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Aetiology-based Management in Paediatric Epilepsy

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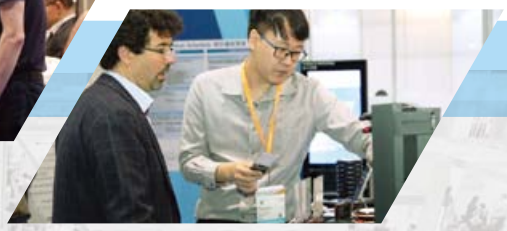

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The Cover Shot

An Orchid

Macro photography opens our eyes to the world of minuscule wonders of colours and shades. It is a form of photography by the original definition - size of subjects captured on negatives or digital sensors in their life size or larger. With the advent of digital photography, image display could be zoomed in to create a macro photograph with decent resolution at ease. But it is not the magnification per se that makes macro photography attractive. The secret is in the lens - close focus distance all the way down to a high reproduction ratio and the narrow depth of field.

Minute details and awe-inspiring texture, often unnoticed with the naked eye, are brought in full view while those outside the focal plane of interest would be blurred and replaced by a colourful bokeh, further supporting and enhancing the whole photograph with substance.

This orchid was shot with a Summilux-M 1:1.4/35 to a Macro-Adaptor-M on a Leica M (Type 240). B & W photography is much easier these days with digital photography. Instead of carrying around the full set of colour filters like in the old days with films, the best effect could be chosen on softwares at the post-production editing. This monochrome, hopefully gives the audience a different feel about the orchid, equally majestic even without its colourful coat.

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Editorial

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Editor

Dr Mario Wai-kwong CHAK

It is my pleasure to serve as the Issue Editor of this May issue of the Hong Kong Medical Dairy. The theme of this issue is "Aetiology-based Management in Paediatric Epilepsy". The reason I have chosen this theme is that paediatric epilepsy is a heterogenous disease with diverse underlying aetiologies. Along with significant advances in understanding the neurobiology of seizures and epilepsy diseases, there have been major paradigm shifts in the concepts underpinning classification. The new, more precise classification of various epilepsy, has led the way to improved diagnosis, better understanding of aetiology, and targeted therapies tailored to the patients' disease. Choice of therapy not only is limited to anti-epileptic medications, but also includes surgical and dietary treatments, especially in children and adolescents with medical refractory epilepsy. Unlike the old days when we managed epilepsy empirically with trails of medical treatment, we now, based on better understanding of the underlying aetiologies, can offer more tailor-made treatments to individual patients, which in turn enables improvement in seizure control, cognitive outcome and hence patients' quality of life. I do hope that from the moment that a patient presents with a first epileptic seizure, the clinician should be aiming to determine the aetiology of the patient's epilepsy. A range of aetiologic groups have been recognised, with emphasis on those with implications for treatment.

Our contributing authors are all distinguished local experts in their respective fields. I myself, a paediatric neurologist/epileptogist, will present the "New ILAE Classification of Seizure and Epilepsies" and share the international recommendation and local experience in how the underlying aetiologies guide the surgical and dietary management of paediatric refractory epilepsy. Dr Liz Yuet-ping Yuen, Dr Hoi-ning Cheung and Dr Yu-kwan Tong, an expert team of chemical pathologists, will share with us their experience in "Early Infantile Epileptic Encephalopathy and Clinical Use of Next-Generation Sequencing-Based Genomic Test"; Dr Sui-to Wong, a paediatric neurosurgeon, will discuss the "Surgical Treatment of Drug-resistant Epilepsy due to Focal Cortical Dysplasia". Dr Amanda Nim-chi Kan, an anatomical pathologist will enlighten us on the "New ILAE Classification of Focal Cortical Dysplasia-Neuropathological Perspective". Ms Yvonne Kwok and Ms Candy Wong, hospital dietitians, will share with us "Ketogenic Dietary Treatment in Epilepsy". Dr Venus Tam, a child psychiatrist, will share with us on "Executive Dysfunction and Psychiatric Co-morbidity in Childhood Epilepsy". Last but not least, I must thank Dr Dawson Fong for his beautiful photo of Orchids as our cover photo of this issue of the Medical Diary. I sincerely hope that you all find these articles interesting and useful in your clinical practice.

The New 2017 ILAE classification of seizure types and the epilepsies; The evolution of concepts and terminologies; How aetiologies guide the management in Paediatric Epilepsy?

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 May 2018.

What is a seizure?

A seizure is defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[1]"

Because current knowledge in seizure is insufficient to form a scientifically based classification, the updated 2017 ILAE Classification of seizure is operational (practical) and based on the 1981 Classification.[2]

Changes in classification of seizure in 2017

On focal seizures

- The term "partial" seizure has been changed to "focal" seizure.
- Focal seizures have been newly classified by first clinical manifestation.
- Awareness is used as a surrogate for consciousness and used as a classifier of focal seizures.[2,3]

On the spectrum of seizures

- The terms "dyscognitive", "simple partial", "complex partial", "psychic", and "secondarily generalized" have been eliminated.
- Atonic, clonic seizure or epileptic spasms and myoclonic or tonic seizure can be either focal or generalized.
- "Focal to bilateral tonic-clonic seizure" replaces "secondarily generalized seizure".
- Certain seizure types can be either of focal, generalised, or unknown onset.
- New focal seizures include automatism, autonomic, behaviour arrest, cognitive (e.g. language impairment, déjà vu, hallucination, perceptional distortions), emotional (e.g. anxiety, fear, joy), hyperkinetic, sensory, and focal to bilateral tonic-clonic seizures.
- New generalisd seizure types include absence with eyelid myoclonic absence, myoclonic-tonic-clonic (e.g. JME), myoclonic-atonic (e.g. Doose syndrome), and epileptic spasms (Infantile spasm).
- Seizure of unknown onset may have features that can still be classified.[2,3]

Fig. 1. ILAE 2017 Classification of Seizure Types Expanded Version[3]

1. Degree of awareness usually is not specified.
2. Due to inadequate information or inability to place in other categories

Epilepsy Classification

Introduction

The ILAE Classification of the Epilepsies has been updated to reflect our gain in understanding of the epilepsies and their underlying mechanism following the major scientific advances that have taken place since last ratified classification in 1989.[4]

Seizure type - First level

- Assuming that the clinician has already made a definite diagnosis of an epileptic seizure.
- Classified into focal onset, generalized onset, and unknown onset.
- In some settings, classification according to the seizure type may be the maximum level possible for diagnosis as there may be no access to EEG, video and imaging studies.[4]

Epilepsy type - Second level

Includes:

1. Generalised Epilepsy

- Typically, EEG shows generalized spike-wave activity.
- It is inclusive of a wide range of seizure types, such as absence, myoclonic, atonic, tonic, and tonic-clonic seizures.[4]

2. Focal Epilepsies

- They include unifocal or multifocal disorders and seizures involving one hemisphere.
- They involve a range of seizure types including focal aware seizures, focal impaired awareness seizures, focal motor seizures, focal non-motor seizures, and focal to bilateral tonic -clonic seizures.
- Typically, the EEG shows focal inter-ictal epileptiform discharges.
- The diagnosis is made on clinical grounds, supported by EEG findings.[4]

3. Combined Generalised and Focal Epilepsies (New Group)

- It requires the presence of both focal and generalised seizures.
- The diagnosis is made on clinical grounds, supported by EEG findings.
- Ictal recordings are helpful but not mandatory.
- Inter-ictal EEG shows both generalisd spike-wave and focal epileptiform discharges, but epileptiform activity is not essential for diagnosis.
- Common examples are Dravet syndrome and Lennox-Gastaut syndrome.[4]

4. "Unknown"

The patient suffers from epilepsy but the clinician could not determine if the epilepsy type is focal or generalised because of inadequate information available.[4]

New Recommendation:

When the clinician is unable to make an Epilepsy Syndrome diagnosis, the epilepsy type may be the final achievable level of diagnosis.[4]

Epilepsy Syndrome - Third level

- Medical syndromes in general are characterised by a constellation of symptoms and signs that tend to occur together.[4]
- Epilepsy Syndrome needs to fulfill the specific criteria in the following aspects: age of onset of seizure, seizure types, patient developmental milestones, patient intelligence and memory function, family history, specific EEG background and inter-ictal +/- ictal EEG findings, neuroimaging findings and aetiology.
- All these clinical details are important to be ascertained because different syndrome are associated with different prognosis and response to treatment.[5]
- A good illustrated example is Landau Kleffner Syndrome, in which patients usually present as acquired language regression with onset around 3-5 year of age with subtle atypical absence seizure and normal MRI brain imaging findings. EEG shows electrical status during slow wave sleep. Apart from using anti-epileptic drug such as valproate and benzodiazepines, these patients require specific treatment include corticosteroid, intravenous immunoglobulin or ketogenic diet in order to normalize EEG, stop epileptic aphasia and improve long term speech outcome. [6]

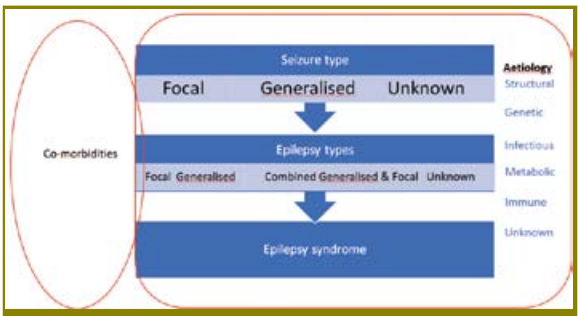


Fig. 2. Framework of Classification of Epilepsies [4]

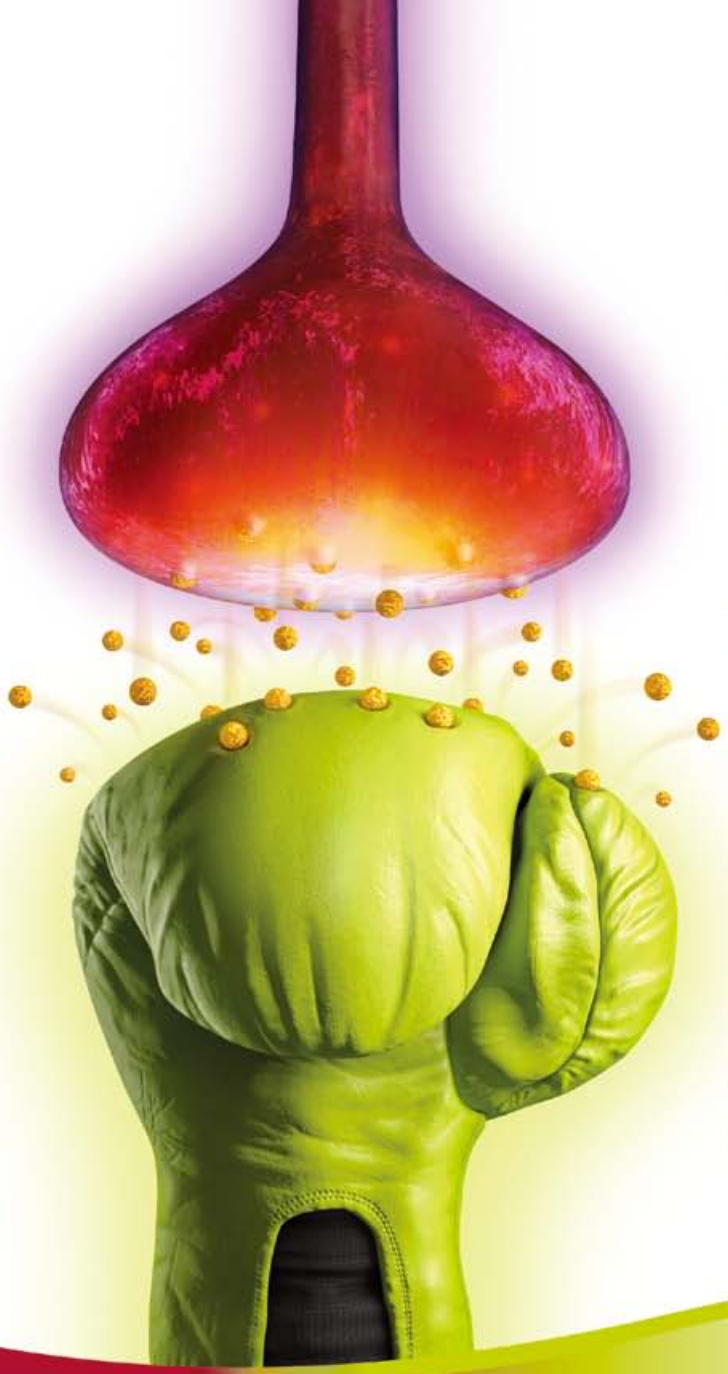
Change of Terminology in Epilepsy Syndrome

The Task Force has decided that

- **Idiopathic Generalised Epilepsy** is used specifically for the group of four epilepsy syndromes: Childhood Absence Epilepsy, Juvenile Absence Epilepsy, Juvenile Myoclonic Epilepsy, and Generalised Tonic–Clonic Seizures Alone.[4]
- **Genetic Generalised Epilepsy** may be used in individual cases where the epilepsy involves a genetic aetiology.[4]
- The term "**benign**" as a descriptor for epilepsy is no longer use because some "benign" epilepsy such as Childhood Absence Epilepsy and Benign Rolandic Seizure have been associated with psychosocial impact and learning problems respectively.[7,8]. "Benign" is now replaced by both "self-limited" and "pharmacoresponsive," each replacing different components of the meaning of benign.[9]
- **"Self-limited" epilepsy syndrome is defined by** the likely spontaneous resolution of a syndrome, usually in the form of sefl-limited focal epilepsies. Examples include epilepsy with centrotemporal spikes, formerly called "benign epilepsy with centrotemporal spikes, self-limited occipital epilepsies of childhood, both the early-onset form and the late-onset.[10]
- **"Pharmacoresponsive" epilepsy syndrome is defined by** the likely control with appropriate antiepileptic drug treatment.[4]
- The terms "malignant" and "catastrophic" are no loinger being used because of their serious and devastating connotations.[4]

Aetiology

- The new classification incorporates aetiology along each stage, emphasizing the need to consider aetiology at each step of diagnosis i.e. seizure level, epilepsy level, and epilepsy syndrome level.[4]
- Owing to potential treatment implications, aetiology is divided into six subgroups.[4]
- A patient's epilepsy may be classified into more than one aetiologic category; the aetiologies are not hierarchical.[4]



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- For example, patients with Rasmussen's encephalitis has both a structural and an immune aetiology; the structural aetiology is critical for epilepsy surgery, whereas the immune aetiology is key for immunotherapy.
- For example, a patient with GLU-1 deficiency has both genetic and metabolic aetiologies.

Structural aetiology

- The presence of visible abnormalities in structural neuroimaging which correlate with electro-clinical findings lead to a reasonable inference that the imaging abnormality is the likely cause of the patient's seizures i.e. epileptogenic lesions.[4]
- The acquired epileptogenic lesions includesuch as stroke, mesial temporal sclerosis, arteriovenous malformations, hypoxic-ischaemic encephalopathy, cavernous hemangioma, post-traumatic lesions, and CNS infections.
- The congenital epileptogenic lesion(s) can arise from tuberous sclerosis or malformation of cortical development, which in turn include a wide range of pathologies such as focal cortical dysplasia, hamartoma, porencephaly, ulegyria, subcortical band heterotopia, lissencephaly, polymicrogyria, schizencephaly, hemimegaloencephaly.
- Specific MRI epilepsy protocols are required to detect a subtle epileptogenic lesion.[11]
- Some of the above epileptogenic lesions are potentially surgically remediable and need to be referred to expert tertiary centre for pre-surgical evaluation and for consideration of early epilepsy surgery if the patient's epilepsy has failed medical therapy.
- In a small local case study, ketogenic diet is effective in seizure control in one patient with medical refractory epilepsy due to post-HIE epilepsy and in another patient with extensive focal cortical dysplasia over dominant hemisphere not amenable to epilepsy surgery.[12]

Genetic aetiology

- If there is positive family history of an autosomal dominant disorder in a neonatal seizure, consider Benign Familial Neonatal Epilepsy with either KCNQ2 or KCNQ3 mutations.[13]
- Clinical research in patients with the same syndrome has revealed genetic conditions such as Childhood Absence Epilepsy or Juvenile Myoclonic Epilepsy.[14,15]
- Use of molecular testing has helped to identify pathogenic copy number variants causation of epilepsy. In 30–50% of infants with severe developmental and epileptic encephalopathies, causative mutation in epilepsy genes, usually sporadic with de novo mutation, has been identified based on molecular genetics.[16] An example in point is Dravet syndrome in which >80% of the patients have a pathogenic variant of SCN1A.
- A monogenic aetiology such as KCNQ2 mutations may cause a spectrum of epilepsy with different degree of severity ranging from mild epilepsy in Benign Familial Neonatal Seizure (BFNS) to severe KCNQ2 encephalopathy with medical refractory epilepsy and psychomotor retardation.[17]
- Dilena et al reported a 10-month old patient with medical refractory epileptic encephalopathy with underlying STXBP1 mutation who showed dramatic response and became seizure-free with normal EEG after having been put on Levetiracetam.[18]

Infectious aetiology

- This aetiology applies to patients with epilepsy but is exclusive of acute symptomatic seizure occurring during CNS infection.[4]
- Examples include neurocysticercosis and tuberculosis, both of which will require specific treatment.[4]
- Other scenarios under infectious aetiology include congenital cytomegalovirus infections and post-infectious development of epilepsy, such as Influenza encephalopathy leading to seizures after the acute infection.[4] In a small local case study, patient with medical refractory epilepsy with cytomegalovirus infection and influenza encephalopathy showed improved seizure control after ketogenic diet.[11]

Metabolic aetiology

- This aetiology refers to a well delineated metabolic defect with manifestations or biochemical changes throughout the body such as GLU-1 deficiency, Succinic semi-aldehyde dehydrogenase deficiency (SSADH), Maple syrup urine disease or Mitochrondrial cytopathy.[4]
- Metabolic aetiology usually reflects an underlying genetic basis, but at times it may be acquired such as in cerebral folate deficiency.[4]
- In a small local case study, ketogenic diet is effective in seizure control of in one patients with medical refractory epilepsy due to SSADH and in another patient with Leigh's disease (complex I & IV respiratory chain enzyme deficiency).[11]

Immune aetiology

- Immune aetiology implies there is evidence of autoimmune-mediated central nervous system inflammation.[4]
- Examples include NMDA receptor encephalitis, for which first-line immunosuppressive treatment include intravenous immunoglobulin, intravenous high dose steroid, +/- plasmapheresis; second-line treatment using rituximab is called for should response to first-line treatment be considered suboptimal.[19]
- In a local case study, high dose steroid together with ketogenic diet has been shown to be effective in reducing seizure in a patient with Familial Haemophagocytic Lymphohistiocytosis initially presenting with neurological manifestation (developmental regression, ataxia and status epilepticus), with neuro-imaging showing extensive grey and white matter inflammation.[12]

Unknown aetiology

- Applied to epilepsy conditions in which the cause of the epilepsy is not yet known.[4]

New Terminology

Developmental Encephalopathy describes the condition where there is only developmental impairment without frequent epileptic activity associated with regression or further slowing of development. There are several different ways of manifestations.[4] Firstly, developmental delay may precede seizure onset. A well-known example is Dravet syndrome, in which developmental slowing or regression occurs between 1 and 2 years of age, at a time when epileptiform activity on EEG is not frequent yet. This suggests a developmental component in addition to an epileptic component.[4] Secondly, even though seizures stop, the developmental outcome is still poor. In some patients with KCNQ2 encephalopathy or STXBP1 encephalopathy, the epilepsy may settle down relatively in early age, but the developmental consequences may remain profound.[4]

Epileptic Encephalopathy refers to the scenario when epileptic activity itself contributes to severe cognitive and behavioral impairment above and beyond that expected from the underlying pathology; these impairments can worsen over time.[20] It strictly refers to an epileptic condition where there is no preexisting developmental delay and the genetic mutation is not thought to cause slowing in its own right.[4]

Developmental and Epileptic Encephalopathy describes the condition where both factors of genetic mutation and epileptic activity play a role in regression or further slowing of development.[4]

Paediatric Epilepsy Surgery

Such surgery refers to the resection/ disconnection of brain epileptogenic tissue with the aim to improve seizure control.

Goal:

At present, the goal of surgery in children is to achieve seizure control, with the potential for the added benefit of improved neurodevelopment.

Indications for referral:[21]

- Children with seizures that are uncontrolled by medical treatment (i.e. failure of two or three appropriate drugs) or are disabling (including medication side effects).
- Patients with MRI findings of a lesion potentially amenable to surgical removal.
- Patients with stereotyped or lateralised seizures or other evidence of focality that cannot be definitely attributed to idiopathic partial epilepsies.
- Childhood epilepsy that cannot be classified as a clearly defined electroclinical epilepsy syndrome (ILAE classification).

Special considerations

Children with intellectual disability, developmental delay, psychiatric disease, or at a very young age should not be excluded from being considered surgical candidates.

- Developmental arrest or progressive disturbances in cognitive function, behaviour, and psychiatric state (epileptic encephalopathy) are common findings in pre-epilepsy surgery assessment and these findings can influence the decision for surgical management.
- Early surgical intervention is critical in infants with catastrophic epilepsy in order to avert developmental arrest/regression.[22,23]
- A subgroup of Paediatric epilepsy surgery candidates, namely those patients with extremely complex presentation or early catastrophic seizures, should be served at Paediatric Surgical centres with advanced technologic capability and multidisciplinary dedicated expertise.[21]

Pre-surgical evaluation

Aims:

- To select candidates for epilepsy surgery.
- To establish the medical intractability of the epilepsy (pharmaco-resistance).
- To confirm the diagnosis of focal epilepsy.
- To identify a possible aetiology for the focal epilepsy.
- To determine the feasibility (i.e. risks and benefits) and safety of possible surgical intervention.

Multi-Modality Evaluation/ Investigations:

- Inter-ictal scalp EEG including natural sleep recording.
- Video-EEG recording for Ictal events .
- Invasive electrode studies are indicated primarily to localizse the epileptogenic region when alternative methods are inconclusive.
- MRI with a specific epilepsy protocol. Specific MRI sequences may be required in the first 2 years of life because of immature myelination, and serial scans may be necessary to identify abnormalities during early postnatal brain development.
- A computed tomography (CT) scan is indicated under specific circumstances (e.g. possibility of calcification).
- Ictal and inter-ictal single photon emission CT (SPECT), PET
- Pre-and post-surgery neuropsychological/developmental/Psychiatric assessment is crucial in view of high incidence of neurodevelopmental and mental health disorders in paediatric epllepsy surgery candidates.[21]

Common Surgical Remediable Syndrome in Children

- Hippocampal Sclerosis
- Developmental Tumour (DNET, Ganglioglioma)
- Hemispheric Syndrome (Rasmussen's Encephalitis, Unilateral Procephalic Cyst/ MCA Infarct, Hemispheric Cortical Dysplasia, Hemimegalencephaly)
- Sturge-Weber Syndrome
- Hypothalamic Hamartoma
- Focal Cortical Dysplasia
- Cavernous Haemangioma

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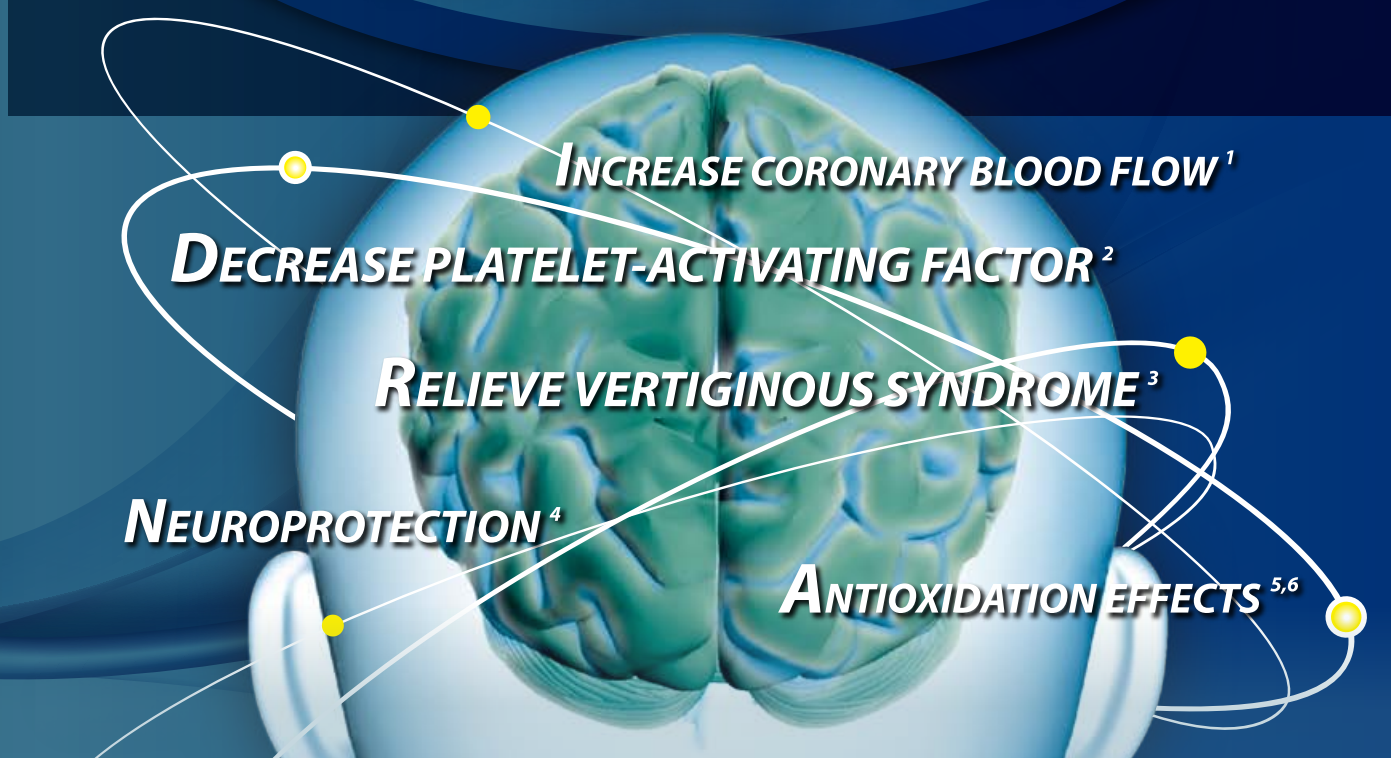

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1. Wu Y, Li S, Cui W, et al. Ginkgo biloba extract improves coronary blood flow in healthy elderly adults: role of endothelium-dependent vasodilation. Phytomedicine 2008;15:164-169. 2. Akisü M, Kültürsay N, Coker I, et al. Platelet-activating factor is an important mediator in hypoxic ischemic brain injury in the newborn rat. Biol Neonate 1998;74:439-444. 3. Haguenauer JP, Cantenot F, Koskas H and Pierart H. (1988) Treatment of disturbed equilibrium with Ginkgo biloba extract. In: Fünfgeld EW. Rökan (Ginkgo Biloba). Recent Results in Pharmacology and Clinic. (pp. 260-268). Springer-Verlag Berlin Heidelberg New York. 4. Lee EJ, Chen HY, Wu TS, et al. Acute administration of ginkgo biloba extract (EGb 761) affords neuroprotection against permanent and transient focal cerebral ischemia in Sprague-dawley rats. J Neurosci Res 2002;68:636-645. 5. Le Bars PL, Kieser M, Itil KZ. A 26-week analysis of a double-blind, placebo-controlled trial of the ginkgo biloba extract EGb 761® in dementia. Dement Geriatr Cogn Disord 2000;11:230-237. 6. Pietri S, Séguin JR, d'Arbigny P, et al. Ginkgo biloba extract (EGb761) pre-treatment limits free radical-induced oxidative stress in patients undergoing coronary bypass surgery. Cardiovasc Drugs Ther 1997;11:121-131.

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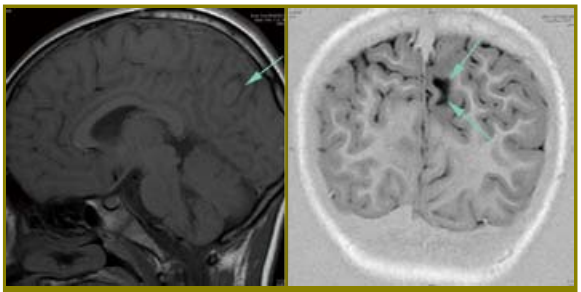

Fig. 3 & 4. MRI brain of a teenager with refractory epilepsy showed suspected Focal Cortical Dysplasia at left cuneus.

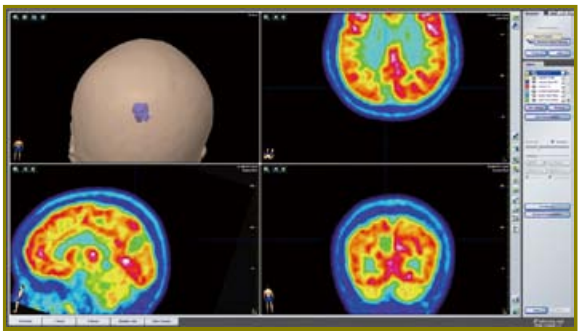

Fig. 5. Inter-ictal FDG PET showed area of hypometabolism in left cuneus in Brain Navigation system. Patient became seizure-free after resective surgery. Pathology showed focal cortical dysplasia IIB.

In patients with medical refractory epilepsy, Continuing trial of anti-epileptic drugs vs surgical treatment; How to choose?

When compared with continued medical treatment, a randomised control study showed that surgical treatment had a higher chance to let patients with refractory temporal lobe epilepsy become seizure free. Children having undergone temporal lobe resections were more likely to achieve seizure freedom than those with extra-temporal lobe resections.[24]

What is the seizure outcome after epilepsy surgery?

According to the retrospective long term study of a local paediatric referral centre, 81% of patients with temporal lobe epilepsy surgery were reported to be seizure-free versus 57% patients with extra-temporal lobe epilepsy surgery. When the patients became seizure-free after epilepsy surgery, their anticonvulsants would be gradually weaned off, but not all would guarantee success. In temporal lobe epilepsy surgeries, 52% of patients were anticonvulsant-free and 24% of patients were with anticonvulsant reduction. While in extra-temporal lobe epilepsy, 12% of patients were anticonvulsant-free and 37% were with anticonvulsants reduction.[25]

Not all medical refractory epilepsy patients are candidates for epilepsy surgery What is the next alternative treatment?

Vagus nerve stimulation (VNS) Implantation

- In children and young people who are refractory to anti-epileptic medications but who are not suitable for resective surgery, VNS is indicated for use as an adjunctive therapy in reducing the frequency of seizures.
- This includes children and young people whose epileptic disorder is dominated by focal seizures (with or without secondary generalisation) or generalised seizures.[26]
- Side effects usually transient and well-tolerated include voice alteration, hoarseness of voice, cough, stomach upset, pain, tingling sensations, nausea, and headache.[27]
- It is a palliative procedure with a response rate of 50% reduction in seizure frequency in one third to one half of patients.[28,29]
- The efficacy may increase with time of post implantation.[28,29]
- VNS may be considered for seizures in children for Lennox Gastaut associated seizure (>50% seizure reduction in 55% (95% CI 46-64%) of 113 patients with Lennox-Gastaut Syndrome in 4 Class III Studies).[29]
- In a small local case series, patients with refractory epilepsy after VNS Implantation had >50% seizure reduction with aetiologies of post-FIRES epilepsy, Lennox Gastaut Syndrome, Symptomatic Generalised Epilepsy; No change in seizure with aetiologies of Subcortical band Heterotropia, Bilateral Mesial Temporal Sclerosis. In terms of seizure type, significant reduction in generalsied tonic clonic seizure, less reduction in complex partial seizure. Apart from potential in improved seizure control, one patient with post-FIRES epilepsy had significant reduction in duration of post-ictal drowsiness, hence improved quality of life. Most patients reported no side effects; only mild transient tolerable side effects of hoarseness of voice and throat discomfort were reported from 2 patients.[28]

Ketogenic diet (KD) in children and young people

- Refer children and young people with epilepsy whose seizures have not responded to appropriate anti-epileptic drugs (AEDs) to a tertiary paediatric epilepsy specialist for consideration of the use of a ketogenic diet.[32]
- Ketogenic Diet is a high fat, low carbohydrate diet that mimics starvation to force the body to use fat as energy instead of carbohydrate and to produce ketones to improve seizure control.
- Ketogenic Diet is a strictly calculated medically supervised therapeutic diet that has proven efficacy for treatment of medical refractory epilepsy. A randomized controlled trial from the United Kingdom found that 38% of children had a substantial (>50%) seizure reduction and 9% had a >90% reduction in seizures.[33]
- KD is the treatment of choice in patients with GLUT 1 deficiency.

- KD is contraindicated in fatty acid oxidation and pyruvate carboxylase disorders.
- KD is the treatment option for patients with Lennox Gastaut syndrome, atonic seizure, myoclonic seizure, and symptomatic focal epilepsy after failure of surgery.[34]
- In a local small case series, KD was found to be effective (>75 % seizure reduction) in refractory paediatric epilepsy patients with Congenital CMV Infection, Focal Symptomatic Epilepsy with suspected extensive Focal Cortical Dysplasia over dominant hemisphere not amenable to epilepsy surgery, Leigh´s disease (Complex I&IV respiratory chain enzyme deficiency), Post-HIE epilepsy, Familial Haemophagocytic Lymphohistiocytosis, Succinic semi-aldehyde Dehydrogenase Deficiency, Influenza Encephalopathy, Landau Kleffner Syndrome.[12] A local case study showed KD is more effective in stopping Electrical Status Epilepticus During Slow Wave Sleep and language regression in Landau Kleffner Syndrome with better patient tolerability and less long-term side effect when compared with monthly Intravenous Immunoglobulin and Pulse Intravenous Methylprednisolone.[6]
- Patients on KD should be taken care of by Paediatric Neurologists and Dietitians who are experienced in dietary management of epilepsy to monitor patient seizure response and look for any side effects.
- Side effects: Constipation, GI upset, hypoglycaemia, metabolic acidosis, hyperketosis, dehydration, prone to infections, renal stone, hyperlipidaemia, hypercalciuria, trace element and Vitamin deficiency, weight change, osteoporosis.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "The New 2017 ILAE classification of seizure types and the epilepsies; The evolution of concepts and terminologies; How aetiologies guide the management in Paediatric Epilepsy?" by Dr Mario Wai-kwong CHAK and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 May 2018 Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. In ILAE Classification of Seizure 2017, the terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalised are eliminated.
2. In ILAE Classification of Seizure 2017, focal to bilateral tonic– clonic seizure replaces secondarily generalised seizure.
3. In ILAE Classification of Epilepsy 2017, it includes Generalised Epilepsy, Focal Epilepsies, Combined Generalised and Focal Epilepsies (New Group) and Unknown.
4. The Epilepsy type may also be the final level of diagnosis achievable where the clinician is unable to make an Epilepsy Syndrome diagnosis.
5. In ILAE Classification of Epilepsy, there are three levels including: Seizure type, Epilepsy type, Epilepsy Syndrome.
6. The new classification incorporates aetiology along each stage, emphasising that there is no need to consider aetiology at each step of diagnosis and carries no treatment implications.
7. In ILAE Classification of Epilepsy, there are six group of etiologies including: Structural, Genetic, Metabolic, infectious, Immune, Unknown.
8. When compared with continued medical treatment, a randomised control study showed that surgical treatment had a higher chance to let patients with refractory temporal lobe epilepsy become seizure free.
9. Children with seizures that are uncontrolled by medical treatment (i.e. failure of two or three appropriate drugs) or are disabling (including medication side effects) is indication to be referred for epilepsy surgery.
10. patients in whom the MRI reveals a lesion amenable to surgical removal is not an indication for epilepsy surgery.

ANSWER SHEET FOR MAY 2018

Please return the completed answer sheet to the Federation Secretariat on or before 31 May 2018 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

The New 2017 ILAE classification of seizure types and the epilepsies; The evolution of concepts and terminologies; How aetiologies guide the management in Paediatric Epilepsy?

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1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No.: _____ (for reference only)

Answers to April 2018 Issue

The Challenges and Opportunities for Treating Obesity (and Diabesity) in Hong Kong

1. T 2. T 3. F 4. F 5. T 6. F 7. T 8. F 9. T 10. T

Dermatology Quiz

Dr Lai-yin CHONG

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Specialist in Dermatology & Venereology

Dr Lai-yin CHONG

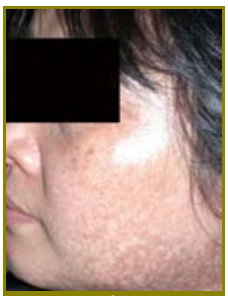

Fig.1: Mottling pigmentary changes and redness

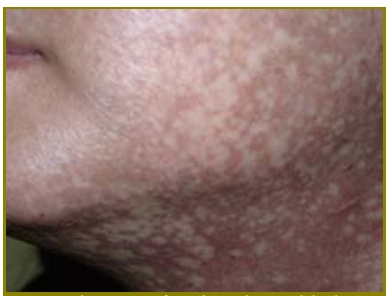

Fig.2: Close-up of neck and mandibular area

A middle-aged woman presented with bilateral mottling skin lesions at her neck and mandibular area of the face (Fig.1 &2), together with erythema and telangiectasia. She is asymptomatic except complaining of the disfigurement. Her past health was otherwise good. She had history of using various types of topical cosmetic products for a long time.

Questions

1. What is the dermatological descriptive term of these skin changes?
2. What is the most likely clinical diagnosis and its differential diagnoses?
3. What is the presumptive underlying cause?
4. How do you treat this disorder?

(See P.37 for answers)

Take back your life
with Keppra

Control seizures with a better quality of life with Keppra[1]

- Let your patients reach the **therapeutic dose in just 2 weeks**[2]
- Keppra has **less influence on cognitive function** to your patients for both children and adults[3,4]
- **Less drug-drug interaction** for your patients[5]
- Improve patients' QoL with a **lower incidence of side effects***[1,6]

Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown. The administration of KEPPRA to patients with renal impairment (especially elderly ≥65 years) may require dose adjustment.[2]

Available in different formulations

* The incidence of adverse effects of LEV was the lowest among CBZ, VPA, TPM, OXC, LTG and LEV and it was significantly lower than TPM, VPA and CBZ

Abbreviation list: CBZ=carbamazepine; VPA=Sodium valproate; TPM=Topiramate; OXC=Oxabazepine; LTG=Lamotrigine; LEV=Levetiracetam; QoL=Quality of life

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Name of medicinal product: Keppra **Qualitative and quantitative composition:** *Tablets* 250 mg / 500 mg / 1000 mg; *Oral Solution* 100 mg/ml; *Concentrate for solution for infusion* 100 mg/ml **Indication:** As monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy OR as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy, myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy, primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy. **Dosage and Route of Administration:** Levetiracetam therapy can be initiated with either intravenous or oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. The total daily dose and frequency of administration should be maintained. *Film-coated tablets* and *Oral solution* may be taken with or without food and the daily dose is administered in two equally divided doses. *Concentrate for solution for infusion* is for intravenous use only and the recommended dose must be diluted in at least 100 ml of a compatible diluent and administered intravenously as a 15-minute intravenous infusion. There is no experience with administration of intravenous levetiracetam for longer period than 4 days. Levetiracetam concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible**Adults** *Monotherapy* Adults and adolescents from 16 years of age Initial dose 250 mg twice daily, then increase to an initial therapeutic dose of 500 mg twice daily after 2 weeks. May increase by 250 mg twice daily every 2 weeks depending upon the clinical response. Max. dose 1500 mg twice daily. *Add-on therapy* Adults (≥18 years) and adolescents (12 to 17 years) weighing ≥50 kg Initial therapeutic dose 500 mg twice daily (can be started on the first day of treatment). May adjust by 500 mg twice daily every 2 – 4 weeks depending upon the clinical response. Max. dose 1500 mg twice daily. **Children** *Monotherapy* No data available. *Add-on therapy* Children aged from 4 years of age and adolescents weighing <50 kg Initial therapeutic dose 10 mg/kg twice daily. Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed adjustments of 10 mg/kg twice daily every 2 weeks. Dose in children weighing ≥50 kg is the same as in adults. **Contraindications:** Hypersensitivity to the active substance or other pyrrolidone derivatives or any of the excipients. **Warnings and Precautions** *Discontinuation* It is recommended to withdraw *KEPPRA* gradually (e.g. in adults and adolescents weighing ≥50 kg: 500 mg decreases twice daily every 2 – 4 weeks; in children and adolescents weighing <50 kg: dose decrease should not exceed 10 mg/kg twice daily every 2 weeks. *Paediatric population* The tablet formulation is not adapted for use in children under the age of 6 years and initial treatment in children weighing <25 kg. Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown. *Renal impairment* The administration of *KEPPRA* to patients with renal impairment (especially elderly ≥65 years) may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection. *Suicide* Suicide, suicide attempt and suicidal ideation have been reported in patients treated with anti-epileptic agents (including levetiracetam). A meta-analysis of randomized placebo-controlled trials of anti-epileptics medicinal products has shown a small increased risk of suicidal thoughts and behavior. The mechanism of this risk is not known. Therefore patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should any symptoms of depression and/or suicidal ideation or behavior emerge. *Excipients – oral solution* Keppra 100 mg/ml oral solution contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions. It also contains maltitol liquid; patients with rare hereditary problems of fructose intolerance should not take this medicinal product. *Excipients – concentrate for solution for infusion* This medicinal product contains 2.5 mmol (or 57 mg) sodium per maximum single dose (0.8 mmol [or 19mg] per vial). To be taken into consideration by patients on a controlled sodium diet. **Interactions:** Enzyme-inducing antiepileptic medicinal products, probenecid, NSAIDs, sulphonamides, methotrexate. **Pregnancy and Lactation:** *Fertility* No impact on fertility was detected in animal studies. No clinical data are available. The potential risk for humans is unknown. *Pregnancy* Keppra is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary. Studies in animals have shown reproductive toxicity. Physiological changes during pregnancy may affect levetiracetam concentration. Decreased in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with levetiracetam should be ensured. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus. *Lactation* Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended. **Ability to perform tasks that require judgement, motor or cognitive skills:** Levetiracetam has minor or moderate influence on the ability to drive and use machines. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected. **Adverse Reactions:** Nasopharyngitis, anorexia, depression, hostility/aggression, anxiety, insomnia, nervousness/ irritability, somnolence, headache, convulsion, dizziness, tremor, balance disorder, lethargy, veretigo, cough, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, rash; asthenia/fatigue. **Overdosage** Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with *Keppra* overdoses. After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60% for levetiracetam and 74% for the primary metabolite. Please read the full prescribing information prior to administration. Full prescribing information is available on request from GlaxoSmithKline Ltd, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong KongAbbreviated Prescribing Information based on PI version NCDS 06.

GlaxoSmithKline Limited
23 / F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong. Tel: (852) 3189 8989 Fax: (852) 3189 8931 hk.gsk.com

HKRx/LTM/0013/17a (07/2019)
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Keppra levetiracetam

Early Infantile Epileptic Encephalopathy and Clinical Use of Next-Generation Sequencing-Based Genomic Test

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Introduction

In infancy and childhood, epileptic encephalopathy (EE) is a devastating condition. Patients are characterised by epilepsy of different seizure types with frequent epileptiform activities on electroencephalography (EEG), leading to cognitive and behavioural impairments that tend to be more severe than expected from the underlying disease pathology alone.[1,2] Common comorbidities include developmental delay or regression, behavioural problems such as autistic features and movement disorders.[3,4] While classification of these disorders is important, it is not an easy task. The age of onset, seizure type and EEG pattern in patients with EE are highly heterogeneous. Variable phenotypes can be observed even among affected members within the same family. As a result, it is often difficult if not impossible to classify the condition based on the electroclinical features.

In 2001, a genetic cause was first recognised for EE in a study of *SCN1A* gene mutations in a group of patients affected by severe myoclonic epilepsy of infancy (SMEI) or Dravet syndrome.[5] Since then, an increasing number of individual genetic disorders are recognised to cause EE.[6-11] For these genetic disorders, establishing the diagnosis by DNA analysis can inform the family about the prognosis of the patient and the recurrence risk in future pregnancies. This also enables better understanding of the disease mechanisms thereby helps to predict the potential triggers and to guide the selection of antiepileptic treatment. Therefore, genetic analysis has become an important clinical tool and forms part of the diagnostic and classification procedures for EE.

In the past, DNA analysis for diagnosis of genetic disorders largely relied on Sanger sequencing, which is highly robust but can only examine a single gene or a tiny proportion of the human genome at one time. This technology would become extremely labour-intensive when multiple genes are to be analysed. Therefore, Sanger sequencing remains suitable for the investigation of single gene disorders where a possible or probable diagnosis can be made on the basis of clinical features and other investigation results. For disorders with a heterogeneous genetic basis, however, a high throughput method which can analyse a large number of genes or even the whole human genome in one go would be highly desirable.

The introduction of next-generation sequencing (NGS) technology in recent years has led to a rapid expansion of genetic and genomic knowledge.[12] Depending on how an NGS experiment is designed and configured, NGS can be used to interrogate tens to hundreds of selected genes (i.e. NGS-based targeted gene panel), to all the 20,000 protein-coding genes in the human genome (i.e. whole exome sequencing) or even the entire human genome (i.e. whole genome sequencing) in one single experiment. Nowadays, NGS is being increasingly used in clinical laboratories and this has made the investigation of genetic disorders with a heterogeneous genetic basis more affordable, faster and more readily available.[12]

NGS-based targeted gene panel analysis for early infantile epileptic encephalopathy (EIEE) is gaining popularity as a diagnostic investigation worldwide including Mainland China and Hong Kong. The reported detection rate in Chinese patients ranged from 18% to 42%, depending on the gene panel design and patient selection criteria.[13-17] For example, Zhang and co-workers used a small targeted panel focusing on 17 genes to test 175 Chinese patients with early-onset EE.[13] Heterozygous *de novo* variants were detected in 56 patients in seven genes, giving a detection rate of 32%.[13] In 2017, Fung and co-workers performed whole exome sequencing and gene panel filtering on a cohort of 31 local patients with non-syndromic cryptogenic neonatal/infantile epileptic encephalopathy.[14] Pathogenic or likely pathogenic variants were identified in 9 patients, giving a diagnostic rate of 29%.[14]

Design of the EIEE panel

We developed a targeted gene panel of 156 genes for EIEE (Table). Most of these genes were known to cause early-onset epilepsy while 14 were candidate genes with causative roles not yet fully established. Case recruitment from all paediatric units under the Hospital Authority (HA) started in 2017. Patients who developed difficult-to-control seizures before 24 months of age with evidence of global developmental delay are eligible to be tested with this targeted gene panel. Patients who have a stronger alternative explanation for their clinical phenotypes e.g. significant perinatal insult, abnormal chromosomal study, structural anomalies detected by neuroimaging are excluded.

After obtaining informed consent, blood samples are collected from the index patients +/- parents and other family members and are sent to our laboratory for

analysis. DNA from the index patients will be subjected to the EIEE panel analysis. Any potential disease-causing genetic variants will be confirmed by a second method such as Sanger sequencing. Samples from the parents and other family members will be used for segregation study when necessary.

In the past year, we have tested 22 families referred from various paediatric units. Ages of the index patients ranged from 2 months to 17 years. Four patients with positive results are described below. All detected variants were classified into pathogenic, likely pathogenic or variant of uncertain significance (VUS) according to the American College of Genetics and Genomics (ACMG) guidelines for interpretation of sequence variants.[18]

Table. The 156 genes included in the early infantile epileptic encephalopathy panel

142 known genes for epilepsy[10,14,16,34-43]
*AARS, ADSL, ALDH7A1, ALG13, AMT, AP3B2, ARHGEF9, ARV1, ARX, ATP1A2, ATP1A3, ATP6AP2, ATRX, BRAT1, CACNA1A, CAD, CASK, CDKL5, CHD2, CLCN4, CLN3, CLN5, CLN6, CLN8, CNTNAP2, COQ4, CTSD, CUL4B, DENND5A, DEPDC5, DLAT, DNM1, DOCK7, DYRK1A, EEF1A2, EFHC1, EHMT1, ETHE1, FGF12 ,FOLR1, FOXG1, FRRS1L, GABRA1, GABRB1, GABRB3, GABRG2, GAMT, GATM, GCSH, GLDC, GNAO1, GRIN1, GRIN2A, GRIN2B, GRIN2D, HCN1, IER3IP1, IQSEC2, ITPA, KCNA2, KCNB1, KCNJ10, KCNQ2, KCNQ3, KCNT1, KCTD7, KIF1BP, KPNA7, LGI1, LIAS, *MAGI2, *MBD5, MDH2, MECP2, MEF2C, MFSD8, MPC1, MTOR, NECAP1, NEDD4L, NPRL2, NPRL3, NR2F1, NRXN1, PC, PCDH19, PDHA1, PDHB, PDP1, PIGA, PIGN, PIGO, PIGT, PIGV, *PLCB1, PNKP, PNPO, POLG, PPT1, PRRT2, PURA, QARS, RELN, SCN1A, SCN1B, SCN2A, SCN8A, SCN9A, SIK1, SLC12A5, SLC13A5, SLC16A2, SLC19A3, SLC1A2, SLC1A4, SLC25A1, SLC25A12, SLC25A15, SLC25A22, SLC2A1, SLC35A2, SLC6A1, SLC6A8, SLC9A6, SPTAN1, ST3GAL3, ST3GAL5, STXBP1, SYNGAP1, SZT2, TBC1D24, TBCE, TCF4, TPP1, TSC1, TSC2, UBA5, UBE2A, UBE3A, UPB117, WDR45, WWOX, ZEB2*
14 candidate genes for epilepsy[10,14,16,36-43]
ARHGEF15, CACNA2D2, CBL, CSNK1G1, GABRB2, GUF1, KCNAB1, KCNH5, KCNMA1, MAPK10, PIGQ, SRGAP2, TUBA8

*Genes in which majority of reported mutations were gross deletions/duplications or complex rearrangements.

Patient 1

The patient developed refractory seizure since the first hour of life. Repeated episodes of apnoeic attacks were also noted. Two novel likely pathogenic variants in the *BRAT1* gene were identified. The parents were confirmed to be carriers. Recessive mutations in the *BRAT1* gene were initially reported to cause lethal neonatal rigidity and multifocal seizure syndrome (OMIM#614498). More than half of the affected patients did not survive beyond the age of 6 months.[19] Although subsequent publications demonstrated a wider clinical spectrum and intra-familial phenotypic heterogeneity, the overall prognosis is still poor.[20] Those who survived longer into childhood had intellectual disability, ataxia and cerebellar atrophy. With the established genetic diagnosis in this baby, the parents were informed of a 25% recurrence risk in their future pregnancies. The genetic result provides important information for the couple as reproductive options such as prenatal diagnosis and preimplantation genetic diagnosis are made possible.

Patient 2

The female patient developed recurrent seizures in clusters since 13 months of age, which were usually associated with febrile illness. She was reported to have frightening sensation and screaming during seizure episodes. A novel heterozygous likely pathogenic variant was found in the *PCDH19* gene. The variant was not found in both parents. The analysis result is consistent with the diagnosis of *PCDH19*-related early infantile epileptic encephalopathy, 9 (OMIM#300088). Patients with *PCDH19* mutations often exhibit fever-sensitive seizures occurring in clusters, and have distinctive features of affective symptoms such as fearful screaming.[21,22] Interestingly, this X-linked condition mainly affects heterozygous female patients while hemizygous males are largely unaffected. Around 70% of reported mutations were *de novo*, as in this patient. Recent researches showed there were generalised decreases in blood levels of neuroactive steroids in girls affected by *PCDH19*-related EIEE.[23] It was hypothesised that therapy aiming to restore steroidogenesis in these patients could result in beneficial effects. For instance, corticosteroid administration has been reported to be efficacious in some pilot studies.[24,25]

Patient 3

The patient developed repeated seizures since 3 months old and had global developmental delay. Seizure semiology was variable and included drop attacks, dystonia, and night-time screaming with increased limb tone. Hyperactive behaviour and autistic features were evident at the age of five. The mother and a maternal uncle both had a history of self-limiting seizure during infancy. Two known pathogenic variants were identified in the *PRRT2* gene of the patient.[26,44] Parental genetic studies are underway. *PRRT2* mutations can cause various clinical phenotypes which include benign familial infantile epilepsy (BFIE, OMIM#605751), paroxysmal kinesigenic dyskinesia (PKD, OMIM#128200) and infantile convulsions with paroxysmal choreoathetosis/dyskinesia (ICCA, OMIM#602066).[27] Large majority of patients with *PRRT2*-related disorders have autosomal dominant diseases with incomplete penetrance and variable phenotypic expression within the same family.[26-28] However, autosomal recessive disease caused by biallelic *PRRT2* mutations are being increasingly recognized, which have been reported to cause a more severe phenotype with other manifestations such as intellectual disability and attention-deficit hyperactivity disorder.[28-30] Choice of medications for this patient's seizure had been complicated by inconsistent parenting with self-manipulation of drug regimen. With the established genetic diagnosis, anticonvulsants proven to be effective for *PRRT2*-related epilepsy can be chosen to provide better patient care.[32]

Patient 4

The patient had progressive microcephaly and severe global developmental delay since infancy. Cortical visual impairmental was evident since 6 months old. Frequent tongue thrusting and involuntary dyskinetic movements were noted before the age of three. Previous *GNAO1* gene analysis was unremarkable. The EIEE panel identified a novel heterozygous likely pathogenic variant in the *GRIN1* gene, which were absent in

both parents and therefore presumed to be de novo. *GRIN1* encodes the GluN1 subunit of the N-methyl-D-aspartate (NMDA) receptor. Patients carrying de novo heterozygous *GRIN1* mutation are characterised by neonatal-onset profound global developmental delay, truncal hypotonia, epilepsy, dystonic or dyskinetic movement disorder, oculogyric crisis and cortical visual impairment, as in this patient.[33] All reported *GRIN1* heterozygous mutations had occurred *de novo* and there were no reports of germline mosaicism.[33] Genetic diagnosis in this patient thus notified an extremely low risk of recurrence in this family and facilitated genetic counselling to the parents.

Summary

The use of NGS technology has greatly facilitated the investigation of complex genetic conditions such as EE. By sequencing tens to a few hundred selected genes, the exact genetic diagnoses can be made in a significant proportion of patients suffered from EE. Our experience with the 156-gene targeted panel showed that this investigation is able to effectively diagnose rare genetic conditions in patients with EIEE and a combination of neurological features such as dyskinesia. Clinical manifestations that are compatible with the underlying genetic diagnosis were often recognised retrospectively after the genetic diagnosis was made by the targeted gene panel analysis. Moreover, it would have taken a much longer time and would have been more costly to reach the final diagnosis if a single-gene analysis approach was used. Results provided by NGS-based genomic analysis have proved to be highly valuable as they inform clinicians and affected families of disease prognosis and recurrence risk. For families planning for another pregnancy, prenatal diagnosis or preimplantation genetic diagnosis are also made possible. As ongoing research uncovers the pathophysiological mechanisms of EE, improved treatment strategy and genetic counselling can be offered.

Acknowledgement
The 156-gene targeted gene panel for early infantile epileptic encephalopathy is part of an HA-funded project for the development of centralised next-generation sequencing services in the Hong Kong Children's Hospital. We sincerely thank our paediatric colleagues who referred patients to us and provided insight and expertise that greatly assisted the interpretation of the genetic variants identified. Specifically, the four patients described in this article were referred to us by Dr Mario Chak of Tuen Mun Hospital (Patient 1), Dr Eva Fung of Prince of Wales Hospital (Patient 2 and 3) and Dr Shelia Wong of United Christian Hospital (Patient 4).

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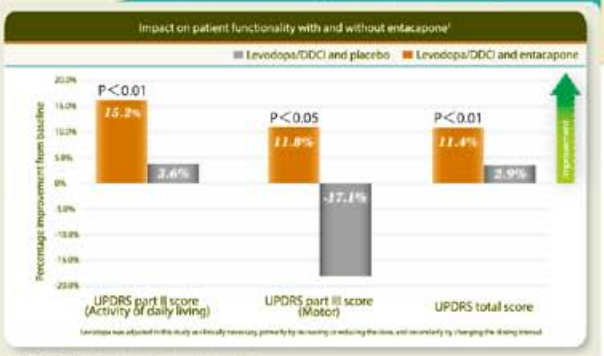

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Reference: 1. Rinne UK, Larsen JP, Siden Å, Worm-Petersen J; and the Nomecomt Study Group. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Neurology. 1998;51(5):1309-1314.
2. Stalevo IISS (Reference: EMEA CPP (May 2012) + CDS (May 2013)

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Drug-resistant Epilepsy due to Focal Cortical Dysplasia – Surgical Treatment

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Introduction

Focal cortical dysplasia (FCD) is the most common diagnosis among children with drug-resistant focal epilepsy requiring surgery, constituting over half of the cases. It is also the second commonest diagnosis among adult sufferers.[1] The histopathological features of FCD, namely cortical lamination disorganisation, large bizarre neurons, and balloon cells, were first recognised as belonging to a distinct entity in 1971.[2] Ongoing efforts to elucidate this entity culminated in a new three-tiered classification in 2011, the Blumcke classification of focal cortical dysplasia.[3] There is limited information on the molecular genetic aspects of FCD. A few monogenic epilepsies have been reported to be associated with FCD, including the protocadherin 19 gene, alpha1-sodium channel subunit gene, syntaxin-binding protein 1 gene, and genes of the mammalian target of rapamycin signalling pathway.[4, 5]

For clinicians, one striking feature of FCD is the great variation in the extent of the affected brain. It can involve a whole hemisphere, and be readily spotted by inexperienced eyes.[5] It can also be so small and inconspicuous that even experts need multi-modality investigations to pinpoint its location.[6] Rarely, it can be multiple, and involves both hemispheres.[7] Therefore, different surgical strategies are required in dealing with FCDs with different clinical and anatomical features.

Pre-operative Evaluation

As a rule, all patients with drug-resistant epilepsy need to be evaluated by a multi-disciplinary epilepsy surgery team.[8] When a suspicion of FCD being the culprit arises, the surgeon needs to know the anatomical location and the extent of the FCD, as well as the anatomy of eloquent brain structures intermingling with it and in its vicinity.

MRI with dedicated epilepsy sequences is essential. The typical MRI findings of FCD are increased cortical thickness or cortical thinning, blurring of the cortical-white matter junction, increased signal on T2-weighted images, a radially oriented linear or conical transmantle stripe of T2 hyper-intensity, and localised brain atrophy (Fig. 1). In general, different subtypes of FCD share many of these radiological features, and cannot be distinguished by MRI; but FCD type IA has a propensity for the temporal lobe and type IB the extra-temporal cortex; type IIB carries the characteristic transmantle sign.[9] The rate of detection of FCD can be increased by using high resolution MRI protocols as well as a higher field MRI machine. A high resolution MRI protocol can show a lesion in more than 50% of patients with non-lesional standard protocol MRI.[10] 3 T MRI can show a lesion in 20% of patients with non-lesional 1.5 T MRI findings, while 7 T MRI can add another 20% to it.[11]

There remain some FCDs that elude MRI detection, and histopathological diagnosis of FCD is made after excision guided by other modalities of investigation such as electroencephalogram, radioisotope scans, and magnetoencephalography. Magnetoencephalography is invaluable for its high temporal and spacial resolution. In one series, one-third of the patients with FCD undergoing surgery had non-lesional MRI but magnetoencephalographic diploes.[12]

For delineating the eloquent structures around a FCD, apart from high resolution 3D MRI, diffusion tensor imaging tractography has become a standard for all age groups, and language functional MRI for patients usually at least beyond age 7.[13]

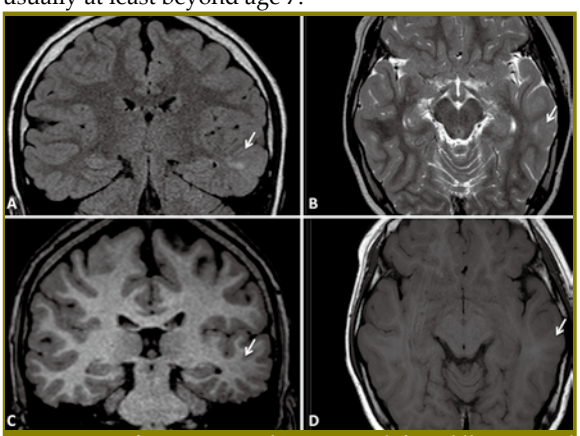

Fig. 1. MRI of a patient with FCD over left middle temporal gyrus (arrows). A: FLAIR sequence. B: T2-weighted sequence. C and D: T1-weighted sequences. Source: From personal collection.

Surgical Strategies

The goal of surgical treatment of drug-resistant epilepsy due to FCD is complete elimination of the epileptogenic effect of a FCD lesion, which often means total extirpation of the lesion, or disconnection of it from the rest of the brain. The first step is to accurately localise the epileptogenic lesion and to define its extent and its relationship with eloquent cortical areas and nerve fibre tracts. A surgical treatment approach for an individual patient can then be planned.

For FCD lesions that are both visible by MRI and surgically accessible, surgical excision should be considered. By surgical accessibility, I refer to not only whether a lesion can be reached without cutting through eloquent brain tissue, but also whether there is a definable border between the lesion and any adjacent eloquent brain tissue. Fortunately, a high percentage of FCDs fall in this category.[14,15] Contemporary neurosurgical techniques allow these FCD lesions to be removed with low complication rates (Illustrative cases 1 and 2; Fig. 2 and 3). Since these lesions are "visible" by MRI, and the completeness of their excision seems to affect seizure control,[16] the use of intraoperative MRI when removing these FCD lesions may prove to be cost-effective.[15]

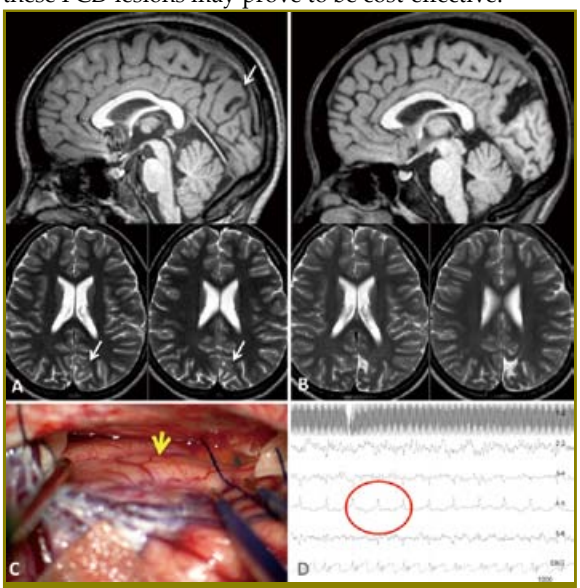

Fig. 2. A 13-year-old girl with intractable epilepsy due to a left medial parietal FCD. Excision of the FCD resulted in complete cessation of seizure (Engel class Ia). A: Pre-operative T1-weighted and T2-weighted MRI images showing the FCD (white arrows). B: Post-operative T1-weighted and T2-weighted MRI images showing complete excision of the FCD. C: Intra-operative photo showing the near-normal gross appearance of the diseased cortex (yellow arrow). D: Intra-operative electrocorticogram showing the typical "ECG-like" discharge pattern at the core of an epileptogenic FCD. Source: From personal collection.

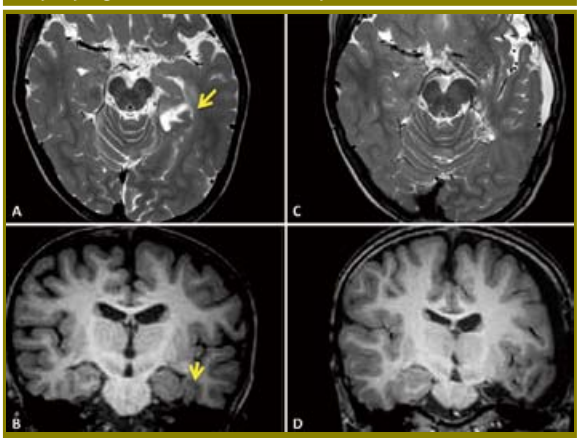

Fig. 3. A 28-month-old child with infantile spasm. She became seizure-free (Engel class Ia) after 2 operations. A and B: Pre-operative T2-weighted axial MRI image, and T1-weighted coronal MRI image showing the mesio-temporal FCD (yellow arrow). C and D: Post-operative MRI images. Source: From personal collection.

For "occult" FCD lesions, i.e. non-lesional by MRI, but epileptogenic foci can be anatomically localised by the combination of other modalities of investigation, invasive monitoring is often the first step, before definitive excision. A group of FCD lesions which often fall in this category is the bottom-of-sulcus dysplasia, which is often very difficult to detect, or not detected at all by MRI. However, the prognosis of seizure control is excellent after successful detection and removal of these lesions.[6] Invasive monitoring techniques including implanted subdural electrodes, depth electrodes and stereoelectroencephalography are usually required when treating these patients[17] (Illustrative case 3, Fig. 4).

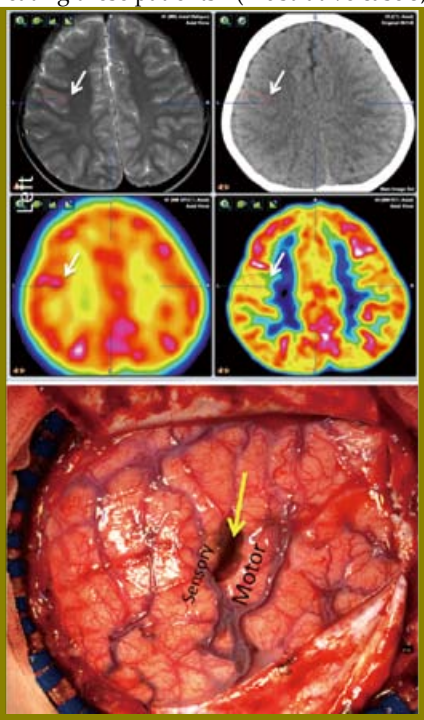

Fig. 4. A 6-year-old child with an "occult" left central sulcus FCD. She became seizure-free after surgery (Engel class Ia), without any permanent neurological deficits. Upper panel: Pre-operative multi-modality imaging studies showing the epileptogenic focus in the left central sulcus (white arrows). Lower panel: Intra-operative photo showing the excision cavity (yellow arrow) at the left central sulcus. Source: From personal collection.

For small, deep-seated FCD lesions, the approach of choice is stereotactic ablation. In this technique, stereotactically inserted probes allow stereoelectroencephalographic recording to confirm the epileptogenic target, followed by thermocoagulation of the target. Currently, there are 2 ablative methods in use, radiofrequency ablation and MRI-guided laser interstitial thermotherapy. The later carries the advantages of real-time imaging and monitoring of thermal dose delivery, and can achieve a larger ablation volume that may require fewer probe targets and placements.[18]

For large multiple lobar, and hemispheric FCD lesions, disconnection procedures are more appropriate. The rationale for disconnection instead of excision of a large portion of the brain is in the reduction of potential complications such as cerebral haemosiderosis and massive intraoperative blood loss. For hemispheric FCD lesions, hemispherotomy is needed, by which the

disease cerebrum is disconnected from the ipsilateral central core (centre core being defined as the extreme, external, and internal capsules, claustrum, lentiform and caudate nuclei, and thalamus). Despite the markedly destructive nature of hemispherotomy, the majority of the patients demonstrate improvement in language and behaviour after surgery[19] (Illustrative case 4, Fig. 5).

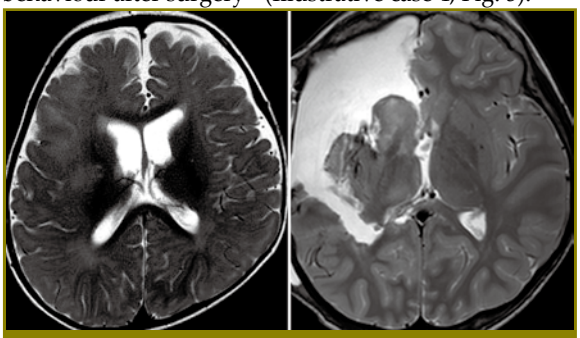

Fig. 5. Right hemispheric FCD. Left panel: Pre-operative T2-weighted MRI image. Right panel: Post-operative MRI image after previous frontal lobectomy, and lastly right periinsular hemispherotomy. Source: From personal collection.

Outcomes of Surgery

Patients being worked up for epilepsy surgery are seizing frequently despite multiple anticonvulsants. Any treatment that can render them seizure-free without medication, or just having Engel class I outcome (defined as seizure free or no more than a few early, non-disabling seizures; or seizures upon drug withdrawal only) is highly rewarding. Surgical series of excisional surgery for drug-resistant epilepsy due to FCD have shown consistently good results. Favourable seizure control (Engel class I) after surgery for FCD as a group ranged between 60 - 70 %.[7, 17, 20] There have been reports looking for differences in outcomes among different FCD subtypes, albeit with inconsistent conclusions. Fauser et al reported more favourable outcome in FCD type I than in FCD type II (Engel class Ia, 55-67% vs 43-50%)[7] ; on the contrary, Isler et al reported a slightly better outcome in FCD type II (Engel class I, 70.4% vs 65.4%).[20] Roessler et al reported a significant difference between FCD type IIA and type IIb (Engel class I, 28% vs 82%, p<0.02)[17]. Bear in mind that these are all small case series.

One factor that has consistently been shown to associate with favourable seizure control is complete excision of a FCD lesion.[15, 16, 17, 20] It however has to be weighted against the risk of causing new and permanent neurological deficits. In Isler et al's series, it amounted to 9%.[20] Here, intra-operative MRI may have a role not only in decreasing the need for re-operation, but also in increasing the safety and completeness of surgical excision.[15, 17] The outcomes in patients undergoing hemispherotomy for multilobar FCD also concur with this "complete excision/ disconnection" observation, for hemispherotomy can achieve Engel class I seizure outcome in 70% of patients.[19]

It is worth noting that in patients with non-lesional MRI, if a localised epileptogenic focus can be inferred from other modalities of investigation, excisional surgery may also bring about favourable seizure control. In 12 patients with non-lesional MRI but positive magnetoencephalographic diploes, 42% could achieve favourable seizure control.[12] Lastly, patients with FCD undergoing thermocoagulation ablation generally demonstrate a much lower rate of Engel class I outcome, which most likely is related to the nature of their disease.

Conclusions

From the surgeon's perspective, patients with drug-resistant epilepsy due to FCD can present with a wide spectrum of clinicopathological complexity. Appropriate surgical strategies, tailored for each individual patient, can achieve good seizure control, and improve quality of life in the majority of these patients.

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Focal Cortical Dysplasia - The Neuropathologic Perspective

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Introduction

Focal cortical dysplasia (FCD) is "a focal cerebral cortical cytoarchitecture abnormality commonly encountered in surgical specimens from patients with poorly controlled epilepsy and likely to represent a malformation of cortical development (MCD)"[1]. There is an increasing number of MCDs described in the literature. In the review series of the German Neuropathology Reference Centre for epilepsy Surgery (n=5603), MCDs represent the third most frequent aetiology, while FCDs are the most common subtypes of MCD identified.[2] MCDs can be intrinsically epileptogenic because of the abnormal arrangement of the synaptic circuitries. "Cortical dysplasia" has been used as a generic term to describe a variety of focal MCDs, including heterotopia and polymicrogyria. However, the term FCD from a neuropathological perspective is generally reserved for the cortical malformation described by Taylor et al.[3] Milder microscopic forms with more subtle histologic changes have been given various terms such as microdysgenesis, mild focal dysplasia, "non-Taylor" dysplasia, hamartias, etc.[1] With recently published ILAE (International League Against Epilepsy) consensus neuropathological classification for FCD, the nomenclature of FCD has been standardised and correlated with clinical findings and outcome.

Development of the brain cortex

Normal histology of the neocortex[4]

The six-layered neocortex forms 90% of the cerebral cortex. On histologic sections, the layers are distinguished by neuronal cell type, density and cellular arrangement.

The main types of cells in the cerebral cortex are pyramidal cells, stellate cells, and fusiform cells. Pyramidal cells are the principal cortical output neurons and exert both inhibitory and excitatory influences within the cerebral cortex. They are pyramidal in shape with heights varying from 10 to 50 um. They possess an apical dendrite pointing towards the pial surface and many horizontal basal dendrites. The axon from the base of each pyramidal cell enters the white matter. The stellate cells are mostly populated in layer IV. They are polygonal in shape and possess scanty cytoplasm, many dendrites and a short axon. Their sizes range from 4 to 8 um. The fusiform cells are mostly in the deepest cortical layers with their long axis perpendicular to the pial surface. Similar to pyramidal cells, the axon from the base of the cell body enters the white matter. Numerous dendrites arise from the poles of the cells. There are also the horizontal cells of Cajal, small horizontal fusiform cells and the cells of Martinotti. Axons of these cells together with the entering afferent projections and association fibres form the radially arranged fibre bundles. There are also tangential fibres running parallel to the pial surface. They are terminal branches of afferent projection and association fibres, axons of horizontal cells and stellate cells, and collateral branches of pyramidal and fusiform cells.

The outermost layer is layer I (the molecular layer) which contains horizontal axons and Golgi type II cells. The layer II (external granular layer) and the layer III (external pyramidal layer) contain dense stellate cells and two sublayers of pyramidal cells respectively. The layer IV (internal granular layer) and the layer V (internal pyramidal layer) are composed of dense stellate cells and medium- and large-sized pyramidal layers respectively.

Apart from the horizontal laminar pattern, radial arrangement cells giving rise to a columnar appearance is also conspicuous except in the frontal lobe. This vertical columnar organisation across the cell types appears functional according to studies of the somatosensory and visual cortex. The interrelation of cortical neurons is also complex and outside the scope this article.

The foetal brain

The foetal cortex develops from progenitor cells from the periventricular zone where the cortical neuroepithelium and the medial and the lateral ganglionic eminences are located. Pyramidal projection neurons in this cortical neuroepithelium migrate radially while inhibitory interneurons migrate non-radially before final radial migration from the medial and the lateral ganglionic eminences. Progenitor cells proliferate in the ventricular and the subventricular zones before radial migration to the future cortex along the radial glial cells which are also neural stem cells. The neuronal identity and the layer fate are determined before radial migration. The radial migration begins with the earliest born neurons. However, they travel the least distance and settle at the deepest level of the cortex followed by the layer V neurons which pass through the deepest layer while the youngest neurons start their migration the last and rest at the most superficial layer, layer II. This is the so-called "the inside-out temporal sequence" of the neocortex development.[5,1] This six-layer cellular arrangement is characteristic of the neocortex.

Pathogenesis and aetiology of FCD

Mutations or insults happen during different stages of the development of the cortical development giving rise to different phenotypes, i.e. same genetic mutations happening at different time of gestation can result in different types of cortical malformation and histology or different diseases sharing the same histology as in the case of FCDIIb and tubers in tuberous sclerosis.

Hemimegalencephaly (HME) is a rare brain malformation with excessive growth of one hemisphere. It may be isolated or syndromic and is typically associated with early onset epilepsy, hemiparesis and developmental delay.[1] The cortical laminae are typically ill-defined with projections of glioneuronal cell aggregate in the layer I. Dysplastic neurons and, sometimes, balloon cells are present.

Histopathology and Classification of Focal Cortical Dysplasia

Taylor et al first described the neuropathologic features of FCDs in surgical specimens from 10 patients in 1971.[3] The most characteristic features are the disruption of the normal cortical lamination with the presence of "large aberrant neurons" and the presence of "grotesque cells" in both cortex and subcortical white matter. The histologic similarities between cortical lesions of patients with tuberous sclerosis complex (TSC) and FCD are discussed and the possibility of FCD being forme fruste of TSC is suggested.

Since then, different FCD classifications have been proposed. The Palmini classification (2004) classified FCD into type I and type II categories mainly based on histopathologic features and was a consensus report of an international workshop. The Palmini classification had been used extensively for scientific reports. However, it "failed to provide consistent associations with clinical and neuroradiological features"[2] and the post-surgical seizure control in the described FCD groups especially the FCD Type I remained ambiguous.[2] It is likely due to the fact that the Palmini Type I FCDs include different entities namely the isolated and the associated FCDs. Moreover, the inter- and the intra-observer agreement for the type I FCDS is poor though the inter-observer agreement on FCD Type II is excellent.[2,6] This suggests a need for refining neuropathologic diagnostic criteria in order to improve reproducibility and enhance insight into the clinicopathologic correlations of FCD subtypes. Therefore, the task force of the ILAE revisited the situation and came up with a new consensus classification of the FCD subtypes based on histopathologic features with large and comprehensive intra-and inter-observer agreement.[7]

The ILAE classification[8]

The ILAE classification is a three-tier system for FCD distinguishing isolated FCDs (Types I and II) from those cortical abnormalities associated with another principal lesions (Type III). Depending on the nature of the associated lesions, the FCD Type III are further subclassified into 4 types; hippocampal sclerosis in temporal lobe (FCD IIIa), glial or glioneuronal tumour (FCD IIIb), vascular malformation (FCD IIIc) and lesions acquired during early life, e.g. trauma, ischaemia, encephalitis (FCD IIId) respectively.

In FCD Type I lesions, disruption of the normal neocortical lamination is the key feature. The pattern of abnormal lamination is subclassified into 3 types; those with mainly abnormal radial cortical organisation (FCD Ia), those with mainly abnormal tangential cortical lamination (FCD Ib) and those with mixed radial and tangential abnormal cortical organisation (FCD Ic). Interestingly, FCD Ic is an uncommon subtype in the German series. This is likely due to the fact that other insults to the brain in early life or lesions associated with abnormal cortical lamination in mixed radial and tangential manner and, hence, they are classified as FCD IIIs. FCDs with dysplastic neurons and those with dysplastic neurons AND balloon cells (Fig.1& 2) are FCD IIa and FCD IIb respectively. Dysmorphic neurons are those neurons with abnormal morphology including cell orientation, position, abnormal shape of soma and neurites and abnormal position of nuclei within the neurons. Balloon cells are often large in size with abundant glassy cytoplasm and exhibit both glial and neuron differentiation and $\alpha\beta$-crystallin by immunohistochemistry. (Fig.1) Binucleation is not uncommon.

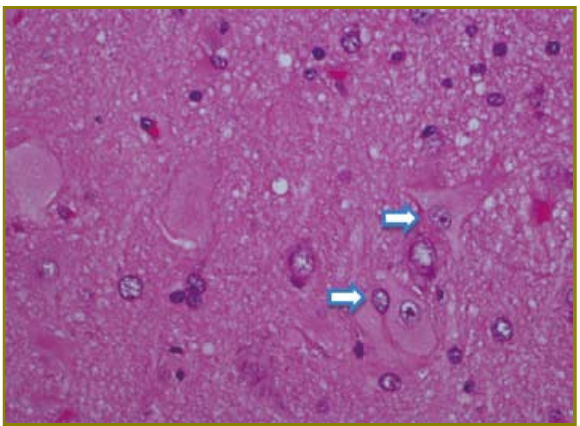

Fig. 1: FCDIIb with scattered balloon cells(arrow). (HE)

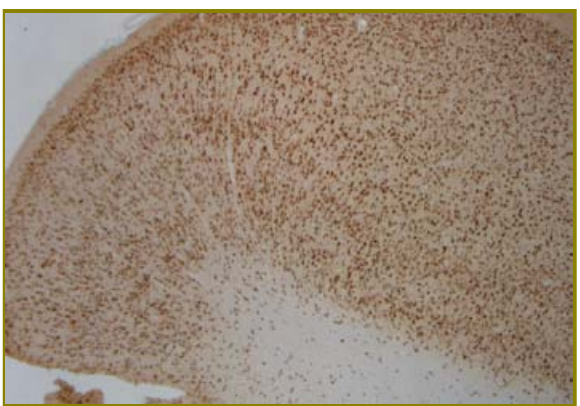

Fig. 2: Transition from relatively normal-looking cortical lamination (left) to disrupted neocortical laminar pattern (right), FCD IIb. (NeuN)

Post-zygotic somatic mutation of some, but not all, neuroblasts developed from the neuroepitheliaum (mosaicism) is believed to be the reason why mixed normal and abnormal neurons are present in the same cortical lesions. Post-zygotic genetic mutations differ substantially from germline mutations that occur at the time of fertilisation and explain why different phenotypes possible for same genetic mutations. Cellular dysmorphism and the abnormal growth of neurons in FCD IIa, FCD IIb, TSC and HME suggest a very early disorder of cellular lineage and differentiation.[2] Tau, one of the many microtubule-associated proteins, is upregulated in an abnormally phosphorylated form in adult degenerative disease and infantile tauopathies, which include FCD II, TSC, HME and ganglioglioma. These infantile tauopathies are disorders of the mTOR signalling pathway. This finding leads to the possibility of use of mTOR inhibitors as therapeutic options.

Specimen Handling – The ILAE guideline

Since histologic diagnosis of FCD relies on identification of abnormalities of the cortical cytoarchitecture as well as cytology, proper specimen handling is of paramount importance. To facilitate standardisation of handling and, hence, reliable histologic diagnosis across laboratories for better communication, research activities and tissue banking, the ILAE developed a consensus standard operational procedure for neuropathology workup of epilepsy specimens.[9] Whenever possible, anatomically intact surgical specimens are preferred to enable systematic analysis. Correction orientation of the tissue sample and the relationship between the tissue sample and the neurophysiologically aberrant sites are essential for the accurate histologic diagnosis of FCD. The latter requires effective communication between neuropathologists and the surgical team. While frozen section has a limited role in histologic diagnosis in epilepsy surgery, sectioning of the tissue sampling along a defined anatomical axis and together with the use of a panel of immunohistochemical stains render a reliable histologic diagnosis in epilepsy surgery. Review of our own cases received between 2001-2015 shows that 13% of the cases without a definitive diagnosis are due to suboptimal tissue orientation or fragmented nature of the specimens. Besides HE section and Luxol Fast Blue, a panel of immunohistochemical stains including GFAP, MAP2, NeuN, neurofilament protein, vimentin and CD34 are recommended in this international guideline.

Concepts in epilepsy surgery differ from those in neuro-oncology surgery, in which non-lesional brain tissue is rarely resected. However, the main goal of epilepsy surgery is to cure the epilepsy and to maintain long-term seizure control. So, the surgical resection field is not surprisingly larger than the lesional tissue detected by brain imaging because the epileptogenic field area defined electrophysiologically can be larger as the abnormal circuitries may be restricted to the malformed cortical area or may extend to the adjacent areas which are anatomically and functionally linked to the disorganised cortex.[2] This implies histologically normal tissue may not be functionally normal. Molecular alterations, e.g. channelopathies, altered glial network etc, that render brain tissue more susceptible to seizure are not detectable at the resolution of light microscopy. Moreover, secondary changes to intracerebral diagnostic procedures such as intracranial electrodes etc, always cause reactive cellular responses which may complicate the histologic interpretation. So, an interdisciplinary approach helps the neuropathologists to understand the clinical questions and subsequently optimal patient care. A standardised histopathologic reporting is helpful for further management of individual patients' epilepsy and understanding of the aetiology as well making available characterized human epilepsy brain tissue sample for brain research.

Conclusion

FCD is one of the commonest pathology in epilepsy surgical specimens. Being a localised pathology in MCD, FCD is amenable to surgery. The recent ILAE consensus classification helps to standardise the nomenclature of the condition, provide prognostic significance, and enhance our understanding of the disease. A standardised approach in specimen handling is mandatory for the effective use of the consensus classification.

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Topic: Current Evidence and Application of Picosecond Laser in Dermatology

Dr. Stephanie Lam
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Ketogenic diet for refractory epilepsy in children

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Introduction

Ketogenic diet is an established, effective non-pharmacologic treatment for drug resistant childhood epilepsy. The diet was first used to treat epilepsy in the 1920s[1], with little variation which constrains its compliance. In the past two decades, methods to achieve a ketogenic diet have been changed, allowing greater diet flexibility and hence better tolerance and compliance.

Ketogenic diet is a high-fat, low-carbohydrate, sufficient-protein diet that mimics the fasting state to maintain chronic ketosis in the body, so that ketones are produced as an alternative fuel source for the brain. It also provides adequate protein and calories for growth and development of the children.

Types of Ketogenic diet

There are four types of ketogenic diet: the classical ketogenic diet (KD), the medium chain triglyceride (MCT) diet, the modified Atkins diet (MAD), and the low glycaemic index treatment (LGIT).

The classical KD is based on a ratio of grams of fat (long chain triglycerides, LCT) to grams of carbohydrate and protein. A ketogenic ratio [fat: (carbohydrate + protein)] of 4:1 provides up to 90% calories from fat with the remaining 10% from protein and carbohydrate.

The MCT diet is a variant of the classical 4:1 KD introduced in the 1970s as an attempt to improve the palatability of the KD by allowing more carbohydrates yet preserving ketosis[2], based on the principle that MCT yields more ketones per calorie than LCT. The MCT diet provides about 75% calories from fat with 45-55% calories from MCT.

The MAD has been used since 2003 as an "alternative", less restrictive type of ketogenic diet[3,4]. This diet allows a free intake of protein, is very low in carbohydrate (about 10g/ day for children), and requires a liberal fat intake of about 70% calories from fat. The ketogenic ratio is about 1:1 to 2:1.

The use of LGIT in treating epilepsy was initially reported in 2005[5]. LGIT allows up to 10% of total calories from carbohydrate. The diet liberalises the extreme carbohydrate restriction of the other types of KD, while restricting the type of carbohydrate-containing foods to those with a glycaemic index of <50. Generous intake of fat (60% of calories from fat) is still required.

Ketogenic diet is an effective treatment for paediatric epileptic patients, as evidenced by the available meta-analysis and systematic review.[6,7] A Cochrane review[7] published in 2016 identified 7 randomised controlled trials (RCTs) which recruited 427 children and adolescents. The RCTs in the review showed promising results for the use of KDs in epilepsy, and concluded that MAD may have a similar effect on seizure control as classical KD.

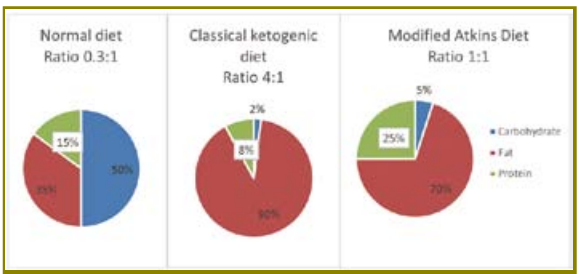

Fig. 1: Differences between the macronutrient compositions among the diets

More about modified Atkins diet (MAD)

In our centre, we have been using MAD in the majority of our children with epilepsy. The efficacy of MAD has been reported in more than 30 studies. A review in 2013 showed that after 3-6 months, approximately 50% of children started on MAD demonstrated a greater than 50% seizure reduction, with about 30% of children experiencing greater than 90% seizure reduction[4]. In a randomised trial on children published in 2013[8], 102 patients aged 2 to 14 years (mean age 5 years) with refractory epilepsy were randomised to receive either the MAD or no dietary intervention for a period of 3 months. The proportion of children with >90% seizure reduction (30% vs 7.7%) and >50% seizure reduction (52% vs 11.5%) was significantly higher in the MAD group. Five children (10%) in the MAD group were seizure free at 3 months compared with none in the control group. These results were comparable to those found for the classical KD. A systematic review and meta-analysis published in 2017 also revealed that classical KD did not differ substantially from MAD in ≥50% and ≥90% reduction of seizure frequency at month-3 and month-6[6]. When the children were maintained on the MAD for more than 6 months, rates of seizure reduction were also found to be similar to those reported for the classical KD, according to studies published in 2017[9].

The MAD allows an unlimited protein and fat intake is a less restrictive alternative to the classical KD. Besides, classical ketogenic meals appear very small in portion size owing to its high fat percentage. Many carergivers and patients find it easier to follow a relatively less restrictive MAD, especially in the adolescent and adult populations.

It was found that MAD did not always achieve long-term high levels of urinary ketosis, and many children and adults could lose ketosis over time yet have preserved seizure control[4]. The MAD has raised questions about the classic belief that persistent, high ketosis is critical. Further studies on this issue are warranted. The precise mechanism of how KD or MAD works to reduce seizures in epilepsy remains unknown. It may be due to the direct action of the ketone bodies producing an anticonvulsant effect, or the metabolic changes associated with ketosis.

Side effects are usually mild while following the MAD and are mostly limited to elevations in the lipid profile and gastrointestinal upsets such as constipation and nausea[8,9]. However, most of these side effects can be resolved with dietary modifications. Micronutrient deficiencies could also be an issue owing to the restrictive nature of the diet. It is therefore crucial for the patients on KD or MAD to have thorough assessments and regular follow-up by a dietitian for careful meal planning.

Before diet initiation

Baseline laboratory and urine testing are checked to ensure no pre-existing contraindications. The types of KD used will be discussed with caregivers, based on the dietary needs and habits of the individual child. In our centre, classical KD is more indicated for patients who need a liquid formula-based diet such as infants who have not started solid or children who are enterally fed, while MAD are more suitable for children and adolescents on oral diet.

Pre diet counselling will be done to caregivers and includes the diet principles, pros and cons of each type of ketogenic diet, possible side effects and the estimated cost for necessary supplements. Caregivers are encouraged to consider the feasibility and practicability of KD at home and share their concerns.

A Nutritional Assessment will be done before the start of diet; calories are typically restricted to 80-90% of the daily recommendations for age, to avoid excessive weight gain. In our centre, an individually estimated requirement is based on the home dietary history.

Ketogenic diet has gained much popularity in recent years,; recipes and meal plans are easily accessible on the website or in the market nowadays. Caregivers are discouraged to follow any meal plan before they have fully understood the details of the diet.

Meal arrangement

In our centre, the child will be admitted to the hospital for close monitoring when KD is introduced, and caregivers will be instructed on meal arrangement and home monitoring by dietitians and nurses. While other centres may involve a period of fasting when initiating KD, retrospective and prospective data showed fasting is not necessary for achievement of ketosis. Moreover, while fluid restriction was previously applied and thought to give a better outcome in KD, over hydration has not been found to exert a negative effect on epileptic seizures. Fasting and fluid restriction are not necessary in our centre.

In classical KD, the ketogenic ratio is increased stepwise from 1:1 to 4:1. In MAD, carbohydrates in the usual diet will be reduced stepwise. While additional oil will be added to the meal, portions will be adjusted according to the ketone production which is monitored daily. Though calculating the ketogenic ratio is not recommended[10], a ratio of 1 to 2:1 is usually achieved in MAD.

Comprehensive dietary counselling will be provided by dietitians. Guiding materials such as a detailed meal plan, a list of food containing carbohydrates, and food label explanations will be given to the caregivers. An emergency plan in case of hypoglycaemia or hyperketosis will also be given.

In view of the limited quantities of fruits, vegetables, enriched grains and dairy, multivitamin supplements with minerals and calcium supplement with vitamin D are recommended11. There are limited choices of paediatric multivitamin available in the market in Hong Kong; hence in our centre, we suggest to our patients that they take the adult formula at dosages of of 2-3 tablets per week, according to the RNI for age.

Monitoring

We recommend that a ketogenic diet, in the form of either classical KD or MAD, is continued for at least 2-3 months to evaluate efficacy.[10] Parents are encouraged to do routine urine ketosis evaluation for the child several times per week and to observe the seizure pattern of their child. Patients are regularly reviewed by dietitians at outpatient clinics, and diet is adjusted based on the nutritional assessment (growth parameters and estimated energy and protein intake), and on laboratory data such as urate, lipid profile and micronutrients levels in the blood.

In patients whose seizure control is successful, KD is recommended to be continued for 2 years. Weaning from KD to the normal diet will be done in a stepwise fashion over 3-4 months, with the ketogenic ratio slowly reduced every few days or few weeks.

Conclusion

A multidisciplinary approach involving neurologists, nurses and dietitians working closely together with regular discussions can provide a more comprehensive understanding of the disease and diet management for individual patients. Establishing a good relationship between caregivers and the team is always the key to successful implementation of the ketogenic diet.

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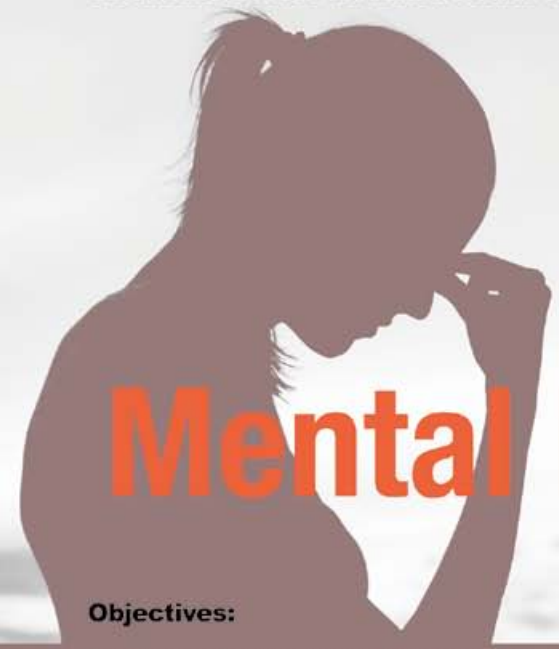
Certificate Course for Allied Health Professionals

CME/CNE Course | Course No. C315



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25 May	Dementia	Dr Candy HY WONG Private Psychiatrist
1 Jun	Insomnia & Management of Sleep Disorders	Dr Yee-him WONG Private Psychiatrist
8 Jun	Common Psychiatric Disorders in Children & Adolescents	Dr Candy HY LIN Private Psychiatrist
15 Jun	Psychosocial Approaches in Psychiatry	Dr Ka-lok TAM Associate Consultant United Christian Hospital
22 Jun	Psychosis	Dr Bruce KT CHAN Private Psychiatrist

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Executive dysfunction and psychiatric co-morbidities in childhood epilepsy

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Dr Fung-ling TAM

Introduction

Epilepsy is one of the most common neurological disorders in childhood. It occurs in approximately 5–7 cases per 10,000 children from birth to aged 15 years, and in about 5 of every 1,000 children in any given year. It is well known that there are increased risks of psychiatric illnesses in children with epilepsy (CWE). Psychopathology occurs in 37% to 77% of CWE, including major depression, anxiety, learning disabilities, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and others[1].

In the Isle of Wight study in 1970, Rutter et al.[2] reported that 7% of children in the general population exhibited a mental health problem compared with 12% of children with non-neurological physical disorders. Significantly higher rates were reported in epilepsy: 29% in children with uncomplicated and 58% in those with complicated epilepsy (i.e. structural brain abnormalities and seizures). Another UK epidemiological investigation conducted by Davies et al. in 1998[3] reported similar findings. Psychiatric disorders were found in 9.3% of the general population aged 5 to 15 years and 10.6% of those with a chronic medical disorder. Higher rates of psychiatric disorders were reported in epilepsy, including 26% in uncomplicated epilepsy and 56% in complicated epilepsy.

Apart from psychiatric co-morbidities, CWE is associated with higher rates of cognitive, behavioural, and academic problems than healthy controls, siblings and other age-matched children with chronic diseases, likely related to subtle cognitive deficits and executive dysfunction, even before antiepileptic drug (AED) treatment when compared with healthy controls[4].

Psychiatric co-morbidities and executive dysfunction in CWE are strongly associated with long-term quality of life, even if seizures are controlled or remit. However, psychiatric and psychological diseases are highly under-diagnosed and under-treated in CWE. One study showed that only 34% of those participants with clinically significant emotional–behavioural or executive functioning difficulties had a history of psychological or counselling services, highlighting the under-served mental health needs of this population[5].

In this article, we will focus on the symptomatology of executive dysfunction and some common psychiatric co-morbidities encountered by CWE.

Executive dysfunction

Executive functions (EFs) include a wide range of cognitive processes and have been defined as a set of inter-related skills often including one or more of the following constructs: a) attention control, b) planning/goal-setting and problem-solving, c) cognitive flexibility of thought and action, d) concept formation/abstraction, e) information processing, and f) working memory. These functions, or processes, are believed to be inter-related, and they are responsible for goal-directed or future-oriented behaviour. Executive functions have been referred to as the 'conductor' which controls, organises, and directs cognitive activity, emotional responses, and behaviour[6,7].

Children with epilepsy (aged 6–12 years) show significantly lower mean values in EFs than controls. CWE show prominent working memory deficits, planning deficits, and executive function deficits more generally[8]. It is worth noting that executive dysfunction is seen not only in those with frontal lobe epilepsies but also in other focal epilepsies of childhood such as temporal lobe epilepsy, as well as generalised epilepsy syndromes. Even children with mild forms of epilepsy (i.e., well controlled with medications and with average intellectual function) may show such difficulties in comparison to healthy children[9].

Cognitive problems are present in idiopathic childhood epilepsies[10]. They are not associated with traditional epilepsy syndromes, but are associated with measures of brain structure, parental IQ, family history, and neurodevelopmental features.

Executive functioning often affects social functioning as well. It is reasonable to hypothesise that children with executive dysfunction may be at higher risks of poor social adjustment and higher rates of stigma.

To assess the executive function, neurocognitive assessment batteries such as the Delis–Kaplan Executive Function System (number-letter switching, letter fluency, and colour-word interference), CNS Vital Signs (CNSVS)[11] and the Biber Cognitive Estimations Test have been used. Parent-rated questionnaires can also be an estimation of the daily executive function. For instance, the Behavioural Rating Inventory of Executive Function (BRIEF) is a standardised questionnaire designed to assess domains and subdomains of executive functioning via parent ratings of observable everyday behaviours. Superordinate indices include the Behavioural Regulation Index (BRI) and Metacognition

Index (MI) as well as the overall Global Executive Composite (GEC) score. The BRI consists of multiple subscales, including Inhibition, Shifting, and Emotional Control, while the MI consists of Working Memory, Initiation, Plan/Organise, Organisation of Materials, and Monitoring subscales. A t-score of ≥ 65 is considered the BRIEF cut-off score for clinically significant elevations.

Moderate correlations were found between neuropsychological deficits and quality of life. In one study, parent ratings of their child's executive functioning, namely problems with working memory, predicted quality of life to a greater degree than intellectual ability and epilepsy-specific factors[12]. Emotional function (Child Behaviour Checklist) and verbal memory (California Verbal Learning Test–Children's Version) emerged as significant predictor variables of Health-related quality of life (HRQoL). Low verbal memory was associated with a twofold risk of low HRQoL, emotional and behavioural difficulty with a 10-fold risk, and the combination of emotional and behavioural difficulty and low verbal memory with a 17-fold risk[12].

There is a relationship between executive dysfunction and psychiatric co-morbidities. Poor EF is significantly more prevalent in the group with a dysfunction within all different subgroups of psychiatric diagnoses (externalising, internalising, and neuropsychiatric disorders) than in the group with no psychiatric disorder[13].

The results reinforce the importance of neuropsychological assessment in clinical care in paediatric epilepsy and suggest important areas of focus for psychological intervention. Children with new-onset epilepsy, even those without severe cognitive or sensory-motor impairment, are at high risk for impaired attention and executive functions even before antiepileptic treatment, when compared with healthy controls. Systematic assessment of cognitive functions in children with new-onset epilepsy is necessary to detect subtle deficits in the early course and adjust treatment accordingly.

When deterioration of cognitive functioning is detected in the early course of paediatric epilepsy, a careful individual analysis of conditions is required.

Attention Deficit Hyperactivity Disorder (ADHD)

Compared with the estimated 2-16% of school-aged children in the general population with ADHD[14,15], rates of ADHD in children with epilepsy range from 30 to 40% with the predominately inattentive subtype of ADHD, making ADHD the most common behavioural problem that is associated with paediatric epilepsy[16]. Another unique phenomenon in this population is the disappearance of the usual gender differences in the prevalence of ADHD. The male to female ratio is 1:1 when co-morbid with epilepsy[17]. In comparison to generalised seizures, focal seizures are associated with a higher risk of ADHD and Depression in children.

The clearest course of diagnosis of ADHD in people with epilepsy is through history-taking. Typical ADHD symptoms occur in multiple settings at home or at school and are usually only mitigated by high degrees of structure. Epilepsy may be less predictable, and symptoms may be more prominent in parietal time periods. Fidgeting and impulsivity are less, and organisational ability may not be affected.

For ADHD, multiple rating scales, such as the Child Behaviour Checklist (CBCL), Conner's Parent/ Teacher Rating Scale and ADHD Rating Scale, have been developed that effectively measure the presence and severity of ADHD. They can be used as screening tools in people with epilepsy.

Anxiety and Mood disorders

The prevalence rates of anxiety disorders in paediatric epilepsy range from 5% to 49%[18] and those of depression vary from 23% to 33%[19]. Regarding frequency in adolescence, the anxiety disorder with the highest lifetime prevalence rate is specific phobia (19.9%), with social phobia (8.5%) and separation anxiety (7.6%) coming in at a close second and third[20].

The diagnosis of anxiety and depression is mainly clinical. Symptoms of depression and anxiety may be associated with the temporal relationship of seizures (pre-ictal, ictal, post-ictal or inter-ictal). Moreover, most anti-epileptic drugs can cause symptoms of depression in young people with epilepsy. If an anti-epileptic drug with mood stabilising properties is discontinued, symptoms of a mood disorder which was in remission because of anti-epileptic drugs can return. The side-effects of anti-epileptic drugs might also include anxiety.

Screening tool such as the Behaviour Assessment System for Children, Second Edition (BASC-2) can be used to screen mood and anxiety symptoms.

Autism Spectrum Disorder (ASD)

ASD and epilepsy are common co-mobidities. It was found that complex partial and generalised seizures were the most common types of seizures, and the abnormal activity usually appeared in the temporal and parietal areas of the brain. Intellectual disability was a risk factor for epilepsy in those with ASD, where the prevalence of epilepsy was 21.5% in those with intellectual disability, and 8% in those without intellectual disability[21]. Epilepsy in ASD was also associated with poorer verbal abilities[22]. Children with seizure disorders scored significantly lower in personal-social, communication scores, social maturity and adaptive scores than children without seizure disorders[23,24,25].

The clinical diagnosis of epilepsy in autism is complicated by the fact that subclinical complex absences may be mistaken for other childhood behaviours such as failing to respond to one's name or to participate in an activity introduced by someone else. The unusual stereotypic behaviours, common in children with autism can be challenging to be distinguished clinically from seizures. It is recommended that structured follow-ups and routine investigations of ASD in children with epilepsy, and of epilepsy in children with ASD[26].

Summary

Executive dysfunction and psychiatric co-morbidities are common in children with epilepsy, but they are usually under-diagnosed and left untreated. The treating physician should have an awareness of the symptoms and perform screening in these children. The general principle of treatment is to optimise the control of epilepsy first with the balance of side-effects of anti-epileptic drugs. Psycho-education to patients and the caregivers, as well as other behavioural and cognitive therapy, are also essential parts of the holistic management. Improving the quality of life is an essential goal in the treatment of children and adolescents with epilepsy, and it should be considered one of the most critical outcome variables.

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1	2	3	4 ★Joint Surgical Symposium – Breast Asymmetry after Surgery	5
6	7	8 ★HKMA Yau Tsim Mong Community Network - Update on Management of Fatty Liver Disease ★FMSHK Officers' Meeting ★HKMA Council Meeting	9 ★Hong Kong Neurosurgical Society Monthly Academic Meeting –Precision Medicine in Neurosurgery ★HKMA Central, Western & Southern Community Network - Recent Advances in Cancer Imaging & Current Trend of Genetic Testings in HK	10 ★HKMA Hong Kong East Community Network – Refining Management for Allergic Rhinitis & Quick Updates for Bell's Palsy ★HKMA New Territories West Community Network - How to Achieve Asthma Control in Primary Care Setting: A Case Approach ★HKMA – HKS&H CME Programme 2017-2018 –"Update in Medical Practice" ★UCH x FM x HKMA KE CN – Certificate Course for GPs 2018 – Assessing Febrile Frail Elderly Patients	11 ★HKMA Shatin Doctors Network and CUHK JC Centre for Osteoporosis Care & Control - The Benefit of LiFE in Fall Prevention in the Community	12 ★Refresher Course for Health Care Providers 2017/2018
13	14	15 ★HKMA Kowloon West Community Network - A Clinical Update in Lipid Management: PCSK9 Inhibitors	16 ★HKMA Shatin Doctors Network - Nutrition Intervention for Mild Cognitive Impairment	17 ★HKMA-Kowloon East Community Network – Local Clinical Experience in Using ARNI in Managing Heart Failure	18	19
20	21	22	23 ★HKMA Central, Western & Southern Community Network - A Clinical Update in Lipid Management: PCSK9 Inhibitors	24 ★HKMA Hong Kong East Community Network - Local Clinical Experience in Using ARNI in Managing Heart Failure ★HKMA New Territories West Community Network - Updates in Mild Cognitive Impairment and Dementia Assessment for Busy Clinicians ★FMSHK Executive Committee Meeting ★FMSHK Council Meeting	25	26
27	28	29 ★HKMA Kowloon West Community Network - Advances in Heart Failure Management - Local Experience with Use of ARNI	30	31 ★HKMA Kowloon East Community Network – Advance in Rheumatic Disease		

Date / Time	Function	Enquiry / Remarks
4 FRI 8:00 AM-9:00AM	**Joint Surgical Symposium – Breast Asymmetry after Surgery** Organizers: Department of Surgery, The University of Hong Kong & Hong Kong Sanatorium & Hospital; Venue: Hong Kong Sanatorium & Hospital; Chairman: Dr. Ava KWONG; Speakers: Dr. Polly CHEUNG and Dr. Dacita SUEN	Enquiry / Remarks Department of Surgery, Hong Kong Sanatorium & Hospital Tel: 2835 8698 Fax: 2892 7511 1 CME Point (Active)
8 TUE 1:00 PM	**HKMA Yau Tsim Mong Community Network - Update on Management of Fatty Liver Disease** Organiser:HKMA Yau Tsim Mong Community Network; Chairman: Dr. LEUNG Wai Fung, Anders; Speaker: Dr. LAU Siu Fai; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
8:00 PM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
9:00 PM	**HKMA Council Meeting** Organiser:The Hong Kong Medical Association; Chairman: Dr. CHOI Kin; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Christine WONG Tel: 2527 8285
9 WED 7:30 AM	**Hong Kong Neurosurgical Society Monthly Academic Meeting –Precision Medicine in Neurosurgery** Organiser: Hong Kong Neurosurgical Society; Speaker: Dr CHAN Shing Kit, Robert Chairman: Dr CHEUNG Fung Ching; Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital	Dr. LEE Wing Yan, Michael Tel: 2595 6456 Fax. No.: 2965 4061 College of Surgeons of Hong Kong 1.5 points
1:00 PM	**HKMA Central, Western & Southern Community Network - Recent Advances in Cancer Imaging & Current Trend of Genetic Testings in HK** Organiser:HKMA Central, Western & Southern Community Network; Chairman: Dr. YIK Ping Yin; Speaker: Dr. LAU Chung Hang, Kevin; Ms Clara FU; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Mr. Ian YAU Tel: 2527 8285 1 CME Point
10 THU 1:00 PM	**HKMA Hong Kong East Community Network – Refining Management for Allergic Rhinitis & Quick Updates for Bell's Palsy** Organiser:HKMA Hong Kong East Community Network; Chairman: Dr. GOH Kim Yeow; Speaker: Dr. Winnie KAN; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA New Territories West Community Network - How to Achieve Asthma Control in Primary Care Setting: A Case Approach** Organiser:HKMA New Territories West Community Network; Chairman: Dr. CHEUNG Kwok Wai, Alvin; Speaker: Dr. CHAN Chung Yan, Anthony; Venue: Pak Loh Chiu Chow Restaurant, Shop A316, 3/F, Yoho Mall II, 8 Long Yat Road, Yuen Long	Mr. Ian YAU Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA – HKS&H CME Programme 2017-2018 –"Update in Medical Practice"** Organiser:The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital; Speaker: Dr. CHAN Wan Pang; Venue: Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central	HKMA CME Dept. Tel: 2527 8285 1 CME Point
1:00 PM	**UCH x FM x HKMA KE CN – Certificate Course for GPs 2018 – Assessing Febrile Frail Elderly Patients** Organiser:United Christian Hospital, Hong Kong College of Family Physians & HKMA Kowloon East Community Network; Chairman: Dr. David VK CHAO; Speaker: Dr.SHA Kwok Yiu, Edmund; Venue: Conference Room, G/F, Block K, United Christian Hospital	Ms. Polly TAI; Ms. Cordy WONG (UCH) Tel: 3949 3430 Tel: 3949 3087 1 CME Point
11 FRI 1:00 PM	**HKMA Shatin Doctors Network and CUHK JC Centre for Osteoporosis Care & Control - The Benefit of LiFE in Fall Prevention in the Community** Organiser:HKMA Shatin Doctors Network and CUHK JC Centre for Osteoporosis Care & Control; Chairman: Dr. MAK Wing Kin; Speaker: Professor Lindy CLEMSON; Venue: Diamond Room, 2/F, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Candice TONG Tel: 2527 8285 1 CME Point
12 SAT 2:15 PM	**Refresher Course for Health Care Providers 2017/2018** Organiser:Hong Kong Medical Association; HK College of Family Physicians; HA-Our Lady of Maryknoll Hospital; Speaker: Mr. Jackie FAN; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin	Ms. Clara TSANG Tel: 2354 2440 2 CME Point
15 TUE 1:00 PM	**HKMA Kowloon West Community Network - A Clinical Update in Lipid Management: PCSK9 Inhibitors** Organiser:HKMA KLN West Community Network; Chairman: Dr. TONG Kai Sing; Speaker: Dr. Wu Kwok Leung, Kenneth; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chune, Mei Foo	Mr. Ian YAU Tel: 2527 8285 1 CME Point
16 WED 1:00 PM	**HKMA Shatin Doctors Network - Nutrition Intervention for Mild Cognitive Impairment** Organiser:HKMA Shatin Doctors Network; Chairman: Dr. MAK Wing Kin; Speaker: Prof. KWOK Chi Yui, Timothy; Venue: Diamond Room, 2/F, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Candice TONG Tel: 2527 8285 1 CME Point
17 THU 1:00 PM	**HKMA-Kowloon East Community Network – Local Clinical Experience in Using ARNI in Managing Heart Failure** Organiser:HKMA KLN East Community Network; Chairman: Dr. AU Ka Kui, Gary; Speaker: Dr. Tsang Kin Keung; Venue: Lei Garden Restaurant, Shop No. L5-8, apm, Kwun Tong, No. 418 Kwun Tong Road, Kowloon	Mr. Ian YAU Tel: 2527 8285 1 CME Point
23 WED 1:00 PM	**HKMA Central, Western & Southern Community Network - A Clinical Update in Lipid Management: PCSK9 Inhibitors** Organiser:HKMA Central, Western & Southern Community Network; Chairman: Dr. YIK Ping Yin; Speaker: Dr. Lee Kar Fai, Victor; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Mr. Ian YAU Tel: 2527 8285 1 CME Point

Date / Time	Function	Enquiry / Remarks
24 THU 1:00 PM	**HKMA Hong Kong East Community Network - Local Clinical Experience in Using ARNI in Managing Heart Failure** Organiser:HKMA Hong Kong East Community Network; Chairman: Dr. YIP Yuk Pang, Kenneth; Speaker: Dr. MIU Kin Man; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA New Territories West Community Network - Updates in Mild Cognitive Impairment and Dementia Assessment for Busy Clinicians** Organiser:HKMA New Territories West Community Network; Chairman: Dr. CHEUNG Kwok Wai, Alvin; Speaker: Prof. Adrian WONG; Venue: Fountain Function Rooms, Lobby Floor, Hong Kong Gold Coast Hotel, 1 Castle Peak Road, Gold Coast, Hong Kong	Mr. Ian YAU Tel: 2527 8285 1 CME Point
7:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
8:00 PM	**FMSHK Council Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
29 TUE 1:00 PM	**HKMA Kowloon West Community Network - Advances in Heart Failure Management - Local Experience with Use of ARNI** Organiser:HKMA KLN West Community Network; Chairman: Dr. TONG Kai Sing; Speaker: Dr. Lau Chun Leung; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chune, Mei Foo	Mr. Ian YAU Tel: 2527 8285 1 CME Point
31 THU 1:00 PM	**HKMA Kowloon East Community Network – Advance in Rheumatic Disease** Organiser:HKMA KLN East Community Network; Chairman: Dr. AU Ka Kui, Gary; Speaker: Dr. TSUI Hing Sum, Kenneth; Venue: V Cuisine, 6/F., Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O	Mr. Ian YAU Tel: 2527 8285 1 CME Point

Certificate Course for Doctors, Midwives, Nurses, Radiographers & Other Healthcare Professionals who preferably have a basic knowledge of obstetric ultrasound

Certificate Course on
Practical Obstetric Ultrasonography

Course No. C318 **CME/CNE Course**

Jointly organised by

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Hong Kong Society for Ultrasound in Medicine

Date	Topics	Speakers
7 Aug	New algorithm in prenatal diagnosis	Dr. WC LEUNG Consultant Obstetrician & Chief-of-service, Department of O&G, Kwong Wah Hospital
14 Aug	Ultrasonography of early pregnancy complications including scar pregnancy	Dr. Vincent CHEUNG Clinical Associate Professor in Obstetrics& Gynaecology The University of Hong Kong
21 Aug	Ultrasonography of placenta, liquor and membranes	Dr. TY FUNG Chief of Service, Obstetrics & Gynaecology Hong Kong Baptist Hospital
28 Aug	How to integrate three- and four-dimensional ultrasonography in obstetric sonography?	Dr. KY LEUNG Consultant and Chief-of-service, Department of O&G Queen Elizabeth Hospital
4 Sep	Nomogram, fetal growth restriction and macrosomia	Dr. Meliza KONG Consultant, Department of O&G United Christian Hospital
11 Sep	Tips in performing routine mid-trimester anomaly scan	Dr. CN LEE Consultant, Department of O&G Pamela Youde Nethersole Eastern Hospital

Date : 7, 14, 21, 28 Aug, 2018 & 4, 11 Sep, 2018 (Every Tuesday)
Time : 7:00 p.m. – 8:30 p.m.
Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Course Fee : HK$750 (6 sessions)
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

Application form can be downloaded from website: http://www.fmshk.org

Answers to Dermatology Quiz

Answer:

1. Poikiloderma is a dermatological term that describes mixed skin lesions of hyperpigmentation, hypopigmentation, atrophy and telangiectasia.

2. Poikiloderma of Civatte is the most likely clinical diagnosis. Civatte was a French dermatologist who first described this condition with mottling or reticulated pigmentation and redness over the neck, mostly in women with fair skin. Other differential diagnoses include Riehl's melanosis, melasma, atrophoderma vermiculata, erythromelanosis follicularis, arsenic poisoning, etc.

   Poikiloderma of Civatte is mainly a clinical diagnosis. Other important underlying causes of poikiloderma should therefore be excluded first. These include collagen-vascular diseases (lupus erythematosus, dermatomyositis, scleroderma), radiodermatitis, poikiloderma atrophicus vascularis in mycosis fungoides, poikiloderma-like cutaneous amyloidosis, and some genodermatoses (Rothmund-Thomson syndrome, Bloom syndrome).

3. The exact aetiology is unknown, but presumptively due to photosensitising components of cosmetics and toiletries (especially perfumes), long term sun exposure and hormonal change.

4. The management includes sun protection and avoidance of all perfumes on or near the affected areas. Hydroquinone and topical retinoid may help to fade part of the pigmentation. Pulsed dye laser and intense pulsed light treatment are useful to reduce the telangiectasia and redness.

Dr Lai-yin CHONG
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Specialist in Dermatology & Venereology

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will not respond adequately
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VNS Therapy® is recommended by guidelines as an adjunctive therapy in reducing seizure frequency in children and adults with DRE who are not suitable for resective surgery

* Not approved in all countries. Consult your label.
The VNS Therapy® Models featured in this page are not approved in all countries. Consult your label.

1. Brodie M.J. Epilepsia. 2013; 54:5–6.

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