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ORIGINAL ARTICLE

Viral infections associated with Kawasaki disease

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Background/Purpose: Kawasaki disease (KD) is a disease of unknown cause. To investigate the infectious etiology of Kawasaki disease, we initiated a prospective case-control study to investigate possible links between common viral infections and Kawasaki disease.
Methods: We enrolled 226 children with KD and 226 age- and sex-matched healthy children from February 2004 to March 2010. Throat and nasopharyngeal swabs were taken for both viral isolation and polymerase chain reaction (PCR) for various viruses.
Results: The mean age of the 226 KD cases was 2.07 years, and the male to female ratio was 1.43 (133 boys to 93 girls). Their mean fever duration was 7.5 days with a mean peak temperature of 39.7°C. In addition to the typical symptoms of fever, neck lymphadenopathy, lip fissure and/or strawberry tongue, skin rash, nonpurulent bulbar conjunctivitis, palm/sole erythema, and induration followed by periungual desquamation, these KD cases also exhibited cough (69%), rhinorrhea (58%), and diarrhea (45%). Cases of KD had a significantly higher positive rate of viral isolation in comparison with the control group (7.5% vs. 2.2%, $p = 0.02$). Compared with the control group, cases of KD were more likely to have overall positive rates of viral PCR (50.4% vs. 16.4%, $p < 0.001$) and for various viruses including enterovirus (16.8% vs. 4.4%, $p < 0.001$), adenovirus (8.0% vs. 1.8%, $p = 0.007$), human rhinovirus (26.5% vs. 9.7%, $p < 0.001$), and coronavirus (7.1% vs. 0.9%, $p = 0.003$).

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: We found that some common respiratory viruses, such as adenoviruses, enteroviruses, rhinoviruses, and coronaviruses, were associated with KD cases.

Introduction

Kawasaki disease (KD) is an acute systemic febrile illness of unknown etiology which predominantly affects children under 5 years of age. Initially described in 1967 by Tomisaku Kawasaki,[1] it is now the most common cause of acquired heart diseases in children in the developed world due to the less frequent occurrence of rheumatic heart disease. There have been reports of differing incidence rates in different countries. Asian countries are supposed to have higher incidences of KD (30—200/per 100,000 children under 5 years of age) than most of the Western countries (3.5—10/per 100,000 children under 5 years of age).[2—10]

The etiology of KD is still controversial and infections are considered to be one of the predisposing factors. The infectious evidence of Kawasaki disease includes temporal clustering and marked seasonality, geographic clustering, family clustering, a high association between Kawasaki disease and infectious disease surveillance, and age distribution, for which the highest incidence rates are seen among 6 month—2-year-old children who have low maternal antibodies and are most susceptible to infections in general.[11—14] We hypothesize that infections with certain viruses may elicit systemic inflammation, and further small and median sized vasculitis, so-called Kawasaki disease, in certain hosts because we found a higher incidence of KD among males, young children, and Asian populations. We thus carried out a prospective case-control study to investigate the association of common viral infections with Kawasaki disease to test the above hypothesis.

Patients and methods

Case enrollment

From February 2004 to March 2010, we enrolled patients who fulfilled the Kawasaki disease criteria at the National Taiwan University Hospital in Taipei City, Taiwan and other collaborative hospitals including Taiwan Adventist Hospital in Taipei City, Far Eastern Memorial Hospital in New Taipei City, and Min-Sheng Hospital in Tao-Yuan County, Taiwan.

We enrolled Kawasaki disease cases that had fever for over 5 days and at least four of the following five manifestations: neck lymphadenopathy, lip fissure and/or strawberry tongue, skin rash, nonpurulent bulbar conjunctivitis, palm/sole erythema, and induration followed by periungual desquamation. The onset of KD illness cases was defined as the 1st day of fever onset.

After informed consent was obtained from the parents, a questionnaire-styled interview was carried out to solicit clinical symptoms and previous contact history with ill household members or with ill people from outside of the household. The illness included sore throat, rash, fever, conjunctivitis, cough, rhinorrhea, abdominal pain, and diarrhea. Clinical laboratory data and coronary arterial lesions were collected from the participants, and all received intravenous immunoglobulin 2 g per Kg plus low-dose aspirin (3—5 mg per Kg). If fever persisted for 2 days after use of intravenous immunoglobulin, retreatment with intravenous immunoglobulin was administered.

Two-dimensional echocardiography was performed in all patients during hospitalization and was repeated at convalescence, 2 weeks, and 8 weeks after discharge. Coronary arterial lesions were defined as coronary arterial dilatation/ectasia, aneurysm, and increased echogenecity, irregularity of vascular wall, or coronary artery aneurysm. A coronary artery aneurysm was defined as having a lumen diameter (inner border to inner border) of $\geq$3 mm in KD cases less than 5 years old and $\geq$4 mm in cases less than 5 years old, and giant aneurysm was defined as a lumen diameter of $\geq$8 mm for any one echocardiography. We took nasopharyngeal swabs and throat swabs from KD cases on the 1st day of hospitalization. These swabs were processed for both viral isolation and polymerase chain reaction (PCR) for various viruses.

Enrollment of control participants

For the healthy control group, we enrolled children who were age- and sex-matched with the KD cases, and who did not have preceding illness for the 2 weeks prior to enrollment. The preceding illness included sore throat, rash, fever, conjunctivitis, cough, rhinorrhea, abdominal pain, and diarrhea. These children were kindergarteners or children who visited our baby wellness clinics for vaccination. Informed consent was obtained from parents of all children in the control group. We also took throat swabs and nasopharyngeal swabs from the control children for viral isolation and viral PCR.

Laboratory methods

Virus isolation

Throat or nasopharyngeal swabs were submitted for virus isolation. Samples were inoculated into human embryonic fibroblast, LLC-MK2, Hep-2, and rhabdomyosarcoma cell cultures. When a cytopathic effect involved more than 50% of the cell monolayer, cells were scraped and subjected to indirect fluorescent antibody staining with specific antibodies or typed by specific methods according to the suspected types of viruses.

Molecular diagnosis for viruses

RNA and DNA extraction from throat swabs, and nasopharyngeal swabs were performed using MagNA Pure LC 2.0 System and MagNA Pure LC Total Nucleic Acid Isolation Kit (Roche Applied Science, Roche Diagnostics, Indianapolis, IN, USA). The primers and probes for enterovirus, adenovirus, influenza B, rhinovirus, metapneumovirus real-time