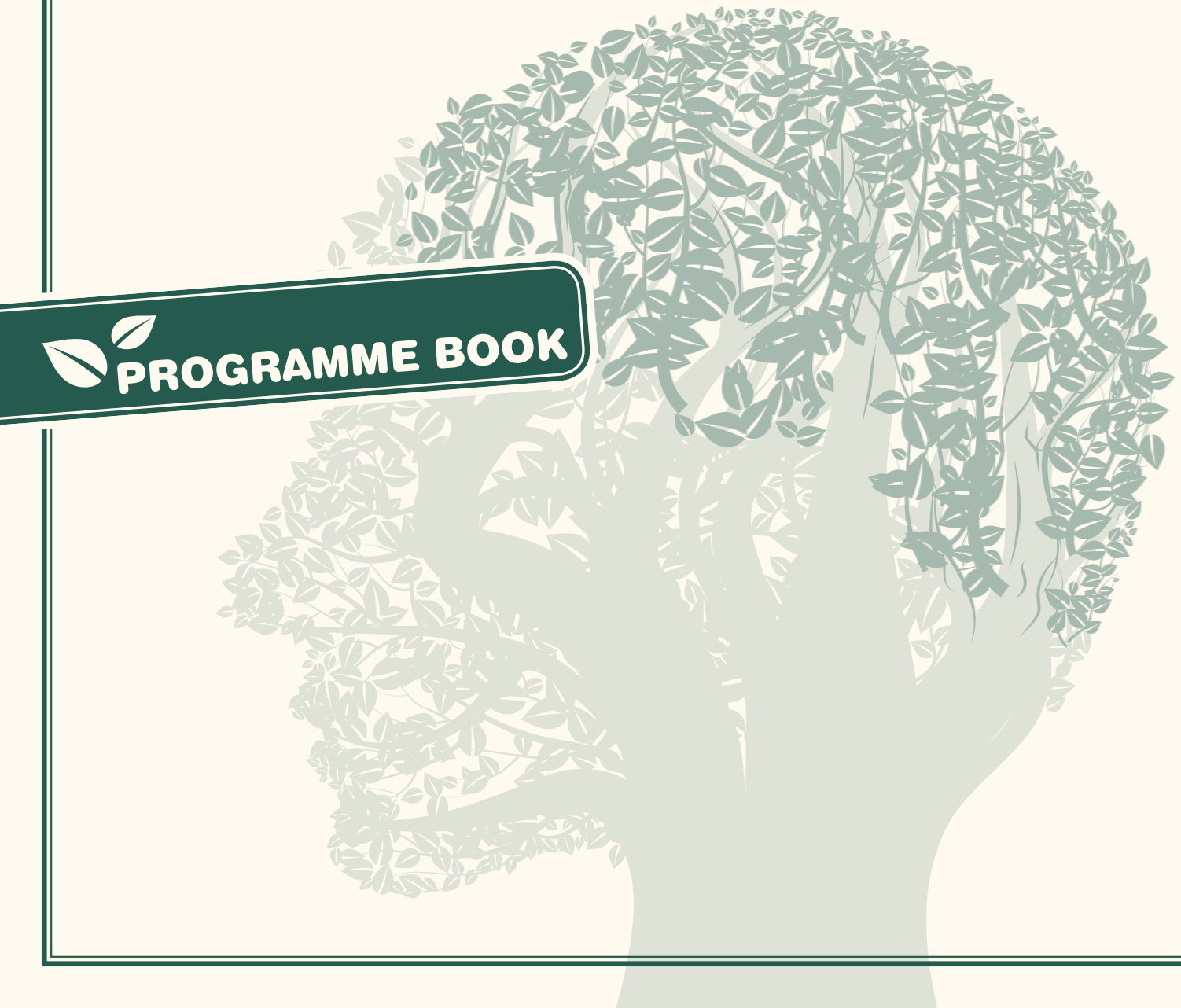
The Hong Kong Society of Child Neurology and Developmental Paediatrics

Annual Scientific Meeting 2013

2 – 4 November 2013 · Hong Kong

"Paediatric Neurometabolic Disorders"



PROGRAMME BOOK

The Hong Kong Society of Child Neurology and Developmental Paediatrics

www.hkcnpd.org

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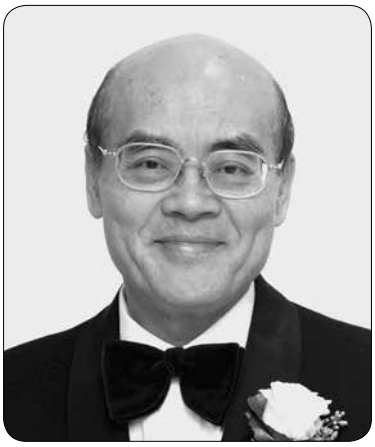
WELCOME MESSAGE



The year 2013 is an important year for Developmental Behaviour Paediatrics (DBP) and Paediatric Neurology (PN) because we have undergone proper accreditation procedures to have both being certified as statutory subspecialties under paediatrics by the Hong Kong College of Paediatricians. The procedure is fair, responsible, accountable and professional. We have well established guidelines for eligible first fellows under direct supervision of Profession Ellen Perrin and Professor Robert Ouvier as external assessors for DBP and PN respectively. All potential first fellows have to go through credential vetting and an interview by the external assessors. Successful candidates would be admitted to the Hong Kong Academy of Medicine for approval of the subspecialty fellowship and further recommended to the Medical Council of Hong Kong for inclusion into the Specialist Register. The PN and DBP subspecialists would be governed by the Subspecialty Boards respectively under the ambit of the Committee for Subspecialty Boards directly under the Hong Kong College of Paediatricians. We have now a full set of working protocols accompanied by documents to smoothly implement our accreditation procedures including the training centres, programmes, trainee status, supporting facilities and certification of trainees in each of the paediatric subspecialties in an orderly and strategic manner. The College has now clear guidelines on the governance of these subspecialties under the subspecialty boards and clear hierarchy for the running of these accreditation procedures. We are pleased that our DBP and PN Boards are pioneers for training of these subspecialties in the Asia-Pacific Region. I would like to congratulate all colleagues involved in these accreditations for their immense achievements and to thank wholeheartedly the External Assessors for their paramount contributions and efforts.

From now on we do have the DBP and PN Boards to take up the standard of practice, quality assurance and research and to carry out our major duties of education, training, certifications, examination and in service training for the subspecialties while the Hong Kong Society of Child Neurology and Developmental Paediatrics continues to perform its original designated mission of professional affairs, education, advocacy, continuous professional developmental and medical fraternity and, most important of all, endeavour to bridge up the gaps between the subspecialties of DBP and PN which are so closely related with each other. This is a time of good tiding for both subspecialties in Hong Kong and I am sure under the seamless collaboration we are going to have a radiant way for the future of both subspecialties.

The Annual Scientific Meeting this year in November 2013 is just in time to celebrate this great event of inauguration of the DBP and PN Boards. The theme is on Paediatric Neuro metabolic Disorders and the course director this year Professor Marc Patterson is a world expert on the subject from Mayo Clinic, United States of America. His immense knowledge, experience and expertise on the subject together with the local faculties will promise all participants a highly instructive and diversified programme for our Annual Scientific Meeting.

I would like to take this opportunity to thank Queen Elizabeth Hospital for providing us with the meeting venue and the following key figures for contributing to the success of this Annual Scientific Meeting: Dr. Catherine Lam, Dr. Tsui Kwing Wan, Dr. Mario Chak, Dr. Eric Yau as well as all speakers at the Meeting. Wyeth Hong Kong Limited is to be commended for their support via an Educational Grant as well as to Ms. Sigourney Liu and her effective team at MIMS (Hong Kong) for their efficient organization of this Meeting. Most important of all, I would like to thank all members for their support and all registrants for their active participation which are always vital for the success of this Meeting. For all your support, I say thank you and I look forward to having your continual support for all future activities of our Society. I wish you all a fruitful and enjoyable Annual Scientific Meeting 2013!

Dr. Chan Chok Wan
President
The Hong Kong Society of Child Neurology and Developmental Paediatrics

COUNCIL MEMBERS

THE HONG KONG SOCIETY OF CHILD NEUROLOGY AND DEVELOPMENTAL PAEDIATRICS (2012 – 2014)

President:	**Dr. Chok-wan Chan**
Vice President:	**Dr. Catherine Chi-chin Lam**
Honorary Secretary:	**Dr. Stephenie Ka-yee Liu**
Honorary Treasurer:	**Dr. Theresa Yee-ling Wong**
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	Dr. Florence Mun-yau Lee
	Dr. Tim Kim-tim Liu
	Dr. Kwing-wan Tsui
	Dr. Eric Kin-cheong Yau
	Dr. Sam Chak-ming Yeung

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Members:	**Dr. Wai-kwong Chak**
	Dr. Chin-pang Chow
	Dr. Catherine Lam
	Dr. Stephenie Liu
	Dr. Kwing-wan Tsui
	Dr. Theresa Wong
	Dr. Eric Yau

COURSE DIRECTOR

Marc Patterson was born and educated in Australia, and trained in neurology and child neurology there, at Mayo Clinic and NIH. He is now Professor of Neurology, Pediatrics and Medical Genetics, Chair of the Division of Child and Adolescent Neurology, and Director of the Child Neurology Training program at Mayo Clinic, having previously served as Professor and Director of Pediatric Neurology at Columbia University. He currently serves as a member of the Neurology topic advisory group for revision of the ICD-10 of the World Health Organization, and leads the Education Core of the NIH-funded Lysosomal Disease Network. He has served in a number of positions in the CNS, AAN, ABPN and ANA. Dr. Patterson's research and practice has focused on rare diseases in children, including multiple sclerosis and neurometabolic disorders, with special interests in Niemann-Pick disease, type C, other lysosomal diseases (including glycoproteinoses) and congenital disorders of glycosylation, areas in which he has published and spoken widely through the United States and internationally.

FACULTY MEMBERS

Name	Affiliation
Dr. Wai-kwong Chak	Associate Consultant Department of Paediatrics and Adolescent Medicine Tuen Mun Hospital
Dr. Chok-wan Chan	Specialist in Paediatrics President The Hong Kong Society of Child Neurology and Developmental Paediatrics
Dr. Josephine Chong	Department of Paediatrics Prince of Wales Hospital
Dr. Cheuk-wing Fung	Associate Consultant Division of Child Neurology Department of Paediatrics and Adolescent Medicine Queen Mary Hospital / Duchess of Kent Children's Hospital
Dr. Joannie Hui	Senior Medical Officer Department of Paediatrics Prince of Wales Hospital
Dr. Catherine Lam	Consultant Child Assessment Service Department of Health
Dr. Florence Lee	Senior Medical Officer Child Assessment Centre Department of Health
Dr. Stephenie Liu	Senior Medical Officer Child Assessment Service Department of Health
Dr. Chloe Mak	Consultant Pathologist Department of Pathology Princess Margaret Hospital
Dr. Sylvia Siu	Department of Paediatrics and Adolescent Medicine Tuen Mun Hospital
Dr. Kin-sing Wong	Department of Paediatrics Queen Mary Hospital / Duchess of Kent Children's Hospital
Dr. Theresa Wong	Specialist in Paediatrics Honorary Treasurer The Hong Kong Society of Child Neurology and Developmental Paediatrics
Dr. Eric Yau	Associate Consultant Department of Paediatrics and Adolescent Medicine Princess Margaret Hospital
Dr. Sam Yeung	Specialist in Paediatrics Council Member The Hong Kong Society of Child Neurology and Developmental Paediatrics

SCIENTIFIC PROGRAMME

Date: **Venue:**	**2 November 2013 (Saturday)** **Lecture Theatre, G/F., Block M, Queen Elizabeth Hospital, 30 Gascoigne Road, Jordan, Kowloon**
13:30 – 14:15	**Registration and Light Buffet Lunch**
14:15 – 15:15	**Seminar I** ***(Chairpersons: Dr. Chok-wan Chan and Dr. Florence Lee)*** **Overview of Neurometabolic Disorders** ***Professor Marc Patterson, USA***
15:15 – 16:15	**Local Presentation I** ***(Chairpersons: Dr. Chok-wan Chan and Dr. Florence Lee)*** **Paediatric Neurotransmitter Diseases** ***Dr. Eric Yau, Hong Kong*** **Glutaric Aciduria Type I: Pre- and Post-expanded Newborn Screening** ***Dr. Joannie Hui, Hong Kong***
16:15 – 16:45	**Coffee Break**
16:45 – 17:45	**Seminar II** ***(Chairpersons: Dr. Wai-kwong Chak and Dr. Eric Yau)*** **Cerebral Organic Acidaemia** ***Professor Marc Patterson, USA***
Date: **Venue:**	**3 November 2013 (Sunday)** **Lecture Theatre, G/F., Block M, Queen Elizabeth Hospital, 30 Gascoigne Road, Jordan, Kowloon**
09:00 – 09:30	**Registration**
09:30 – 10:30	**Seminar III** ***(Chairpersons: Dr. Catherine Lam and Dr. Eric Yau)*** **Congenital Disorders of Glycosylation** ***Professor Marc Patterson, USA***
10:30 – 11:30	**Local Presentation II** ***(Chairpersons: Dr. Eric Yau and Dr. Sam Yeung)*** **Newborn Screening of Metabolic Disease in Hong Kong** ***Dr. Chloe Mak, Hong Kong*** **Neurometabolic Diseases: Current Scenario and Hope** ***Dr. Cheuk-wing Fung, Hong Kong***
11:30 – 12:00	**Coffee Break**
12:00 – 13:00	**Seminar IV** ***(Chairpersons: Dr. Wai-kwong Chak and Dr. Sam Yeung)*** **Lysosomal Storage Diseases – Clinical Presentations, Diagnosis and Management Strategy** ***Professor Marc Patterson, USA***
13:00 – 14:00	**Light Buffet Lunch**

14:00 – 15:30	**Case Presentation** *(Chairpersons: Dr. Catherine Lam and Dr. Stephenie Liu)* Case 1: MELAS: Clinical Approach and Management *Dr. Josephine Chong, Prince of Wales Hospital, Hong Kong* Case 2a: A Baby with Unexplained Syndrome (Multisystem Disorder with Unknown Origin) *Dr. Sylvia Siu, Tuen Mun Hospital, Hong Kong* Case 2b: A Baby with Developmental Regression and Leukodystrophy *Dr. Wai-kwong Chak, Tuen Mun Hospital, Hong Kong* Case 3: An Adolescent with Progressive Neurodegeneration *Dr. Kin-sing Wong, Queen Mary Hospital / Duchess of Kent Children's Hospital, Hong Kong*
15:30 – 16:00	Coffee Break
16:00 – 17:00	**Seminar V** *(Chairpersons: Dr. Stephenie Liu and Dr. Theresa Wong)* Niemann-Pick Disease, Type C – Overview and Recent Progress in Therapy *Professor Marc Patterson, USA*
Date: Venue:	4 November 2013 (Monday) Pearl Ballroom, 2/F., Eaton Hong Kong, 380 Nathan Road, Jordan, Kowloon
18:30 – 19:00	Registration
19:00 – 20:00	**Keynote Lecture** *(Chairpersons: Dr. Chok-wan Chan and Dr. Theresa Wong)* Universal Newborn Screening for Metabolic Disorders *Professor Marc Patterson, USA*
20:00 – 22:00	Chinese Banquet

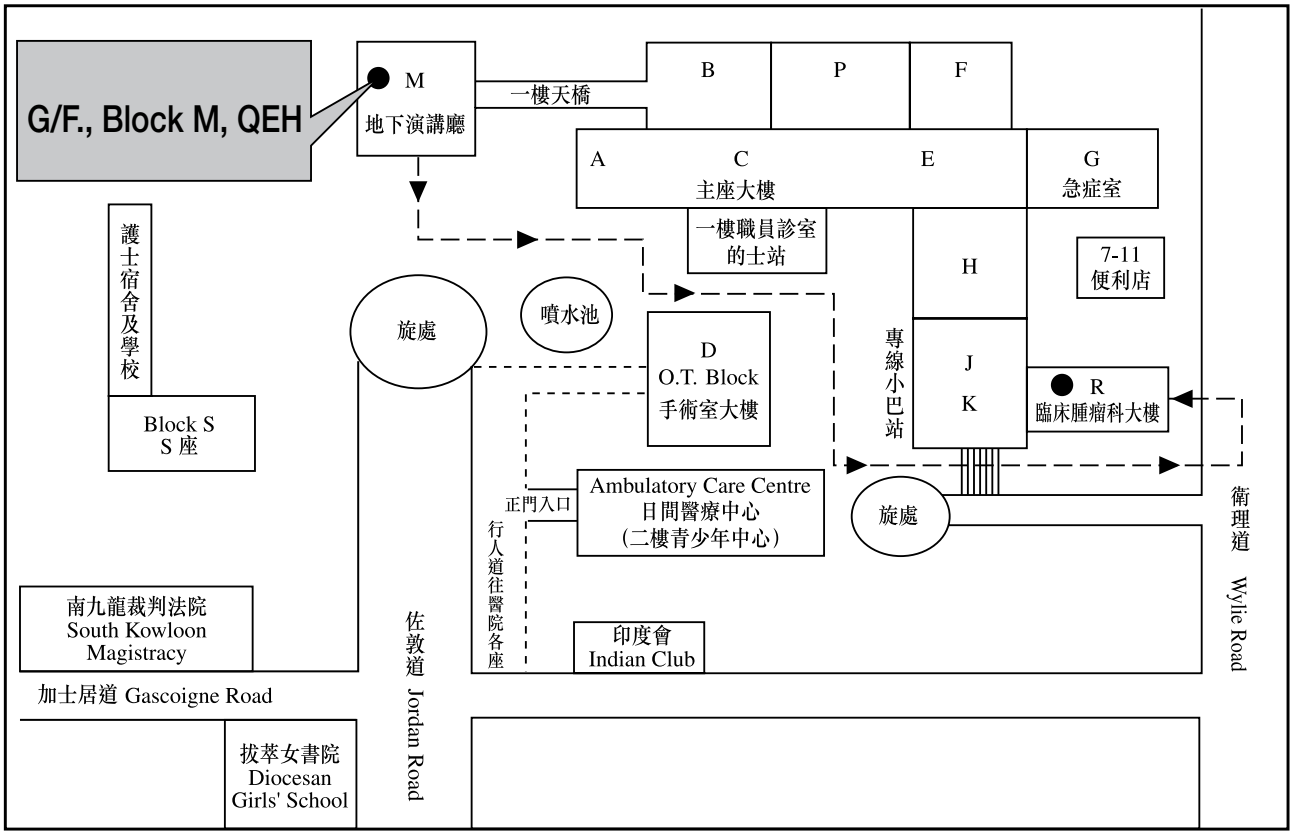
ACADEMIC ACCREDITATIONS

College / Association	2 Nov	3 Nov	4 Nov
Hong Kong College of Family Physicians (Category 5.2)	TBA	TBA	TBA
Hong Kong College of Paediatricians (Category A)	3 points	6 points	1 point
Hong Kong College of Physicians	3 points	5 points	1 point
Hong Kong College of Radiologists (Category A)	TBA	TBA	TBA
MCHK Programme	TBA	TBA	TBA
Hong Kong Occupational Therapists Association	TBA	TBA	TBA
Hong Kong Physiotherapy Association	TBA	TBA	TBA

VENUES

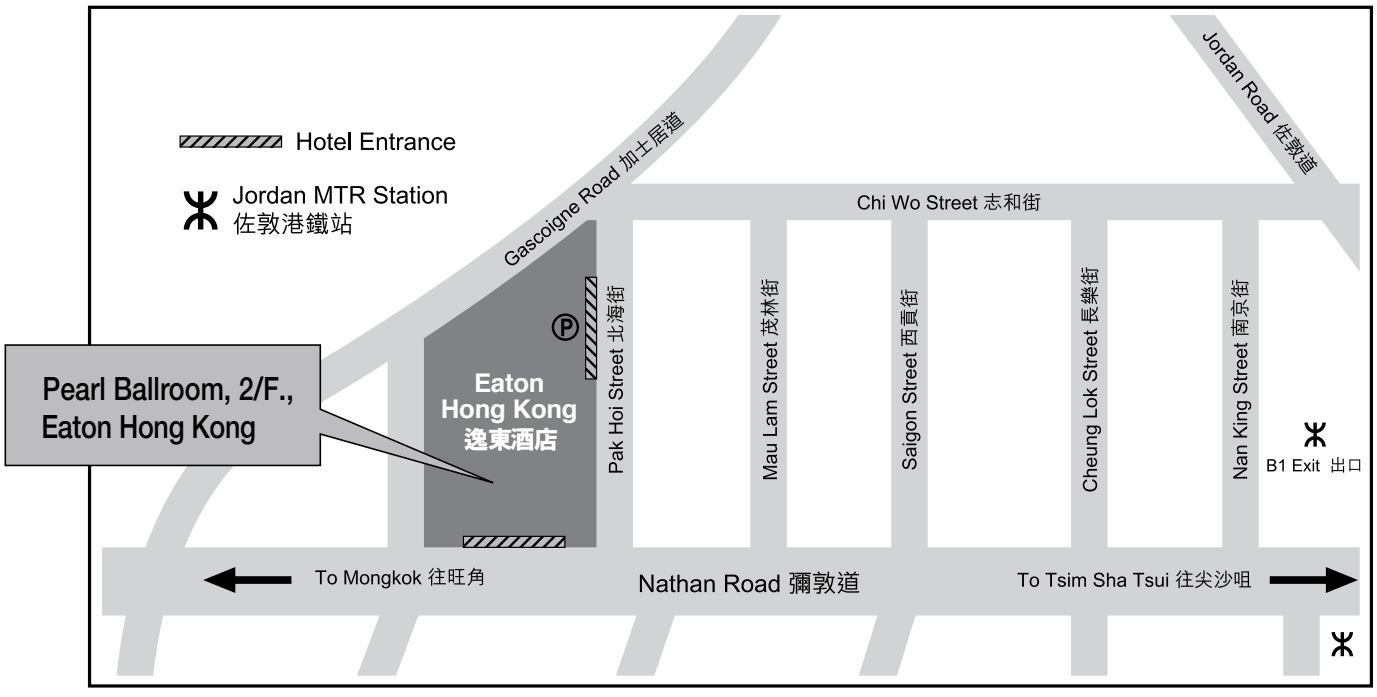
QUEEN ELIZABETH HOSPITAL 伊利沙伯醫院

2 – 3 NOVEMBER 2013



EATON HONG KONG 香港逸東酒店

4 NOVEMBER 2013



SEMINAR I

Overview of Neurometabolic Disorders

Marc Patterson
Chair, Division of Child and Adolescent Neurology, Professor and Neurology, Pediatrics and Medical Genetics, Director, Child Neurology Training Program, Mayo Clinic Children's Center, USA

Neurometabolic disorders are inborn errors of metabolism, most of which area inherited in an autosomal recessive fashion, although X-linked recessive, dominant and mitochondrial inheritance patterns have been described. These disorders are individually rare, but because of their severe phenotypes and the large number of such diseases, they constitute a significant disease burden worldwide. Conventionally, one can think of these disorders as small molecule diseases, such as the amino and organic acidopathies and urea cycle disorders, or large molecule disorders such as the lysosomal storage diseases. There is an overlap group of disorders which have features of both categories, which I refer to as complex diseases. These are perhaps best exemplified by the congenital disorders of glycosylation.

The typical phenotype of small molecule disorders is one of catastrophic metabolic decompensation in the face of metabolic stressors such as an increased load of substrate, or increased catabolism, as may occur in the face of intercurrent infection. The extent of such decompensation and the severity of the stressor are proportionate to the degree of residual activity of the defective gene product. Large molecule diseases, on the other hand, tend to have a slowly-progressive course, characterized by inexorable loss of neurologic function. The precise neurologic systems involved and the symptoms that they exhibit are specific to particular metabolic pathways.

A thorough history and examination will generally allow the astute clinician either to make a precise diagnosis or to narrow the range of diagnostic possibilities. As our ability to sequence the genome and interpret the results improves, there are an increasing number of direct molecular assays available to complement the more traditional approach to biochemical investigation, which involves the assay of specific analytes, enzymes and other gene products. A wide variety of therapies are already available for small molecule diseases, and as our understanding of the pathophysiology of large molecule diseases increases, their repertoire of disease-modifying therapies is also expanding.

LOCAL PRESENTATION I

Paediatric Neurotransmitter Diseases

Eric Yau
Associate Consultant, Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, Hong Kong

Paediatric Neurotransmitter Disease (PND) is a group of rare genetic neurometabolic disorders resulting from defect in synthesis, breakdown or transport of neurotransmitters.

Monoamine neurotransmitter disease is a heterogenous group of disorders primarily due to deficiency of cerebral dopamine and / or serotonin. Both of these neurotransmitters have key roles in central nervous system including control of locomotion, mood and behaviour.

These disorders include:

Defect in BH4 synthesis
- Autosomal dominant GTP cyclohydrolase 1 (AD GTPCH1) deficiency
- Autosomal recessive GTP cyclohydrolase 1 (AR GTPCH1) deficiency
- Sepiapterin reductase (SR) deficiency
- 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency

Defect in BH4 Regeneration
- Pterin-4α-carbinolamine dehydratase (PCD) deficiency
- Dihydropteridine reductase (DHPR) deficiency

Defect in Monoamine synthesis
- Tyrosine hydroxylase (TH) deficiency
- Aromatic L-amino acid decarboxylase (AADC) deficiency

Defect in Dopamine transport
- Dopamine transporter deficiency syndrome (DTDS)

Clinical phenotypes and severity of diseases may vary but many of these diseases have onset in childhood and are predominantly presented with neurological symptoms. They may mimic other neurological disorders such as epilepsy, cerebral palsy, developmental delay, movement disorders, etc. and are therefore frequently misdiagnosed.

Cerebrospinal fluid (CSF) analysis for neurotransmitters is an important tool for accurate diagnosis. Molecular study of specific genes can be performed for diagnostic confirmation. More than 30 cases with monoamine neurotransmitter diseases have been diagnosed in Hong Kong.

Some of these diseases are amendable to treatment and if left untreated, patient may develop severe neurological dysfunction and quality of life will be much compromised. Clinical suspicion and targeted investigation may allow early diagnosis and intervention for those treatable and potentially treatable neurotransmitter disorders.

LOCAL PRESENTATION I

Glutaric Aciduria Type I: Pre- and Post-expanded Newborn Screening

Joannie Hui
Senior Medical Officer, Department of Paediatrics, Prince of Wales Hospital, Hong Kong

Glutaric aciduria Type I (GA1) is an organic aciduria caused by inherited deficiency of glutaryl-CoA dehydrogenase (GCDH) which is involved in the catabolic pathways of L-lysine, L-hydroxylysine and L-tryptophan. If not diagnosed and treated timely, this disease is devastating for most patients. It often manifests as acute encephalopathic crises during infancy and early childhood resulting in irreversible cerebral damage.These encephalitis –like acute encephalopathic episodes are often precipitated by febrile illness, immunization or surgical intervention. The characteristic neurological sequel of these crises is a bilateral striatal damage and subsequently movement disorder manifesting as extrapyramidal syndrome with focal, segmental or generalized dystonia, orofacial dyskinesia, choreoathetotic movements, dysarthria and a degree of spasticity. Therapy for GA1 consists of a low lysine and tryptophan diet, L-carnitine supplementation and prompt treatment of intercurrent illnesses. Yet despite the above treatment regimen, the striatal damage that has occurred during the initial encephalopathic crisis cannot be reversed in most patients.

Expanded newborn screening by tandem mass spectrometry introduced since the late 1990s has revolutionalised and brought hope to these patients. Presymptomatic diagnosis and early treatment have been shown to prevent significant complications and improve neurologic outcomes. The enormous difference in neurologic outcome between the pre-symptomatic (diagnosed through expanded newborn screening) and symptomatic (diagnosed after clinical presentation) GA1 patients argues strongly for the implementation of expanded newborn screening locally here in Hong Kong.

SEMINAR II

Cerebral Organic Acidaemia

Marc Patterson
Chair, Division of Child and Adolescent Neurology, Professor and Neurology, Pediatrics and Medical Genetics, Director, Child Neurology Training Program, Mayo Clinic Children's Center, USA

Most organic acid disorders present with acute or intermittent metabolic decompensation. The cerebral organic acidemias constitute a family of diseases which have some features suggestive of a large molecule disease, including structural abnormalities of the brain and in many cases a slowly-progressive course that may also be complemented by episodic decompensation in the face of specific stressors. The disorders typically included in this category include glutaric aciduria Type 1, N-acetyl aspartic aciduria (Canavan disease), L-2- and D-2-hydroxyglutaric aciduria and succinic semialdehyde dehydrogenase (SSADH) deficiency.

All of these diseases have characteristic clinical and radiologic signatures. For example, patients with glutaric aciduria type 1 typically have macrocephaly associated with enlarged extra-axial spaces, with or without striatal signal hyperintensity. L-2-hydrohyglutaric aciduria is characterized by subcortical white matter changes, with relative sparing of deep white matter; the dentate nuclei are also involved. Canavan disease shows a similar pattern of preferential involvement of the subcortical white matter and sparing of the deep white matter. Direct molecular testing is now available to confirm specific suspected diagnoses and all of these disorders are amenable to disease-modifying therapy with diet and/or cofactors. As with all such disorders, early diagnosis is essential in order that disease-modifying therapies maybe deployed before irreversible tissue damage has occurred.

SEMINAR III

Congenital Disorders of Glycosylation

Marc Patterson
Chair, Division of Child and Adolescent Neurology, Professor and Neurology, Pediatrics and Medical Genetics, Director, Child Neurology Training Program, Mayo Clinic Children's Center, USA

Almost all biologic molecules are modified by glycosylation. Since the first description of what is now known to be phosphomannomutase 2 deficiency by Jaak Jaeken in 1980, the family of congenital disorders of glycosylation has rapidly expanded. There are now more than 60 diseases that can be so characterized. Congenital disorders of glycosylation may be subclassified according to their biochemistry, into N-linked, O-linked and GPI anchor disorders. In all cases, co- or post- translational modification of glycoconjugates is impaired. Because glycosylation is essential for trafficking of macromolecules, for cell to cell signaling and for protection of such molecules in potentially hostile chemical environments, hypoglycosylation leads to widespread downstream impairment of function. It is characteristic of these disorders that with rare exceptions, the central, and in some cases peripheral nervous system, are involved. There are typically protean systemic abnormalities which may involve the coagulation system, liver, integument, bones, heart and other viscera.

Screening tests are now available for the N-linked glycosylation disorders and for some of the O-linked disorders. For the more common of these disorders, enzyme assays are available, but in other cases, direct molecular diagnosis is usually more efficient. Diagnosis of the extremely rare forms of these disorders will typically require collaboration with a glycobiologist.

Highly specific and effective disease-modifying therapy in the form of oral mannose supplementation is available for one disorder, phosphomannose-isomerase deficiency (PMI-CDG); fucose supplementation is also helpful in leukocyte adhesion deficiency Type 2 (SLC35C1-CDG). A variety of therapeutic strategies are being investigated for other disorders in this family.

LOCAL PRESENTATION II

Newborn Screening of Metabolic Disease in Hong Kong

Chloe Mak
Consultant Pathologist, Department of Pathology, Princess Margaret Hospital, Hong Kong

Inborn errors of metabolism (IEM), a term first coined by Sir Archibald Garrod in 1902, comprise a phenotypically and genetically heterogeneous group of more than 1000 disorders caused by defective enzymes or transporters in metabolic pathways. Such defects lead to malfunctioning metabolism and accumulation of toxic intermediate metabolites, resulting in burdensome morbidities and mortalities.

In recent years, expanded newborn screening has been widely implemented as an effective preventive measure worldwide. This is made feasible with the advent of tandem mass spectrometry. The technology allows inexpensive and simultaneous detection of 20 to 50 different metabolic disorders in one single blood spot specimen, at a cost of less than USD 25 per patient.

Many of these potentially fatal metabolic disorders are amenable to effective treatment upon timely diagnosis. Early detection and intervention upstream could lead to favorable clinical outcomes.

In 1998, the New South Wales Newborn Screening Program was the first centre to implement expanded NBS based on electrospray ionization TMS followed by the New England Newborn Screening Program of the University of Massachusetts Medical School in the subsequent year. Since then, more and more conditions have been added to the list. In 2006, the American College of Medical Genetics issued a consensus statement with recommendations of a core panel of 29 disorders and 25 additional secondary target disorders in their newborn screening program. In considering the appropriateness of which diseases to be screened, the expert panel developed 19 criteria from clinical characteristics, analytical characteristics, diagnosis, treatment and management and established a scoring system. Cost was considered as a non-essential criterion among all.

In contrast, Hong Kong has yet to adopt a similar expanded newborn screening program. At present, using the sampling of cord blood at birth, only two conditions are being screened, namely congenital hypothyroidism and glucose-6-phosphate dehydrogenase deficiency. We will discuss on the update of expanded newborn screening in metabolic diseases and its relevance to Hong Kong.

LOCAL PRESENTATION II

Neurometabolic Diseases: Current Scenario and Hope

Cheuk-wing Fung
Associate Consultant, Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital / Duchess of Kent Children's Hospital, Hong Kong

Neurometabolic diseases were a group of inborn errors of metabolism with neurological involvement. Most of these diseases were once thought to be untreatable and patients could end up in a neurodegenerative process. In recent years, the field of neurometabolic diseases has been rapidly expanding:

1. Advances in understanding the underlying biochemical and molecular mechanisms allow some "old and non-metabolic" diseases to be re-classified into inborn errors of metabolism
2. Novel diseases have been discovered
3. Atypical and milder phenotypes are reported
4. The number of potentially treatable neurometabolic diseases is increasing
5. Novel treatment strategies are either available or under trials

However, diagnosing neurometabolic diseases remain a major challenge to front-line clinicians. Phenotypic overlap does occur with other non-neurometabolic neurodegenerative or neurogenetic diseases. Use of a panel of laboratory tests for screening within a well-defined clinical context remains a useful approach especially targeted for those diseases that are potentially treatable. Unfortunately, negative screening does not rule out neurometabolic diseases. Diagnosis relies on a close collaboration between clinical and laboratory specialists aiming at:

1. Precise and accurate clinical phenotyping
2. Understanding false positivity and false negativity of an individual neurometabolic investigation
3. Use of one or a battery of biochemical and / or molecular test(s) to make the final diagnosis

Through case illustrations and data from a tertiary referral centre for neurometabolic diseases in Hong Kong West Cluster, "HOPE" would be the future for our patients.

SEMINAR IV

Lysosomal Storage Diseases – Clinical Presentations, Diagnosis and Management Strategy

Marc Patterson
Chair, Division of Child and Adolescent Neurology, Professor and Neurology, Pediatrics and Medical Genetics, Director, Child Neurology Training Program, Mayo Clinic Children's Center, USA

Lysosomal storage diseases comprise a family of more than 50 disorders resulting from defective activity of hydrolytic enzymes, which function in the acidic environment of the lysosome, or other molecules which assist acid hydrolases in their catalytic function, or are involved in the trafficking of macromolecules in the endosomal-lysosomal system. The net result of deficiencies of any of these gene products is the accumulation of one or more macromolecular substrates within the lysosome, leading to a cascade of downstream effects including premature cell death by apoptosis, inflammation and activation of a variety of alternative pathways. For example, calcium homeostasis is dysregulated in a variety of fashions specific to different disorders. The lysosomal storage diseases are traditionally subclassified according to the nature of the stored substrate. Thus, the mucopolysaccharidoses, mucolipidoses and glycoproteinoses are characterized by excessive storage of ground material which leads to characteristic facial appearance, involvement of the bones (dysostosis multiplex) and variable degrees of involvement of the nervous system, heart and other connective tissues. The sphingolipid storage diseases may or may not be accompanied by enlargement of the viscera, but in the vast majority of cases, there is primary central nervous system involvement and there may be specific diagnostic clues, such as the cherry red spot typically seen in GM2 and GM1 gangliosidosis, as well as some cases of Niemann Pick A, or the characteristic eye movement abnormalities of Niemann Pick Disease, Type C (vertical supranuclear gaze palsy) or Type 3 Gaucher's disease (horizontal supranuclear gaze palsy).

As for other inborn errors of metabolism, a comprehensive history and examination will usually permit the clinician either to make a specific diagnosis or to narrow down the range of diagnostic possibilities. In a majority of cases, the diagnosis can be confirmed by directly assaying the activity of the gene product, most commonly a lysosomal hydrolase, although an increasing number of disorders can be diagnosed directly by molecular analysis.

The nonneurologic manifestations of many lysosomal storage diseases can be effectively addressed by enzyme replacement therapy, first introduced by Rosco Brady for Gaucher disease in the early 1990s. Alternative small molecule strategies, including substrate inhibition therapy and chaperone therapy, are also being investigated in these diseases. The small molecule strategies have the potential to modify the neurologic phenotypes, which in general have not responded to enzyme replacement strategies. Moreover, the progress in molecular diagnostics now opens the possibility of both newborn and carrier screening for a wide range of these diseases which could ultimately lead to their primary prevention.

SEMINAR V

Niemann-Pick Disease, Type C – Overview and Recent Progress in Therapy

Marc Patterson
Chair, Division of Child and Adolescent Neurology, Professor and Neurology, Pediatrics and Medical Genetics, Director, Child Neurology Training Program, Mayo Clinic Children's Center, USA

Niemann Pick disease, Type C is an unconventional lysosomal storage disease. It is caused by mutations in either of the NPC1 or NPC2 genes, whose dysfunction leads to impaired endosomal-lysosomal trafficking and the accumulation of a variety of macromolecular substrates within the lysosome. As with other lysosomal storage diseases, the accumulation of these substrates leads to premature cellular death by apoptosis, as well as a cascade of downstream effects. Niemann Pick disease, Type C can present at any age, beginning in utero with fetal ascites, to maturity with a slowly-progressive dementia or psychiatric syndrome. The visceral manifestations may be severe and lethal in the neonate, but beyond infancy, Niemann Pick disease, Type C is predominantly a neurodegenerative disorder. Although the disease affects virtually all subsystems of the central nervous system, the cerebellum is disproportionately affected, causing ataxia, dysarthria and dysphagia. Vertical supranuclear gaze palsy, localizable to the dorsal midbrain, is typically the first neurologic manifestation of this disease, although it is often over looked. As many as one-half of children with this disorder may experience seizures of a variety of types and as many as a third of patients exhibit gelastic cataplexy, which in this setting is quite characteristic. All patients who survive long enough will develop progressive global cognitive impairment, i.e., a dementia, although this term is often not employed in children. In adolescents and adults, psychiatric symptoms may overshadow other features of the disease, although careful examination will usually disclose characteristic clues as described above.

Recently, measurement of a specific oxysterol in the blood has found to be highly sensitive and specific for the diagnosis of this disorder, and will likely supplant other initial diagnostic testing in the near future. In addition, a variety of potential disease-modifying therapies are now either available or under investigation. Miglustat has been studied and is an approved therapy in many countries. Clinical studies suggest that this agent can at least transiently slow progression of the disease in selected subsets of patients. Cyclodextrin infused directly into the nervous system is currently being studied at the National Institutes of Health and there are plans to study an HSP70 analog and an HDAC inhibitor in this disease based on some promising laboratory investigations.

KEYNOTE LECTURE

Universal Newborn Screening for Metabolic Disorders

Marc Patterson
Chair, Division of Child and Adolescent Neurology, Professor and Neurology, Pediatrics and Medical Genetics, Director, Child Neurology Training Program, Mayo Clinic Children's Center, USA

Newborn screening was introduced in the United States approximately 50 years ago. Newborn screening is now available throughout the world, although the precise disorders which are screened vary from country to country. Newborn screening was initially advocated for disorders in which early diagnosis would permit the introduction of disease-modifying therapy and thus significantly ameliorate the phenotype. The prototype disorder for newborn screening is phenylketonuria, and the dramatic change in the course of this disease since the introduction of newborn screening is one of the great genetic success stories of the 20th century. Since that time, advances in technology, in particular the wide availability of tandem mass spectroscopy, has permitted an increase in the number of analytes which can be reliably detected on blood spots. As a consequence, in certain areas of the United States, as many as 50 disorders may be screened for using blood spots obtained at the time of birth. With few exceptions, these are disorders for which disease-modifying therapy is available and for which there is either clinical data or a logical basis to assume that early intervention will significantly improve the patient's outcome.

In recent years, there has been increasing pressure from advocacy groups to further expand newborn screening to include disorders which have not traditionally been part of the panel, specifically lysosomal storage diseases. The first such disorder to be added to a newborn panel was Krabbe disease in New York. Studies at Duke University had shown that transplantation of children with the early infantile form of this disease before three weeks of age could lead to prolonged survival and, in at least a subset of children near normal development. Because of this, advocacy groups lobbied the legislature and Krabbe disease screening has now been in progress for several years in New York State. Interestingly, this has confirmed the rarity of the early infantile form of Krabbe disease but has also detected a substantially larger number of individuals who would be predicted to have later onset disease. New challenges have arisen in counselling these individuals and in designing protocols for followup. In many years, the New York experience can serve as a model if not a caution in the more widespread introduction of such screening techniques.

In addition to the traditional biochemical screening, advances in molecular technology, in particular the availability of massively parallel sequencing opens up the possibility of direct genetic analysis of blood samples obtained around the time of birth. There are, of course, significant technical challenges in isolating and sequencing the DNA from such a small volume of blood. Perhaps the even greater challenge, however, will be interpreting the massive amounts of data potentially obtained from such screening and providing appropriately qualified personnel to counsel the parents of children found either to be affected with such disorders or to be carriers of mutations in potentially-deleterious genes.

We live in interesting times in the world of newborn screening. There is great potential to improve the health of the population, but the expansion of newborn screening will require very careful consideration of ethical, financial and medical issues as well as an intense program of education of professionals and the public.

PAST ANNUAL SCIENTIFIC MEETINGS

Since the inauguration of our Society in 1994, Annual Scientific Meetings were held each year:

2012

Date: 16 – 19 November 2012
Theme: Augmentative and Alternative Communication
Course Director: Dr. John Costello, USA
Keynote Lecture: Breaking the Silence for Children with Complex Diffculties

2011

Date: 18 – 21 November 2011
Theme: Paediatric Neuro-Radiology
Course Director: Professor Paul Griffiths, UK
Keynote Lecture: An Approach to Imaging Children with Cerebral Palsy

2010

Date: 26 – 29 November 2010
Theme: Neuro-Immunology
Course Director: Professor Russell Dale, Australia
Keynote Lecture: Auto-antibodies in Paediatric Neurology

2009

Date: 13 – 16 November 2009
Theme: Autism Spectrum Disorders: Updates on Management
Course Director: Professor Lonnie Zwaigenbaum, Canada
Keynote Lecture: Complementary and Alternative Medicine in Autism Spectrum Disorders: Public Forum

2008

Date: 21 – 24 November 2008
Theme: Neuro-Genetics
Course Director: Professor Alan Percy, USA
Keynote Lecture: Exploring the Neurogenetics of Mental Retardation

2007

Date: 16 – 19 November 2007
Theme: Energy Crisis of Nervous System
Course Director: Dr. Ingrid Tein, Canada
Keynote Lecture: Approach to the Diagnosis and Management of Muscle Cramps, Exercise Intolerance and Recurrent Childhood Myoglobinuria

2006

Date: 10 – 13 November 2006
Theme: Attention Deficit Hyperactivity Disorder
Course Director: Professor Drake Duane, USA
Keynote Lecture: Treatment of ADHD: Medical Behavioural and Educational and Prognosis

2005

Date: 11 – 14 November 2005
Theme: Neuromuscular Disorders of Infancy, Childhood and Adolescence
Course Director: Professor Royden Jones, USA
Keynote Lecture: Childhood Neuromuscular Disorder from the Perspective of Adult Neurology

2004

Date: 19 – 22 November 2004
Theme: Paediatric Rehabilitation
Course Director: Dr. Chok-wan Chan
Keynote Lecture: Evolution of Developmental Paediatrics in Hong Kong

Course Director: Professor Robert Armstrong, Canada
Keynote Lecture: Developmental Paediatrics in the 21st Century

2003

Date: 19 – 22 September 2003
Theme: Paediatric Neurocritical Care
Course Director: Dr. Robert Tasker, UK
Keynote Lecture: Head Injury and Neuroscience – Inside Fragile Minds

2002

Date: 8 – 11 March 2002
Theme: Paediatric Neuro-Ophthalmology
Course Director: Professor David Taylor, UK
Keynote Lecture: The Apparently Blind Child

2000

Date: 8 – 11 December 2000
Theme: Language Development, Learning Disorders and Brain Plasticity: Research and Clinical Implications
Course Director: Professor Albert Galaburda, USA
Keynote Lecture: Language Development, Learning Disorders and Brain Plasticity: Research and Clinical Implications

1999

Date: 20 – 22 November 1999
Theme: Paediatric Neuro-Epidemiology
Course Director: Dr. C. M. Verity, UK
Keynote Lecture: What Happens to Children who Suffer with Febrile Convulsions

1998

Date: 14 – 16 July 1998
Theme: Paediatric Epilepsy
Course Director: Professor Brian Neville, UK
Keynote Lecture: Epilepsy: A Potential Reversible Cause of Developmental Disability

1997

Date: 11 – 13 November 1997
Theme: Neonatal Neurology
Course Director: Professor Alan Hill, Canada
Keynote Lecture: Brain Injury in Premature Newborn – An Overview

1996

Date: 29 October – 1 November 1996
Theme: Paediatric Neurorehabilitation
Course Director: Professor Joe Watt, Canada
Keynote Lecture: Recent Advances in Paediatric Neurorehabilitation

1995

Date: 14 – 16 November 1995
Theme: Neurometabolic Diseases
Course Director: Professor Kenneth Swaiman, USA
Keynote Lecture: Update on Neurometabolic Diseases in Childhood

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