

KDRP 225

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Long Term Outcome

Kawasaki Disease Long Term Outlook

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10:11:39

I have been taking care of patients with Kawasaki Disease for 31 years now. I saw my first patient in 1972 and I am still in contact with some of those patients. So it's been quite a journey to work with people over the time and the... really wonderful thing is that a group of doctors who are interested in Kawasaki Disease is relatively small. But really quite cohesive.

10:12:07

And we have learned an extraordinarily amount in the 35 years or so that we have become aware of this disease. So sometimes you may feel

discouraged that we don't have the vaccine, we don't have the etiologic agent, but I look at it with great wonder at what we've learned about the way the disease behaves, how it affects the body. And we have a remarkably effective treatment, which Dr. Burns talked about and which has really changed everything.

10:12:41

I'm going to talk to you a little bit about the way I talk with my patients because I still see a large number of patients, and I still have a clinic at least once, sometimes two days a week depending on how many patients that we have.

Nature of Kawasaki Disease

- Self Limited Illness with blood vessel inflammation
- Active Inflammation resolves by 2-3 months
- Majority of children recover with no *detectable* permanent damage
- The proportion of children who recover without coronary damage after IVIG treatment is now over 95%
- Dr. Kato and many others have demonstrated that echocardiogram at 1 to 2 months is capable of determining if there has been significant alteration of coronary arteries

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I think it's important for you to understand what Kawasaki Disease is and what it isn't. And I know that you are very well educated group of parents. But Kawasaki Disease in spite of little nibbles here and there that something else might be going on, is basically a self-limited disease of young children.

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That means that you have it you get over it, and there's not strong evidence that it sets you up for other problems in life, except those that are related to coronary damage, and vascular damage that occurs when you have Kawasaki Disease.

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It's also important to understand that children with Kawasaki Disease have, are almost always healthy before they develop Kawasaki Disease, they are, this is not a disease of immunologically impaired children, children who have difficulty with, medical problems. And they are not abnormal after they have Kawasaki Disease except as relates to damage that occurred to their vascular system during this time.

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This is important to understand both in terms of; you don't really want to overprotect your children. And you don't want to think of them as somebody particularly strained or different or who requires, a different kind of, of child-rearing.

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The active inflammation resolved by two to three months. , And the markers for that are C-Reactive proteins sedimentation rates, the return of the white cells to normal, and the return of the platelets to normal.

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Today particularly but at all times the majority of children recover with no detectable permanent damage to their coronary arteries. And now because of IGIV treatment, we can expect that children, who are treated in the first week of, will have less than a 5% chance of having coronary artery damage. And of, now that we are re-treating and having new protocols for those that are refractive to IVIG, this can potentially be decreased even further.

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And also non-invasive testing with echocardiogram early if the echocardiogram is good at detecting coronary artery abnormalities, and determining whether there has been a significant alteration.

Long Term Outlook depends on Coronary Artery Status at 1-2 m

- Evidence shows that nearly all children with KD were healthy before their illness
- Children who have recovered from KD are normal with respect to immune function, arthritis, brain function, emotional problems, diabetes and other chronic or long term problems except those relating to coronary artery or other blood vessel damage which occurred during the KD illness.

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Nearly all children, as I mention they were nearly all healthy before they had Kawasaki Disease, and after they've recovered they're normal with respect to a new function. They are not necessarily more set up for arthritis, diabetes and other chronic or long-term problems except those relating to coronary arteries. Their brain function is usually normal. Emotional problems are not necessarily more common in children who have recovered from Kawasaki Disease.

Spectrum of Blood Vessel Damage

- There is now very secure knowledge about the outcome of KD over the next 20 years
- In any illness where the outcome can range from death at one extreme to full recovery without any minor or microscopic damage at the other extreme any one person will end up on one particular spot on that line.

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We have quite mature knowledge about the outcome or the natural history or the way that children behave over the next 20 and maybe 30 years. But 20 years at least. So we have a 20-year follow-up, with good studies, the patients have been carefully looked at.

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Now what I always try to tell people then is you have to realize that there is a spectrum of blood vessel damage. In any illness where you can die, at one extreme, or you could recover with no damage whatsoever. Any one patient will fall somewhere along that line. And it's important to find out, and you find this out at the one to two month period after Kawasaki Disease, where the child fell on that line.

Outcome Categories

- No coronary abnormalities on any echo
- Short term coronary dilation disappearing within 2-6 months
- Moderate sized aneurysms 7mm or less
- Giant coronary artery aneurysms
- Death in early KD

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So the outcome categories that we're going to talk about are, children who have never had any coronary artery abnormalities on any echocardiogram taken at the time of first seen, maybe one or two weeks later, one month later, and maybe two months later.

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There's the second category of children who have short term, coronary artery dilation that disappears, within two to six months, to one year, after Kawasaki Disease. We have patients who have moderate sized aneurysms, six, seven millimeters or less, mostly less. And then you have the patients who are at the highest risk with giant coronary artery aneurysms.

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And finally of course, we do recognize that there, are some patients who die in the early stages after Kawasaki Disease. And we certainly can't talk about long-term outcome in those patients except to develop strategies to try to prevent that from happening.

No Coronary Abnormalities on any Echo

- No evidence of increased risk of death or cardiac problems over the next 20-30 years
- Minor or microscopic artery changes may or may not be present
- Stop low dose aspirin at 2-3 months when platelets and ESR/CRP are normal again
- Healthy heart living counseling at 2 months to one year after KD onset to prevent atherosclerosis
- Blood fat and cholesterol or “lipid profile” if over 2 years old
- Special cardiac follow up not needed after 2 m to 1 year

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Now for those children who have no coronary artery abnormalities on any echocardiogram and there have been echocardiograms taken at the right windows of opportunities, when they are first seen, when the fever comes under control and one to two months later.

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There's no evidence of increased risk of death or cardiac problems over the next twenty to thirty years.

10:18:19

Minor, or microscopic artery changes, might or might not be present, in any one child that's in this category. It's not worth it to do the kinds of invasive testing that you would have to do to determine if there were minor or microscopic abnormalities. They're certainly not going to suggest a biopsy of the coronary arteries in children who have no evidence of a coronary abnormality.

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These patients will have been treated with some dose of aspirin. And their low dose aspirin can be discontinued at 2-3 months when platelets and sedimentation rate C-reactive protein have been found normal.

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I'm involved with patient's need to understand what healthy heart living is all about, and should have counseling for health heart living at two months or

one year, after the diagnosis of Kawasaki Disease. This is to prevent atherosclerosis, this is good advice for everyone, but its particularly good advice for someone who might have minor or microscopic abnormalities.

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Because as Dr. Kato has shown, there may be only a few ways that arteries can show damage. They'll damage from Kawasaki Disease can end up looking quite a bit like damage from atherosclerosis. Some of the same mechanisms must be going on. We do the need more research in that area, but we don't want to add insult to possible injury, that may have already occurred.

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I think all of these patients who are over two years of age should have blood-fat and cholesterol or lipid profiles and a sophisticated one. Not one of the quick ones you get at the health fair. But one that tells you what the HDL is like what the LDL, the DLDL. And so on.

10:19:57

And I think a growing consensus that special cardiac follow-up is not needed after two months to one year. Some of us are group agree, and we, we don't find this in the major disagreement point. Would say I end my follow-up on two to three months, and some would say I end my follow-up at one year, and some would say I see them at five years and ten years and 15 years. But this group does not necessarily need close follow-up.

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And it's really important not to overprotect the child. Because, not necessarily even you, but the grandparents will say, "Well gee you have a terrible illness don't you remember that? How can you let him go to gym class? You know he should probably become a computer expert." Well all of our children can't become computer experts, but the ones that spend too much time in front of the computer are the ones who are not going to develop their cardiovascular fitness.

Healthy Heart Living Basics

- No Smoking Tobacco *throughout life*
- Monitoring and treatment of high blood pressure *throughout life*
- Habit of regular vigorous physical exercise
- Avoidance of Obesity
- Prudent diet: 20-30% of calories from fat
- Further diet change if lipids are abnormal
- Promote emotional well being
- Healthy stress management practices

PP7

So this is healthy heart living basics.

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No smoking tobacco throughout life. I don't care what you tell your children when they are getting to be teenagers say, "If you don't believe me call Dr. Melish. You can't smoke because you had Kawasaki Disease. I don't generally threaten them much. But in that case I would say, no matter how cool it looks you don't do it.

10:21:11

Monitoring and treatment of high blood pressure throughout life, most of these children have normal blood pressure at the time we see them when they are young. But we know it's a the silent thing that can come on, particularly in late school age, particularly if they are a little overweight. Adolescent and then that period from 20 to 30, when they still think they are invulnerable and when they hardly ever see the doctor, they need to have their blood pressure monitored.

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They need to have it, regular vigorous physical exercise. They need to avoid obesity. They need a prudent diet and the Heart Association of Canada and the United States have wonderful cookbooks and they can tell you about how to design a diet where 20 to 30 percent or less of calories come from fat.

10:21:54

At this point I always remind my patients that American adults have improved their eating habits. American children's eating habits are still stuck in the '50's! If you have give a child their druthers they would have McDonalds for lunch every day, and Pizza with Pepperoni for supper every night, and that is not the diet that their parents are eating. So we need to see that they do follow through with diet.

10:22:23

Further diet changes if their lipids are abnormal. , Dr. Dean Ornish has shown us how important it is to promote emotional well-being. To keep your heart and your arteries open. And children need to learn like the rest of us, healthy stress management practices. So everyone needs to know these healthy heart living basics.

Short Term Coronary Dilation Normal by 2-6 months

- No evidence to date of cardiac death or problems in next 20-30 years
- Low dose aspirin 1 year to long term Rx
- Healthy Heart Living
- Repeated echos at 6 mos to 1 year until at least 2 are normal
- Need for special cardiac follow-up uncertain or optional

PP8

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Second category the child with short-term coronary dilatation. Now any sort of something has happened, we don't really know what it is. There is no evidence to date that this group has an increased incidence of cardiac death or problems over the next twenty to thirty years, so in that way they are like the children who have, no evidence whatever of coronary dilatation.

10:23:08

For me, I would like to keep these children at a low dose of aspirin. I see almost nothing wrong with taking one baby aspirin per day for long term. And

many people advocate that as the male children as soon as they get into their 20's or 30's they should probably take one baby aspirin every day. So other people would disagree but I discuss this with parents, if they feel they need the closure, when the coronary artery abnormalities have resolved. They want to stop, I don't get too excited about it, but I personally if it was my child I would probably say, long term aspirin would be a good thing.

10:23:43

Healthy heart living, repeated echoes at 6 months to 1 year, until at least two in a row are normal. EKG's probably at the same time and the need for special cardiac follow-up in this group, which doesn't have much wrong going on, is uncertain or optional and probably should be worked out with someone that you trust.

Moderate Sized Aneurysms

- 50% of these aneurysms resolve within 2 years
 - Areas of resolved aneurysm are not quite normal with decreased ability to dilate with exercise
 - No progression to stenosis over 20 years
- 50% of aneurysms persist
 - Depending in part on size, shape and location of the aneurysm, progression to stenosis or partial blockage of the blood vessel may develop over 20 years
- So...

PP9

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The moderate type aneurysms. , Dr. Kato has shown in his long-term follow-up of studies which, span the same period as mine but then in a far more sophisticated way with many more patients. Show that 50% of children with moderate sized aneurysms will have regression to normal lumen size within two years.

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These areas of resolved aneurysms are not quite normal. There is decreased ability to dilate with exercise and some paradoxical or unusual reactions to drugs that normally cause dilation. So there is something abnormal about these vessels. They are stiffer, they are more like pipes, and they are less

like an elastic tissue area. This is not the entire cardiovascular coronary tree; this is only those sections that were aneurysmal.

10:25:01

But at least he has shown there is no progression to stenosis over 20 years in these groups. So regression is a good thing, it's a form of healing. It's a type of healing that you can have when you've had this degree of insult.

Moderate Size Aneurysm Care

- Indefinite low dose aspirin and/or other “anti-platelet” drugs such as persantine or clopidogrel (Plavix)
- Healthy Heart Living
- Periodic echocardiograms, EKGs, exercise and/or drug stress echos and Thallium SPECT tests
- Individually tailored exercise program
- Regular cardiac follow-up indefinitely
- **DRUG AND FOLLOW-UP COMPLIANCE IS ESSENTIAL AND MUST START EARLY**

PP10

10:25:15

The other group of patients has, 50% of these aneurysms persist. And the persistence can depend on the size of the aneurysm, the shape of the aneurysm, the location, or which vessel it's in. Whether there is progression to stenosis or a partial blockage of the blood vessel. And this can develop over the next 20 years.

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So for this group of patient, moderate sized aneurysm care, is going to involve indefinite low-dose aspirin at least and or, and this may change over the next few years, other anti-platelet drugs, such as Persantine, or Plavix or other drugs that may be developed. The anti-platelet drugs that we have now work at different sites, in terms of platelet interaction. And we know that interaction of these platelets with these walls of the blood vessel with may be abnormal, and not as smooth as a child that never had Kawasaki Disease. This may cause development of stenosis. It's a very active area for research.

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Of course these children follow healthy heart living. And many of these children should be involved in regular active exercise. Once gain on an individual basis.

10:26:32

These people will need periodic echocardiograms. They will need probably; they will need angiograms, EKG's exercise and or drug stress echos. And Thallium SPECT spec tests particularly as they get older. Individually tailored exercise programs. Regular cardiac follow-up will be needed indefinitely with transition to care for adult cardiologists.

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And here, you as a parent, especially if you can start with children who are three, four, not already 13. Drug and follow-up compliance is essential and you need to start it early. It has to become part of the child's life. Because compliance is going to be important in their period from say ten to thirty until they get their sense back.

10:27:21

I used to think that it was only teenagers but now that a couple of my children have grown into their 20's, I know that they have not rejoined the human race!

Giant Aneurysms

- At risk for myocardial infarction for first 1-2 years
- At risk for development of stenosis over 30 years depending on size, shape, location of aneurysms
- Risk of aneurysm rupture is low and appears to be limited to the first 1-2 years
- SO...

PP11

10:27:32

Okay, giant aneurysm. This group of patients is at risk for myocardial infarction, for the first one to two years. This seems to be a period of risk of coronary rupture. This is important because if you have a child with an

enlarged aneurysm, all of the people who surround you are going to be telling the story of Uncle Joe who was 75 and had an abdominal aneurysm and it suddenly burst and he dropped dead and this was horrible, and how are you going to deal with that?

10:28:02

It's really a very uncommon thing to have coronary rupture and it occurs early. And Dr. Kitamura pointed out that this is not something that we can predict. Even with a giant aneurysm these vessels can continue to serve a patient well for a long long time, even though they are abnormally damaged. But rupture is not that big of a problem. But they are at risk for myocardial infarctions particularly in their early years. And then later again a stenosis may develop.

10:28:32

They are at risk for development of stenosis, which goes up on a gradual level over 20 to 30 years depending once again on size, shape, location, of the aneurysm. So for this group of patient.

Giant Aneurysm Care

- Anticoagulation with warfarin plus an antiplatelet agent such as low dose aspirin or clopidogrel (Plavix) – This has been proven to prevent bad cardiac outcomes
- Periodic imaging with exercise and drug stress echo and SPECT tests
- Regular cardiac followup with cardiologist
 - Obtain referral to a special Kawasaki disease center
- Healthy Heart Living with individual exercise Rx
- May need interventional treatment
- ENFORCE COMPLIANCE – DRUGS & VISITS

PP12

This group of patients is going to do better with anti-coagulation. Which is more than anti-platelet therapy. Probably together with anti-platelet therapy.

10:29:05

This has been proven to prevent the bad cardiac outcomes. So this is how you live, long and well with giant aneurysms. At the present time you do better if your blood can be anticoagulated. Anticoagulation will carry it's own

special list for exercise in terms of avoidance of contact sports and situations where you may have a hemorrhage.

10:29:28

This patient will clearly need periodic imaging with exercise and drug stress and spec tests. They need regular cardiac follow-up with cardiologist. And my prejudice is that patients with this problem, which is now a rare problem in the United States, should be seen at a place that has special interest and expertise in Kawasaki Disease. And people can give you referrals for that. But these are the people like Dr. Takashi, like Dr. Kitamura in Japan. People who have the most interest and are going to our international meetings and are keeping up and who know what the options are because this is a group that needs very special attention.

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Clearly they need healthy heart living. With individual exercise prescription. They may need interventional treatment and they must do compliance with drugs and visits. It's very hard for doctors to chase after patients. And the patients have to keep coming when they are supposed to keep coming. And I find that that's a problem. Oh, he's doing so well, Dr., I know I should have seen you last year, but you know it's now two year and three years. And the kids will be more likely to do that than the adults.

Giant Aneurysms

- At risk for myocardial infarction for first 1-2 years
- At risk for development of stenosis over 30 years depending on size, shape, location of aneurysms
- Risk of aneurysm rupture is low and appears to be limited to the first 1-2 years
- SO...

PP13

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So imaging, some of you are all too familiar with all of these imaging methods, but imaging has some credible change in the last five years, it's likely to credibly improve in the next five years. So a lot of these things are

going to become better and better and we'll be able to understand the individual anatomy of patients in this group that are at the highest risk. And be able to monitor them better and better as time goes on.

Imaging Methods

- Echocardiography
- Electrocardiograms
- Holter Monitors
- Thallium and Technetium Perfusion Tests
- MRIs
- Ultrafast CT
- Intravascular Ultrasound

PP14

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And the biggest problem for this group, as we mentioned is not coronary rupture, but it's the later development of stenosis. Which seems like a double whammy. Bad enough that they got dilated coronary arteries, how the hell did they get stenotic coronary...? But what happens is the abnormal flow through these large vessels causes changes in the walls of the vessel. Particularly at the outlet of the aneurysm, there is the buildup of clotting and recanalization.

Interventional Treatments for Stenosis and Insufficiency

- Clot dissolving drugs such as TPA
- Balloon Angioplasty
- Stent Implantation
- Rotoblader Ablation
- Coronary Artery By-Pass Grafting
 - Needed rarely and only for severe stenosis
 - Relatively safe and effective
- Cardiac Transplantation
 - Rarely needed

PP15

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So stenosis ends up being the serious, most serious problem. For people who have clots that develop within their coronaries, this can be detected by echo. Clot dissolving drugs can be given, people who are progressing toward myocardial infarction and have had one, can be treated with a, clot-dissolving drugs such as TPA.

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Balloon angioplasty can relieve stenosis. Stents, particularly now the new drug implanted stents can keep stenotic areas of arteries open. For the calcified areas, rota-bladers can break down the calcification. Coronary artery bypass grafting is not needed that often, in the United States. I think you should be very careful about who does it in children. If the person becomes older then, that's probably not so important. So this is very individual. But, as Dr. Kitamura shows, that it's relatively safe and effective, but he is doing it on a group of patients, half of whom have already had myocardial infarctions, all of who have evidence of severe stenosis. This is a very serious decision.

10:33:12

And cardiac transplantation may not be as effective at the present time as we would like it to be. And fortunately it is rarely needed. It is, and has been and is being performed, and sometime it is needed in catastrophic cases.

Outcome

- Outlook has improved greatly over the past decade. There are now many treatments available and your child's life expectancy will be extended
- Find a doctor or center that is knowledgeable and work with them.
- Children with severe and unique problems should be seen at a specialized center

PP16

10:33:30

I just wanted to say that outlook has improved greatly and especially over the past ten year. There's now many many treatments available, the child's life expectancy will be extended. You need to find a doctor or a center that's knowledgeable and work with them, and the children with severe and unique problems need to be seen at a specialized center.

10:33:54

And it's very important for you to develop a relationship with the doctor that you trust that you can talk with. It's amazing to me, Jane gets this too. We have calls two or three or four times a week, from people we've never heard of from places we don't know, asking us questions about what they should do about their child with cardiac disease or their child with Kawasaki Disease.

10:34:17

I always ask them, "Well if you don't think your doctor knows quite what to do, have your doctor call me." Because it's very hard for me to even know what's going on to talk to them over the phone. I almost never get calls from these people's doctors. Clearly these people are not able to talk with their doctors. , They are getting their information on the side. You have to find someone that you can work with and you should be able to find it. Because this is going to be, the people that really need this kind of attention are the severe and unique patients that we talk about.

10:34:47

So thank you very much.