## 47

### ACE I/D AND AT1 1166A/C POLYMORPHISM AS A RISK FACTOR FOR CORONARY ARTERY STENOSIS IN KAWASAKI DISEASE

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Gene polymorphism is considered to become the individual risk factors for the disease developments. We studied the gene polymorphism of Angiotensin Converting Enzyme(ACE) I/D, and Angiotensin II Receptor1 (AT1) 1166A/C polymorphism in Kawasaki disease patients and examined whether these polymorphism associate with coronary artery stenosis. ***(Subjects and Methods)*** 195 Kawasaki disease patients were enrolled in this study. Written informed consents were acquired from all patients. We divided the patients into three groups. Group N (n=122); no coronary artery changes, Group C (n=40); coronary artery dilation and/or stenosis without myocardial ischemia, Group S (n=33); coronary artery stenosis with myocardial ischemia. Genomic DNA specific primers were designed and Polymerase Chain Reaction (PCR) were performed. PCR products were separated on the agarose gel directly (ACE I/D polymorphism), or after the sequence specific restriction enzymes digestion (AT1 1166A/C polymorphism). ***(Results)*** We could not detect any significant differences in specific genotypes between the groups. However, when we evaluated the patients whether they possess D allele of ACE I/D polymorphism and/or C allele of AT1 1166A/C polymorphism, the patients who own both ACE polymorphism D allele and AT1 polymorphism C allele were significantly higher in Group S ($\chi^2$ test ; $p<0.05$). We concluded the Kawasaki disease patients who have both D allele in ACE I/D polymorphism and C allele in AT1 1166A/C polymorphism are exposed to the higher risk for coronary artery stenosis.

## 48

### CORRELATION OF MPO-ANCA EPITOPE BETWEEN PATIENTS WITH KAWASAKI DISEASE AND THEIR MOTHERS

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Recently, the activated neutrophils and the antibodies against neutrophils, anti-neutrophil cytoplasmic antibody (ANCA), have been demonstrated in relation to the development of vasculitis. The elevation of neutrophil counts in peripheral blood in Kawasaki disease is believed to cause the development of aneurysm in coronary artery. Elevation in the levels of myeloperoxidase specific ANCA (MPO-ANCA) in sera of patients with Kawasaki disease has also been observed. In order to investigate the role of MPO-ANCA in the progression of vasculitis, epitope analysis of MPO-ANCA have been reported (1, 2). MPO-ANCA reacted with N-terminus and C-terminus in the heavy chain of MPO, suggesting correlation of specific monoclonal/oligoclonal MPO-ANCA with the progression of vasculitis. In coronary arteritis in Kawasaki disease the epitope of MPO-ANCA was also analyzed. Furthermore, we analyzed correlation of MPO-ANCA epitope(s) in sera of between patients and their mother in order to know source of the antibody. Most of healthy mothers showed MPO-ANCA positive in their sera and about epitope in sera of patients were coincident by 50% with that of mothers, but not father's. These results suggest that source of auto-antibody MPO-ANCA may be same to that of patient's mother's. 1)Tomizawa et al. J Clin. Immunol. 18, 142-152, 1998. 2) Fujii et al. Clin. Nephrology 53, 242-252, 2000.

## 49

### RETROSPECTIVE SURVEY ON KAWASAKI DISEASE BETWEEN 1940 AND 1965 AT TOKYO UNIVERSITY HOSPITAL

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Kawasaki disease (KD) was first reported by Dr. Tomisaku Kawasaki in 1967 in Japan. Large-scale nationwide epidemiological surveys have been continuously conducted by the Japan Kawasaki Disease Research Committee, however, there were few reports of KD before 1967. Because the causative agent of KD has not been elucidated yet, it is important to clarify when KD first broke out in Japan and what kind of environmental changes took place at that time around young children. To study when KD outbroke in Japan, we investigated medical charts of patients who had been hospitalized at Tokyo University Hospital, which is the oldest university hospital in Japan, from 1940 to 1965. We identified 10 patients whose symptoms fulfill the clinical criteria for KD. The ages of the patients ranged from 8 months to 5 years, and their final diagnosis were either Stevens-Johnson syndrome, allergic toxic erythema, Izumi fever, scarlet fever or cervical lymphadenitis. These 10 patients were found from 1950 to 1964, and none was found from 1940 to 1949, suggesting that some factors triggering the outbreak of KD emerged before 1950.

## 50

### CLINICAL CRITERIA FOR THE RISK OF PEDIATRIC CAA IN HISTORICAL PERSPECTIVE

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The objective of this paper is to examine the clinical criteria for the risk of pediatric coronary artery aneurysms from a historical perspective. In the late 1970s IPN was re-categorized as the fatal outcome of KD. Pathologists welcomed the connection between the observable rash/fever sign complex described by Kawasaki and coronary artery abnormalities (CAA). This had both research and clinical implications. Investigations shifted from exploring the mechanisms of the vasculitis to a search for an infectious agent predicted to be responsible for the sign complex. By the early 1980s, the CDC case definition, based on Kawasaki's clinical signs, was adopted as the diagnostic criteria for authorizing diagnoses and treatment to prevent coronary artery abnormalities (CAA). However, the KD case definition was designed as an epidemiological tool to authenticate the existence of the syndrome for research purposes rather than as a diagnostic tool for the detection of CAA. Based on clinical experience described in the literature and confirmed by our experience at San Diego Children's Hospital, we have found increasing numbers of children with CAA who failed to meet the KD clinical criteria. Treatment of these atypical cases is often delayed and they develop CAA. The goal of a clinical case definition should be to alert physicians to institute immediate treatment. Instead, the current case definition often serves to construct a barrier to effective intervention. This paper (re)examines the historical evidence that persuaded clinicians that IPN and KD are the same disorder. We suggest that while the merging of these two syndromes initially served a useful diagnostic purpose, continued reliance on the KD sign complex has resulted in delay of treatment of CAA in atypical cases that earlier would have been included in the designation of IPN.

## 51

### KAWASAKI DISEASE: A CLIMATE CONNECTION?

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The winter/spring seasonality of KD has been recognized for over two decades and a recent study found that KD incidence in San Diego (SD) County was positively associated with average monthly precipitation ($r=0.52$, $p<0.001$) (Bronstein et al., Ped Inf Dis J. 2000;19:1087-91). Based on this observation, 246 KD cases from SD County over 6.75 yrs were analyzed for additional climate associations. Fifty-eight clusters (=2 pts within 4 d) were identified and 15/58 had 3 or 4 pts. These 15 clusters were temporally associated with strong, anomalously negative 700mb heights (lower than average pressure), in a broad lower midaltitude swath offshore of California, indicating an active storm track and quite likely wet conditions in SD County starting 6 days prior to the onset of the first case in the cluster and waning by 4 days after onset. Rainfall tended to precede the onset of a KD cluster. In 10 of the 15 clusters, we found preceding precipitation of at least 0.1" recorded in the 6-day interval before the first case in the cluster. Analysis of an additional 23 consecutive SD County cases from 2000-2001 revealed distinct clusters associated with weather patterns similar to those described above. Examination of 278 pts from Los Angeles Children's Hospital from 1994-2000 revealed similar patterns of atmospheric circulation but without the distinct wet signature that was noted for the SD cases. Analysis of 36,955 cases from Japan (1993-1998) for clustering and climate associations is in progress. Additional parameters including wind, humidity, cloud cover, weather type, visibility, barometric pressure, and dry-wet transitions will be explored in relation to KD clusters in California and Japan. The accurate specification of weather patterns related to the onset of KD may lead to formulation of new hypotheses regarding etiology.

## 52

### ROLES OF CORONARY ANGIOGRAPHY FOR PATIENTS WITH KAWASAKI DISEASE IN THE RECENT DECADE

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