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General Summary

We have 10 subspecialty research groups, which are the Inherited Metabolic Disease group, the Endocrinology group, the Neurology group, the Hematology and Oncology group, the Infectious Diseases and Immunologic Disorders group, the Nephrology group, the Cardiology group, the Allergy group, the Neonatology group, and the Pediatric Psychiatry group. The final aim of each subspecialty groups is supplying practical benefits to patients and their families through basic and translational research and clinical study.

Research Activities

Inherited metabolic disease group

1. We developed a novel gene therapy for Krabbe disease and mucopolysaccharidosis (MPS) type VII.
2. We showed the effectiveness of preconditioning, such as with interferon and an anti-c-kit antibody, for bone marrow transplantation in a murine model of MPS type II.
3. We found that enzyme replacement therapy has an additive effect to bone marrow transplantation in MPS II mice.
4. Induction of a molecular chaperone enhanced the activity of α-glucosidase in Pompe disease fibroblasts.
5. We showed that oral administration of α-glucosidase induced immune tolerance in enzyme replacement therapy for Pompe disease.
6. A database was created of patients in our clinic with Fabry disease.
7. We performed genetic diagnoses with a comparative genomic hybridization array and next-generation sequencing in patients with congenital anomalies and intellectual disabilities.

Neurology group

We investigated the clinical records of 142 children after traumatic brain injury to evaluate the outcomes of posttraumatic epilepsy. The risk factors for post-traumatic epilepsy were abuse, subdural hematoma, consciousness disturbance (severe, prolonged), and complications (poor mobility, cognitive impairment). We evaluated the efficacy of fosphenytoin in 24 patients with status epilepticus. The

efficacy of fosphenytoin was 70%. Transient hypotension was observed as an adverse effect in 1 patient. The optimal serum concentration of fosphenytoin could be maintained for 15 hours with a dose of 22.5 mg/kg but could not be achieved with a dose of 7.5 mg/kg. Our findings suggest that fosphenytoin is safe and effective for patients with status epilepticus who are younger than 2 years.

Nephrology group

The Division of Nephrology provides a full range of services for the evaluation and management of children with simple or complex nephrologic or urologic disorders, including:

1. Hematuria or proteinuria or both
2. Glomerulonephritis
3. Urinary tract infections
4. Electrolyte or acid-base disorders
5. Hypertension
6. Complex and severe disorders resulting in end-stage renal disease requiring dialysis or transplantation or both

Our staff is well equipped to provide both acute and chronic management of various kidney problems and to provide consultative services to other departments within the hospital and to community physicians. Inpatient and outpatient consultations are available for children with electrolyte and acid-base disorders. Staff members work closely with urologic and pediatric surgeons to provide comprehensive management of patients.

Infectious diseases and Immunologic Disorders group

We focused on the identification of causative pathogens by means of polymerase chain reaction techniques for the genetic diagnosis and treatment of primary immunodeficiency syndrome, especially chronic granulomatous disease (CGD). The multiplex polymerase chain reaction assay was faster, more sensitive, and more specific than the gold-standard culture-based method in inflammatory diseases and respiratory infectious diseases.

We found a significantly lower incidences of *Bacteroides* and *Bifidobacterium* in patients with CGD and colitis than in patients with CGD and no colitis. The results suggest that compositional change is a useful diagnostic tool in CGD colitis.

We reported that thalidomide was effective for treating bowel inflammation in patients with CGD but did not cause progression of fungal or bacterial infections. Thalidomide is an efficacious therapeutic option for patients with CGD colitis.

Hematology and Oncology group

We reported familial cases of *MYH9* disorders. The patients were a 1-year-old Japanese boy, who presented only with macrothrombocytopenia, and his father, who had refractory chronic idiopathic thrombocytopenia purpura, hearing loss and, chronic renal failure. Sequence analysis of exon 1 of the *MYH9* gene identified heterozygous S96L mutations in both the child and the father, resulting in the diagnosis of familial cases of *MYH9* disorders.

We performed and presented a cross-sectional survey of pain management during bone marrow aspiration and biopsy to institutions belonging to the Tokyo Children's Cancer Study Group. Through the acquisition of relevant pharmacological knowledge and the sharing of information with palliative care teams, the "Guide to the Pharmacological Management of Symptoms in Children with Cancer" was established.

Cardiology group

The pediatric cardiology group is interested in both basic and clinical cardiology research to improve outcomes for children with congenital or acquired heart diseases. The results of our research have been presented at the annual meetings of the Japan Pediatric Society, the Japan Pediatric Cardiology and Cardiac Surgery, and the Pediatric Academy Society. Ongoing projects are as follows.

1. The effects of telmisaltan in heart failure
2. The effects of bisoprolol in right heart failure
3. The effects of carperitide in monocrotaline-induced pulmonary hypertension
4. Assessment of cardiopulmonary function in metabolic heart disease
5. Urocortin and angiopoetin evaluation in congenital heart disease
6. Early diagnosis of renal dysfunction in patients with congenital heart disease
7. Risk factors for atrial tachycardia in Wolff-Parkinson-White syndrome

Allergy group

The main subjects of our research are as follows: 1) the role of eosinophils, mast cells, and epithelial cells in the pathology of allergic diseases; 2) pediatric asthma; 3) food allergy; 4) atopic dermatitis; and 5) treatments for allergic diseases. We have organized and performed the following multicenter clinical studies: 1) The Preventive Effect of Tulobuterol Patch for the Long-Term Management of Infantile Asthma study (PET study); 2) Pediatric Asthma Research for Guideline study (Pediatric Asthma Research for Guideline Update: Add-on use of tulobuterol patch on unstable asthma treated with leukotriene receptor antagonist); 3) The Continuous Inhalation Treatment study (A comparison of continuous inhalation treatment with salbutamol and isoproterenol for severe pediatric bronchial asthma: A multicenter, double-blind, randomized study); and 4) the Optimal Stepdown Therapy for Controlled Pediatric Asthma Responded to SFC (OSCAR) study; Effect of Oral Immunotherapy in Preschool Children with Milk Allergy study (ORIMA study).

Endocrinology group

Accomplishments of our group this year are as follows.

1. We analyzed the expression of urocortin 2, urocortin 3, corticotropin-releasing factor receptor 2, nesfatin-1, and inflammatory cytokines in the brains of a rat model of left ventricular heart strain. Furthermore, we are performing immunohistochemical and behavior analyses.
2. We studied insulin insufficiency in infants with acute gastroenteritis due to *Rotavirus* infection.
3. We investigated the efficacy of treatment with growth hormone in children who are

small for gestational age, have short stature, or had extremely low birth weight. Both good responders and poor responders to growth hormone treatment were clearly identified.

4. We have just started an educational program for young pediatric endocrinologists. We are now sending each young resident to the Departments of Endocrinology and Metabolism of Saitama Children's Medical Center and of Tokyo Metropolitan Children's Medical Center.

Publications

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