Subsequent development of Kawasaki disease following acute human adenovirus infection among siblings

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SUMMARY

We report a middle-childhood girl presented with high-grade fever and headache for 4 days. Following this, the child developed mucocutaneous symptoms. She had a notable family history of autoimmune disease. Tests revealed increased inflammatory markers. On the sixth day of illness, a two-dimensonal echocardiogram showed an enlarged coronary artery, diagnosed as incomplete Kawasaki disease (KD) and treated with IVIG and aspirin. Within a week, her younger sibling, an early-childhood girl presented with features of viral prodrome, developed mucocutaneous lesions and subcutaneous oedema of limbs. Her investigations also showed elevated inflammatory markers and echocardiographic changes, diagnosed as incomplete KD.

The subsequent development of KD in siblings, both showing initial viral symptoms and a family history of autoimmune disease, led to the suspicion of a potential viral trigger. This was confirmed through viral PCR studies for human adenovirus (type 3). These cases highlight an unusual occurrence of KD developing in siblings following acute adenoviral infection.

BACKGROUND

Kawasaki disease (KD) is an acute febrile illness of childhood and affects children aged less than 5 years. It is a type of medium-vessel vasculitis with more predilection for coronary arteries. The first case of KD was reported by Kawasaki from Japan in 1967.[1] KD is one of the leading causes of acquired heart disease among children in many developed countries.[2]

As there is no specific laboratory test for this illness, a diagnosis of KD is established on clinical grounds, for which American Heart Association criteria have been implemented in the diagnosis of KD.[3] There are only a few reported cases of KD among siblings[4 5] and no reported cases of KD among siblings from India.

The aetiology of KD remains unknown. Underlying genetic predisposition with some infectious trigger may initiate the development KD.[6 7] Here, we are describing case reports of subsequent development of KD following acute human adenoviral infection, which was confirmed by PCR sequencing. Our is the first case report of KD among siblings following acute adenoviral infection.

CASE PRESENTATION

The patients were female siblings, early and middle childhood apparently healthy with a significant family history of myasthenia gravis in maternal grandmother and Guillain-Barré syndrome in maternal great grandmother.

Case 1

A middle childhood girl child from south India immunised up to date as per national immunisation schedule of India, presented with fever for 2 days, high-grade continuous associated with chills, had history of non-projectile vomiting and headache, diffuse in nature, with no red flag signs, normal general physical and systemic examination, investigation suggestive no evidence of infection, child been treated symptomatically on outpatient basis and the child continues to have high-grade fever spikes with no localising signs for which child was hospitalised. On day 4 of fever, the child had bilateral conjunctival congestion, and on day 5, the child had strawberry tongue, thought of possibility of incomplete KD, investigated on same line.

Case 2

Five days following diagnosis of incomplete KD in the first sibling, the second sibling, early childhood girl child presented with high-grade fever and cold for 3 days, vomiting and lose stools for 2 days. On examination, the child had cheilitis and bilateral non-purulent conjunctivitis. The child on day 4 of fever developed strawberry tongue and oedema involving hands and feet. As second sibling also had features suggestive of incomplete KD, developed within a span of 1 week. the possibility of viral trigger for KD was thought and evaluated on same line.

The patient received IVIG 2 g/kg and aspirin 5 mg/kg/day for 8 weeks.

INVESTIGATIONS

Investigations: (case 1)

A complete blood count revealed haemoglobin concentration of 126 g/L, haematocrit of 37.7 %, a mean corpuscular volume of 80 fL, total leucocyte counts 9.9×10^9/L, with 66% neutrophils, 13% lymphocyte, 21% monocyte, platelet count of 187×10^9/L, erythrocyte sedimentation rate (ESR) 38 mm per hour, C reactive protein (CRP) was 17.07 mg/L, serum ferritin was 280 ng/mL. D-dimer was 642 g/L, serum lactate dehydrogenase (LDH) was 270 IU/L and serum triglycerides were 111 mg/dL. Urine analysis was within normal limits. Blood and urine cultures were negative. Rapid antigen detection test (RADT) and throat

culture for group A streptococci (GAS), suspected scarlet fever, were negative. PCR for rickettsia and viral pannel was only positive for human adenovirus (type 3). Two-dimensional (2D) echocardiography—proximal dilatation of left main coronary artery (LMCA) with diameter 3 mm and right coronary artery measured 2 mm, mild tricuspid valve regurgitation and good biventricular function.

Investigation: (case 2)

A complete blood count revealed haemoglobin concentration of 115 g/L, haematocrit of 37.1 %, a mean corpuscular volume of 85 fL, total leucocyte counts of 14.5×10^9/L, with 77% neutrophils, 10% lymphocyte, platelet count of 169×10^9/L. ESR was 40 mm per hour. CRP was 42 mg/L. Serum ferritin was 273 ng/mL. D-dimer was 685 g/L. Serum LDH was 387 IU/L. Liver enzymes serum glutamic-oxaloacetic transaminase(SGOT) was 39 IU/L and serum glutamate-pyruvate transaminase(SGPT) was 18 IU/L. Serum albumin was 3.7 g/L. Urine analysis was within normal limits. Blood and urine cultures were negative. RADT and throat culture for GAS were negative. 2D echocardiography—proximal dilatation of LMCA with diameter 3 mm and normal calibre of right coronary artery, mild tricuspid valve regurgitation, mild circumferential pericardial effusion and good biventricular function. PCR for rickettsia and viral pannel was only positive for human adenovirus (type 3) in both the siblings.

With subsequent development of KD among siblings within a week, with a significant family history of autoimmune disease, possible genetic association for development of KD was thought. As there is no single gene identified among Indian children, genetic testing was not done.

DIFFERENTIAL DIAGNOSIS

Case 1

As the child had fever for 2 days with prodromal symptoms, followed by development of maculopapular rash, possibility of viral exanthematous fever (such as adenovirus, measles, coxsackie), rickettsial fever and scarlet fever was thought off. Investigated in the same line, Weil-Felix test, RADT and throat swab for GAS were negative. Serum PCR pannel for rickettsial and viral was sent which was positive only for human adenovirus (type 3) and child was managed accordingly. As the child continues to have fever spike, repeat investigation suggestive of elevated inflammatory markers and echocardiography suggestive of dilated coronary arteries, diagnosis of incomplete KD was made (two clinical criteria, strawberry tongue and bilateral non-purulent conjunctivitis and positive 2D echocardiogram features).

Case 2

Subsequently, younger sibling also developed fever with prodromal symptoms, as clinical features were similar to elder sibling possibility of human adenovirus infection was thought off. Evaluated in same line, investigation showed, serum PCR was positive for Human adenovirus (type 3). The child continues to have fever spikes, in the background of family history of autoimmune disease, with the elder sibling being diagnosed as incomplete KD, further evaluated, showed high inflammatory markers and dilated coronary arteries. Hence, diagnosed as incomplete KD (three clinical criteria, strawberry tongue, bilateral non-purulent conjunctivitis and oedema of hands and feet and positive 2D echocardiogram features).

TREATMENT

Both the patients received IVIG 2 g/kg and aspirin 5 mg/kg/day for 8 weeks.

OUTCOME AND FOLLOW-UP

After treatment, fever subsided within 24 hours in both the siblings. Children were discharged with antithrombotic dose of aspirin for 8 weeks. Follow-up 2D echocardiogram showed normal coronary artery and on examination had no periungual peeling of figure and toes in both the patients.

DISCUSSION

The aetiology for development of KD remains unclear. Certain factors such as genetics, ethnicity and viral aetiology as considered as possible aetiology. Genetic susceptibility can attribute for development of KD.[8 9] Some functional single-nucleotide polymorphisms (SNPs) such as inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) and caspase 3 (CAPS3) significantly increase susceptibility to KD.[8] A large study done by Onouchi *et al*, among Japanese population identified following genes such as FAM167A-BLK region at 8p22-23, human leucocyte antigen region at 6p21.3, CD40 region at 20q13 and SNP of FCGR2A among children with KD.[6] Another study done by Onouchi *et al*, among US and Japanese children identified, SNP in the ITPKC gene on chromosome 19q13.2 showed increase susceptibility of coronary artery lesions among children with KD.[10]

Infections such as group A Streptococcus, Staphylococcus, Bacillus cereus, Yersinia, adenovirus, coxsackievirus, measles, Epstein–Barr virus have been reported as trigger for development of KD. The patient's microbiome stimulates innate immunity fallowing any infection may trigger development of KD. Risk of exposure is high in children with siblings, as compared with children without.[8 11] In our case, a week following infection in the elder sibling, features of KD developed in younger sibling.

2.4% of children diagnosed to have KD, had upper respiratory tract infection secondary to adenovirus.[12] Adenovirus infection mounts strong inflammatory response, so mimic bacterial infection and KD. Adenovirus infection presents with high fever, upper and lower respiratory tract symptoms, conjunctivitis, gastrointestinal and hepatic symptoms and can also have mucocutaneous involvement, cervical lymphadenopathy and encephalitis. The various clinical manifestations of adenovirus infection mimics KD.[13] In our case, both siblings had similar clinical features, within 1 week of illness, possibility of infectious trigger was suspected, viral pannel (PCR) for respiratory infection was sent, was reported positive for human adenovirus type 3. The risk of development of KD increases by 10-fold if mother had any autoimmune disease.[8] In our case, there is a family history of autoimmune disease in first-degree relative.

The aove studies quote significant association for the development of KD following viral trigger and also family history of autoimmune disease, independently. None of the studies showed

Learning points

- Infectious trigger for Kawasaki disease (KD) should be considered if a sibling develops KD in a short span.
- Early assessment for coronary artery involvement should be warranted in children with suspected KD.
- High index of suspicion for KD should be considered among siblings, with a strong family history of autoimmune disease.

association of both viral trigger and genetic susceptibility in development of KD.

KD is an acute self-limiting illness, occasionally inflammatory cascade affects coronary walls and leads to detectable macroscopic and microscopic alterations, which presents with severe complications, such as coronary artery aneurysm, acute myocardial infraction, heart failure, arrhythmias and haemodynamic instability.[14–17] The coronary involvement is uncommon within first week of illness.[2] In our case, the coronary dilatation was noted in the first week of illness in both siblings. With timely diagnosis and treatment, subsequent resolution of coronary artery involvement was noted on follow-up.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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