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General Summary

We have 8 subspeciality research groups: 1) the Medical Genetics, Congenital Metabolic Diseases, Endocrinology, Gastroenterology and Hepatology group, 2) the Allergy and Immunology group, 3) the Neurology group, 4) the Hematology and Oncology group, 5) the Cardiology group, 6) the Infectious Diseases group, 7) the Neonatology group, and 8) the Nephrology group. The ultimate aim of these subspecialty groups is to supply practical benefits to patients and their families through basic and clinical research. Realizing this aim requires cooperation and a high motivation for research.

Research Activities

Medical genetics, congenital metabolic diseases, endocrinology, gastroenterology and hepatology

We focused on research concerning medical genetics, congenital metabolic diseases, endocrinology, gastroenterology, and hepatology. In the field of medical genetics and congenital metabolic diseases, we analyzed the clinical manifestations and natural history of Japanese heterozygous females with Fabry disease. Furthermore, we studied the effect of antibody formation on the reduction in urinary levels of globotriaosylceramide during agalsidase beta therapy in patients with Fabry disease. In the field of endocrinology, we performed molecular analysis of autosomal dominant hypoparathyroidism in a neonate and studied intrauterine therapy for fetal goiterous hypothyroidism during late gestation. In the field of gastroenterology and hepatology, we performed a retrospective multicenter study to examine the association between gastric atrophy and *Helicobacter pylori* infection in Japanese children.

Allergy and immunology

We have been measuring several types of marker in exhaled breath condensate from young children with asthma. Next, we measured the levels of exhaled nitric oxide in young children with asthma and compared them with levels in control subjects without asthma (4.8 ± 0.7; age range, 2 to 6 years). We found that levels of exhaled nitric oxide were negatively correlated with symptom-free periods ($r = -0.239$, $p = 0.044$).

The mechanism of asthma exacerbation induced by upper respiratory infection with rhinovirus has also been investigated.
We developed a questionnaire for caregivers of children with atopic dermatitis (Quality of Life of Caregivers of Children with Atopic Dermatitis) which has been submitted for publication.

Neurology
We focused on 2 research activities concerning human herpes virus (HHV) 6 encephalopathy and West syndrome last year. First, we investigated HHV-6 encephalopathy, to classify HHV-6 encephalopathy based on the findings of magnetic resonance imaging and single-photon emission computed tomography. HHV-6 encephalopathy can be classified into 4 types: 1) the frontal predominant type, 2) the hemispheric type, 3) the acute necrotizing encephalopathy type, and 4) the diffuse type. The hemispheric type predominantly affected the occipital lobes. The diffuse type showed decreased blood flow in all areas of the cerebrum and had a frontal predominance similar to that of the frontal predominant type. All patients with the hemispheric type had frequent clusters of hemiconvulsions both in the initial febrile period and in the defervescence period, which were followed by transient hemiplegia. Patients with the frontal predominant type or the diffuse type had generalized convulsions, including secondary generalized seizures, in clusters in the defervescence period. This imaging-based classification of HHV-6 encephalopathy suggests that each type of encephalopathy has characteristic manifestations. Pathophysiologic changes, such as direct viral invasion, vascular changes, cytokine storm, and secondary immunological response, seem to be reflected in the type of HHV-6 encephalitis, and each type may be associated with characteristic manifestations.
Next we describe our study of West syndrome. We studied factors affecting developmental outcomes in patients with cryptogenic West syndrome. Medical records of 32 patients with West syndrome were reviewed for clinical features: treatment lag, electroencephalography findings, and seizure evolution. Those features were compared between a good outcome group and a poor outcome group. The duration from onset to any treatment was longer in the poor outcome group than in the good outcome group. Evolution of electroencephalography findings showed that paroxysmal discharges reappeared in frontal regions more frequently in the poor outcome group than in the good outcome group. Frequency of other type of seizure except spasms was higher in the poor outcome group than that in the good outcome group. Focal epilepsy developed more frequently in the poor outcome group than in the good outcome group. In conclusion, shorter treatment lag is associated with a favorable outcome in cryptogenic West syndrome. Reappearance of paroxysmal discharges in the frontal regions and the evolution to other types of seizure may be associated with undetectable lesions in the frontal region.

Hematology and oncology
We demonstrated the molecular mechanism of the antitumor activity of the G-quadruplex-interacting agent 5,10,15,20-tetrakis (*N*-methyl-4-pyridyl) porphyrin

(TMPyP4) through G-quadruplex stabilization in guanine-rich DNA sequences in K562 leukemic cells. Moreover, we reported that the effects of an inhibitor of epidermal growth factor receptor were dependent on the EGFR mutation pattern. We investigated the expression of E-cadherin and N-cadherin in paraffin-embedded sequential surgical specimens and autopsy specimens from a 4-year-old girl with recurrent ependymoma and subsequent cerebrospinal fluid dissemination. Expression of E-cadherin was low in all surgical specimens and autopsy specimens, whereas expression of N-cadherin was high level in all surgical specimens but was decreased in autopsy specimens. These results suggest that the expression of N-cadherin is a marker for cerebrospinal fluid dissemination in ependymoma.

Cardiology

Our cardiologic studies were as follows.

1. Prenatal diagnosis of congenital heart disease
2. Diagnosis, treatment, and long-term postoperative follow-up of congenital heart disease
3. Basic assessment of right ventricular failure
4. Multidetector-row computed tomography in congenital heart disease
5. Evaluation of respiratory circulation dynamics with expired gas analysis for children with heart disease
6. Strategy for the treatment of acute-phase Kawasaki disease
7. Evaluation of respiratory function in congenital heart disease
8. Treatment of arrhythmia detected with cardiac screening in school-aged children
9. Epidemiology of Kawasaki disease
10. Magnesium dynamics in pediatric cardiology
11. Magnesium therapy for arrhythmia in childhood
12. Molecular biology in congenital heart disease
13. Dynamics of nitric oxide in children with congenital heart disease
14. Secretion kinetics of atrial and brain natriuretic peptides in children with congenital heart disease
15. Catheter intervention for congenital heart disease
16. Thyroid function in congenital heart disease
17. Ventricular function in patients who have undergone the Fontan procedure
18. Assessment of cardiac function in metabolic disease

We perform research after finishing our daily practice. We presented many findings at annual meetings.

Infectious diseases

Our research focuses on primary immunodeficiency, infectious diseases, and collagen diseases in children. We have been studying new methods of diagnosis and treatment based on our clinical experiences. Our research studies were as follows.

1. The diagnosis and gene therapy of chronic granulomatous disease
2. Surveillance of respiratory infection
3. Efficacy and safety of vaccines

4. Disease activities and prognosis of juvenile idiopathic arthritis and systemic lupus erythematous
5. Effect of molecular intervention against refractory collagen diseases

Neonatalogy

We studied risk factors for patent ductus arteriosus (PDA) with and without spontaneous closure of the ductus arteriosus in very low birth weight infants. Gestational age and surfactant administration were identified as risk factors for PDA. Birth weight, 1-minute Apgar score, mechanical ventilation, respiratory distress syndrome, and red blood cells were also identified as significant risk factors for PDA.

Publications

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