Brainchild

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Hong Kong Society of Child Neurology & Developmental Paediatrics
香港兒童腦科及體智發展學會

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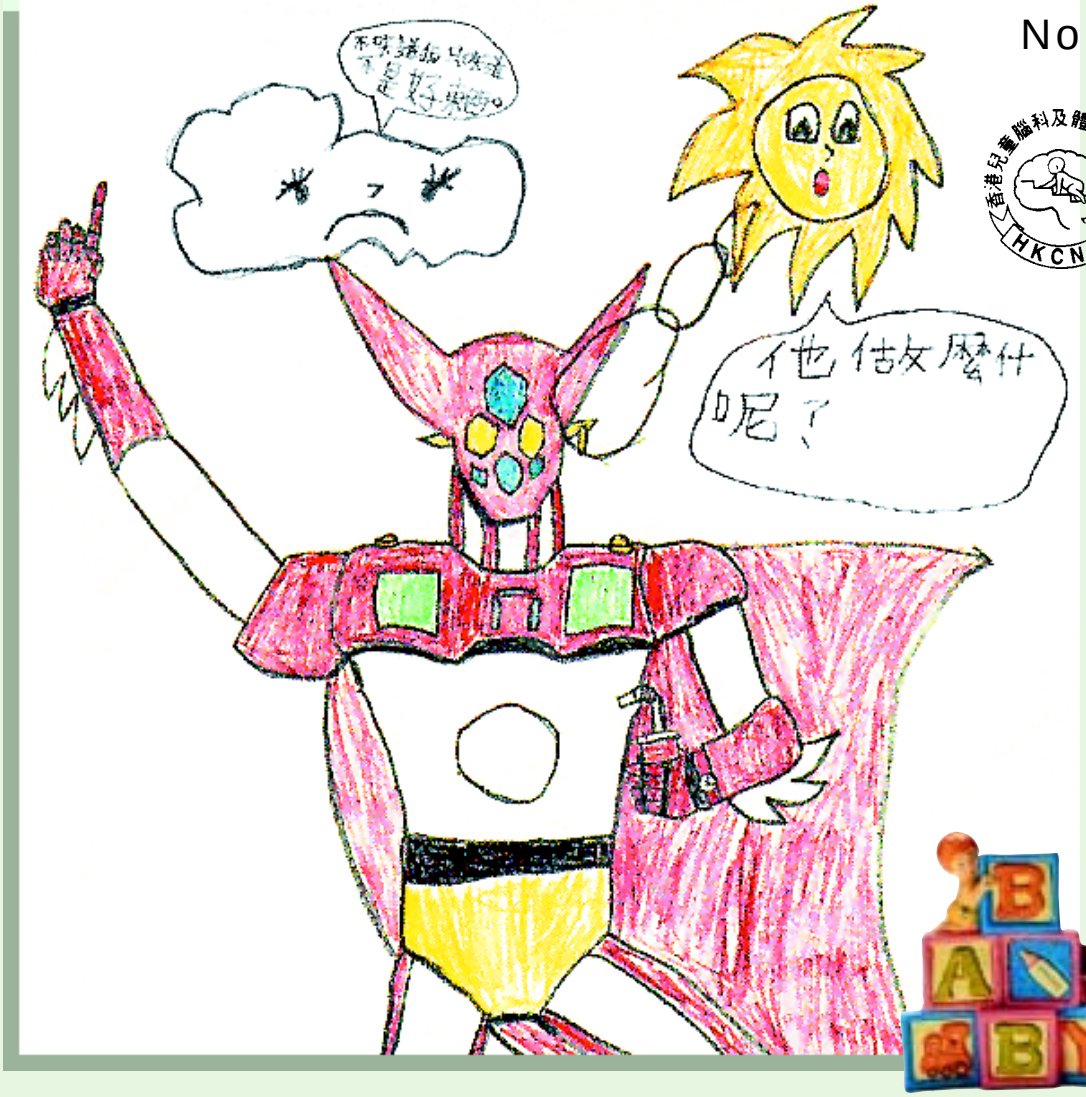

Hong Kong Society of
Child Neurology & Developmental Paediatrics
香港兒童腦科及體智發展學會

The Council

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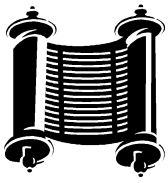
Cover

The cover picture is a drawing from an artistically inclined dyslexic child. Note the reversal of words in the Chinese phrases in his handwriting on the picture.

The Hong Kong Society of Child Neurology & Developmental Paediatrics
Brainchild - December 2001 Issue



Message from the President

Dr. CHAN Chok Wan

We are pleased to witness that the current issue of Brainchild covers a wide range of articles for our readers including a timely reviewed article on Epilepsy Surgery (Ada Yung), report on survey on the use of Botox in Hong Kong (Wu Shun Ping), and a concise and informative account of the Society's Child Neurology Conference hosted in December 2001 where we were extremely encouraged to see so many colleagues coming forth with their clinical materials for professional sharing. The sections on journal review and letters to the editor are especially innovative and create new channels for future development. I would like to thank all contributors for the effort they have devoted despite heavy commitments in their daily clinical duties. This illustrates the good saying "where there is a will, there is always a way!"

The Hong Kong Society of Child Neurology and Developmental Paediatrics is well known for the large quantity and diversified pattern of scientific activities in Hong Kong throughout these years. It currently runs regular clinical and didactic meetings, including the Child Neurology Conference, Neuro-Developmental Conference, Bimonthly Scientific Meeting, as well as the major Annual Scientific Meeting. In addition, there are ad-hoc scientific meetings organized when overseas experts passing through Hong Kong, major themed conferences such as the upcoming "International Conference on Dyslexia in Children using the Chinese Language" of October 2002, and participation in activities of other professional bodies such as the Hong Kong College of Paediatricians 10th Anniversary Celebration Scientific Meeting where we presented the position paper on "Neuro-Developmental Paediatrics Interfacing with Primary Health Care". All these render our scientific activities full, comprehensive and exciting. We are proud of such endeavours to date!

Under the guidance of the Society Council, we have a significant number of working groups operating, including the working groups on Specific Learning Disabilities, Epilepsy, Epilepsy Surgery, and Cerebral Palsy. The objectives of these groups are to study common yet complex clinical problems

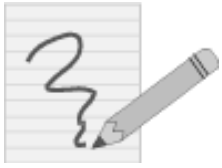
within the realm of child neurology and developmental paediatrics. Through these groups, we hope to establish local incidence, morbidity patterns, special local features, treatment protocols and position papers on management, and others. We firmly believe that all these are not only vital for proper management of such conditions in Hong Kong, but will also be valuable for advancement in international reference and sharing.

It is widely agreed that health education to professionals, parents and the general public provides foundation to success in the management of clinical problems in childhood. Here at the Society, we are proud to have jointly organized with the Federation of Medical Societies of Hong Kong this year three Certificate Courses on "Developmental Paediatrics and Child Neurology" for all professionals, "Specific Learning Disabilities" for teachers and special educators, and "Update on Epilepsy" for the general public. It was impressing to witness the enthusiastic response to all three courses by the targeted audience and the favourable comments as well as the call for more sessions on the course evaluation questionnaires. May we thank convenors and course lecturers for the good missions accomplished!

Judging from the above long list of activities and the understanding that our Society is but a small one with less than thirty full members and limited resources, the Society Council is very grateful for the dedicated hardwork and outstanding contribution of all members. Needless to say, we are indebted to our sponsors for their generous support which is always essential for our success. As for Brainchild, we are thankful to Wyeth (Hong Kong) Ltd. for their staunch financial support since its inauguration, and we look forward to their continual support to render this publication a permanent icon in the local scene.

Finally on behalf of the Society, I would like to take this opportunity to wish you all "Merry Christmas, Happy and Fruitful New Year of 2002".

Editor-in-Chief, Brainchild
President, HK Society of Child Neurology & Developmental Paediatrics



Education Section

An Overview on Epilepsy Surgery in Children

Dr. Ada YUNG
Department of Paediatrics, Queen Mary Hospital

Introduction - An Overview on Management of Epilepsy

Goals of Any Treatment for Epilepsy

The goals of treatment for epilepsy are (1) to maximize normal function, and (2) to minimize adverse effects, which are either seizure related or treatment related.

Complications due to seizures are different in the adult and the paediatric population. In an adult, epilepsy is associated with an increase in mortality, either due to an increase in accidents or SUDEP (sudden unexplained death of epileptic patients). Repetitive seizures are also associated with cognitive, linguistic, motor, sensory, psychiatric, and social impairments.

In children, the problems arising from very frequent seizures are slightly different. Our main concern is the prevention of cognitive decline. Cognitive dysfunction and decline during the developmental phase of the brain can be irreversible.

Complications from treatment include various life-threatening idiosyncratic reactions associated with the use of individual anti-epileptic drugs; the complications arising from brain surgery, in cases when epilepsy surgery is considered; gastro-intestinal upset and severe acidosis associated with ketogenic diet.

Making a Diagnosis - Seizure Semiology

An accurate diagnosis of epilepsy and categorization of the epileptic seizures and syndromes are the pre-requisite for successful treatment (Tables 1 and 2). One can obtain important information on the epileptic focus from the clinical symptomatology. For example, a complex partial seizure (CPS), preceded by epigastric discomfort, followed by dystonia on one side and stereotypic movement on the other side may suggest mesial temporal seizures. Depending on the functional cortex involved, one can have some clues on the seizure onset, based on the type of aura the patient has.

However, one should also be aware of the limitation of seizure semiology. Differentiating CPS from absence seizures with automatism or eye-lid myoclonus may be difficult. The response to carbamazepine (CBZ) can be totally different. While useful in cases of partial epilepsy, CBZ is known to aggravate seizures in cases of idiopathic epilepsies. Defining primarily versus secondarily generalised seizures can be difficult, especially in very young children when aura cannot be described, or when the seizures arise from sleep.

Table 1.

International Classification of Epileptic Seizures (ICES) - Commission on Classification and Terminology of the International League Against Epilepsy (revised - 1981)

Classification of Partial Seizures
A. Simple partial seizures (consciousness not impaired)
   1. w minor signs (focal motor w or w/o march, versive, postural, phonatory)
   2. w somatosensory or special-sensory symptoms
   3. w autonomic symptoms
   4. w psychic symptoms
B. Complex partial seizures (with impairment of consciousness)
   1. SPS - CPS, w or w/o automatism
   2. CPS at onset, w or w/o automatism
C. Partial seizures evolving to secondarily generalised seizures
   1. SPS - SGTC
   2. CPS - SGTC
   3. SPS - CPS - SGTC

Classification of Generalised Seizures
A. Absence seizures
   1. Typical absence - impairment in consciousness only, mild clonic, w atonic, w tonic, w automatism, w autonomic component
   2. Atypical absence
B. Myoclonic seizures
C. Clonic
D. Tonic
E. Tonic-clonic
F. Atonic

Table 2.

International Classification of Epilepsies and Epileptic Syndromes - Commission on Classification and Terminology of the International League Against Epilepsy (revised - 1981)

1. Localisation-related
   1.1 Idiopathic (with age related onset)
      - BECT, BOE, reading epilepsy
   1.2 Symptomatic
      - EPC
      - Frontal/temporal/parietal/occipital
2. Generalised epilepsies and syndromes
   2.1 Idiopathic (age-related onset) - benign N/N convulsion, benign myoclonic epilepsy in infancy, childhood absence, JAE, JME, GTC on awakening
   2.2 Cryptogenic or symptomatic
   Infantile spasms, LGS
   2.3 Symptomatic
   myoclonic-astatic, progressive myoclonic sz
3. Epilepsies and syndromes undetermined whether focal or generalised - NNS
4. Special syndromes - FS, eclampsia

Another example on the limitation of clinical symptomalogy is the classification of neonatal seizures. So far, the definition and classification of neonatal seizures remain confusing. There are clinical neonatal seizures without EEG correlation, or electrical seizures without clinical correlation.

Making a Diagnosis - EEG

The indications of EEG include (1) classification of seizures and epilepsy syndromes and (2) lateralisation and localisation of epileptogenic focus.

In certain epilepsy syndromes, the EEG diagnosis is mandatory. Examples include the finding of 1-2 Hz slow spikes and slow wave complexes in Lennox-Gastaut syndrome; Hypsarrhythmia in infantile spasms; sleep activated centro-temporal spikes with tangential dipole, in the absence of background slowing, in benign partial epilepsy of childhood.

In other patients, especially in the presence of a normal inter-ictal EEG, repeating an EEG under sleep deprivation (sleep for 4 hours or less) may improve yield for inter-ictal discharges. The use of additional electrode leads in the sub-temporal area (T1, T2) or special sphenoidal leads improve the pick-up of discharges in the mesial temporal region.

Finally, in-patient EEG continuous monitoring with video recording may be indicated for certain cases, especially when the response to treatment is unsatisfactory.

The Choice of Anti-epileptic Drug (AED)

The choice of AED depends, to a certain extent, on the dominant seizure types and epilepsy syndromes. Carbamazepine and phenytoin, being the first line AED for partial epilepsies, are best to be avoided in cases of primary generalised or idiopathic partial epilepsies of childhood, due to the tendency to aggravate seizures and increase myoclonic jerks in latter cases. Another example on AED use is ethosuximide (ESM) in the management of absence seizures. ESM, having a more benign side effect profile, is a good drug for absence seizures. However, in the presence of co-existing generalised tonic-clonic (GTC) seizures, epilim will be better choice, since ESM has not been shown to be effective against GTC seizures.

A detailed description on the indication of various AEDs is beyond the scope of this review. The use and indication of the use of ketogenic diet will not be discussed here.

When is Epilepsy Surgery Considered in Children?

The goals of treatment of epilepsy, as mentioned earlier, is a balance between achieving normal function of the patient and minimizing complications from the disease and the treatment.

One has to stress the difference in the definition of normal function in the adult and paediatric population. In the adult population, independence, employment and driving are major issues. The decision to go for epilepsy surgery is made when the use of AEDs alone can no longer achieve the degree of independence an adult epileptic patient desires.

In the cases of epileptic children, independence is, however, not a major issue. The decrease in seizure number is equally important as the improvement in development and behaviour. Early epileptic surgery also provide an advantage because developmental plasticity of an immature brain offers modified risks for new post-operative risks.

When is Surgery Indicated?

The indications for epilepsy surgery include:

Curative Surgery

1) Absolute indication - favorable surgical outcome
   Surgically remediable syndromes
   a) Focal resection
      (i) Mesial temporal lobe epilepsy
      (ii) Lesional partial epilepsy (lesional on MRI brain)
   b) Hemispherectomy
      Disturbances confined to one hemisphere
      (i) Hemimegalencephaly
      (ii) Sturge-Weber syndrome
      (iii) Rasmussen's encephalitis
      (iv) Large unilateral developmental abnormalities - cortical dysplasias and porencephalic cysts
2) Relative indication - variable outcome
   Intractability versus operatability
   In focal epilepsy with normal MRI brain
   Consider:
   a) Medical Intractability
   b) A well localised epileptogenic zone
   c) A low risk of new post-operative deficits

Palliative Surgery

1) Vagal nerve stimulator
2) Corpus callosotomy

Surgically Remediable Syndromes

In surgery remediable syndromes, epilepsy surgery offers a good chance (70% or greater) of abolishing disabling seizures.

Across all ages, patients with mesial temporal lobe epilepsy due to hippocampal sclerosis, and partial epilepsy due to structural lesions are good candidates for epilepsy surgery.

Specific to the paediatric age group, catastrophic unilateral or secondary generalized epilepsies of infants and young children due to disturbances confined to one hemisphere (various examples as listed as above) respond well to hemispherectomy.

Intractability vs Operatability

The majority of our paediatric patients with partial epilepsy are extra-temporal in origin, in contrast to a majority of mesial or neocortical temporal epilepsy in the adult population. Careful selection of surgical candidates is mandatory because surgical outcome for non-lesional frontal lobe or posterior quadrant epilepsy is known to be poor.

When patients with intractable, non-lesional partial epilepsies are considered for epilepsy surgery, there are several issues that need to be considered.

A. Medical Intractability
B. A Well Localised Epileptogenic Zone
C. A Low Risk of New Post-operative Deficits

A. Medical Intractability

Medical intractability means the failure of medical treatment. It is difficult to give an absolute definition when seizures are intractable. This is because seizure treatment is highly individualized and requires optimal medications and optimal serum therapeutic concentrations.

Medical intractability can be established after (1) adequate drug trial with maximally tolerated dosage, given for an adequate duration (duration being the function of pre-existing seizure frequency) and (2) adequate number of drug trials, usually 2-3 of the established and newer AEDs.

Risk factors for a low probability of seizure remission include: high seizure frequency (daily or weekly episodes, seizure clustering); early seizure onset, particularly in infancy; the presence of organic brain damage. In the presence of infrequent seizures or short duration of epilepsy, surgical option, however, can still be considered, especially when there is recurrent status epilepticus or epilepsia partialis continua, or there are yearly infrequent seizures that affect driving or work.

However, one has to be aware of the possibility of deficient medical management that can simulate medical intractability.

Conditions that simulate medical intractability include (1) patient non-compliance or intermittent compliance; (2) failure of the doctor to administer appropriate AED at an adequate therapeutic concentration and (3) failure of the patient to respond due to non-epileptic disorders / psychogenic seizures.

Exclusion of neurodegenerative disorders and inborn errors of metabolism is mandatory for they are associated with structural brain abnormalities. Aggressive treatment and surgical intervention are relatively not indicated in such cases for the patients will deteriorate due to their underlying metabolic problems.

B. A Well Localised Epileptogenic Zone

In order to perform focal lobar or multi-lobar resection, one has to lateralise the epileptic focus to one hemisphere and then further localise the epileptogenic focus to a particular region. Please refer to Table 3 for pre-surgical work-up.

C. Risk for New Post-op Deficits

Epilepsy surgery is all about the balance between the removal of cerebral dysfunction caused by an epileptic focus and the creation of new functional deficits when a resective area involves an eloquent cortex.

Paediatric epilepsy surgery is unique due to neuronal plasticity in a growing brain and therefore shifting of function. The concern about the epileptic focus overlying the eloquent cortex may be lessened due to the congenital nature of pathology causing intractable paediatric epilepsy in children. There may be shifting of function early on when a developmental malformation is located in or near a functional region.

Table 3.

Pre-surgical work-up
- Phase 1
  - Non-invasive EEG monitoring
    - Inter-ictal
    - Ictal
  - MRI brain with epilepsy protocol
  - Isotope scans - inter-ictal and ictal SPECT, (± inter-ictal PET, ± MEG)
  - (WADA)
- Phase 2
  - Intra-operative ECoG (before and after resection)
  - Extra-operative ECoG - ictal, inter-ictal
  - Functional brain mapping - sz focus vs functional area

When Should Surgery be Considered? – Importance of Early Intervention

There is evidence for neuronal injury & cellular changes associated with chronic epilepsy. A child who has medically refractory epilepsy may outgrow the seizures. However, the loss of critical, formative years and the potential for lasting deficits in cognition and learning are alarming.

To weigh against the danger of surgery versus cognitive decline due to intractable epilepsy, one has to take into account of the window of neural plasticity.

Conclusions

In summary, there are special considerations for children with intractable epilepsy undergoing pre-surgical evaluation. Assessment of risk / benefit analysis for surgery may be difficult in children and infants. The predominance of extra-temporal localisation poses great challenge for localisation of the epileptogenic zone. The underlying cause of intractable epilepsy is mainly developmental pathology. Apart from dealing with seizures which are difficult to be controlled, the benefit of an improvement in development and behaviour should be taken into consideration. Finally, developmental plasticity may offer modified risks for new post-operative deficits after surgery.

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1. Wyllie, E. The Treatment of Epilepsy: Principles and Practice. Second edition. Williams & Wilkins.
2. Engel, J, Pedley, T. Epilepsy. LW&W.

Survey of the Use of Botulinum Toxin A in Paediatric Departments in Hong Kong

Dr. WU Shun Ping
Department of Paediatrics, Queen Elizabeth Hospital

Botulinum toxin A (BTA) is used in treatment of childhood spasticity and dystonia. It produces transient relaxation of muscles and hence increase the range of movement of the joint which these muscles exert their action. There are two commercial brands of BTA. A standard vial of BTA of either brand costs about HK$2,400.

In order to find out the usage of BTA amongst various paediatric departments of the Hospital Authority Hospitals, a questionnaire regarding the use of BTA in the year 2000 was administered to the neurologists of all paediatric departments of the territory in July 2001. All departments have responded to the questionnaire.

Amongst the 12 paediatric departments, 9 departments have prescribed BTA in 2000. The total number of injections given amounted to 124 during the twelve-month period. The percentage of patient receiving repeated BTA injection ranged from 10% to 80% in various departments.

More than 90% of patients received BTA to treat spasticity. Less than 10% of patient received BTA for focal dystonia. Lower limb was the commonest site of injection, accounting for about 90% of all injections. Gastrocnemius, hip adductors and hamstrings were the three most commonly injected muscles. Flexor digitorum superficialis, flexor digitorum profundus and flexor carpi radialis muscles were also injected in a few hospitals. Other rarer sites of injection included sternomastoid muscles, adductor pollicis, pronator muscles of forearm, biceps and temporalis muscles.

As the body size of children is smaller, most hospitals would arrange to allow sharing of a vial of BTA amongst two to three patients in order to save cost.

Gait analysis is seldom done for evaluation of BTA treatment. EMG guided injection is not adopted at all as revealed in the study. These auxiliary investigations, while might be useful in research setting, would increase the time and cost of BTA treatment.

On a more personal level, the questionnaire looked into the personal perspectives of all paediatric neurologists whether their prescription of BTA has met any restriction. Only three neurologists reported a presence of restrictions limiting the amount of BTA they could prescribe in year 2000.

Estimating from the number of injections, the local paediatric neurologists have used a total of HK$290,000 of BTA in treating children with spasticity and dystonia. However it should be pointed out that it is likely to be an under-estimation of the need of BTA treatment in the local paediatric population. There is a significant proportion of children with spasticity and dystonia who are not attending paediatricians who offer BTA as an adjunct therapy to physiotherapy and splintage.

Conclusion

Botulinum toxin A treatment is adopted widely in Hong Kong for the treatment of childhood spasticity and dystonia. Lower limb remains the most commonly injected area. The treatment incurs a significant expenditure and the expenses on BTA, as an adjunct therapy to physiotherapy, splintage and orthopaedic management, is likely to increase in the coming years as the treatment becomes more widely available.

A Hypotonic Baby with Intractable Seizure: A Rare Diagnosis

Dr. Louis C. K. MA
Department of Paediatrics, United Christian Hospital

A female baby was born to non-consanguineous parents with a birth weight of 3.01kg. The antenatal history was remarkable. She developed lethargy and repeated desaturations on day 2, necessitating ventilator support. On physical examination, she was hypotonic and weak but all her reflexes were normal. A few days later, her reflexes became brisk and she started to have intractable seizures.

Based on the clinical findings of non-paralytic hypotonia and hyper-reflexia, we suspected that the lesion lied in the central nervous system. Computed tomogram of the brain revealed decreased attenuation of white matter (Figure 1). In view of the absence of obvious structural lesions to account for the clinical picture, we proceeded to perform metabolic screening in order to elucidate the underlying cause. There were no acidosis or hypoglycaemia. Ammonia, lactate, pyruvate levels and amino acid pattern were all normal. Urine for metabolic screening was non-contributory. We performed a quantitative assay of serum and CSF glycine levels. The blood glycine level was only mildly elevated but the CSF glycine was very high (15 times the upper limit of normal). The CSF/blood glycine ratio was 0.18 (normal range is 0.02-0.03). The result is compatible with the neonatal or classical form of non-ketotic hyperglycinaemia (NKH).

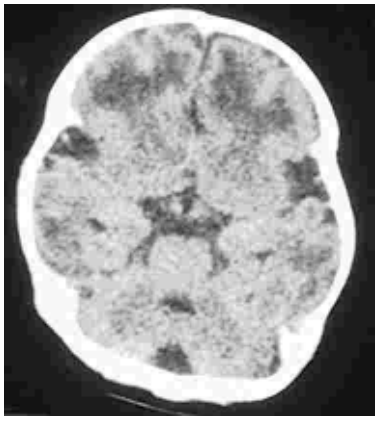


Figure 1. Axial CT Brain showing decreased white matter attenuation.

The baby is now being treated with sodium benzoate to reduce the CSF glycine level. She is on a multitude of anti-convulsants (Vigabatrin, phenobarbitone and clobazam). Moreover, Dextromethorphan (a non-competitive inhibitor of NMDA receptor) is added to help seizure control. The control of seizure is far from being satisfactory and her EEG remains hypsarrhythmic (Figure 2). As a result, ACTH has been started recently.

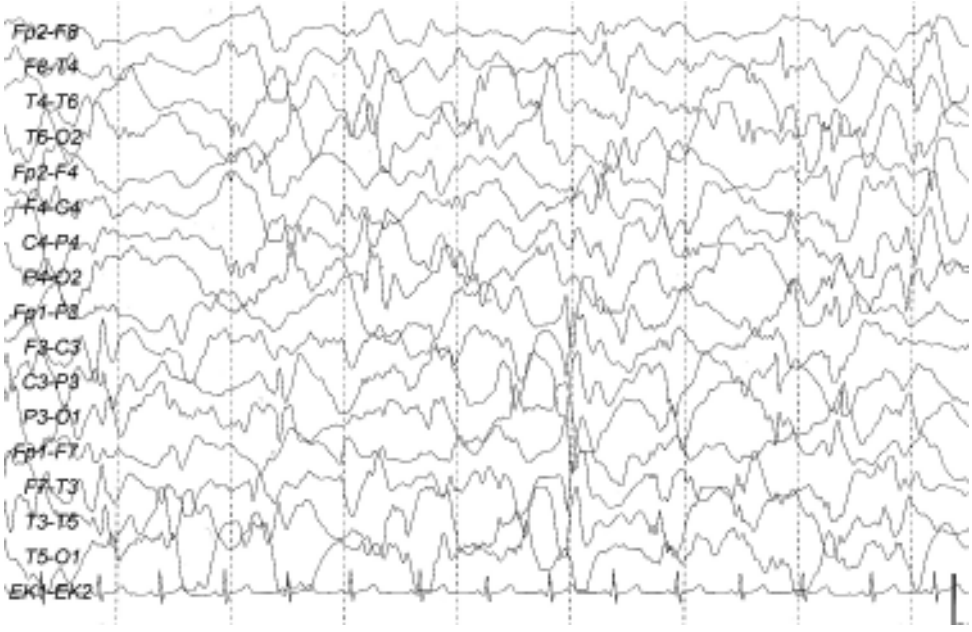


Figure 2. EEG showing hypsarrhythmia with disorganized background activity and random sharp wave/spike discharge.

Key Messages

- Consider NKH as the cause of intractable seizures in a neonate.
- The diagnosis of NKH requires CSF glycine level and CSF/blood glycine ratio, as the blood glycine level could well be normal.
- Sodium benzoate and dextromethorphan are useful in the management of NKH, in addition to a multitude of anti-convulsants.

A Pairs of Sibs with Dentatorubropallidoluysian Atrophy

Dr. WU Shun Ping
Department of Paediatrics, Queen Elizabeth Hospital

The index patient, a girl who presented to a paediatric department at 5 years old because of frequent falls, was noted to have regressed insidiously over the past 8 years. She exhibited moderate grade mental retardation, myoclonic epilepsy and increasing ataxia. Walking has become increasingly unsteady and difficult.

Her younger brother, who required resuscitation after birth with a diagnosis of "hypoxic-ischaemic encephalopathy", exhibited dystonia during the first year of life. His development is also significantly delayed. He is unable to speak or walk. His posture is increasingly dystonic. Choreo-athetosis is present.

Their parents are non-consanguineous. A first cousin of the patients (Figure 1) also suffers from severe grade developmental delay, severe dystonia and rigidity and epilepsy. She was found to have 3-methylglutaconic acid in the urine on several occasions. Non-specific type of 3-methyglutaconic aciduria was diagnosed basing on this finding.

MR brain study showed marked cerebellar atrophy (Figure 2). However there is no other diagnostic changes. EEG of the younger brother showed features compatible with myoclonic epilepsy.

DNA analysis was done for the index patient and her brother. They both showed abnormal expansion of CAG repeat in the DRPLA loci. The sister has 63 repeats and the brother has 64 repeats. Normal asymptomatic individuals would have less than 30 repeats. Thus the diagnosis of dentatorubropallidoluysian atrophy is made for the two patients. The parents of their cousin refused the DNA study. However in hindsight it is likely that their cousin also suffers from the same disease.

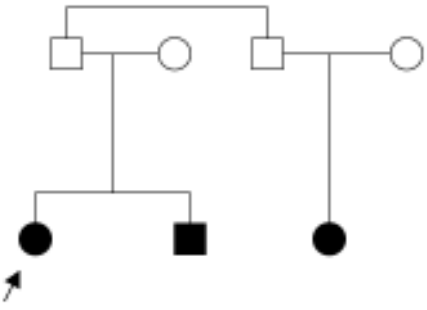


Figure 1. Pedigree of the index patient.

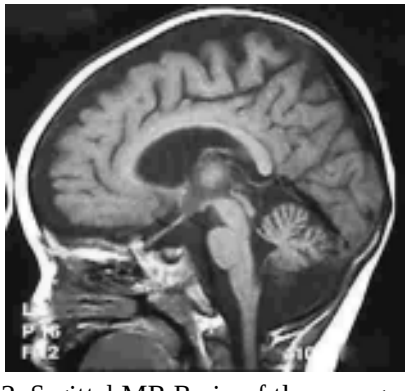


Figure 2. Sagittal MR Brain of the younger brother showing cerebellar atrophy.

Dentatorubropallidoluysian atrophy is a tri-nucleotide repeat disease. It shows the characteristic of anticipation, i.e., the symptoms become increasingly severe and the presentation became earlier and earlier as the number of CAG repeat increases down the family tree. This disease usually presents in teenage. The clinical presentation is a variable combination of dementia, dystonia, myoclonus, epilepsy, ataxia, chorea and athetosis. Thus this diagnosis should be considered when a combination of two or more these signs and symptoms. The two patients in this report are amongst the earliest presenters in the medical literature.

Addendum

The Clinical Genetics Service, Department of Health offers molecular genetic tests for a number of neurological conditions. The following is a list of them:

Disease	Gene(s) involved	Investigation
Fragile X syndrome	FMR 1	CGG expansion
Fragile XE syndrome	FMR 2	GCC expansion
Huntington's disease	IT15	CAG expansion
Friedreich Ataxia	X25	GAA expansion
Myotonic dystrophy	DMPK	CTG expansion
Spinocerebellar ataxia 1,2,3,6,7,12	SCA 1,2,3,6,7,12	CAG expansion
Spinocerebellar ataxia 8	SCA 8	CTG expansion
Dentatorubropallidoluysian atrophy	DRPLA	CAG expansion
Duchenne muscular dystrophy	DMD	Exon(s) deletion/duplication and carrier status/linkage analysis
Hereditary Sensorimotor neuropathy 1A	PMP22	Gene duplication
Pelizaeus-Merzbacher disease	PLP	Gene duplication
Prader-Willi syndrome	Chromosome 15	Microdeletion
Angelman syndrome	Chromosome 15	Microdeletion
Spinal Muscular atrophy	SMN	Exon deletion/carrier status
α-thalassaemia	α- globulin	Gene deletion/point mutation
Achondroplasia	FGFR 3	Point mutation
Hypochondroplasia	FGFR 3	Point mutation
Thanaophoric dysplasia	FGFR 3	Point mutation
Crouzon syndrome	FGFR 2	Point mutation
Neonatal Marfan syndrome	Fibrillin	Point mutation
Waardenburg syndrome type 1	PAX 3	Point mutation
Deafness	Connexin 26	Point mutation
MELAS, MERRF, NARP	Mitochondria	Point mutation
Adult polycystic kidney disease	PKD 1	Linkage analysis
Leri-Weill syndrome	SHOX	Deletion
Glutaric aciduria type 1	GCDH	Point mutation
Haemophilia A	Factor VIII	Gene inversion/linkage analysis
Familial incontinentia pigmenti	NEMO	Exon deletion/linkage analysis
Alport syndrome	COL4A5	Linkage analysis
Neurofibromatosis type 1	NF1	Premature termination
Pyruvate dehydrogenase deficiency	PDHA 1	Point mutation
Rett disorder	MECP 2	Point mutation
Gaucher disease	GCB	Point mutation

(Courtesy of Clinical Genetic Service, Department of Health)

Management of a Boy with Late Onset Ornithine Transcarbomylase Deficiency

Dr. C. H. KO
Department of Paediatrics, Caritas Medical Centre

A 7-month-old male infant presented with one day's history of repeated vomiting and increasing lethargy. The child had a change of milk formula to a high protein formula three days before admission. The total protein intake increased from 1.8 g/kg/day to 2.6 g/kg/day. He had no fever or evidence of intercurrent illness. He became progressively lethargic and developed coma 8 hours after admission. On examination, the child was hypotonic and was hyperventilating. His fundi were normal. There was no hepatosplenomegaly.

For his past heath, he was born in St. Teresa hospital at full term by vacuum extraction with a birth weight of 8 lb 2 oz. He had an uneventful perinatal history. He was the first child of the family. His parents were non-consanguineous.

Preliminary investigations were as follow:

- Urea 1.4 mmol/l, creatinine 41 μmol/l, Na 142 mmol/l, K 4.0 mmol/l
- pH 7.532, pCO_2 20.7, pO_2 136, HCO_3 17 mmol/l , BE -3.2 mmol/l
- Total bilirubin 16 μmol/l, ALP 331 iu/l, ALT 26 iu/l, albumin 40 g/l, glucose 6.1 mmol/l
- PT 16.1 s, APTT 35.8 s, INR 1.44
- CBP, ESR: normal
- Alpha thalassaemia trait
- Viral serology, sputum & blood culture: negative
- EEG: acute encephalopathic picture
- BAER & VEP: normal
- CT brain: normal
- NH4 = 484 μmol/L (reference 21-50)

The provisional diagnosis was urea cycle defect. The child was admitted to ICU and was put on mechanical ventilation. Sodium benzoate and arginine infusion were given. No dialysis was required. His serum ammonia decreased to 101 μmol/L 7 hours later, and further decreased to 25 μmol/L at 25 hours later. He regained full consciousness and was extubated on the next day.

Further investigations revealed:

- Plasma amino acid profile: glutamine 883 μmol/L (333-809), alanine 415 (120-600), citrulline 15 μmol/L (8-47), arginine 59 μmol/L (12-112), arginosuccinate <4 μmol/L (normally undetected), ornithine 15 μmol/L (20-136)
- Urine orotic acid = 2530 μmol/mmol Cr (0-3.7)
- Urine amino acid by HPLC: moderate hyperaminoaciduria with remarkable hyperexcretion of glutamine
- Molecular study: De novo mutation at codon 129 (CGT to CAT i.e. Arg129His) at the last nucleotide of exon 4 of ornithine transcarbomylase (OTC) gene, affecting splicing of intron 4 (reported residual OTC activities 2-3%). Both parents' genes do not contain the mutation.

The biochemical & molecular studies are diagnostic of late onset ornithine transcarbamylase deficiency. The child was then referred to the dietitian for counseling and maintained on protein restriction at 1.5 g/kg/day. He was also started on oral sodium benzoate, arginine, metabolic mineral mixture, and multivitamins. Subsequent follow up showed that the child suffered from no residual neurological sequelae. His neurodevelopment was appropriate for chronological age according to Child Assessment Centre assessment. His body weight was along 25% centile and his height at 97% centile. He had no further hyperammonemia attacks. Repeated plasma amino acid pattern 2 months later showed improvement: glutamine 750 μmol/L (333-809), alanine 685 μmol/L (120-600), arginine 56 μmol/L (12-112), ornithine 43 μmol/L (20-136).

The plan of management was to prevent hyperammonemia (keep normal plasma NH4, glutamine and arginine [both <800]), and provide adequate protein to support normal growth and development. Dietary protein restriction is the mainstay of treatment.

Dr CH Ko then shared with us the management protocol for suspected acute hyperammonemia:

1. Identify precipitating factors: infections, high protein intake, surgery, immunization. Identify clinical signs: recurrent vomiting, drowsiness, lethargy, irritability, ataxia, slurring, headache, opisthotonos, convulsions, hepatomegaly, deranged LFT, or coma.
2. Keep nil by mouth and allow no nitrogen intake. Start 10% dextrose infusion.
3. Confirm hyperammonemia by Ammonium Checker or at main laboratory. Discrepancy between the Ammonia Checker and the laboratory assay should always be correlated.
4. Priming infusion containing 0.2 to 0.8 gram/kg arginine hydrochloride, 0.25 gram/kg sodium benzoate in 20 ml 10% dextrose/kg over 1-2 hours.
5. Continuing infusion of 0.25 gram/kg sodium benzoate and 0.2 to 0.8 gram/kg arginine hydrochloride in 10% dextrose per 24 hours.
6. Avoid raised intracranial pressure. Administer mannitol.

7. If ammonia concentration rises during pharmacotherapy, start a second priming infusion while preparing to institute dialysis.
8. Consider haemodialysis if NH3 concentration not lowered within 8 hours. Peritoneal dialysis may also be useful though less

Dr. Ko highlighted the importance of maintaining a high index of suspicion for inborn error of metabolism in children presenting with impaired conscious state. A clue for the urea cycle defect would be the presence of low urea and/or hyperventilation. When a rapid diagnosis is made, appropriate treatment would reduce the incidence of subsequent neurological morbidity.

There was another case of ornithine transcarbomylase deficiency in a ten years old girl now under shared care by PWH & TMH. The girl first presented at six years old with confusion. There was on and off vomiting for several years before admission. NH3 was around 500 at first presentation. Dr. Ko explained to us that OTC deficiency in boys usually presented with acute decompensation and had relatively normal period in between, whereas the presentation would usually be subacute in girls. However the neurological outcome might be less optimistic in girls. This case was unusual in that OTC in boys classically presented at the newborn period and the ammonia level would be higher (~1000 μmol/L). This might be related to the particular mutation found in the molecular study. Correlation between the phenotypic presentation (such as severity of the disease) and the type of mutation had been reported.

Dr. Ivan Lo, from the Genetic Service, explained to us that molecular study for urea cycle defect was currently available from CUHK on a research basis.

Dr. Ko lastly shared with us a web-site for family support group at www.nudcf.org

Does He Need a Liver Biopsy?

Dr Winnie K. L. YAM
Department of Paediatrics, Alice Ho Miu Ling Nethersole Hospital

A 3 years boy, incidentally found to have raised ALT and AST during an episode of URI, had persistently elevated ALT & AST over a 6 months period (ALT 289-425 IU, AST 244-288 IU). Examination showed no stigmata of chronic liver disease. Splenomegaly of 2 cm was found.

Investigation ruled out infective, immunologic and metabolic causes (including α1AT). The only abnormal findings were:

1. CT abdomen: diffuse deposition disorder, L lobe of liver enlarged, spleen normal
2. CK 28240, LDH 3740

Further questioning reviewed that the child walked without support at 15-16 months of age, but had a history of easy falling and mild balancing problem. Parents and teachers were not worried. Examination showed pseudohypertrophy of calf. Gower sign was negative. Muscle biopsy confirmed Duchenne Muscle Dystrophy.

Discussion and Conclusion

1. Colleagues shared their experience that it was not uncommon for the elevated ALT to be due to muscle problem (such as muscular dystrophy or rhabdomyolysis) even though ALT was generally considered to be specific for hepatocellular injury. According to literature, the increase in ALT might be even greater than that of AST.
2. Occult muscular diseases should be considered in cases of isolated elevation of ALT/AST. The neurological findings might not be remarkable especially if the child was young.
3. Liver involvement or the CT finding of liver in DMD were not mentioned in most neurology textbooks. Literature search reviewed only one report of histologically confirmed hepatitis in children suffering from DMD. The long term prognosis of such cases were not known. It was suggested that the CT abdomen should be reviewed and/or repeated. Liver biopsy should be proceeded if the CT findings were persistent.

References

1. The role of liver in muscular dystrophy. - 1993 Italy
   "...Kin the presence of muscular dystrophy, a disease caused by structural defects of muscular membranes, also hepatocytes show ultrastructural defects. ...histological findings of hepatitis..."
2. Elevated aminotransferase activity as an indication of muscular dystrophy: case reports and review of the literature. - 1996 Canada
   "Five male children....ALT, generally considered to be specific for hepatocellular injury, was increased two to 25 times above normal in all the reported cases. Paradoxically, the increase in ALT activity was greater than that of serum aspartate aminotransferase... children with elevated serum ALT, in the absence of other signs and symptoms of hepatic injury, may have occult muscular disease--most frequently muscular dystrophy. ..."
3. Persistent hypertransaminasemia as the presenting findings of muscular dystrophy in childhood. - Taiwan 1999
   "....Five children (all boys)... between 4 months and 5.5 years. The neurological findings were all not remarkable. ..."
4. Diagnosis of occult muscular dystrophy: importance of the "chance" finding of elevated serum aminotransferase activities.-1993 USA
   ".... four children, including one girl...."
5. An unusual association: alpha-1-antitrypin deficiency and muscular dystrophy - Letter to editor:
   "...four cases.... Duchenne type of muscular dystrophy while two were of Becker type. ...in one of these patients, alpha-1-antitrypsin (alpha-1-AT) deficiency was also diagnosed...alpha-1-AT 0.24 (normal values: 0.8-2.1 g/L). .... Liver biopsy was also performed which showed chronic active hepatitis (hepatitis activity index: 8 according to Knodell). ..... "
6. Raised serum transaminases: not always liver disease - Letters to the editor - Arch Dis Child - 2000
   "...normal serum bilirubin, glutamyl transpeptidase, alkaline phosphatase, and albumin. The only abnormality was a persistently raised alanine aminotransferase (507 IU/litre) ... ...His liver, which was not enlarged, was palpable probably because of visceroptosis seen on ultrasound scan. ..."

Journal Watch

Early Development of Intractable Epilepsy in Children: A Prospective Study

Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B.

Neurology 2001;56(11):1445-62.

Early prediction of development of intractable epilepsy would allow physicians to consider patients for alternative treatment earlier. The authors set out to determine the risk of intractable epilepsy in newly diagnosed epileptic children prospectively and compare the relative importance of traditional epilepsy outcome predictors and other factors in the context of epilepsy syndrome.

This is a cohort study of children who were first diagnosed to have epilepsy (first unprovoked seizure between 1 month and 15 years of age, have at least two unprovoked seizures on separate days and be newly diagnosed during recruitment period) (n=613) recruited in paediatric/adult neurology practices (academic/private/community clinics) in Connecticut between January 1993-December 1997. They were followed for the development of intractable epilepsy (failure of >2 first line anti-convulsants, >1 seizure/month for over 18 months or intolerable adverse reaction from two anti-convulsants and poor control from one other).

The mean follow period was 36 months (median 4.8 year) and 97.7% of the total were followed for longer than 18 months. 10.0% met the criteria of intractability within two years of initial diagnosis of epilepsy. Four children who developed intractability after four years or more excluded.

Factors including epilepsy syndrome, aetiology and the traditional epilepsy outcome predictors like age, sex, neuro-imaging abnormality, seizure types, initial seizure frequency, seizure numbers, history of neonatal seizures, selected EEG abnormalities were compared. Syndromic grouping ($p<0.001$) and aetiology ($p<0.001$) were strongly correlated with the risk of intractability. The risk was highest in the cryptogenic/symptomatic group (34.6%), lowest in the idiopathic group (2.7%); and intermediate in the other location-related (10.7%) and unclassified group (8.2%) ($p<0.001$). After multivariable adjustment for epilepsy syndrome, initial seizure frequency ($p<0.001$), acute symptomatic or neonatal status epilepticus ($p= 0.001$) and focal EEG slowing ($p=0.02$) were associated with increase risk of intractability whereas absolute number of seizures initially was not.

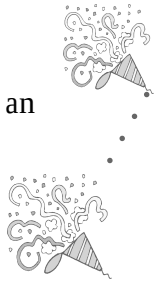
This is a well-conducted prospective cohort study with well-defined sample of patients and clear outcome criteria. It provided useful criteria in identifying children at greatest risk of intractable epilepsy. However it was not clear whether all the subjects were at the pre-treatment stage i.e. at the similar point in the course of the disease, when they were recruited as previous treatment may alter the outcome. The authors adopted a clear and simple and sensible definition of intractable epilepsy. Unfortunately there has been no uniformly accepted definition of intractable epilepsy, the diagnosis of which often needs to be individualized with factors like patients age, seizure type, developmental status and lifestyle. The age distribution of the subjects recruited showed a highest incidence in the 5-9 year

age group. This is different from the common observation that the incidence of paediatric epilepsy shows a bi-modal distribution, highest in the infancy and late childhood. The extent of representation of the patient sample needs to be considered. As the authors noted there were four children who developed late intractability after 4 years. The average follow up period of 36 months in the study would potentially fail to capture children with late intractability. A longer term follow study would be useful. It would also be interesting to analyze and compare the characteristics of those patients who develop late intractability versus early intractability.

(Reviewed by Dr. Sharon Cherk, Department of Paediatrics, Kwong Wah Hospital, Kowloon)

News of the Society

Welcome New Members



The Council welcomes a new Affiliate member, Miss YUE Yee Wah, Eva, an occupational therapist of United Christian Hospital.

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New Council Service Term in 2002

During the Annual General Meeting 2002, scheduled for May 2002, new Council members will be selected to serve a new term when the current Council abdicates. All full members are eligible for bearing office. Please consider volunteering your service to the community of child neurologists and developmental paediatricians. The Society is, after all, advocating for the welfare of all children with neurological and developmental problems. Your service is therefore of utmost importance to them.

The nomination will soon be open. Please watch for upcoming notices.

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Neurology Conference (previously known as the Case Management Study Group)

This conference is a platform for bringing up difficult and interesting cases to discuss amongst colleagues from various hospitals and private sector. The next meeting is scheduled for 9 April 2002, 7 pm at the Lecture Theatre, D Block Ground Floor, Queen Elizabeth Hospital. If you would like to share your intriguing clinical cases with your colleagues please contact Dr Winnie Yam at wusp@ha.org.hk at least one week prior to the meeting.

Annual Scientific Meeting 2002

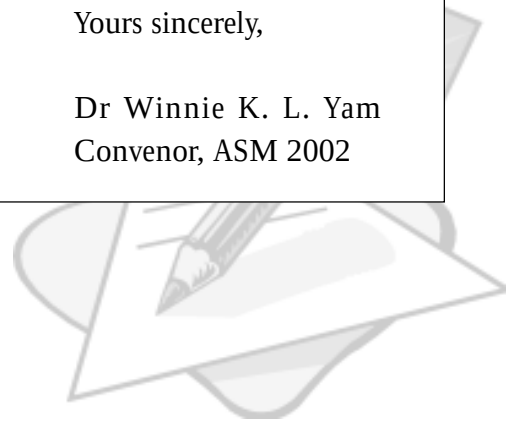
Re: HKCNDP – Annual Scientific Meeting 2002
"Paediatric Neuro-Ophthalmology"

It is our pleasure to inform you that our Annual Scientific Meeting, originally scheduled on 12-15 October, 2001, will now be held on 8-11 March, 2002. The theme of the meeting will remain "Paediatric Neuro-Ophthalmology". Our Course Director will be the world famous Dr David S. I. Taylor from the Visual Sciences Unit, Institute of Child Health, London, UK. He is also currently the Consultant at the Department of Ophthalmology, Great Ormond Street Hospital for Children NHS Trust, UK. There will be a series of seminars on topics of interest to be held on 8-11 March, 2002. The highlight of the meeting will be a Plenary Lecture on "The Apparently Blind Child" to be held in the evening of 11 March, 2002 at the Great Eagle Hotel, Kowloon. Enclosed please find the preliminary scientific programme of the meeting.

You will soon receive the posters, scientific programme, registration form and call for abstract. Please kindly mark your dairy first! We look forward to meeting you at this coming academic function!

Yours sincerely,

Dr Winnie K. L. Yam
Convenor, ASM 2002



HKCNDP
Annual Scientific Meeting 2002
8-11 March 2002

Scientific Program
Topic : "Paediatric Neuro-Ophthalmology"

	Friday 8 March	Saturday 9 March	Sunday 10 March	Monday 11 March
Venue	G/F, Block M QEH	G/F, Block M QEH	G/F, Block M QEH	Great Eagle Hotel
AM			Seminar III (9:30-12:30) "Peculiar Visual Images" - Dr David Taylor Local Presentation 1."Developmental Management of Severe Visual Impairment - Experience of Child Assessment service" - Dr Iris Lau 2. "Assessment and Management of Strabismus and Amblyopia in Children" - Ms Frenchy Chiu	
Lunch		12:30-14:00	12:30-14:00	
PM		Seminar II (14:00-17:00) Local Presentation: 1. "Acquired VI n Palsy in Children - a Benign Case and a Not-so-benign Case" - Dr CY Ko 2. "Paediatric Ophthalmic Assessment for Children with Severe, Multiple Disabilities" - Dr CH Ko "Eye Movement Disorders and Strabismus Syndromes" - Dr David Taylor	Seminar IV (14:00-17:00) Free Paper Session "Retinal Disease - When Do I Call the Neurologists?" - Dr David Taylor	
Evening	Seminar I (20:00-22:00) "Optic Nerve and the Brain" - Dr David Taylor			Plenary Lecture (20:00-22:00) " The Apparently Blind Child" - Dr David Taylor