GCY Fong 方頌恩
JKY Fong 方嘉揚

Recent advances in the diagnosis and management of epilepsy

癲癇症診斷和處理新進展

Epilepsy is the second most common neurological disorder in developed countries. Recent advances in the understanding of pathogenetic mechanisms and in the diagnosis and management of epilepsy over the past decade have had a significant impact on every aspect of epilepsy management. A simple diagnosis is inadequate for both patients and physicians. A full diagnostic investigation to classify the type of epilepsy is now mandatory for appropriate care. In this review, current views on pathogenetic mechanisms, controversies in classification, advances in neuroimaging techniques, the use of novel antiepileptic drugs, and non-pharmacological treatment options for intractable epilepsy will be discussed.

癲癇症是發達國家中第二種最常見的神經性疾病。過去十年中，對癲癇症的病理機製的瞭解，和診斷處理中的新進展在癲癇症護理的各方面都產生顯著影響。簡單的診斷對於患者和醫生都是不足夠的。對於採取適當護理而言，一個完整的診斷檢查以區分癲癇症類型是必須的。本文將討論癲癇病理機製上的新觀點，分類中的爭論，神經圖像技術的新進展，新抗癲癇藥物的使用，以及對於難處理的癲癇症的非藥理治療方法。

Key words:
Epilepsy/classification;
Epilepsy/diagnosis;
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關鍵詞：
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Division of Neurology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong
GCY Fong, MRCP, FHKAM (Medicine)
JKY Fong, MRCP, FHKAM (Medicine)

Correspondence to: Dr GCY Fong

Introduction

The term epilepsy is derived from the Greek word epilamvanein or epilepsia, which means ‘to be seized’, ‘to be taken hold of’, or ‘to be attacked’. Famous historical figures such as Alexander the Great, Julius Caesar, Napoleon Bonaparte, Charles Dickens, and Vincent Van Gogh were affected by epilepsy. Possession by evil spirits was once considered the aetiology of epilepsy, thereby causing significant social handicap. The magnitude of medical, social, and economic problems arising from chronic epilepsy is staggering.

Epilepsy is the most common neurological disease worldwide and is second to stroke in causing neurological morbidity in developed countries. Approximately 45 to 100 million people worldwide are estimated to have active epilepsy.[1] In the United States, the age-adjusted mean annual incidence of epilepsy ranges from 28.9 to 53.1 per 100 000.[2] Given a proposed 7% rate of underreporting, there would be a total of 70 000 to 12 800 new cases of epilepsy every year.[3] The projected number of new cases of epilepsy in Hong Kong is approximately 2000 per year. The cumulative incidence of epilepsy is 1.3%[4] to 3.1%[5] for people aged up to 80 years.

This review discusses current views on epilepsy pathogenesis and controversies of epilepsy classification. In particular, the role of

molecular discoveries in the diagnosis of various epilepsy syndromes will be highlighted. In addition, advances in neuroimaging techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), as well as the use of novel antiepileptic drugs (AEDs) and non-pharmacological treatment options for intractable epilepsy are addressed.

Classification of seizures and epileptic syndromes

Hughlings Jackson divided chronic epilepsies into focal and generalised seizures, and this important distinction is now embedded in the International League Against Epilepsy (ILAE) classification of the epilepsies.[6,7] The ILAE classification provides a taxonomic scheme for the analysis of individual seizure attacks. Apart from the fundamental concept of 'generalised' versus 'partial' epilepsies, the aetiological distinction between 'idiopathic' versus 'symptomatic' is also emphasised. The term idiopathic carries with it the implication of normal intelligence and neurological status, whereas the term symptomatic is associated with abnormal neurological findings, and commonly, brain lesions. An intermediate term, cryptogenic, has been used to describe syndromes that are presumed to be symptomatic but where the aetiology remains unidentified. Dozens of idiopathic epilepsies—both generalised and partial—have now been shown to be the consequence of genetic defects. Examples include juvenile myoclonic epilepsy and autosomal-dominant nocturnal frontal lobe epilepsy syndrome. Despite the intensive effort spent in revising the first ILAE classification, only about one third of adult epilepsy cases fit into a diagnostic category of the current ILAE classification.

The practicality of the ILAE classification in routine clinical practice has been called into question.[8] Hence, newer classifications for seizures and epilepsy, which incorporate neurogenetic, neuroradiological, and neurosurgical advances have been proposed.[8-10] These classifications emphasise different aspects of epileptic seizures (Tables 1 and 2).[9-11] As a result, an ILAE task force is evaluating the need to revise the current ILAE classification, the following four specific areas will be considered:

(1) descriptive terminology for ictal phenomena;
(2) classification of epileptic seizures based on known or presumed pathophysiological and anatomic substrates;
(3) classification of epileptic syndromes and epileptic diseases due to unique aetiologies (eg single gene defects); and
(4) an additional category for classification of functional disability due to seizures or epilepsy.[12]

Table 1. Semiologic classification of seizures[9,10]

Paroxysmal event	
Epileptic seizures	Non-epileptic paroxysmal event
Auras	
Somatosensory auras*	
Auditory auras	
Olfactory auras	
Abdominal auras	
Visual auras*	
Gustatory auras	
Autonomic auras*	
Psychic auras	
*Autonomic seizures**	
Dialeptic seizures	
Typical dialeptic seizures (typical absence seizure in ILAE† classification)	
*Motor seizures**	
Simple motor seizures*	
Myoclonic seizures*	
Epileptic spasms*	
Tonic-clonic seizures	
Tonic seizures*	
Clonic seizures*	
Versive seizures*	
Complex motor seizures	
Hypermotor seizures	
Automotor seizures	
Gelastic seizures	
Special seizures	
Atonic seizures*	
Hypermotor seizures	
Negative myoclonic seizures*	
Astatic seizures	
Akinetic seizures*	
Aphasic seizures	

* Indicates the seizure has a somatotopic distribution
† ILAE International League Against Epilepsy

Genetic epilepsy syndrome

Advances in molecular genetics have fostered new understanding of the pathogenesis of epilepsy. In the past decade, about a dozen genetic defects and over 30 genetic loci have been identified. Mutation of the sodium channel β-1 subunit in febrile convulsions,[13] and a potassium channel mutation in benign familial neonatal convulsions[14] are two examples.

Up-to-date genomic locations that are associated with epilepsy syndromes are summarised in Fig 1 and Table 3. Genetic counselling should be provided when laboratory support can confirm the gene defect. Completion of the human genome project, micromanipulation of embryos, transfer and 'knock-out' of genes, and gene therapy may be possible in the future to correct these underlying primary defects.

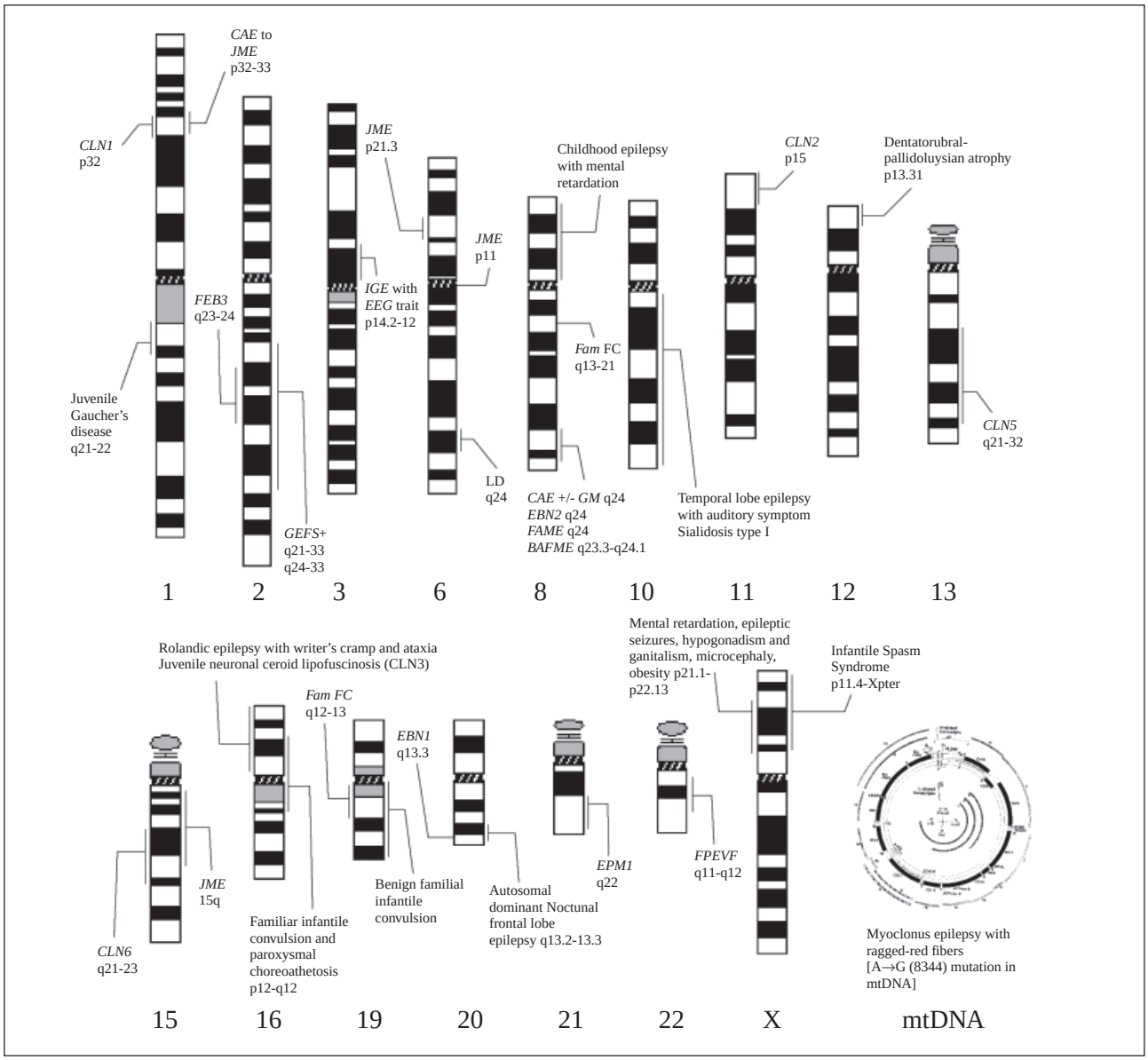
Table 2. Modern and revised version of the ILAE classification of the epilepsies[11]

Genetic epilepsies	Symptomatic or acquired epilepsies
Genetic epilepsies whose primary symptoms/signs are exclusively generalised and/or partial seizures Benign neonatal familial convulsions in chromosome 20q and 8q24 Benign infantile familial convulsions in chromosome 19q Infantile spasms—X-linked Benign infantile familial convulsions and paroxysmal choreothetosis in chromosome 16p12-q12 Childhood absence epilepsy (pyknolepsy) with or without grand mal tonic clonic seizures in chromosome 8q24 Childhood absence epilepsy (pyknolepsy) with grand mal tonic clonic and myoclonic seizures during adolescence in chromosome 1p Juvenile myolonic epilepsy in chromosome 6p and chromosome 15q Epilepsy with generalised tonic clonic seizure on awakening in chromosome 6p Childhood epilepsy with centrotemporal spikes and writer's cramp/ataxia in chromosome 16p12-q12 Temporal lobe epilepsies in chromosome 10q Febrile convulsions in chromosome 8q and 19q and 2p *Genetic epilepsy syndromes with severe neurological deficits and/or progressive degenerations and/or malformations* Cortical dysplasias Progressive myoclonus epilepsies Landau-Kleffner syndrome *Idiopathic epilepsies with generalised seizures—undetermined aetiology but suspected to be of genetic origin* Benign neonatal convulsions Benign myoclonic epilepsy in infancy Idiopathic West syndrome Lennox Gastaut Dravet syndrome with normal psychomotor development Early childhood primary myoclonic epilepsy Severe myoclonic epilepsy of infancy Juvenile absence epilepsy Epilepsy with myoclonic absence Epilepsy with generalised tonic clonic seizure on awakening	*Symptomatic epilepsies with mainly generalised seizures* West syndrome Lennox-Gastaut Dravet syndrome Epilepsy with myoclonic-astatic seizures Early myoclonic encephalopathy Early infantile epileptic encephalopathy with suppression bursts (Ohtahara syndrome) *Symptomatic epilepsies with partial seizures and/or secondary generalised seizures* Epilepsia partialis continua of childhood (Kojewnikow syndrome) Rasmussen's encephalitis Benign epilepsia partialis continua Temporal lobe epilepsies Frontal lobe epilepsies Parietal lobe epilepsies Occipital lobe epilepsies

Epileptogenesis and seizure expression

Basic research in epilepsy has focused on focal epileptogenesis and seizure spread for more than half a century, with recent findings clarifying the pathogenesis of chronic epilepsy. The basic mechanism is likely to be due to abnormal cell-to-cell communication, which results in chronically enhanced states of excitability. Long-term potentiation,[15] mirror or a secondary focus,[16] and the kindling phenomenon,[17] are the most widely accepted paradigms that explain such hyperexcitability. All postulated theories share the common view that repeated seizures facilitate the development of chronic epilepsy—that is, that seizures beget seizures.

When applied to clinical practice, this view implies that epilepsy may become intractable to AEDs if seizure control is suboptimal. This implication is in concordance with the clinical dictum, 'partial control equals no control.' Mesial temporal sclerosis is offered as a clinical illustration. The current pathogenetic model for this condition consists of initial neuronal death and selective cell damage caused by status epilepticus or recurrent seizures. This subsequently results in mossy fibre sprouting and reorganisation, which leads to chronic epilepsy.[18,19] Repeated seizures have also been implicated in hippocampal damage and impaired recent memory.[20,21] There is accumulating evidence suggesting the induction of chronic epilepsy by infantile febrile seizures, although debate is still ongoing.[22,23] Given current data, long-term follow-up after complex febrile convulsions appears advisable. Effective prophylaxis of recurrent febrile seizures and aggressive treatment of status epilepticus appear to be potentially useful strategies of reducing the subsequent emergence of hippocampal sclerosis.



* Disease/gene abbreviations and genetic loci are listed in Table 3

Fig 1. Gene map of epilepsy syndromes

Diagnostic evaluation of epilepsies

Correct diagnosis is the cornerstone of appropriate management. Diagnostic evaluation begins with good history-taking and is supplemented by physical examination and routine electroencephalography (EEG) (Table 4). Clinical signs, such as subtle body part asymmetry consistent with early focal cerebral insult, visual field defect, and neurocutaneous stigmata, can be overlooked without a high index of suspicion. Whenever identified, such signs are strongly indicative of focal epilepsy, and active search for the underlying pathology is required.

A simple diagnosis of epilepsy is inadequate for both patients and physicians. A simplified and practical scheme for providing a more specific epilepsy diagnosis is outlined in Fig 2, and effort should be made to classify the epilepsy into one of these categories. Step 1 involves differentiating epileptic seizure from non-epileptic events, and reactive seizures from spontaneous recurring seizures. Seizures induced by alcohol intoxication, sleep deprivation, and metabolic encephalopathy in general do not require AED prophylaxis. Rational treatment is simply elimination of the precipitating factors. Observation for a period of 6 months to 1 year, however, may be necessary to determine whether seizures are spontaneous or reactive.

For those patients who have spontaneously recurring seizures, neuroimaging is almost always indicated in the search for the underlying aetiology. Epileptogenic lesions conform to specific disease categories, such as tumour, arteriovenous malformation, or

Table 3. Summary of disease/gene abbreviations and genetic loci

Disease/gene abbreviation	Genetic loci
Infantile neuronal ceroid lipofuscinosis (CLN1) or Santavuori-Hattia's disease	1p32
Childhood absence epilepsy to juvenile myoclonic epilepsy (CAE to JME)	1p32-33
Juvenile Gaucher's disease	1q21-22
Familial generalised epilepsy with febrile seizure plus (GEFS+)	2q21-q33
Febrile seizure (FEB3)	2q23-24
Generalised epilepsy with febrile seizure plus	2q24-q33
Idiopathic generalised epilepsy (IGE) with electroencephalogram trait	3p14.2-12
Juvenile myoclonic epilepsy (JME)	6p11
Juvenile myoclonic epilepsy	6p21.3
Lafora's disease (LD)	6q24
Childhood epilepsy with mental retardation	8p
Familial febrile convulsion (Fam FC)	8q13-21
Benign adult familial myoclonic epilepsy (BAFME)	8q23.3-q24.1
Childhood absence epilepsy and grand mal epilepsy (CAE +/- GM)	8q24
Benign neonatal familial convulsions (second locus) [EBN2]	8q24
Idiopathic generalised epilepsy trait	8q24
Familial adult myoclonic epilepsy (FAME)	8q24
Temporal lobe epilepsy with auditory symptom	10q
Sialidosis type I	10q
Classical late infantile neuronal ceroid lipofuscinoses (CLN2)	11p15
Dentatorubral–pallidoluysian atrophy	12p13.31
Late infantile Finnish variant neuronal ceroid lipofuscinosis (CLN5)	13q21-32
Juvenile myoclonic epilepsy	15q
Late infantile variant neuronal ceroid lipofuscinosis (CLN6)	15q21-23
Rolandic epilepsy with writer's cramp and ataxia	16p
Juvenile neuronal ceroid lipofuscinosis or Batten's disease (CLN3)	16p
Familial infantile convulsion and paroxysmal choreathetosis	16p12-q12
Benign familial infantile convulsion	19p
Familial febrile convulsion	19q12-13
Autosomal dominant nocturnal frontal lobe epilepsy	20q13.2-13.3
Benign neonatal familial convulsions (EBN1)	20q13.3
Progressive myoclonus epilepsy of Unverricht Lundborg type (EPM1)	21q22
Familial partial epilepsy syndrome with variable foci (FPEVF)	22q11-q12
Mental retardation, epileptic seizures, hypogonadism and ganitalism, microcephaly, obesity	Xp21.1-p22.13
Infantile spasm syndrome	Xp11.4-Xpter
Myoclonus epilepsy with ragged red fibres	8344 mtDNA

hippocampal sclerosis. The pathology and location of the epileptogenic zone (temporal versus extratemporal) are both important in determining the subsequent management, especially when epilepsy surgery is contemplated.

Electroencephalography

Electroencephalography remains the most important investigation for epilepsy. It involves the recording and analysis of electrical signals generated by the brain. These signals are small and surrounded by a variety of large electrical potential from the environment. Good equipment, meticulous technique, and informed interpretation of data are all equally important for the proper use of this neurodiagnostic tool.

Video-EEG synchronises ictal behaviour and electroencephalogram changes so that the actual seizure attacks can be recorded for semiological analysis. This method permits the best classification of seizure type, along with localisation of the epileptogenic focus as part of the presurgical evaluation. Depth or subdural intracranial electrodes are sometimes used with video-EEG for better definition of the seizure onset and its route of propagation. Although this procedure carries some morbidity (including intracerebral haemorrhage), mortality is seldom reported. Invasive-EEG is useful for guiding successful surgical resection and can be safely performed by an experienced neurosurgeon.

Magnetic resonance imaging

Magnetic resonance imaging is currently the most sensitive and specific structural neuroimaging procedure for epilepsy.[24] Advantages of MRI include noninvasiveness, high resolution, multiplanar imaging, and the absence of biological toxicity and ionizing radiation.[25] Brain study by MRI reliably identifies the pathological findings responsible for the epileptogenic zone and indirectly suggests the localisation of the epileptic brain tissue.[25] Lesions, including tumours, vascular malformations, hippocampal sclerosis,[24] and neuronal migration defects,[25-27] can readily be detected on the MRI scan (Box).

Table 4. Diagnosis of epilepsy syndromes: factors to be considered

Factors	Examples
Age of seizure onset	Benign familial neonatal convulsions Benign neonatal familial convulsions (second locus) Childhood absence epilepsy Juvenile absence epilepsy Juvenile myoclonic epilepsy Benign adult familial myoclonic epilepsy
Remission of epileptic seizures	Childhood absence epilepsy
Interictal neurological status	Progressive myoclonus epilepsy of Unverricht Lundborg type
Causes and trigger mechanisms of epileptic fits	Juvenile myoclonic epilepsy (photic stimulation) Childhood absence epilepsy (hyperventilation)
Interictal and ictal electroencephalogram findings	Lennox-Gastaut syndrome Lafora's disease of Unverricht Lundborg type (EPM1)
Different response to anti-epileptic drugs	Childhood absence epilepsy Juvenile myoclonic epilepsy
Remission rate after treatment	Childhood absence epilepsy
Pattern of hereditary transmission	Autosomal dominant nocturnal frontal lobe epilepsy Neuronal ceroid lipofuscinosis (CLN1-6) Myoclonus epilepsy with ragged red fibres
Clinical semiology and ictal electroencephalogram correlation	Partial epilepsy syndromes (temporal, frontal, parietal, and occipital lobe epilepsies), myoclonic epilepsy, absence epilepsy

Hippocampal sclerosis is now recognised as a distinct epileptic syndrome, characterised by recurrent complex partial seizures, a positive history of febrile convulsions, adolescent onset, hippocampal atrophy on MRI (unilateral or sometimes bilateral), CA1 and CA4 subsector gliosis, and often intractability to AED treatment. Hippocampal sclerosis can be treated surgically, and its detection by neuroimaging is thus of vital interest. New MRI techniques have been used to enhance diagnostic sensitivity and specificity (up to 95%). Such techniques include T_2-relaxometry,[28] and fluid-attenuated inversion recovery sequence.[29] High-resolution MRI provides detailed anatomical landmarks so that volumetric MRI can then be applied to quantify (with the aid of sophisticated computer software) the extent of hippocampal atrophy.[30] Magnetic resonance spectroscopy (MRS) is another new method that can be used to study changes in neurotransmitters,[31-33] and functional MRI studies can be used to map the sensorimotor strip and language cortex.[34]

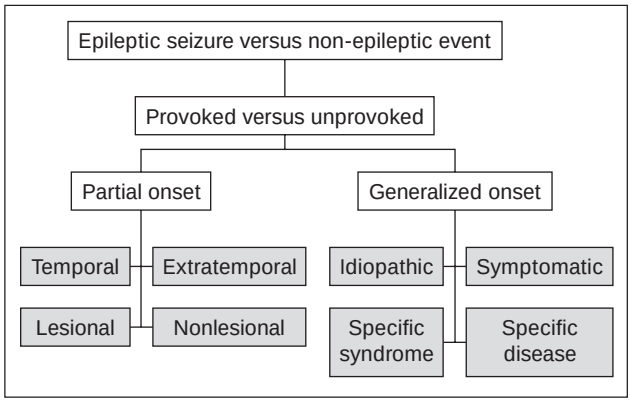


Fig 2. A clinical approach to classification of seizures and epilepsies

Functional neuroimaging

Functional neuroimaging plays an important role in epilepsy management, particularly in identifying surgically resectable foci. Two kinds of functional neuroimaging are currently available commercially—namely, single-photon emission computed tomography (SPECT) and PET. Functional neuroimaging is the product of a radioactive tracer, imaging hardware, and data-analysis software. Different tracers and neurotransmitter ligands can be used in PET scan studies

Commonly detected magnetic resonance imaging lesions in patients with intractable epilepsies

- Mesial temporal sclerosis
- Neoplastic lesions, eg oligodendroglioma, meningioma
- Vascular malformation, eg arteriovenous malformation, cavernous haemangioma
- Developmental lesions
  - Diffuse neuronal migration disorders
    - Diffuse pachygyria
    - Lissencephaly
    - Subcortical laminar heterotopia (double cortex syndrome)
  - Focal
    - Focal cortical dysplasia
    - Polymicrogyria
    - Schizencephaly
    - Focal nodular subcortical heterotopia
    - Hemimegalencephaly
    - Harmatoma eg dysembryoblastic neuroepithelial tumour

(^{18}F-2-deoxyglucose [FDG], ^{15}O, $C^{15}O_2$, ^{11}CO and $H_2{}^{15}O$) and SPECT study (^{99m}hexamethylene-propyl-eneamine-oxime [^{99m}Tc-HMPAO], ^{123}I-iodoamphetamine [IMP] and ^{99m}Tc-ethyl cysteinate dimmer [ECD or Neurolyte®]). The choice of tracer depends on the physiological process of interest, such as oxygen consumption, glucose metabolism, or cerebral blood flow. It is important to know the clinical status of the patient, because a seizure prior to isotope injection can alter cerebral metabolism and hence the test result.

Two commonly used functional neuroimaging studies for epilepsy are FDG-PET and ECD SPECT. The sensitivity of detecting unilateral temporal hypometabolism by interictal FDG-PET is 70% to 80%.[35,36] Well-localised hypometabolism may be slightly less frequent in cases of extratemporal partial epilepsy.[37] On rare occasions, ictal FDG-PET scan may inadvertently show a hypermetabolic signal over the seizure focus.[38] In contrast, the sensitivity of interictal SPECT scan for extratemporal lobe epilepsy is only about 50%.[39-41] As the half-life of the isotopes involved is much longer than the duration that occurs in FDG—6 hours for ^{99m}Tc HMPAO versus 2 minutes for FDG—ictal study can be done in video-EEG monitoring units.[42] This technique increases the sensitivity of cerebral SPECT study to between 65% and 90%,[40,43,44] with rare false-positive results.[44] Findings from a ictal SPECT study correlate well with MRI, video-EEG, and depth EEG localisation investigations.[43]

Treatment

Advances in treatment modalities for epilepsy are encouraging. Until the advent of a 'cure' for epilepsy, perhaps through advances in molecular genetics, novel AED therapies, epilepsy surgery, and neuroprosthesis implantation provide therapeutic options for the management of intractable epilepsy.

Antiepileptic drugs: an overview

Since bromides were first used to treat seizures in the 19th century, research to discover better-tolerated and more effective drugs has been continuous. Antiepileptic drugs remain the treatment of choice for chronic epilepsy. Mechanisms of drug action include decreasing neuronal excitability; or enhancing inhibition by altering sodium, potassium or calcium conduction; or by affecting the activities of neurotransmitters such as γ-aminobutyric acid or glutamate. Specific AEDs launched after valproate in 1980 were classified as new AEDs in contrast with conventional AEDs (eg phenytoin, carbamazepine, phenobarbital, benzodiazepines ethosuximide, and valproate). Vigabatrin was first introduced in European countries in 1989. Gabapentin, lamotrigine, felbamate, clobazam, oxcarbazepine, tiagabine, topiramate, zonisamide, and levetiracetam are also examples of new AEDs. Most of these are indicated as add-on therapy for refractory partial seizures, and there now increasing data to justify their use as monotherapy, or in generalised epilepsy syndromes. The safety profile for using these new AEDs in pregnancy however, is still unknown.

Antiepileptic drug treatment—new better than old?

In the past decade, a number of new AEDs have been studied in clinical trials. Marson et al[45] reported a meta-analysis of new drug trials in 1997. Pooled data from 4091 patients were included, and the efficacy and side effects of new AEDs are summarised in Table 5. Overall, the efficacy is comparable to conventional AEDs but central nervous system side effects (ataxia, dizziness, somnolence) are still noted, especially when high drug dosages are used. Apart from seizure type, the side effect profile is the most important factor in determining the choice of AED. The following examples will illustrate how the side effect profile of individual AEDs affects their clinical usage.

Oxcarbamazepine

Carbamazepine has proven efficacy in the treatment of partial and secondary generalised epilepsy. Its 10-keto analogue, oxcarbamazepine, has a low propensity to inhibit or induce oxidative enzymes and does not produce carbamazepine epoxide. Oxcarbamazepine can be given twice daily with a dose equivalence of 3 to 2 when switching from carbamazepine.

It has been advocated as monotherapy for patients with newly diagnosed epilepsy or as an alternative to carbamazepine, if side effects are troublesome (eg Stevens-Johnson syndrome). There is 30% cross-hypersensitivity with carbamazepine, however.

Lamotrigine

The median daily dose of lamotrigine ranges from 200 to 400 mg/d. Lamotrigine is as effective as carbamazepine or phenytoin, but it has a better side effect profile.[46] Hypersensitivity rash, the most troublesome side effect, appears to be dose related. A rash similar to Stevens-Johnson syndrome was noted in approximately 0.2% of patients treated, and the incidence of non-serious rash was approximately 7%.[47] Consequently, it was recommended that a low starting dose of lamotrigine (eg 25 mg/d or 25 mg on alternate days when combined with valproate) should be used,

Table 5. Pooled efficacy and side effects data from randomized studies of new antiepileptic drug

	Odds ratio (95% CI)					
	50% responders	Withdrawal (any reason)	Ataxia	Dizziness	Fatigue	Headache
Gabapentin	2.29 (1.53-3.43)	1.36 (0.75-2.49)	2.03 (1.00-4.13)	2.25 (1.28-3.95)	2.25 (1.09-4.63)	0.67 (0.33-1.36)
Lamotrigine	2.32 (1.47-3.68)	1.19 (0.79-1.79)	2.98 (1.86-4.77)	2.38 (1.63-3.48)	0.71 (0.26-1.24)	1.15 (0.72-1.85)
Tiagabine	3.03 (2.01-4.58)	1.81 (1.21-2.70)	1.24 (0.33-4.64)	1.88 (1.18-2.99)	1.45 (0.88-2.40)	-
Topiramate	4.07 (2.87-5.78)	2.56 (1.64-4.00)	1.84 (0.97-3.49)	1.89 (1.20-3.28)	2.52 (1.47-4.31)	-
Vigabatrin	3.68 (2.45-5.51)	2.58 (1.26-5.27)	1.44 (0.51-4.03)	1.61 (0.80-3.22)	1.50 (0.81-2.76)	1.08 (0.45-2.59)
Zonisamide	2.47 (1.36-4.47)	4.23 (1.71-10.49)	6.86 (2.63-17.85)	2.58 (1.11-5.96)	2.66 (1.14-6.22)	-

with slow dose escalation (eg increasing 25 mg every week) until the desired target range is achieved.

Topiramate

Topiramate shows a plateauing of therapeutic effect with doses greater than 600 mg/d. A significantly higher percentage of patients enter remission with add-on topiramate therapy, and the long-term retention rate is among the highest for the new drugs. Approximately 30% of patients continue topiramate into the third year. Patients taking near-maximal dosages were less likely to withdraw from therapy due to side effects than with alternative agents.[48] The side effect of 'thinking abnormality' in relation to this drug refers to problems with concentration, in contrast to the psychotic thought disorder associated with vigabatrin use. Hence, topiramate is not usually contraindicated for patients with psychiatric disorders.

Vigabatrin

Vigabatrin was introduced in 1989 in Europe, and various studies subsequently established that a dose of 2 to 4 gm/d was effective in controlling infantile spasms (West syndrome), and complex partial seizures. The efficacy of vigabatrin has been reconfirmed in a large, recent, randomised, double-blind study,[49] and it is considered comparable to carbamazepine therapy.

Drug-induced psychosis and an aggravation of myoclonus are among the side effects reported, and constitute relative contraindications for patients with previous psychiatric disorder, severe depression, or myoclonic seizure. Recently, there has been increasing concern about permanent visual field constriction, with a reported incidence approaching 40% in both paediatric and adult series.[50] Although reversibility was reported in one patient 10 months following withdrawal of vigabatrin, such a high incidence would warrant judicious use in newly diagnosed patients with epilepsy. Infantile spasms or partial seizures that have failed to respond to combinations of alternative AEDs are indications for prescribing vigabatrin. Under such circumstances, visual field examination with a Goldmann perimeter 6 monthly is recommended.[51]

Sodium valproate

Sodium valproate has been widely used for patients with idiopathic generalised epilepsies, but its association with polycystic ovaries and obesity is a major concern for adult women.[52] A cause and effect relationship is far from clear, however, with the confounding effect of epilepsy on reproductive hormonal changes. A recently published article suggests that valproate started at prepubertal age, had an increased chance of leading to polycystic ovaries and hyperandrogenism in adulthood.[53] Caution should be exercised when giving sodium valproate to female patients who are overweight, with a history of irregular menstrual cycles, or who have shown signs of hyperandrogenism.

Another rare side effect from sodium valproate is encephalopathy, accompanied by hyperammonaemia. This usually occurs in children with congenital enzyme defects, patients with liver disease, or those taking combinations of AEDs. This encephalopathy has recently been reported in two patients who were taking sodium valproate and topiramate.[54] This observation serves to alert clinicians to the emergence of rare side effects when combination AEDs are used.

Epilepsy surgery—where to resect and how much is enough?

Epilepsy surgery usually employs a resection or disconnection procedure aiming at eradicating or isolating the epileptogenic zone, while sparing functional cortex. Presurgical evaluation consists of a series of investigations (eg video-EEG recording with or without

Odds ratio (99% CI)						
Nausea	Somnolence	Diplopia	Tremor	'Thinking abnormal'	Depression	Anorexia
0.75 (0.32-1.72)	2.04 (1.21-3.44)	-	-	-	-	-
1.70 (1.08-2.68)	1.50 (0.88-2.54)	3.39 (2.05-5.61)	-	-	-	-
1.26 (0.67-2.37)	1.21 (0.73-2.03)	-	3.17 (1.15-8.75)	-	-	-
1.38 (0.68-2.81)	2.86 (1.71-4.79)	-	-	3.95 (1.88-8.39)	-	-
0.92 (0.29-2.90)	1.24 (0.59-2.62)	-	-	-	2.59 (0.99-6.75)	-
1.91 (0.69-5.31)	-	-	-	-	-	4.29 (1.69-10.92)

invasive EEG, neuroimaging studies, intracarotid or highly selective amytal test, and cortical mapping) to map out the epileptogenic zone and determine adjacent cortical function. Appropriate candidate selection for epilepsy surgery is vital for success.[55]

Lesional epilepsy constitutes the largest group of adult-form epilepsy that is amenable to surgery. Different surgical approaches target different sites of the lesion (temporal versus extratemporal), and underlying pathologies (neoplastic, vascular, infective, or developmental malformations). Simple lesionectomy, if complete, can achieve a seizure remission rate comparable to that of formal epilepsy surgery. For certain pathologies such as dysembryoblastic neuroepithelial tumour, even a partial resection has been reported to achieve good result.[56] The underlying pathology and the completeness of lesion resection appear to be the two most important factors governing subsequent seizure remission.

Anterior temporal lobectomy is the surgical treatment of choice for temporal lobe epilepsy, with a success rate of 60% to 70% worldwide.[55,57] It often comprises excision of mesial temporal structure (including the amygdala, hippocampal head and body, uncus, entrorhinal region, and the parahippocampal gyrus), and a variable portion of the tip of the temporal lobe. The use of the amytal test has largely prevented the complication of global amnesia, but there has been some concern about resection of the temporal neocortex, which carries a higher risk of specific memory deficits. Following the preliminary success of highly selective amygdalohippocampectomy, surgical techniques have been modified and refined using the neuronetvigation approach[58] or radiofrequency technique.[59] Initial results appear promising and reinforce the critical role of the mesial temporal structures in the epileptogenic process. In selected cases, it may be justified to spare the temporal neocortex during surgical resection.

For extratemporal epilepsy, presurgical evaluation usually requires a highly specialised and experienced team of experts, including epileptologists, neurosurgeons, neuropsychologists, and neuroradiologists. Tailor-made surgery is the rule rather than the exception. Cortical mapping may be necessary to determine the adjacent eloquent cortex (eg sensorimotor strip, visual cortex). Subdural grids or strips electrodes in ictal EEG recordings provide coverage of a wide area and also allow schematic cortical stimulation to determine functionally important eloquent cortex. If this area overlaps with the identified epileptogenic tissue or the MRI identified lesion, this may preclude complete surgical resection and thus limit the chance of seizure remission after surgery. Under such circumstances, a disconnection procedure (eg multiple subpial transection or corpus callosotomy) may be considered.

Radiosurgery

Radiosurgery has treated more than 100 000 patients throughout the world since Leksell first described the technique in 1951.[60] Radiosurgery is considered an effective and non-invasive treatment method for intracranial vascular malformations and many tumours. Patients with lesion-associated epilepsy often showed an improvement in seizure control following irradiation, irrespective of whether there was angiographic obliteration or tumour shrinkage. This observation suggests a beneficial effect of irradiation on epileptogenic tissue.[61,62] Mori et al[63] described the effect of radiosurgery on rat hippocampal epilepsy, demonstrating a significant reduction of seizures following subnecrotising (20 Gy) irradiation. At about the same time, Regis et al[64] reported preliminary success in seven patients with classical temporal lobe epilepsy who had received Gamma knife surgery. This procedure used a marginal

dose of 25 Gy given at the 50% isodose line, using a cobalt 201 source. The average irradiated volume was 6.5 mm^3, which included most of the mesial temporal structures. Six of the patients became seizure-free approximately 10 months following irradiation, which coincided with the MRI appearance of target destruction. Major side effects were not encountered but larger studies are required to confirm the efficacy and safety profile of this new treatment modality.

Neuroprosthesis and vagal nerve stimulation

There are other treatment modalities that may benefit patients who have medically intractable seizures and who are not candidates for surgery. Vagal nerve stimulation was introduced in 1988.[65] This technique involves intermittent stimulation of the cervical portion of the left vagus nerve by implanted electrodes connected to a subcutaneous generator underneath the left clavicle, similar to a cardiac pacemaker. The mode of action is not entirely understood but is believed to involve inhibition of the brainstem and other subcortical structures. Side effects include hoarseness of voice, throat discomfort, and cough, which occur more commonly with a higher frequency of stimulation but otherwise the technique is well tolerated.

In 1999, Morris and Muller[66] reported the largest series so far investigating this technique. A total of 440 patients were studied. Overall, there was a 50% seizure reduction at 2 years and a 43% reduction at 3 years post-treatment. It should be noted, however, that most patients were also taking AEDs during this time and that adjustments of dosage were permitted.

Conclusion

Epilepsy research, including the development of innovative diagnostic and therapeutic interventions is ongoing. Advances stand to benefit the estimated 45 to 100 million patients with epilepsy worldwide. The considerable morbidity, the side effects of epilepsy therapies, and the social stigma of having epilepsy can hopefully be alleviated by further understanding of the underlying pathophysiology and hence the eventual emergence of a ‘cure’. Gene mapping and positional cloning techniques have been successful in demystifying the spectrum of epileptic syndrome and have led to a potential revolution in epilepsy classification.

The understanding of these mechanisms has also initiated novel therapeutic strategies during the past decade. These advances in neuroimaging techniques for both structural and functional localisation have rendered seizure-free status to thousands of patients with intractable partial epilepsy syndrome through neurosurgical intervention. Nevertheless, many patients with intractable chronic epilepsy currently will only achieve better seizure control by the introduction of novel AEDs that have better side effect profiles.

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