

PEDIAPOD MARCH TRANSCRIPT 2023

Geoff Marsh

Hello and welcome back to PediaPod for March 2023. In this episode, we look at cardiovascular outcomes in children with Kawasaki disease.

Kawasaki disease is a common childhood vasculitis and its global incidence appears to be increasing. Although this disease is self-limiting and more recent treatments with intravenous immune globulin have drastically improved outcomes, the associated vasculopathy can cause cardiovascular complications with serious long term implications. In this episode of PediaPod, I speak with Early Career Investigator Cal Robinson at the Hospital for Sick Children, Toronto, Canada. He and his team performed a population based cohort study using Ontario Health administrative databases to determine the risk of cardiovascular events and mortality after Kawasaki disease.

Cal Robinson

Okay, so I'm Cal Robinson. I grew up in Toronto, Canada and after I finished high school here I moved to the UK where I completed medical school at the University of St. Andrews, Scotland and the University of Manchester, England. I then worked for a year as a junior doctor back in Scotland and then went back to Canada for pediatric residency which was at McMaster University in Hamilton. And it was really there at McMaster during my pediatric residency that I became interested in looking at doing research into different childhood diseases such as Kawasaki disease using population-based healthcare administrative databases that we have available to us here in Ontario. So after my pediatric residency at McMaster, I then moved back to Toronto to complete a fellowship in pediatric nephrology at SickKids. Currently, I am in the process of completing a master's degree in clinical epidemiology at the University of Toronto, working with Dr. Rulan Parekh and we're looking at different treatment options for childhood nephrotic syndrome.

Geoff Marsh

So you look like you're heading into nephrology but you've just recently published a paper on Kawasaki disease and cardiovascular outcomes. So you've got a few different interests?

Cal Robinson

Yeah. So I think the hard thing for me as a medical student and as a pediatric resident was deciding what I wanted to do. I kind of loved everything that I did. And in my first few years as a pediatric resident, I knew I wanted to pursue a subspecialty but whether that was rheumatology, nephrology, or something else, I wasn't sure. So I ended up getting involved in research in a number of different conditions across different specialties, which I think was great. It certainly broadened the experience that I had and introduced me to new people and new research methods in these different areas. So the research that we did in Kawasaki disease has certainly benefited the research I'm doing now in kidney diseases. But yes, I'm by no means a subject matter expert in pediatric rheumatology.

Geoff Marsh

Okay, but I suppose one thing that binds them both together is a population-based approach to studying the disease?

Cal Robinson

Yes, absolutely. So I think that for all of my research, I've been interested in trying to leverage the datasets that we have available to us. And I think that's a huge strength in Canada, that for each province with a single payer health care system, we have a huge amount of data that's collected. And we can use this data to study long term outcomes of different pediatric diseases. And that's a real strength. I think that the power of these databases is that we can get large cohorts, sometimes thousands of children with a condition and then we can follow them for ten, twenty or more years.

Geoff Marsh

It raises the question with regards to Kawasaki disease, how common is it? And what's the global trend of incidence?

Cal Robinson

Kawasaki disease is the most common childhood vasculitis, but it's still relatively rare. For our study, we included all children across the province of Ontario. So for the twenty year period that we were looking at there would have been about four to five million children in the province during that period. And of those children, we found that about four and a half thousand of them had Kawasaki disease. So you can get a sense for the numbers there in terms of the incidence overall. So we previously published a paper looking at the incidence here in Ontario, and we found that it has been increasing, which is consistent with some other authors here in Canada, as well as some other countries around the world, particularly in Asia where they have quite robust surveillance data nationally.

Geoff Marsh

Kawasaki disease itself is what you call self-limiting, isn't it? But what you were interested in was the knock-on effects on cardiovascular health. Can you just give us a sense of the routine course of this disease?

Cal Robinson

Yeah, so we know that during the acute phase of Kawasaki disease, there's inflammation happening within the arteries. And that inflammation causes damage to the structure of the arteries and sometimes ballooning of the artery or coronary aneurysm. And we know from other studies that those children with large coronary aneurysms are at increased risk of heart attacks and other cardiac complications longer term.

Geoff Marsh

Let's talk about your results then. You had this really great big cohort, what precisely were you measuring as your primary and secondary outcomes?

Cal Robinson

The primary outcome we were really focused on was major adverse cardiac events. So that was a composite of developing a heart attack, a stroke, or transient ischemic attack, or death. And those are

well coded in the databases that we have available in Ontario. So we can be confident in those outcomes. In terms of some of the secondary outcomes, we looked at individual cardiac events, we looked at the risk of needing a cardiac surgery or other cardiovascular procedures to get a sense for what the individual risks of those would be as well.

Geoff Marsh

The headline result was that those major adverse cardiac events were, as you'd expected, higher in children who were exposed to Kawasaki disease...

Cal Robinson

Yes. We saw the children that had experienced Kawasaki disease were at increased risk of developing these cardiac complications in the long term after their initial diagnosis. So up to ten years after developing Kawasaki disease, we still saw that they were at increased risk. But I think one of the other key takeaways is that the absolute risk actually of these events was quite low. It was less than 2% of them that developed these major adverse cardiac events throughout the follow up that we had in our study, which was compared to just under 1%. For pediatric control, we looked at a few other things as well, to get a sense for both the timing as well as which children with Kawasaki disease were at greater risk. And in those analyses, we found that the risk of these cardiac events was highest in the first year after diagnosis. And gradually the risk for children with Kawasaki disease decreased over time back towards the general population level. The other thing we found, which again was not entirely surprising, was that children that had coronary aneurysms during their initial illness were at the highest risk of subsequent cardiac complications. And for these children, about 10% of them developed major adverse cardiac events throughout our follow up.

Geoff Marsh

We'll come to what we can do with that information in a moment. But there was one surprising result in your paper, which was that the Kawasaki disease-exposed infants actually had a lower mortality in your cohort?

Cal Robinson

Yeah, agreed. This was a bit of an interesting finding and not one that we had expected. It has actually been seen in some other studies too. So in the nationwide survey in Japan, which is a large survey of Kawasaki disease patients that's conducted annually, they have also shown before that children with Kawasaki disease that don't have coronary involvement don't have an increased risk and may actually have a decreased risk of mortality long term. Authors from the Japanese studies have previously hypothesized that this may be due to decreased risk-taking behaviors and lower rates of accidental death. Unfortunately, with the data we had in our study available to us, we weren't able to look into that.

Geoff Marsh

You mentioned that certain Kawasaki disease patients were at significantly higher risk than those that had had coronary aneurysm. So how can that help clinicians to surveil these populations? What can we do with that information?

Cal Robinson

Yeah, I think this data can help in a number of ways, both for patients and families as well as healthcare providers. In terms of patients and their families I think that this gives us information that we can use to counsel them better, we can talk to the timing and the risks of these cardiovascular complications after the child has recovered from Kawasaki disease illness. Now, our data, based on how long we're able to follow these children up, really only provides data into adolescence and young adulthood. So future studies are going to be needed to better understand these individuals' risk of heart disease. And these sort of complications later in life, say in their fifties or sixties at more typical ages for experiencing problems like heart attacks or stroke. As healthcare providers, I do think that it provides information to us about which patient populations are at the highest risk. And for these patients, certainly, we need to be closely monitoring for signs and symptoms of cardiovascular disease, particularly outside of typical ages. So we see that these individuals could be experiencing heart attacks in their teenage years or young adulthood years. So we need to be mindful of that when considering what the risk of those problems could be. And then also the surveillance we do, so whether these children need to be followed more closely in terms of blood tests or things like cholesterol or imaging and there is good information on best practices for that in Kawasaki disease guidelines.

Geoff Marsh

Are we any closer to preventing Kawasaki disease or treating the inflammation or whatever's causing the vasculitis?

Cal Robinson

So certainly huge steps have been made in the last 2030 years in terms of the treatment of Kawasaki disease. Historically, there were really very few treatments, children were treated just with aspirin alone. More recently, we started treating children with intravenous immunoglobulin and other immunosuppressive agents and really the risk of developing coronary aneurysms has fallen dramatically. So, whereas historically, maybe 20 to 30% of children could have had coronary involvement during their initial illness, now that number is reported as being typically less than 5%. There may be studies that come out in the future looking at different immunosuppressive options, combinations that could reduce that risk even further. But there will always be children that are diagnosed a bit later, or have developed aneurysms already by the time they've presented to a healthcare setting. So for these individuals, we know that they are at increased risk. And it's about understanding exactly what the timing of that risk is and what strategies we can use to try and mitigate that risk long term.

Geoff Marsh

These healthcare databases sound like a bit of a goldmine. Are there any limitations to using that sort of dataset?

Cal Robinson

There are some limitations in terms of the data that we have available to us. So we are confident that we can define Kawasaki disease in these databases, as well as the outcomes, particularly the major adverse cardiac events. One area where there's a limitation to this data is defining coronary aneurysms, and there are diagnostic codes that we can use to define this but these codes haven't been validated in other studies. So with the data we have available to us, unlike clinical research, where you

could go into each patient's chart and actually confirm the presence of the aneurysm, the size, other characteristics, we're not able to look at that level of detail.

Geoff Marsh

I suppose that's the trade off with the fact that you were able to get such huge numbers and therefore more power in your statistical analysis?

Cal Robinson

Yeah, absolutely. I think that the big trade off using these healthcare administrative databases is that you have much larger sample sizes, longer follow up periods, and there's huge advantages to doing that. But you are limited in terms of the depth that you can go in and that this data has been collected, not for research purposes but for healthcare administrative purposes. So you have to be able to work within the limitations of the data and what you have access to.

Geoff Marsh

Are you going back to nephrology or what's next?

Cal Robinson

To be determined! I would say I am still very interested in Kawasaki disease and vasculitis. For the moment my research is mostly in common childhood kidney diseases such as nephrotic syndrome, which actually has some overlap with Kawasaki disease in terms of potential causes of it. It's also an immune-mediated condition treated with similar medications. So we'll see!