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LONG-TERM ISSUES AND MANAGEMENT OF KAWASAKI CORONARY ARTERY DISEASE

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The cardiovascular involvement in Kawasaki disease (KD) are most important clinical issues. However, the long-term consequence of cardiovascular sequelae in KD remains uncertain at the present time. In 1973 we introduced coronary angiography (CAG) as a routine cardiac examination. From 1973 to 2000 we experienced 1,970 consecutive patients of acute KD, of which 302 (15.3%) had coronary aneurysms. These patients had been followed for more than 2 years with longest 28 yrs (mean: 7.5 yrs.). Follow-up(2nd) CAG was performed in 280, of which 151 demonstrated the regression of coronary aneurysms (54%). Further follow-up CAG (3rd, 4th, 5th) was done in 130 cases. In the long-term pathological study the regressed aneurysms revealed the marked initial thickening mainly caused by proliferation of medial smooth muscle cells and well degenerated endotherium. Those findings were also demonstrated by intravascular ultrasound imaging in the follow-up patients. Long-term endothelial function in those patients was impaired. From this long-term follow-up study we review our data and discuss the following issues in the long-term problems of pediatric through adults in KD. 1) Cardiovascular spectrum in Kawasaki disease. 2) Fate of coronary aneurysms; Regression of aneurysms and progression to coronary artery disease. 3) KD vasculitis may be an atherosclerotic risk factor. 4) Kawasaki disease is a part of causes of adult coronary artery disease. 5) Therapeutic recommendations, particularly for the catheter interventional treatment.

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A NATIONAL SURVEY OF PEDIATRIC CARDIOLOGISTS REGARDING CLINICAL MANAGEMENT OF KAWASAKI DISEASE IN THE USA

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To compare the current practice of US Pediatric Cardiologists with the 1994 guidelines of the American Heart Association (94-AHA) in the management of Kawasaki disease (KD), a multiple-choice survey was sent to those practicing in US fellowship programs. Opinions of 97/350 (28%) physicians practicing in 29/40 (73%) programs are summarized: Years of practice in pediatric cardiology (average±SD) was 13.2±10 for respondents vs. 13.6±10.5 for non-respondents ($p=0.69$). In contrast to 94-AHA guidelines, 10% of respondents use low- or moderate-dose Aspirin in the acute phase of KD and another 12% are aware of colleagues who do so. Another 50% who use high-dose, recommend clinical trials to evaluate Aspirin dose recommendation. Clinical criteria (validated in Japan) for patient selection to administer IVIG are followed by 3% of the respondents, and another 18% feel that similar criteria need to be evaluated for use in the US. In contrast to 94-AHA recommendations, 70% advise follow-up for risk-level I patients. For risk-level II, only 20% follow the 94-AHA no-follow-up option while 80% provide regular follow-up, 34% utilizing advanced diagnostic testing. For risk-level IV patients, 84% prefer periodic stress-echo (45%) or stress-perfusion scan (40%) vs 15% who prefer periodic echo at rest or stress ECG (94-AHA does not provide clear recommendation). For asymptomatic patients, 24% do not council for healthy lifestyle habits unless patients have persistent coronary aneurysms or other known coronary risk factors. For persistent coronary aneurysms 36% perform cardiac catheterization periodically, the others catheterize in presence of coronary symptoms (9%), abnormal stress echo (20%), or abnormal stress myocardial perfusion (18%). Conclusion: The respondents' opinion was in concert with data from the most recent literature, but in contrast with many 94-AHA recommendations. The current trend in KD cardiovascular management in US teaching institutions suggests a need for an update in the current official guidelines.

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VASCULAR WALL MORPHOLOGY AND VASCULAR ELASTICITY OF CORONARY ANEURYSMS IN LONG-TERM AFTER KAWASAKI DISEASE: INTRAVASCULAR ULTRASOUND STUDY

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The coronary artery (CA) lesion in Kawasaki disease (KD) may be a long term coronary risk factor. We examined the CA wall morphology and elasticity of CA itself using intravascular ultrasound (IVUS) imaging in 70 KD patients (pts) and 10 controls. Consecutive KD pts were followed over more than 10 years from KD onset. The 70 pts comprised 4 groups: Group 1:18 pts with persistent aneurysms. Group 2: 18 pts with CA stenosis. Group 3: 28 KD pts with regressed CA aneurysms, Group 4 :6 pts with normal CA angiography findings at the acute stage of KD. We carefully examined the CA wall morphology on IVUS imagings. The % area change (%AC) of CA lumen in one cardiac cycle was calculated using IVUS imaging to examine the elasticity of the CA wall. The IVUS imaging in Groups 1 and 2 showed intima hyperplasia and various degree of calcification at sites of both persistent coronary aneurysms (intima-media complex (IMC):0.71± 0.22mm, % calcification area (%CA):55.4± 21%) and stenosis (IMC:0.88± 0.44mm, %CA:81.4± 20%,). However, IVUS imaging in Group 3 showed various degrees of the intimal thickening without calcification (IMC:0.48± 0.12mm, %CA:0 %). All IVUS findings in the Group 4, the CA wall echo had a single layered appearance, were similar to that in the control pts. In Group 1 and 2, the CA demonstrated poor elasticity, almost no change in the lumen area (%AC, Group 1:2.4± 1.9%, Croup 2:0.8± 1.5%). In Group 3, A significant poorer elasticity was fond compare to the control pts (Group 3:8.1± 3.7% vs. control 22.0± 13.2%, $p<0.05$). Group 4 showed no significant difference of elasticity of CA from control (Group 4:21.2± 11.3%). We conclude that long-term persistent coronary aneurysm and regressed coronary aneurysms after KD have abnormal vascular wall morphology and poor vascular elasticity.

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MORTALITY AMONG PERSONS WITH A HISTORY OF KAWASAKI DISEASE IN JAPAN: THE FIFTH LOOK

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To clarify whether patients with Kawasaki disease have a higher death rate than the age-matched healthy population after the disease occurrence, 6576 persons with a history of Kawasaki disease have been followed-up by the Research Committee. Between July 1982 and December 1992, 52 collaborating hospitals collected data on all patients having a new definite diagnosis of Kawasaki disease. Patients were followed until December 31, 1999, or death. The expected number of deaths was calculated from Japanese vital statistics data and compared with the observed number. Of 6576 patients enrolled, 27 (19 males and 8 females) died. The standardized mortality ratio (SMR) was 1.25. In spite of the high SMRs during acute phase, the mortality rate was not high after the acute phase for all patients. Although the SMR after the acute phase was 0.76 for those without cardiac sequelae, 6 males (no females) with cardiac sequelae died during this period and the SMR for the male group with cardiac sequelae was 2.35.Conclusion. The mortality rate among males with cardiac sequelae due to Kawasaki disease was 2.4 times as high as in general population, whereas mortality rates for females with the sequelae and both males and females without sequelae were not elevated.

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THIRTY YEAR PERSPECTIVE OF CARDIAC SEQUELAE OF KAWASAKI DISEASE (KD) IN HAWAII

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We reviewed all 950 cases of KD at our center from 1971 to 2001. Of these, 190 patients developed coronary artery abnormalities (CAA) diagnosed by serial echocardiograms. Among patients treated with either 400mg/kg of IVIG times 4 doses or a single dose of 2 grams/kg, the overall CAA rate was reduced from 19% in untreated patients to 6% ($P< 0.001$). For patients under 1 year of age, the CAA rate decreased from 25% of untreated patients to 9% ($P<0.002$). There was no significant difference in CAA rate between the two IVIG regimens. Three of the first 88 patients encountered during 1971 to 1978 died within 1 month of onset (8, 21, and 23 days). Three other children who died from sudden cardiac death had autopsy findings consistent with KD. None of these patients had been diagnosed before death, although one had compatible symptoms for 14 days while the other had an illness compatible with KD 17 years prior, as documented by another hospital's record. The early death at 8 days had acute inflammatory pancarditis, severe coronary intimal and adventitial inflammation with inflammatory infiltrates separating myocardial fibers but no coronary thrombosis. 4 deaths had thrombosis in aneurysmaly dilated coronaries. The sudden death 17 years after presumed KD had extensively remodeled coronaries and multiple braided lumina with remote and acute thrombosis.Six patients have required advanced cardiac interventions. One child with giant aneurysm had massive thrombosis 2 months after onset and was successful treated with thrombolytics. Two children developed severe peripheral gangrene and were treated with heparin, corticosteroid pulse therapy, and Prostaglandin-E infusion. Two other children with giant aneurysms which progressed to stenosis 12 and 15 years later had angioplasty (1) and stent (1). One child, who had asymptomatic myocardial infarction 1 year after KD, underwent successful coronary artery bypass.

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ASSOCIATION OF FC Γ RECEPTOR POLYMORPHISMS IN KAWASAKI DISEASE

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Introduction: Inadequate handling or clearance of microbial antigens is one of the explanations for the beneficial effect of IVIG in Kawasaki Disease. In case of antigen clearance by IgG, Fcγ-receptor (FcγR)-dependent mechanisms were logical targets for study. There are various FcγR types, each with a different expression pattern among leukocytes. Relevant amino acid substitutions or polymorphisms are known in the FcγRIIa, FcγRIIIA and FcγRIIIB genes, which define receptor affinity for IgG. Materials and Methods: Gene polymorphisms were determined by PCR techniques using specific primers for the FcγRIIA, FcγRIIIA and FcγRIIIB alleles. Results: In a cohort of Caucasian KD patients (n=106), FcγR polymorphisms showed differences in genotype distribution compared to a group of 87 healthy controls. A clear shift towards FcγRIIIA-158F/F was seen in our group compared to the control (41% versus 32%, $p=0.08$). No such differences in the genotype distribution of FcγRIIA-131R/H and FcγRIIIB-NA (1,2) were detected. A relation to IVIG efficacy and the occurrence of CAA was not found. The FcγRIIIA is expressed on Natural Killer cells and macrophages. The FcγRIIIA-158F isoform is known to have a lower affinity for IgG (1, 3, 4 subclasses) than the FcγRIIIA-158V isoform. Overexpression of this isoform might therefore result in a less effective handling of endogenous IgG or IVIG and a higher risk for the development of KD.