Kawasaki Disease in Two Cousins with Atypical Presentation: Case Report

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**ABSTRACT** Etiology of Kawasaki disease could not be fully understood, it is believed that there is a genetic susceptibility related to a number of genetic associations; and familial cases have been reported. Hereby we present a 7 year-old boy who had high fever, lymphadenopathy, rash, low acute phase reactants due to secondary hemophagocytosis. He also had a cousin who developed Kawasaki disease 10 years ago with a similar presentation who was eventually diagnosed as having Kawasaki Disease. This is the first familial case presented from Turkish population which reminds us that genetic susceptibility does exist in pathogenesis of Kawasaki disease.

**Key Words:** Mucocutaneous lymph node syndrome; vasculitis; lymphohistiocytosis, hemophagocytic


**Annotat Kelimeler:** Mukokutanöz lenf nodu sendromu; vaskülit; lenfohistiyositoz, hemofagositik


Kawasaki disease has been described nearly 40 years ago, although etiology of disease could not be fully understood, it is commonly believed that there is a genetic susceptibility and the inflammatory process is triggered by an infectious agent. Genetic susceptibility to Kawasaki disease are based on the observations that it is seen much more common in the same ethnic group, especially Asians and Asian Americans, a few reports of occurrence between siblings and in people whose parents had a history of Kawasaki disease. Several factors have been associated with genetic predisposition, including IL-4, colony stimulating factor 2, IL-13 and transcription factor. Although parental or sibling cases are not uncommon, complex families with Kawasaki disease seen not only in siblings but also in cousins are rarely reported. We suggest that the occurrence in...
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two cousins with many years apart supports the genetic predisposition to this disease in our population as well.

CASE REPORT

A 7 year-old boy was admitted to emergency room with a history of cough and fever for 12 days that did not remit with non steroidal anti-inflammatory drugs. Cefuroksim therapy had been started but his fever was still high. His hemoglobin level (Hb): 11.4 mg/dL, white blood cell count (WBC): 5600/uL, thrombocyte: 211.000/uL, sedimentation rate: 12 mm/h, CRP: 1.3 mg/dL, ASO: 138.5, Brucella Agglutination (-), X ray of lungs was normal. After 2 days, his temperature was still high with repeated physical examination revealed hepatosplenomegaly, therefore his laboratory tests were repeated. His blood count showed Hb: 10.8, WBC: 1920/uL, thrombocyte:138.000/uL, CRP: 4.7 mg/dL, sedimentation: 6 mm/h, fibrinogen: 308 mg/dL, ferritin: 1484 ng/dL, LDH: 1493 U/L, Salmonella agglutination (-) Brucella agglutination (-) EBV IgM (-) IgG (-) CMV (-). His bone marrow aspiration examination revealed hemophagocytosis therefore he had been transferred to our medical center.

When he was admitted to our hospital, his physical examination showed left anterior cervical 2 x 1.5 cm lymphadenopathy, maculopapular rash especially prominent on trunk, hyperemia of oropharynx, tonsiller hypertrophy, hepatosplenomegaly. His blood count showed Hb: 10.3 mg/dL, WBC: 3800 u/L, thrombocyte:186.000, sedimentation: 8 mm/h, CRP: 0.3 mg/L, ALT: 302U/L, AST: 362 U/L, other biochemical values were normal. Hepatitis serology was negative, EBV VCA IgM (-) , IgG (+), EA (-) , EBNA (+). Brucella agglutination (-), Salmonella agglutination was (-) except O ag Group B 1/160 (+). None of the cultures revealed any bacteria. Bone marrow aspiration was examined but no specific pathology was present. Abdominal ultrasonography did not show any pathology except hepatosplenomegaly. Echocardiography was normal. A skin biopsy was done from his rash, but there were only nonspecific changes. His bone marrow aspiration showed hemophagocytosis, and his laboratory results from the referring center were compatible with secondary hemophagocytosis.

At 6th day of his stay, his fever was still unremitting despite antibiotic therapy, his lips become fissured. Also he had peeling of his fingertips. At the same time his sedimentation rate elevated up to 77 mm/h. His echocardiography was repeated showing dilatation of coronary arteries: therefore he was accepted to have Kawasaki disease and secondary hemophagocytosis. Intravenous immunoglobulin (IVIG) therapy was started as 2 g/kg as a single dose. Aspirin was also added to therapy protocol. After the IVIG, he was afebrile, his sedimentation rate decreased to 40 mm/h so he was discharged 3 days after IVIG treatment. When he returned for control 3 days after discharge, he was afebrile, his lymph node was smaller, his rash almost disappeared and his blood count and biochemistry was completely normal.

From his history it was learned that his cousin had Kawasaki disease 10 years ago when she was 5 years old. She had unremitting fever, macular rash and cervical lymphadenopathy. She did not benefit from antibiotics, her sedimentation rate was high-then she was referred to our center. Her ecocardiography showed dilatation of right coronary artery, and she had diagnosis of Kawasaki disease and treated with intravenous immunoglobulin successfully.

DISCUSSION

Previous studies have showed that occurrence of Kawasaki disease in families is significantly higher, there is a 2 fold increase in children whose parents had Kawasaki disease and 10 fold increase in siblings in Japan but no clear pattern of inheritance could be found, thus multiple genetic associations could have a role.

Burns et al showed asymmetric transmission of 5 alleles including IL-4, CSF 2, IL-13, TCF7, all located on 5q31. IL-4 plays a role in differentiation of Th2 cells and secretion of IL-4, IL-5, IL-6, IL-10, IL-13, upregulation of CD23 and VCAM-1, levels of IL-4, VCAM-1 and CD23 in serum of Kawasaki
patients are elevated, so genetic variation in IL-4 allele is thought to play an important role in genetic susceptibility to Kawasaki disease.\(^7\)

Furthermore, genomewide linkage analysis showed strongest linkage on 12q24 but also 5q31, 5q33, 6p21 where HLA genes are located, supporting the genetic susceptibility to Kawasaki disease but further studies should be done to understand the exact role of genes in the pathogenesis of the disease.\(^9\)

CD180, is another molecule, shown to be overexpressed on B cell lymphocytes of Kawasaki patients, this molecule is activated in viral infections and induce an immune response.\(^10\)

In our case 2 cousins were diagnosed as Kawasaki disease 10 years apart from each other, almost with the same complaints. Time difference between 2 cases suggests a genetic susceptibility rather than an infectious etiology. This is one of the rare presentations of Kawasaki disease between cousins. In addition, the diagnosis delayed because of low levels of sedimentation rate and C-reactive protein which most likely is the result of secondary hemophagocytosis. This case was also one of the rare Kawasaki disease patients who developed secondary hemophagocytosis; only seven cases with this type of presentation were reported in the literature so far.\(^11\)

Familial cases of Kawasaki disease had been rarely reported outside Japan and these could be the first familial cases of Kawasaki disease reported from Turkey.

It has also been reported that coronary artery abnormalities and risk of recurrence is significantly higher in siblings,\(^12\) but our patient has been followed without recurrence for 4 months.

In conclusion a genetic susceptibility may be operative in Kawasaki disease similar to the other rheumatic diseases. Possible occurrence in family members should be remembered.

### REFERENCES