SY2.1 RECOGNITION OF KAWASAKI DISEASE
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This presentation explains the historical background and details how the author introduced the recognition of Kawasaki disease. It discusses the establishment of the disease's diagnosis and the early years of its research.

SY2.2 EPIDEMIOLOGIC FEATURES OF KAWASAKI DISEASE AND LESSONS FROM THEM
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Since 1970, four years later to the first report publication of Kawasaki disease by Dr. Tomisaku Kawasaki in 1967, 23 nationwide surveys of the disease have been conducted every two years in Japan, and now we are conducting the 24th one. The surveys have revealed the epidemiologic features of the disease in Japan as follows:

1. Three nationwide epidemics were in 1979, 1982, and 1986.
2. Currently, the yearly number of patients and incidence rate increased.
3. Male/female ratio is about 1.4.
4. Seasonal variations, high in January and slightly high in summer season, have been observed.
5. Age-specific incidence rate was monomodal distribution with the peak in late infantile period (0-year-old).
6. Chronologic and geographic clustering has been observed.
7. Sibling cases and parent-child cases existed.

Through these findings, the hypothesis about the etiology of Kawasaki disease that some infectious agent(s) play a role as a trigger of the disease on a susceptible child. The findings suggesting infectious agent(s) are: (1) three times nationwide epidemics, (2) geographic movement of the epidemic, (3) age-specific incidence rate with a peak on the late infant age, (4) chronologic and geographic clustering, (5) seasonal variation, (6) sibling cases, and (7) clustering of the disease in small areas. High peak in January and increasing the number of patients in summer seasons indicate more that than one agent related. Different seasonal variations among countries and areas also indicate the cluster agent theory. In addition, the disease has been observed in more than 60 countries and areas around the world, which include countries under the equator and those close to poles. This fact also indicates the trigger of the agents.

On the other hand, (1) lower incidence rate than measles and chicken pox in the era without vaccinations, (2) different incidence rates among races, and (3) existence of sibling cases and parent-child cases, indicate host susceptibility about the disease. Many etiological hypotheses have been proposed about this disease, but the etiology is still unknown. We have to criticize newly proposed hypotheses from the view point whether the hypothesis is consistent with these epidemiologic features.

SY2.3 GENETIC FACTORS OF KAWASAKI DISEASE
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Previous studies have suggested that Kawasaki disease (KD) is a systemic vasculitis syndrome which affects susceptible individuals when they experience events, such as infection by microorganisms or exposure to environmental materials, those can trigger the disease. Genetic factors, along with age and gender, are believed to be host factors, influencing individuals’ susceptibility to KD. Recognizing that clarification of all the host and environmental factors and elucidation of their interactions is the definitive way for development of a causal therapy and preventive measure against KD as well as its coronary complications, efforts have been continuously made. As for genetic components, genome-wide studies based on the ‘Common disease common variant’ hypothesis identified 6 definitive susceptibility loci (TPKC, CASP3, BLK, CD40, FCGR2A and HLA-c2 gene regions) and knowledge on expression and function of the genes have provided important insights into the KD pathogenesis and partly been contributed to an understanding of the mechanism of IVIG resistance, however, a large part of genetic etiology of KD has been unexplained yet and, above all, the reason for its marked predilection for the East Asian populations still remains unknown. In this symposium, I would like to overview the current knowledge of genetic factors of KD and introduce our present approach.

SY2.4 ACUTE MANAGEMENT OF KAWASAKI DISEASE
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Kawasaki disease is an acute febrile illness affecting especially in infants. Coronary artery abnormality occurs approximately 25% of Kawasaki disease if not treated. Recent advance regarding acute management such as high-dose intravenous immunoglobulin, corticosteroids, infliximab, or cyclosporin A decreases its incidence less than 3%. In Japan, a guideline for the medical treatment of acute Kawasaki disease was revised in 2012 and proposed an acute management algorithm based on risk stratification using risk scores to predict non-response to intravenous immunoglobulin therapy. In 2016, the American Heart Association also updated their guidelines for managing Kawasaki disease patients. In this lecture, I am going to explain about the guidelines especially focused on acute management of Kawasaki disease and discuss future directions.

SY2.5 MicroRNA-145-5p and MicroRNA-320a upregulate inflammatory cytokine expression in acute Kawasaki disease
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Objective: Kawasaki Disease (KD) is an acute inflammatory disease that takes the form of systemic vasculitis. Endothelial microparticles (EMPs) have been recognized as an important transcellular delivery system. The purpose of this study was to elucidate whether EMPs are involved in vasculitis in acute KD.

Methods: Fifty patients with acute KD (aged 4 months to 14 years) and 50 controls (25 non-KD febrile and 25 healthy children) were enrolled for the study. Patients with KD were divided into two subgroups: those...
with coronary artery lesions (CAL, Z-score > 2.5, n = 5) and those without CAL (NCAL, Z-score ≤ 2.5, n = 45). Blood samples were collected three times: first, at the time of diagnosis before the initiation of IVIG treatment; second, immediately after the first IVIG infusion; and finally, at 2-4 weeks after the onset of the disease. EMPs were measured using flow cytometry, and microRNA (miR) expression profiling was performed by microRNA array. In situ hybridization analysis of miRNA expression in a tissue sample from a CAL patient was performed, while the biological effects of miRs on gene expression were investigated in THP-1 monocytes.

Results: The percentage of EMPs among small vesicles of patients with KD prior to treatment was 1.31 ± 0.16 %, which was significantly higher than in controls (0.09 ± 0.03 %, P < 0.0001). Furthermore the number of EMPs in patients with CAL rapidly increased after the initial treatment, and was significantly higher than those of NCAL (P < 0.001). We identified 2 miRs, hsa-miR-145-5p and hsa-miR-320a, which were specific to patients with CAL, and these are predicted to affect the monocyte/macrophage function by in silico analysis. In situ hybridization confirmed that hsa-miR-145-5p was preferentially expressed in coronary artery endothelial cells. We also demonstrated that these 2 miRs could upregulate inflammatory cytokine miRNAs, including interleukin-6 and tumor necrosis factor-α in THP-1 monocytes.

Conclusions: EMPs may serve as a sensitive marker for the severity of endothelial dysfunction and vasculitis in acute KD. Moreover, hsa-miR-145-5p and hsa-miR-320a, encapsulated in EMPs, might be involved in inflammatory cytokine regulation and the pathogenesis of vasculitis in acute KD.