinflammation. So these patients can present with fever, they can present with hypotension, they can present with difficulties breathing. They can have multiorgan system failure, liver failure, kidney failure, respiratory failure, and become quite ill. They can also have involvement in their CNS, central nervous system or brain and that can present as delirium, as all the way to cerebral edema and even death from that. And so it's a very serious disease, and if you don't recognize it early enough to prevent the end-organ damage these patients can do quite poorly and that accounts for the high death rate that is still seen with this disease in a significant number of patients.

**Dr. Narloch:**
Thank you so much for that explanation. There’s certainly a lot going on here. Thinking about the cytokines that drive HLH and the associated hyperinflammation, I wonder if we could take a closer look at some of the key players in this story. Which cytokines have

been found to play an important role in HLH pathogenesis, and how do they factor into the manifestations of HLH?

**Dr. Hermiston:**
Good question. So, there's been a lot of work and profiling of cytokines from patients who have HLH. And this is another example where collaborative research has really been key. This is rare, and so these have really been done as multi-institutional studies really at a global level and very much moved our insight and understanding of this disease forward.

We think one of the key initiating factors is a cytokine called interferon gamma, which is produced and released by T cells when they recognize something that is inappropriate for our bodies, so infection or malignant cell. The role of the interferon gamma is to act, among many things, is to activate macrophages. Macrophages then can phagocytose and try to eat up things in the microenvironment that are bad for us. And in doing that process, and when they become activated, they themselves release cytokines, key ones being, IL-1, IL-6. There's also production of TNF alpha in this inflammatory microenvironment. Those cytokines lead to increased activation and recruitment of additional inflammatory cells. And all of that is a good thing, um, provided that you are able to terminate and clear the infection or the malignant cells once this inflammatory process has started.

If you can't do that, then the cytokine levels build up. And it's really the buildup of these cytokines and their effects that cause the clinical manifestations of HLH.

So if you imagine – what I often tell patients is, if you imagine when, you know, think about when you have the flu and you feel achy and you hurt, and you have a fever, all of that is due to cytokines. And it's those same cytokines, but at much higher levels, that mediate the effects, that we see clinically in HLH. So the fever is driven by high levels of IL-1, IL-6 can contribute to that, as can TNF alpha, what we call capillary leak, um, where you start to have, hypotension because your blood vessels are leaky and then you get leaking of fluids, and that leads to – can lead to organ failure, including lung failure, heart failure was really due to that. We see an increased risk of bleeding in these patients. That's thought to be due to release of plasminogen activator inhibitor type 1 if you're ever in a trivia game that can increase breakdown of the proteins that are essential for preventing you from bleeding. And so these patients often have a bleeding predisposition because of too much production of that – of that agent.

So all of that is initiated essentially by unchecked cytokine production. And over time, those macrophages aren't very specific in what they kill. And so instead of just attacking the infection or the malignancy that has triggered this whole process, they start to target and eat up normal cells in the body. So you can get infiltration with inflammatory cells and particularly macrophages. And this is where the word hemophagocytosis comes from. You start to get ingestion non-specifically of your blood cells. It can infiltrate really any tissue in the body, but liver failure is not uncommon. In this disease, kidney failure is not uncommon, um, respiratory failure is not uncommon. And it really is all because of this initial triggering by cytokines that's a normal part of an immune response that, in this case, has gone unchecked.

**Dr. Narloch:**
Such a good explanation. Dr. Hermiston, thank you so much for that. There's still a lot being discovered about the two classifications of HLH, often referred to as primary and secondary. At a high level, primary HLH is generally understood to manifest because of a genetic abnormality that predisposes someone to developing the HLH syndrome, while secondary HLH occurs in response to another condition, like an infection or malignancy. Could you tell us a little more about these two classifications, including the similarities and the differences between them?

**Dr. Hermiston:**
Yeah, this is a great question. And I think one of the most confusing things in this field, and also one of the things that I think is really evolving as we – as our technology gets better and as we start to understand more. So historically, primary, also called familial HLH, um, it has been attributed to an identifiable genetic mutation usually homozygous or X-linked and thought to infect primarily young children, babies. And in these individuals, when people have looked at the genes that are involved in familial or primary HLH they tend to map to genes that are important for release – reduction or release of cytolytic granules. And so these patients – and they've taught us a tremendous amount about how the immune system works – but in these patients, they're able to start an immune response appropriately, but they can't turn it off because they can't get those granules that are toxic to the target cell, either produced or released into the target cell. And so it's really that defect of not being able to terminate or put the brakes on an immune response that causes familial HLH.

I think one of the things that is important to appreciate is that even in patients with primary HLH, HLH doesn't happen spontaneously, at least in the animal models. You still need something to trigger it, whether it be infection or malignancy. And so, individuals with primary HLH we still, even in those patients, we always want to look for what was the trigger so we can eliminate that, because that's – if you don't eliminate the trigger, then you've got what the, you know, essentially the spark that starts the hyperinflammation continuously

present.

Also important to note that primary or familial HLH can happen in patients who are not babies. And in fact, there's a study from the group in Cincinnati that looked at all of the referrals. And the oldest patient who had homozygous perforin mutations, which is one of the defects in this kind of killing pathway, was 72 years old when he presented. So it's important, even in older patients, to look. And certainly, something that's evolved in my career is this recognition by my adult colleagues that this can be inherited. And they are doing more and more transplants on particularly young and middle-aged adults with familial HLH, that historically probably was unrecognized simply based on age. We said everybody was secondary HLH, if you were more than, you know, a young kid.

Secondary HLH is how we classify it when we can't find a genetic mutation underlying the disease. Sometimes this can happen in response to just overwhelming presence of a trigger. So if you have lots of stimuli for the immune response, you can get something that looks like HLH without having a genetic mutation, because it's so hard for the immune system to keep up. So you end up with lots of cytokines as it's trying to do its best to eliminate the harmful trigger. That can happen in patients who have autoimmune disease. And so the autoantigen is the trigger in that case. It can happen in the context of some infections, Leishmania, Dengue fever, a lot of the viral infections, particularly of the herpes virus class, are classic triggers in those instances. And it can also happen in the context of malignancy.

I think one of the things that's really interesting and evolving in the field, and why I'm personally not a huge fan of calling it, is it primary or secondary? To me, that doesn't matter. The question really should be, is there hyperinflammation? And is the immune system in this patient helping them or hurting them? And when you answer that question, that guides what you should do next from a therapy standpoint, what we are learning is that many patients who present at older ages, or what we thought was classically secondary HLH, likely have what we call digenic mutations. So they have mutations in the pathways that lead to that are important for cytolytic function, killing target cells that may be crippled, but not completely eliminated. And so the patients who have familial primary

HLH tend to have more homozygous both you know, copies of that gene and all of that protein are eliminated. And individuals that we historically have classified as secondary HLH, I think we're recognizing now that many of them have proteins in the pathways that are important for killing cells that aren't completely eliminated, but don't quite work appropriately. And so I think that's one of the evolutions in the field at the current time.

Also important to note and I think one of the things that has made it confusing in this field is that HLH gets – is maybe not the best name for this disease; it comes from the historic use of how this field evolved. There is related, and I kind of think of as an umbrella or cousin of this called macrophage activation syndrome, which is essentially an HLH-like phenotype that we see in patients who have autoimmune disease. It tends to be triggered by the antigen the autoantigen in that case but many of the manifestations are similar. Some of those patients probably have defects in not the cytolytic granule pathway, but actually in the inflammasome, which is another piece of machinery within our cells that's important for terminating an immune response. Those patients tend to have higher levels of IL-18 whose downstream target is interferon gamma. So you can imagine that if you lead to you know, IL-18 leads to activation of interferon gamma, then you end up with more IL-1 and IL-6 using those same circuits it's just started in a somewhat distinct way.

**Dr. Narloch:**
Thank you for walking us through this, doctor. This has been great. There's certainly a lot to digest, and I really appreciate you sharing your knowledge with us. We've covered a fair amount so far, starting from the first case studies describing HLH and leading all the way up to the field's current understanding of this complex disease. We've discussed the mechanisms behind the dangerous immune dysregulation as well as the similarities and differences between primary and secondary HLH.

During our next episode, we will discuss the challenges associated with identifying and diagnosing HLH, which can be difficult when patients are presenting in such critical condition. I think it's important to remember that consulting an expert such as yourself can be extremely helpful when suspecting a patient may have HLH, is that right?

**Dr. Hermiston:**
Oh, I think it's definitely helpful. In fact, in our institution, we have a weekly conference that is multidisciplinary of all of our different subspecialists. It's led by one of my colleagues, Dr. Matt Zinter, um, in our – who's a critical care specialist, where we discuss these very complex children. And, um, even though I view myself as someone who is because of my interest in this disease, have a lot of experience with it, I still always involve colleagues. I think these are very, very complex patients, and having a sounding board to think about how to best treat and manage these patients is just crucial in providing the optimal care.

I think one of the biggest challenges in treating patients with HLH is that there is a trigger that's often an infection, and giving immunosuppression to a patient who has infection is a really hard decision to make, and making that decision as a group is helpful. I'm a Bay Area basketball fan, and you know, we say there is strength in numbers, but I think this is really one of those cases where

collaborating with your colleagues so that we can collectively make the best decisions for these complicated patients is very important.

**Dr. Narloch:**
Thank you so much for taking the time to share your experience and knowledge about HLH. Is there anything else you would like to add before we wrap things up?

**Dr. Hermiston:**
I just want to thank you again for the opportunity to chat with you about one of my favorite diseases today and to be invested in increasing physician knowledge about this very challenging and difficult disease. And I think, you know, most importantly if you see a patient where you're thinking – you know, first you have to think about hyperinflammation, and then I really believe the next step is to think about, is the immune response in this patient helping them or hurting them, which will guide what you do next in terms of a therapeutic approach.

**Dr. Narloch:**
Thank you, Dr. Hermiston, and thank you for being with us today.

**Dr. Hermiston:**
Thank you.

**Dr. Narlock:**
Thank you for joining us today on Investigating HLH. If you liked this podcast and think someone else might as well, please forward it along. Our next episode will feature more experts to dive deeper into the diagnosis and management of HLH. Once again, my name is Adam Narlock, and I'll see you next time.