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THE STUDY OF SERUM VASCULAR ENDOTHELIAL GROWTH FACTOR AND CARDIAC TROPONIN I IN ACUTE FEBRILE PHASE OF KAWASAKI DISEASE

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Purpose: Kawasaki disease is a febrile disease with acute multisystemic vasculitis associated with early development of acute myocarditis and coronary artery abnormalities. The study was performed to investigate the levels of VEGF and cTnI in acute stage of KD before IVGG therapy to confirm and find early diagnostic method of KD by serologic test. **Method**: The patients group was consisted of 61 cases who were hospitalized from jan. 1998 to feb. 2001. The control group was consisted of 24 cases who suffered from non KD. The obtained sera were measured the levels of VEGF and cTnI by using Chemoluminoimmunoassay method, and compared with the results of both groups. **Results**: 1) The sex ratio of male to female was 1.6:1.0, and mean age was 2.6+/-1.6 years old. 2) The levels of VEGF were 143.64+/-115.38 pg/ml in patients group, which were significantly increased as compared to control group(26.55+/-13.75 pg/ml)($P<0.05$). 3) The level of cTnI was significantly increased 19 cases(31%) among patients group(0.21+/-0.14 ng/ml) as compared to within normal range of it(<0.1 ng/ml) in control group($P<0.05$). 4) Acute phase reactants such as CRP, ESR were positive, and leukocytosis was seen in acute stage of both groups. However, there were no singificance on both groups(P0.05). **Conclusion**: The measurement of serum VEGF and cTnI can be one of useful method for early diagnosis and confirmation of vasculitis and acute myocarditis in KD, and can help to early treatment of IVGG to reducing cardiovascular abnormalitis of it.

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NF-KAPPA B ACTIVATION IN PERIPHERAL BLOOD MONOCYTES/MACROPHAGES AND T CELLS DURING ACUTE KAWASAKI DISEASE

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Kawasaki disease (KD) is a febrile disease of childhood characterized by systemic vasculitis, and the levels of many proinflammatory cytokines are elevated in the serum at the acute stage. We investigated the activation of transcription factor NF-kappa B for genes that encode the proinflammatory cytokines in CD14+ monocytes/macrophages and CD3+ T cells in peripheral blood by means of Western blot and flow cytometric analyses. Western blot analysis demonstrated that NF-kappa B activation was more increased in CD14+ monocytes/macrophages than in CD3+ T cells in all children during the acute stage. Flow cytometric analysis revealed NF-kappa B activation in CD14+ monocytes/macrophages was significantly higher than in CD3+ T cells at the acute stage (30.0 ± 16.0% vs 11.4 ± 5.0%, $p < 0.01$, Wilcoxon test). NF-kappa B activation in CD14+ monocytes/macrophages was significantly decreased after high-dose intravenous immunoglobulin therapy ($p < 0.05$). The present findings suggest that CD14+ monocytes/macrophages play an important role in the cytokine production during acute KD.

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A NOVEL MARKER FOR DISEASE ACTIVITY IN KAWASAKI DISEASE

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A previous study on Kawasaki Disease (KD) revealed an interesting new marker to monitor disease activity: human neutrophil elastase (HNE). HNE is released by granulocytes, and their plasma levels are a good representation of the activity of those cells in vivo. Materials and Methods: A cohort of patients was screened prospectively. Blood was collected at sequential time-points, starting before IVIG administration. We determined plasma HNE and CRP, as routine inflammatory marker, by ELISA. Results: Preliminary data showed an increase of HNE levels in all KD patients in the acute phase of the disease. These levels remained high for a period of weeks only slowly returning to normal. Levels of HNE were 1155 ng/ml [95% C.I.: 703-1607 ng/ml] before IVIG administration. After 1 week, 6 weeks and 3 months the levels were 475 ng/ml [95% C.I.: 210-740 ng/ml], 300 ng/ml [95% C.I.: 158-442 ng/ml] and 386 ng/ml [95% C.I.: 69-702 ng/ml] respectively. Levels below 50 ng/ml are considered normal for children. Levels of CRP were only elevated until 1 week thereafter: 113 mg/L [95% C.I.: 70-157 mg/L] and 25 ng/ml [95% C.I.: 6.7-44 mg/L] respectively. After 6 weeks and 3 months the levels had normalized: 2.3 mg/L [95% C.I.: 0.1-4.8 mg/L] and 2.7 ng/ml [95% C.I.: 0.1-5.9 mg/L] (Normal value <5.0 mg/L). Conclusion: Human neutrophil elastase appears to be useful to monitor the acute phase of the disease activity. This finding indicates that inflammation proceeds for a longer period than has been suggested previously. A relation between prolonged inflammation and premature atherosclerosis warrants further evaluation.

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SERUM GRANULOCYTE COLONY-STIMULATING FACTOR IS INCREASED IN ASSOCIATION WITH CORONARY ARTERY DILATATION IN KAWASAKI DISEASE

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The major pathology of Kawasaki disease (KD) is systemic vasculitis that is caused by inflammatory cytokines. In KD, increased neutrophils are supposed to be responsible to the injury of coronary arterial endothelium by producing elastase. We studied the correlation between the serum levels of G-CSF and cardiac complication in KD to prove the involvement of G-CSF in stimulation of the proliferation of granulocytes and eventually causing coronary artery lesion. Thirty patients diagnosed as having KD (17 males and 13 females, aged 2 months to 5 years) were enrolled in this study. Gammaglobulin (400mg/kg/day for 5 consecutive days) and aspirin (30mg/kg/day) were administered to all. Ten patients exhibited transient mitral or aortic valve regurgitation and 6 had transient or persistent coronary artery dilatation. Blood samples were collected weekly. Serum levels of G-CSF ware monitored by ELISA assay. The mean serum G-CSF was 247.2±339.1 pg/ml in the first week, decreased to 18.3±49.4 pg/ml in the second week, to 14.2±26.5 pg/ml in the third week, and to 15.2±21.8 pg/ml in the fourth week of acute phase KD. Serum G-CSF in patients with coronary artery dilatation (400.5±194.3 pg/ml) was significantly higher than in patients without dilatation (125.0±97.8pg/ml) in the first week ($p<0.05$).Mean number of neutrophils in patients with coronary artery dilatation (8856±2916 /μl) was not significantly different from that in without dilatation (10006±3810/μl) in the first week. The present study revealed that serum G-CSF was significantly higher in patients with coronary artery dilatation than in patients without dilatation in the first week of KD. G-CSF may play an important role in coronary artery dilatation through activating neutrophil function or other unknown processes in acute phase KD.

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HYPERCYTOKINEMIA IS NOT ORIGINATED FROM PERIPHERAL MONONUCLEAR CELLS AT ACUTE PHASE OF KAWASAKI DISEASE

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Immune activation and generalized vasculitis are two central features of Kawasaki disease (KD). Recent observations indicated that serum levels of cytokines including interferon(INF)- γ, tumor necrosis factor (TNF)- α and interleukin (IL)-1 are remarkably increased, and that the administration of intravenous γ-globulin (IVGG) reduces the levels of elevated cytokines. **Objective**: We examined whether the plasma exchange (PE) for intractable KD cases reduces the elevated serum cytokines, and whether hypercytokinemia is originated from peripheral mononuclear cells at acute phase. **Materials and Methods**: We first compared the serum levels of cytokines between pre- and post-treatment of IVGG (8 cases) and PE (8 cases), using ELISA and cytometric bead array (CBA) system (Becton & Dickinson). For 4 cases among them, we investigated the messenger RNA levels of several cytokines in peripheral mononuclear cells at acute phase, using ribonuclease protection assay (RPA) system (Becton & Dickinson). Results: In sera of the children intractable to IVGG, increased levels of cytokines were detected such as INF-γ, IL-6, IL-10 and soluble TNF receptor (sTNFR). After PE therapy, serum levels of them markedly decreased to the normal ranges (INF-γ: 9.1 ± 13.4 →4.0 ± 6.4 pg/ml, IL-6: 67.5 ± 74.3→6.6 ± 8.4 pg/ml, IL-10: 14.1 ± 5.1→7.4 ± 2.1 pg/ml, sTNFR: 2521.9 ± 728.2→1338.2 ± 575.9 pg/ml). However, RPA analysis demonstrated that messenger RNA levels of several cytokines at acute phase were undetectable in both pre- and post-treatment of PE in peripheral mononuclear cells. **Discussion**: These findings suggested that the effectiveness of IVGG and PE treatment for KD will be attributed to the reduction of proinflammatory cytokine levels in serum, and that the increased levels of proinflammatory cytokines were originated not from the circulating mononuclear cells, but presumably from in situ lymphocytes and macrophages located at inflammatory lesion such as vasculitis lesion.

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FACTORS PREDISPOSING TO THE CORONARY ARTERY RISK IN KAWASAKI DISEASE

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To assess predisposing factors of coronary artery abnormalities(CAA) in Kawasaki disease, clinical records of patients with a discharge diagnosis of Kawasaki disease at Korea University Medical Center from 1999 to 2001 were reviewed. A total of 99 patients were diagnosed and 11 patients developed CAA (11%). Variable factors including clinical manifestations, laboratory measurements, treatment and its responses were evaluated to predict CAA. Sixty five patients met complete American Heart Association (AHA) criteria (typical KD) whereas 34 patients did not (atypical KD). CAA were developed in 5 of typical KD compared to 6 of atypical KD (7.7% vs 17.6%). Intravenous immune globulin (IVIG) were administrated in 91 patients and 9 of them developed CAA compared to 2 of 8 who did not received IVIG (10% vs 25%). When the IVIG responsiveness was defined by the presence or absence of defervescence within 5 days after IVIG therapy, 75 were IVIG-responsive and 16 were not. Six in the IVIG-responsive group developed CAA compared to 3 in the IVIG-non-responsive group (8% vs 19%). A total of 62 patients were male and 8 of them developed CAA compared to 3 of 34 female patients (13% vs 8%). Total duration of fever, a duration of fever before the initiation of IVIG and the level of C-reactive protein (CRP) at onset were significantly higher ($p=0.0018$, $p=0.0095$, $p=0.002$) and the hemoglobin level at onset was significantly lower in CAA group ($p=0.0009$). Conclusively, predisposing factors of CAA in Kawasaki disease are male gender, atypical manifestations, no IVIG therapy, no IVIG-responsiveness, longer duration of total fever, longer duration of fever before the initiation of IVIG, the higher level of CRP and the lower level of hemoglobin at onset.