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Kawasaki Disease – An Update

Developed by Annie Cheung and Dr. Mercedes Chan for PedsCases.com.
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Introduction:

AC: Hello everyone. My name is Annie Cheung and I am a final year medical student from Imperial College London in England. I am about to start my foundation year, the equivalent of residency, in Edinburgh.
MC: I am Dr. Mercedes Chan, and I work as a pediatric rheumatologist in BC Children's Hospital in Vancouver, Canada and am a Clinical Associate Professor of Pediatrics at the University of British Columbia.
AC: Today, we want to discuss Kawasaki disease. The learning objectives of this podcast are:

1. To define KD and its differential diagnosis from other paediatric condition
2. To outline the management of KD
3. To discuss KD in relation to MIS-C Multisystem Inflammatory Syndrome

AC: This podcast will be similar to bedside teaching: I will present a case, and we will discuss the differentials and pathophysiology. We will then move on to investigations and treatment.
MC: I will ask Annie some questions throughout the podcast. If you would like, feel free to pause and think of the answers yourself. Also, keep it in the back of your mind that I will ask what are 3 things you learnt today.
MC: Now, we want to include a high yield summary before we begin.

1. KD is a medium vessel vasculitis affecting young children. It is a clinical syndrome characterised by the CRASH&BURN acronym. There are 3 phases, and the most significant consequence is coronary artery aneurysms.
2. All children with KD must have an echocardiogram to assess their risk of having an aneurysm. KD is treated with IVIG and aspirin.
3. KD is a known phenotype of MIS-C, which has its own characteristic findings.

Case Presentation

MC: So, Annie, could you please summarise the case you saw?
AC: Of course
I saw this 2-year-old male in the ED with his father. We will refer to him with a pseudonym George.
George presents with a 4-day history of fever, rash, and red hands.
The fever was continuous and lasted 4 days. His father gave him paracetamol, but this was not very effective in reducing his fever.
He also had an erythematous rash that covered his trunks and limbs. He said it was not pruritic.
Also, George's hands were swollen and erythematous.
On further questioning, parents also noticed red eyes 2 days ago, but there was no change in appearance of the lips and tongue.
Systems review showed that he had a reduced appetite and fluid intake. He was not as playful.
He did not have any difficulty moving his head and neck. He also did not pull at his ears or experienced weight loss.

He was previously healthy and well male with no known drug allergy.
Birth and developmental history are non-contributary.
In terms of social history, he lives with his immediate family, who are all healthy. They have not had any recent travels. He is up to date with vaccinations, including COVID.

On examination, George appeared irritable, toxic, and not playful. Because of this, I assessed his ABCs.
Vitals showed a temperature of 39.5 degrees Celsius. His blood pressure was 90/60. George's heart rate was 110. Respiratory rate was 25, and his oxygen saturation was 99% in room air.
For his airways, he was speaking so this was assumed to be patent.
Breathing: his respiratory rate was 25, and auscultation of his chest revealed normal vesicular breath sounds.
In terms of circulation, his cap refill was less than 2 seconds. He had normal heart sounds with no added sounds or murmur.
His GCS was 15/15, and pupils were equal and reactive. I did not appreciate any conjunctivitis, but his parents showed me a picture that showed previously injected conjunctiva with a rim of clearing around the iris.
On head and neck exam, there was a single cervical lymph node that was palpable. It was in the upper anterior cervical chain and measured about 1.5cm.
His lips and tongue had a normal appearance. There were no oral ulcers, enlarged tonsils or spots.
George had an erythematous rash throughout, in particular trunk and limbs. It was a fine macular rash, and was non-bullous.
His palms and soles were erythematous, and his hands and feet were swollen. There was no peeling of his skin.
Abdominal examination was normal.

In summary, George is a 2-year-old male with a 4-day history of fever, erythematous rash, swollen hands, conjunctivitis, and cervical lymphadenopathy.

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Differentials

MC: At this point, what was your top differential?

AC: My top differential, unsurprisingly, was Kawasaki disease. We learnt in medical school this acronym: CRASH&BURN. C for: Conjunctivitis R for rash A for Adenopathy (cervical) S for Strawberry tongue and H for Hand (red, swollen). The BURN part stands for a fever lasting longer than 5 days. The A in CRASH can also stand for acetylsalicylic acid (ASA or Aspirin), which is part of the treatment and we will chat about that later on.

MC: The picture here was very classic, so I can see why you were able to identify Kawasaki's as a differential so quickly.

MC: Can you tell me more details about the classic presentation of these features?

AC: Absolutely. We talked a little bit about these symptoms in our case.

- The conjunctivitis is injected but spares the rim around the iris, which is known as the limbus. It is non-exudative, and is not painful.
- The cervical lymphadenopathy is often unilateral and is greater than 1.5cm. It is usually firm and fixed.
- The strawberry tongue has a characteristic look. It may be associated with changes to the lips and oral cavity such as cracking and drying.
- The hands and limb changes include oedema, erythema, and periungual desquamation but the peeling usually doesn't come until later in the disease[1,2]

MC: Now, remember that Kawasaki disease is a diagnosed of exclusion and some symptoms that the patient experienced may have already run its course, so it is important that you take a full history!

MC: Let's talk about the rash now.

MC: While the rash of a KD is polymorphous, classically it is non-bullous and non-vesicular. If the rash is bullous or vesicular, the child may have a different diagnosis.

MC: Did you think of some other differentials for the rash?

AC: Yes.

- scarlet fever presents similarly with a rash and cervical lymphadenopathy; it can also present with a strawberry tongue and fever. But characteristically, the rash feels like rough sand paper
- hand foot and mouth disease will lead to a rash on the palms, soles, and mouth.
- Another infection is chickenpox. But this will present with pruritic blisters, which our case did not present with

MC: Those are some good differentials. Are there any other dangerous differentials we would not want to miss?

AC: I would want to rule out any malignancies, such as acute lymphoblastic leukaemia, which can present with lymphadenopathy and fevers

AC: Another differential is Multisystem Inflammatory Syndrome in Children, also called MIS-C. This syndrome has developed from the COVID pandemic.

- MIS-C presents very similarly to Kawasaki disease. Patients often also experience a fever, rash, cervical lymphadenopathy, and limb changes
- However, patients with MIS-C typically also have gastrointestinal symptoms such as diarrhoea as well as shock and coagulopathy.
- In our case, the patient did not experience these other symptoms, so it is more likely to be classic Kawasaki disease[3]

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MC: Other differentials I would include are:

- other infections – tropical diseases such as tuberculosis and dengue especially if there is history of travel or sick contacts
- Measles is another differential – recently, there has been some outbreaks due to low vaccine uptake. Measles have characteristic Koplik spots – white spots on the mucous membrane in the mouth.
- drug reaction to antibiotics – for example Steven Johnson's syndrome
- Systemic Juvenile Idiopathic Arthritis and inflammatory bowel disease can also present with a rash and fever as well as changes to the hands and feet
- Children with Kawasaki disease may have a concurrent infection – this happens in up to 30% of children, so remember to consider different differentials. In the case where you can identify an infection AND feel a patient has Kawasaki disease, it is important to treat both.

Kawasaki Disease & phases

MC: Before moving on to investigations and management, let's talk about the phases of Kawasaki disease. This will help us to formulate and understand why we manage Kawasaki the way we do.
MC: Can you briefly tell me about your understanding of the disease, and what the phases are?
AC: Kawasaki disease is a medium sized vasculitis, resulting in the CRASH&BURN acronym symptoms. It is also called mucocutaneous lymph node syndrome.
AC: There aetiology of KD is unknown, but the leading theory is an infection leading to activation of the immune system.
MC: This is both the innate and adaptive immune systems. Many pro-inflammatory cytokines such as IL-1, a major protein responsible for fever and inflammation, have been shown to be associated with KD.
AC: The most important consequence of Kawasaki disease is coronary artery aneurysms.
MC: The chronic narrowing and sclerosis of arteries caused by inflammation of KD damages vessels, leading to a variety of cardiac complications. Apart from coronary aneurysms, KD also causes myocarditis in up to 50% of cases. In the worst-case scenario, a child can end up having a myocardial infarction.
MC: In the developed world, KD is the number 1 cause of acquired heart disease in paediatrics, whereas in the developing world it is rheumatic fever.
AC: Typically, KD affects children under 5, with boys of East Asian background affected more than other groups. There are 3 phases:
AC: Phase 1 is the Acute phase, occurring in weeks 1-2. The symptoms experienced fulfils the CRASH&BURN criteria.
AC: So that would include: Conjunctivitis Rash Adenopathy (cervical) Strawberry tongue Hand (red, swollen) Fever 5+ days.
MC: And at end of phase 1, the palms/soles - the periungual area - can start to peel. It peels like a banana, from the tips of the palms downwards.
MC: Often, when I take a history, I ask if their skin has started to peel. This can be counted as part of the criteria.
AC: Phase 2 is the subacute phase, and is typically weeks 2-6.

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MC: In phase 1, within the coronary arteries, there is transmural inflammation, which leads to a weakened blood vessel wall. This inflammation decreases during phase 2, so this is when aneurysms typically start to develop. This can also explain why an initial ECHO may be normal.
AC: Lastly, phase 3 is the convalescent phase, and usually occurs from week 6 onwards.

- We will know by 6 weeks if an aneurysm has developed
- This is why patients are kept on the treatment – aspirin - until their 6 week follow up with a cardiologist who will perform an echo.

MC: Another way of classifying Kawasaki disease would be via the types: classic and incomplete.
MC: Classic (also called complete) would present as the CRASH & BURN acronym, fulfilling with fever and 4 of 5 criteria.
MC: Incomplete (also called atypical), as the name suggests, would present with fever, less than 4 criteria, and positive labs or echo findings. We are moving away from the term "atypical" KD as it can be confusing.
MC: It's important to remember that patients presenting with incomplete KD are usually less than 1 years old, and are more likely to have aneurysm[4]

Investigations

MC: How would you investigate and why would you choose each test?
AC: Considering the consequences of Kawasaki disease, the most important investigation would be an Echocardiogram as soon as possible to assess the aneurysm
MC: Echo is used to calculate the Z score, which classifies the condition into 5 levels of risks. 5 is the highest level of risk, and the child will require cardiac monitoring and long term anticoagulation.
MC: The z score is an age and gender matched score of norms. Normal would be 0-2 (within 2 standard deviations). Dilatation is a score of 2-2.5, and CAA would be >2.5. So children who are categorized as Grade 5 in terms of risk usually have a Z-score >10.[5]
AC: What would you do if you do not have access to echo?
MC: If echo cannot be done straight away but you have high suspicion for KD, treatment should be started straightaway.
AC: Some other investigations include throat swab, COVID swabs, and skin swabs to rule out other differentials. I would also get some labs, including CBC, LFT, U&Es, CRP, ESR and ASOT. I would expect to see high inflammatory markers.
MC: With a CBC, you may find normocytic anaemia, neutrophilic leucocytosis, and thrombocytosis.
MC: Now, thrombocytosis usually presents later (in phase 2), so you may not see it at this point in our case but if you see it especially towards the end of the acute phase, it can support a diagnosis of KD. Overall, CBC gives us a baseline that we can follow through with treatment
MC: I would also add on albumin because albumin can become low when there is inflammation.
MC: Urinalysis will also show sterile pyuria in 80% of children due to a urethritis that can occur. Because of this, when you take the urine sample, this is one instance where you would NOT want a catheter specimen.

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Management

MC: Moving onto the management of Kawasaki disease, if you are confident with your diagnosis, you can start to manage Kawasaki straight away.

MC: How would you treat this patient?

AC: There are 3 main ways to treat Kawasaki:

AC: First, IVIG is the gold standard because it has been shown to decrease the risk of coronary artery aneurysms.[6]

AC: How does IVIG actually work?

MC: There are lots of theories of how IVIG works, but generally, it's believed that IVIG eliminates non-specific Fc receptors and inhibiting binding of Fc receptors on cells. It can also "mop up" proinflammatory proteins known as cytokines, and neutralize toxins and other antigens.

MC: In practice, you give 2g/kg once, and wait as it is given over hours. After 36 hours, if the patient no longer has a fever, you can discharge home

MC: There is a risk of HF/oedema since IVIG infusions are a large fluid load – so if a gallop is present, or if there are concerns about heart failure, you would either reduce the rate of the infusion or you may want to consult rheumatology and talk about giving steroids first to control the inflammation which can be helpful. Other than affecting the coronary artery aneurysms, KD can also affect the heart muscle and can cause myocarditis or Kawasaki shock which is why some children may present in heart failure or shock. We consider these cases high-risk or challenging KD patients.

AC: IVIG has side effects. Immediate SEs include: fever, sweating, nausea, tachycardia. And Delayed SEs include: aseptic meningitis, haemolytic anemia, renal failure, eczematous reactions.

MC: Something else to note is IVIG resistance. Do you know what this is?

AC: IVIG resistance is if a patient remains febrile after 1st dose IVIG + aspirin ("recrudescent or persistent fever at least 36 hours following completion of the first dose of IVIG.")

MC: Up to 20% of patients may experience this, and they have higher risks of aneurysms

AC: How do you treat IVIG resistance?

MC: Generally we would give a 2nd dose of IVIG first then reassess again after 36 hours. If there is ongoing fever or signs of inflammation despite the second dose, we would consider steroids or more potent anti-inflammatories including biologics that specifically counteract pro-inflammatory proteins. One example of this is infliximab which is an anti-TNF biologic.[7]

AC: The second key treatment for Kawasaki disease is Aspirin.

This is one of the only uses of aspirin as treatment in children due to the risk of Reye syndrome. Reye's syndrome is a rare syndrome, characterised by acute encephalopathy with hepatic dysfunction due to mitochondria damage.

AC: High dose is given initially for its anti-inflammatory activity to reduce the chances of having aneurysms.

AC: After the fever subsides, the child is kept on low dose aspirin for its anti-platelet effects until they have a repeat echo

MC: Yes, so just a few words about ASA you're absolutely right you can give high-dose ASA during the inflammatory phase then reduce to low-dose once the fever has subsided and this is what has been taught for many years and in guidelines, etc. However, there is emerging evidence that now there is not one perfect dose of ASA in terms of their effects on outcome, so

many hospitals are now treating with lower doses throughout the entire course of KD. For example, at my hospital we treat with 3-5mg/kg/day until the 6-week ECHO but I want to stress there is no perfect dose in terms of reducing IVIG resistance or coronary artery aneurysm formation.
AC: Thirdly, I know there is starting to be more discussion around use of steroids but this is not routine.
MC: You're absolutely right – there are now some studies looking at use of steroids earlier on in Kawasaki disease, for example, if they present with shock or if children are very young or if they were able to get an ECHO soon after diagnosis and have aneurysms, but generally I would suggest consulting rheumatology if giving steroids from the get-go.
AC: What happens if the IVIG and aspirin combination does not work?
MC: If a patient still has aneurysm despite this treatment plan, they should be referred to cardiology. The treatment option then may be anticoagulation and activity restriction.

AC: Going back to our case, George received IVIG and aspirin. His echo fortunately did not show any dilatation, and he was discharged.
MC: What discharge instructions would you provide to his family?
AC: I would suggest for George follow up with paediatrician in 5-7 days, and to monitor for fever/signs of KD. The child needs to stay on ASA until the 6-week ECHO with cardiology and usually cardiology will decide if he needs to stay or can stop the ASA depending on the ECHO result.
MC: Yes, prior to discharge I would also ensure that the bloodwork is normalizing. If the CRP is not yet normal, I would recommend getting bloodwork within a week of discharge/before/at pediatrics follow-up to ensure that it is normal. Sometimes a persistently raised or rising CRP post-discharge may mean that there is still some inflammation present.

MIS-C

AC: I mentioned MIS-C earlier as a differential and know that the biggest difference to KD are the gastrointestinal symptoms. Can you please tell me a bit more about MIS-C?
MC: MIS-C is an exaggerated immune response to the COVID viral spike proteins. It has 3 recognized phenotypes, one of which is KD. Its other 2 presentations are shock and hyperinflammation. These symptoms usually occur about 3-6 weeks after a COVID contact or infection.[8]
MC: Even though there is a KD phenotype with MIS-C, it presents a little differently than "classic" KD. Usually, older children are affected by MIS-C compared to KD. You do not need to have 5 days of fever to make the diagnosis. Children also tend to have more GI and cardiac involvement at presentation such as abdominal pain, vomiting, diarrhoea, or hemodynamic instability and shock.[9]
MC: Apart from the differences in clinical presentation, KD can also be differentiated from MIS-C via lab findings. For example, MIS-C patients develop lymphopenia and less significant thrombocytopenia. Also, MIS-C will cause significant troponin and BNP increase, whereas KD would cause a mild increase. Of note, both can be associated with a hyperinflammatory state with macrophage activation syndrome being seen more commonly in MIS-C than in KD.
MC: MIS-C is treated similarly to KD with ASA, steroids and IVIG.

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AC: If you are interested in learning more about MIS-C as I am, there is a dedicated podcast on PedsCases.

Q&A

MC: Do you have any questions for me?

AC: How often does KD reoccur? And does the treatment change if it reoccurs?

MC: In Japan, the rate of recurrence is around 3%, whereas the rate of reoccurrence in America is around 1.75%.[10]

MC: The treatment for reoccurrence depends on the timeline. If it has been months or years since the last episode, we would treat it as a new incident. If the recurrence occurs within a few weeks, the management plan would be to escalate therapy as we have talked about.

Take home points

MC: Our learning objectives today were:

1. To define KD and its differential diagnosis from other paediatric condition
2. To Outline the management of KD
3. To Discuss KD in relation to MIS-C Multisystem Inflammatory Syndrome

MC: And Annie what are 3 things you have learnt?

AC: I learnt:

1. Some investigations for KD besides echo include: albumin, which would be low due to inflammation; and urine analysis, which would show sterile pyuria.
2. There is emerging evidence for lower doses of ASA as well as use of steroids at an earlier phase of the disease course.
3. MIS-C only require 1 day of fever for diagnosis, and is associated with different lab findings such as troponin and BNP increase.

MC: Lastly, the take home points today are:

1. KD is a medium vessel vasculitis affecting young children. It is a clinical syndrome characterised by the CRASH&BURN acronym. There are 3 phases, and the most significant consequence is coronary artery aneurysms.
2. All children with KD must have an echocardiogram to assess their risk of having an aneurysm. KD is treated with IVIG and aspirin.
3. KD is a known phenotype of MIS-C, which has its own characteristic findings.

Outro

AC: If you would like to learn more about Kawasaki disease, please browse the resources on PedsCases. There is a transcript of this podcast and further reading.

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Many hospitals have their own treatment protocol – that may be something to discuss with the pediatrician or rheumatologist.
AC: Thank you so much for joining us today!

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Useful links

- https://www.pedscases.com/kawasaki-disease-0
- https://www.pedscases.com/mis-c
- https://www.pedscases.com/approach-recurrent-fevers
- https://www.pedscases.com/kawasaki-disease
- https://www.pedscases.com/viral-rashes-children

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- https://www.pedscases.com/approach-lymphadenopathy
- https://soundcloud.com/goshpods
- Guidelines: https://pubmed.ncbi.nlm.nih.gov/28356445/
- https://www.pmmonline.org/doctor/arthritis/multi-system-disease/vasculitis/kawasaki-disease/

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