Current approach to adult epilepsy

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Abstract

Epilepsy is one of the commonest serious brain conditions affecting over 70 million people worldwide. Its incidence has a bi-modal distribution with the highest risk in infants and older age groups. Recent progress in genomic technology are exposing the complex genetic architecture of the common epilepsies, and are driving a paradigm shift. Epilepsy is a symptom-complex with multiple risk factors and a strong genetic predisposition rather than a condition with a single expression and a single cause. These advances have translated into the new classification of epileptic seizures and epilepsies. A detailed clinical history and a reliable eyewitness account remain the cornerstone of the diagnosis. Ancillary investigations can help determining aetiology and prognosis. Brain imaging is making great progress in identifying the structural and functional causes and consequences of the epilepsies. Comorbidities are increasingly recognised as important aetiological and prognostic markers. Antiseizure medication may suppress seizures in up to two thirds if not more of all individuals but do not alter long term prognosis. Epilepsy surgery is the most efficacious way to achieve long term seizure freedom in selected individuals with drug-resistant focal epilepsy, but is still likely underutilised. With improved understanding of epileptogenesis, epigenetic determinants and pharmacogenomics comes the hope for better, disease-modifying or even curative pharmacological and non-pharmacological treatment strategies. Other developments include the clinical implementation of seizure detection devices and new neuromodulatory techniques including responsive neural stimulation.

Introduction

Epilepsy, one of the commonest brain conditions affecting over 70 million people worldwide, is characterized by an enduring predisposition to generate spontaneous epileptic seizures and has numerous neurobiological, cognitive and psychosocial consequences.[1] Nearly 80% of people with epilepsy live in low- and middle-income countries. In many parts of the world, epilepsy is stigmatised and people may not get treatment. Over three-quarter of those with active epilepsy are untreated and this constitutes a major treatment gap, mostly concentrated in low- and middle income countries.[2] Epilepsy should be a global health priority, as cost-effective treatments are available that can substantially reduce morbidity, disability and mortality.[3,4] In 1997, the WHO in conjunction with the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy launched the Global Campaign Against Epilepsy, which resulted in the 2015 World Health Assembly urging all states to address the specific needs of people with epilepsy.[5]

Epidemiology

Epilepsy incidence in high-income countries is overall consistent across different regions with an incidence around 50 (range 40-70) per 100,000 per year.[6–10] It is bi-modally distributed with two peaks at both extremes of life: in the very young and in people over the age of 50 years. In the elderly, incidence goes up with increasing age with the highest incidence in those over the age of 70 years. Incidence is higher in low-income countries, and usually above 80-100 per 100,000 persons per year for unknown reasons, but sub-standard health-delivery system, poor hygiene, lack of basic sanitation, and a higher risk of infections and traumatic brain injury may contribute.[8,11] Regardless of geographical location the prevalence of active epilepsy is usually between 4 and 12 per 1000.[6–9] Risk factors vary per age-group. Brain

development malformations usually present with epilepsy before adulthood. Epilepsy associated with head trauma, infections and tumours may occur at any age. Cerebrovascular disease is the commonest risk factor in the elderly. Geographical location is important as parasitic conditions such as falciparum malaria, neurocysticercosis and onchocerciasis are amongst the commonest preventable risk factors worldwide.[11]

In high income countries over two-thirds of people achieve long-term remission, usually soon after diagnosis.[12] The overall good prognosis is often attributed to the widespread use of antiseizure medication. In poor settings, however, many people enter long-term remission without medication, supporting the suggestion that prognosis is for some independent of drugs.[13] Up to one third of people have drug-resistant epilepsy. The increasing number of available drugs has had only a minor, if any, benefit in terms of improved outcomes such as people becoming seizure-free.[14] It is possible that these numbers somewhat overestimate the true number of people with ‘drug-resistant epilepsy’. Determining outcome in epilepsy is fraught by the problems which beset all epidemiological studies. ‘Pseudo drug resistance’ may result from misdiagnosis, non-adherence or inappropriate treatments. For some, epilepsy is a dynamic condition alternating between drug-responsive and drug-resistant states and this may alter numbers depending in which state someone is at time of case ascertainment.[15]

Classification

Epilepsy is defined by as: (1) two unprovoked seizures occurring more than 24 hours apart; or (2) a single unprovoked seizure if recurrence risk is high (i.e. > 60% over the

next 10 years) or (3) a diagnosis of an epilepsy syndrome.[1] Epilepsy is considered resolved for people who had an age-dependent syndrome but have past the applicable age and are seizure-free, or those who have remained seizure-free for the last 10 years with no medication for the last 5 years.[1] Proper classification schemes are needed to guide the best possible management: what may the best medication for one syndrome may be deleterious for another. ILAE recently updated the classification and terminology of seizures[16,17] and epilepsy.[18] The new scheme incorporated progress in the understanding of the epilepsies. Too often people are categorised as simply having 'epilepsy' while diagnosis should be as specific and as precise as possible. Classification is made at three levels: seizure type, epilepsy type and syndrome (Figure 1). At each stage aetiology and comorbidities should be identified as these may have important therapeutic implications. Aetiologies are divided into categories: genetic, structural, metabolic, infectious, immune, or unknown.[18] Seizures are first classified by onset: focal, generalised or unknown. Level of awareness subdivides focal seizures in those with retained and impaired awareness. Focal seizures are further categorised by the earliest and most prominent motor or non-motor manifestation (Figure 2).[16,17] All classifiers are optional and depend on available level of detail. Generalised seizures are divided into motor and non-motor (absence) seizures. Seizures of unknown onset may have features which can still be classified. A common scenario includes someone presenting with convulsions without clinical evidence for a focal or a generalised onset. These seizures can be classified as 'unknown onset tonic-clonic seizures'. In those presenting with convulsions of presumed focal onset, the term "focal to bilateral tonic-clonic" is recommended while 'generalised tonic-clonic seizures' are restricted to those with generalised epilepsy. Epilepsy types are divided into four categories: focal,

generalised, combined generalised and focal and unknown. The new category of "combined generalised and focal epilepsy" is used for those presenting with both seizure types. Common examples are Dravet or Lennox-Gastaut syndrome. The highest level of precision can be obtained by identifying an epilepsy syndrome. This diagnosis results from a cluster of clinical features including age of onset, seizure types, comorbidity, EEG and imaging features. ILAE's educational website (epilepsydiagnosis.org) provides guidance for the diagnostic work-up.

Mortality

Premature mortality among people with epilepsy poses a significant public health problem as some deaths are preventable. Comorbidities are the most important cause of death particularly soon after diagnosis.[19,20] Mortality in low-income countries is higher than in high-income countries,[21] but its causes differ. Deaths due to external causes (e.g. accidents) seem more prevalent in low-income countries. Up to one third of all premature deaths are either directly (e.g. status epilepticus, injuries, sudden unexpected death in epilepsy (SUDEP)) or indirectly (e.g. aspiration pneumonia, suicide, drowning) attributable to epilepsy.[22] SUDEP is one of predominant causes of epilepsy-related death and has recently attracted substantial attention.[22] The cause is yet unknown and effective preventative measures are lacking.[23] The diagnosis requires an autopsy to rule out an underlying cause of death.[24] SUDEP is mostly unwitnessed and sleep-related.[25] Many victims are found in prone position[26] with evidence of having had a recent seizure. Rare cases occurring during video-EEG monitoring suggest that SUDEP is preceded by a convulsion followed shortly by apnoea and then asystole.[27] Incidence is 1.2 per 1,000 person-years[28,29] with a peak for those aged 20-40 years. The young average age at death explains why SUDEP,

despite its low incidence, is the second neurological cause of potential years of life lost.[30] Frequent convulsions are the major risk factor,[28] particularly if nocturnal.[25,31] There are suggestions that nocturnal supervision could be protective.[31,32] Reducing seizure frequency seems the best way to reduce SUDEP risk.[33] An open discussion about the consequences of epilepsy, including death, is recommended as an essential part of counselling particularly of those at high risk.[28]

Pathophysiology

Epileptogenesis is the process converting a non-epileptic brain into one capable of generating spontaneous, recurrent seizures.[34,35] The process is conceptualised to result from an imbalance between excitatory and inhibitory activity within a neuronal network, becomes more disposed to fire in an excessive, hypersynchronous, oscillatory manner which when sustained, disrupts normal neuronal processing and is capable of recruiting other neuronal networks.[34] For generalised epilepsies, epileptogenic networks are widely distributed involving thalamocortical structures bilaterally.[17,36] For focal epilepsies, networks involve neuronal circuits in one hemisphere, commonly limbic or neocortical.[17] The imbalance between excitation and inhibition resulting in epileptogenic circuits is not necessarily simply an increase of excitation or a loss of inhibition, but an aberrant increase in inhibition can be pro-epileptogenic in some circumstances such as absence,[37,38] or limbic epilepsies in the immature brain.[39] It has long been believed that most generalised epilepsies have a genetic basis.[40] In contrast, focal epilepsies were thought to be mostly underlined by structural cerebral abnormalities, in particular drug-resistant epilepsy.[41–43] Recently, however, an increasing number of genetic mutations inherited and de-novo, have been found in non-lesional focal epilepsy.[44–48]

The pathophysiological mechanism by which structural abnormalities cause seizure activity is not fully understood. It is accepted that seizures result primarily from abnormal activity in cortical neurones, although glial cells and axons in the white matter may become secondarily involved.[49] Much of the understanding derives from animal models involving an epileptogenic brain insult, using proconvulsant chemicals, or electrical stimulations or traumatic brain injury.[49,50] The relevance of extrapolating these models to humans has been questioned.[51]

The best ascertained epileptogenic lesion is mesial temporal sclerosis, often found in resected brain tissue from people who had surgery.[52–54] The characteristic pathological findings are: loss of excitatory and inhibitory neurons in specific subfields, axonal sprouting and synaptic reorganisation and alterations in glial function and structure.[52,55–58] It was hypothesised that an initial insult results in hippocampal cell loss, followed by collateral axonal sprouting and a resultant reorganisation of synaptic circuitry, eventually affecting the balance between inhibition and excitation in limbic circuits until spontaneous seizures ensue. Many different neurobiological processes have been implicated as potential targets for anti-epileptogenic or disease-modifying therapies.[59,60] These include accumulation of neurodegenerative proteins (such as h-tau and β-amyloid), neurogenesis, pro-inflammatory processes (such as IL-1β, TGF-β/ALK), changes in neuronal voltage and ligand gated ion channels, neurotransmitter release/uptake characteristics or intracellular signalling cascades (such as BDNF/TrkB, the mTOR pathway, adenosine/ADK, microglia activation).[60] It has been proposed that many of these are driven by epigenomic changes induced by the epileptogenic insult.[61,62] Which, if any, of these are fundamental to epileptogenesis is still to be established and there is no clinically validated anti-epileptogenic therapy.

Genetic basis and contribution

More than 30 different genes have been found in families with rare autosomal dominant monogenic epilepsies with high penetrance.[63,64] The initial genes discovered were primarily in those coding for ion channels, however, recently a number of non-ion channel genes including genes for neuronal receptors, transcription factors and enzymes have been found. People with familial monogenic epilepsies represent a small percentage of all genetic epilepsies.[65,66] The underlying causes of the majority of individuals with presumed genetic generalised epilepsies, such as juvenile myoclonic epilepsy, are still unknown despite intensive investigations.[64,67,68] The genetic cause of these common epilepsies is likely to be complex, involving contributions from multiple genes –within individuals and between different individuals with the same syndrome.[65,66]

Traditionally genetic abnormalities were believed to cause mainly generalised epilepsies, in particular the idiopathic generalized epilepsies and developmental epileptic encephalopathies.[40] Recently, it has become clear, however, that focal epilepsies can also have a genetic basis.[44,45] Mutations associated with focal epilepsies often involve genes in the mTOR pathway, but can involve voltage gated (e.g SCN1A) or ligand gated channels (e.g. GABRG2).[46–48] There is also evidence that the presence of an epilepsy family history increases the risk for the development of focal acquired epilepsy such as those following traumatic head injury.[40,69] There is probably a spectrum in the genetic contribution to the aetiology from those where genetics is the primary cause through to those where an underlying genetic background predisposes to the development of epilepsy after an acquired brain insult, i.e. a “second hit”.

Recent advances such as Genome Wide Association Studies (GWAS),[70] Whole Exome Sequencing (WES)[71] and Whole Genome Sequencing (WGS), are beginning to uncover the genetic architecture of some of these epilepsies.[68] The contribution of common variants versus multiple rare mutations has been long debated,[66] but recent evidence suggest both are likely to play a role.[68] Most advances were made in severe developmental and epileptic encephalopathies, where WGS approaches identify genetic mutations in 30-50% of subjects with more than 60 genes implicated with a wide range of cellular processes including ion channels, synaptic proteins, and transcriptional regulators.[72] Most commonly these are due to de novo mutations, but recessive or X-linked mutations, mosaicism and copy number variants also contribute.[72,73]

Comorbidities

Epilepsy rarely stands alone and the presence of co-morbidities is the norm; well over half of people with epilepsy have one or more additional medical problems. Psychiatric conditions (e.g. depression, anxiety disorder, psychosis, autism spectrum disorder) have long been associated with epilepsy, but more recently somatic conditions (e.g. type 1 diabetes mellitus, arthritis, digestive tract ulcers, chronic obstructive pulmonary disease) have also been linked to epilepsy.[74] Several possible associative mechanisms have been identified. Artefactual associations or merely a chance association may not be ruled out as people with more illnesses are more likely to be referred onwards thus leading to selection bias. The associations, however, do not explain the whole picture. A causative relationship (e.g. stroke causing epilepsy) is the most unequivocal mechanism of association. Some conditions can be resultant of epilepsy or its treatment (e.g. the effects of antiseizure

medications or the consequences of seizures such as fractures). A shared risk factor is an underlying factor or condition, which results in the development of two or more distinct conditions. The risk factor can be environmental, genetic, neurochemical, physiological or structural origin.[75] Genetic factors can impact the relationship between epilepsy and comorbidities in various ways. They can be the basis for developing epilepsy or a comorbidity, or the source of a shared risk factor for epilepsy and a comorbidity (e.g. epilepsy, cortical tubers and cardiac rhabdomyoma in a subject with a TSC2 mutation).

Comorbidity affects quality of life, results in more frequent health care visits and higher health-related costs.[76] The prevalence of some comorbidities is up to eight times higher in people with epilepsy than in the general population. These include dementia, migraine, depression, anxiety, heart disease, peptic ulcers, and somatic auto immune diseases. Epilepsy management should include screening of comorbidities as the efficacy and tolerability of antiseizure medications is often affected by comorbid conditions.[75]

Diagnostic work-up

Epilepsy is a complex diagnosis lacking an easy accessible gold standard. A detailed history and a reliable eyewitness account remain the key. The decision as to whether a seizure has occurred is based on a combination of symptoms and signs, as no single feature is epilepsy-specific (Panel 1).[77,78] Adding to complexity epilepsy is polymorphic with many presentations and a myriad of imitators. Non-epileptic paroxysmal events should always be ruled out as epilepsy misdiagnosis rates are high and potentially damaging.[79] Transient loss of consciousness (TLOC) is the most

common presentation with syncope, and psychogenic or functional causes are the most important epilepsy mimics.[80] An ECG should be considered in all adults with possible seizures particularly if presenting with TLOC.[78,81] Home videos of events can be of great diagnostic help, yet require expertise to differentiate epileptic from non-epileptic events.[82–84] An abnormal EEG does not define epilepsy but interictal epileptiform discharges may provide support for a clinical diagnosis.[78] An abnormal EEG is most helpful to determine the likely epilepsy type (focal vs. generalised), to diagnose an epilepsy syndrome and to assess recurrence risk.[85,86] Newly developed computerized tools might improve quality of EEG assessment and reporting.[87] In those who present diagnostic difficulties after clinical assessment and standard EEG, long-term video-EEG monitoring may provide a definitive diagnosis particularly if attack frequency is high.[88]

Immunology

The recent discovery of neuronal antibodies has led to the identification of previously unknown encephalopathies and epilepsies.[89] The prevalence of 'autoimmune epilepsy' is yet unknown but it appears to affect a significant minority of those presenting with focal epilepsy.[90] Encephalitis linked to antibodies targeting glutamic acid decarboxylase (GAD)-65, LGI1, CASPR2 and NMDA receptors seems the most common causes. Antibody testing should be considered if the initial evaluation fails to identify an underlying cause and subject presents with symptoms or signs of limbic encephalitis.[89,90] Diagnostic cues include cognitive decline, personality changes, autonomic seizures, dyskinesia, comorbid autoimmune conditions and mesial temporal changes on MRI (which may evolve into mesial temporal sclerosis).[89–95] Some features may be suggestive for a specific cause including faciobrachial

dystonic seizures as an early sign of LGI1 encephalitis.[96] The course is mostly subacute but may be insidious. Swift recognition is important as early immunotherapy in NMDA and LGI1 encephalitis appears more efficacious than antiseizure treatment and improves cognitive outcome.[94,97] Anti GAD65 encephalitis is the exception to the rule as it seems poorly responsive to immunotherapy.[90,95] Serological testing is increasingly valuable but additional CSF analysis should always be considered especially when NMDA encephalitis is suspected.[98] Some results should be interpreted with caution including VGKC positivity in the absence of LGI1 and CASPR antibodies[99] or low GAD-65 titres.[90] In those with a definite autoimmune cause, neoplastic screening is recommended, although the yield is generally low except for NMDA.

Imaging

MRI is the standard imaging tool, revealing epileptogenic lesions in about 20% in people with newly diagnosed epilepsy and more than half of people with drug-resistant focal epilepsy.[43,100,101] People in whom a MRI lesion is detected have a higher risk for recurrence after a first seizure[102] or to continue to have seizures after treatment than those without.[103] It is critical that MRI is performed using a epilepsy-appropriate protocol comprising at least 1mm three-dimensional volumetric T1-weighted imaging, T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences (including hippocampal angulation) and axial T2* gradient echo or susceptibility-weighted sequences.[104] Expert evaluation is probably equally important as some subtle lesions such as hippocampal sclerosis or focal cortical dysplasia can otherwise be missed.[105] In people with drug-resistant focal epilepsy with previous

seemingly normal MRIs, it is often worthwhile to rescan using a different scanner or sequences (Figure 3).

Drug treatment

For most, antiseizure medications are the main treatment modality aiming at stopping seizures at the earliest opportunity without causing side effects as these affect quality of life. Seizure remission is also likely to reduce the morbidity and to decrease the risk of premature mortality associated with continuing seizures, particularly convulsions.[12,22] With over 25 medications licensed world-wide, one could expect there would be no one still having seizures. This is, however, far from the truth. In high income countries, it is often said that current available drugs are effective in about two thirds of individuals[106] although more recent data, however, suggest that up to 80% could potentially be seizure free.[12] In reality, it is likely that much less people are actually seizure free and a recent US study found that more than half are still having seizures.[107] Those who are unemployed, who live alone or are in low income households are at higher risk of active seizures.

Despite the extensive number of available drugs only a few are considered first line. Mechanisms of drug action are outside the scope of this review and can be revised elsewhere.[108,109] Many drugs can be used for focal and generalised seizures but other are specific for particular forms of epilepsy such as sodium channel modulators which are mainly appropriate for focal epilepsies (Table 1). For those who may require treatment, an individualised management plan needs to put in place promptly. Medication choice is influenced by individual circumstances such as age, gender, child bearing potential, comorbidities and tolerability issues in one hand and seizure

type and epileptic syndrome in the other (Figure 4).[78,110] In the elderly, who often are in many concomitant drugs for comorbidities, drugs with potential drug-to-drug interactions should be avoided. An example of a positive association would be the choice of an antiseizure medication with anti-migraine potential in someone with a history of migraine. The individualised management plan should also incorporate strategies to prevent status epilepticus in those with repeated or prolonged convulsions. Various non-injectable medications can be used at home to terminate prolonged seizures or clusters. Buccal or intranasal midazolam seems a safe and effective alternative for rectal diazepam.[111,112]

An important question is at what stage or after how many seizures treatment should be started as starting treatment after a first seizure will not alter prognosis (Figure 4).[78,110] It is probably good practice to wait for a recurrence before commencing treatment. Those who seem to a higher risk of recurrence due to the presence of a structural abnormality, an abnormal EEG, or a pre-existing neurological deficit should, however, have treatment started as soon as possible. This may also be valid for those who wish to minimise the risk of a further seizure due to personal circumstances (e.g. need to operate vehicle, work requirements) and fully understand the scope and limitations of drug treatment and the risks of recurrence. An exemption to consider is when an individual has very infrequent seizures; this usually requires an informed decision about the gap between seizures, limitations of drug treatment and risk of recurrence on and off treatment.

Antiseizure medication should be introduced slowly and dose up-titration in symptom-led steps expect. The drug should be titrated up to the maximum tolerated dose if seizures are still happening. If tolerability issues appear at any point, a dose reduction is required. If the individual derives no benefit at the maximum tolerated

dose, a switch to an alternative first-line drug should be initiated. If all first-line drugs fail, then second-line options should be added. In those with frequent and high-risk seizures add-on medication could be considered at an earlier stage. It is better to make only one drug change at a time as it is then possible to determine causality if there is any improvement or deterioration.

Monotherapy is usually the best option as polytherapy may increase the risk of poor adherence, drug interactions and long-term toxicity. There is also patchy evidence of synergetic interactions between drugs regardless of mechanism of action. It is important to discontinue drugs if their use has not been of benefit in terms of seizure control and if they are suspected of giving rise to tolerability issues. Drug withdrawal should also be a consideration in those who achieve long term seizure freedom while taking antiseizure drugs; nomograms have been developed to predict reliably recurrence risk and the chance of long-term seizure freedom.[113]

Drug-resistant epilepsy is assumed after the “failure of adequate trials of two tolerated, appropriately chosen and used antiseizure drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”.[114] In those cases it is good practice to rule out all possibilities for treatment failure and to ensure diagnosis is correct. This may require new investigations, or a referral to a specialised centre. If the diagnosis is confirmed, alternative non-pharmacological treatments including surgery and neurostimulatory interventions should be considered. Dietary treatments (e.g. ketogenic diet) could improve seizure control in some. Dosing should depend on whether or not the person continues to have seizures and/or dose-related side effects. Drug levels should not be use as a guide to dosing but only for a specific purpose (e.g. when non-compliance or drug-drug

interactions are suspected or to adjust dosing to hormonal effects (e.g. oral anticonceptives and pregnancy) on certain antiseizure medications).

Side effects

Treatment with antiseizure medications is frequently associated with side effects.[115,116] Neuropsychiatric symptoms (e.g. fatigue, dizziness, unsteadiness, irritability) are the most frequent side effects but they can affect every organ system. Side effects are often insidious and may go unrecognised. It is good practice to maintain a high level of vigilance for adverse effects. In women of childbearing potential risk of teratogenicity should always be taken into account and weighed against all available alternatives.[117] Where possible, valproate should be avoided in view of the high risk of malformations and developmental problems of the exposed child.[118] Counselling should also include the possibility of interaction with oral contraceptives. Certain antiseizure medications may induce contraceptive failure, whereas oral contraceptives may also reduce levels, particularly of lamotrigine, leading to recurrence. Antiseizure medications with enzyme-inducing properties may not only reduce efficacy of co-administered drugs such as oral anticoagulants but also induce deficiencies (e.g. folate deficiency), endocrine, metabolic disturbances or affect bone health.[119,120] Screening for human leucocyte antigen (HLA) should be considered prior to initiation of carbamazepine in people of Asian descent, as life-threatening cutaneous adverse reactions are strongly associated with HLA-B*15:02.[78] Screening for comorbidity may help to prevent side effects, e.g. avoiding drugs which may promote depression in someone with a mood disorder.

Surgery

People with drug-resistant focal epilepsy may benefit from removal, or disconnection of a circumscribed brain region by achieving full seizure-control or at least abolishing disabling seizures. Seizure-freedom rates after surgery range from 50-80% in well selected groups.[121] Surgery seems cost-effective and better than best medical treatment in terms of seizure-control and quality of life.[122–125] Benefits of successful surgery also include reduced risk of injury or premature death, opportunity to drive, greater independence and perhaps improved vocational options. Surgical treatment, however, is still underutilized and potential candidates are often not referred or referred late possibly because of misconceptions and fears (e.g. ambiguous view on pharmacoresistance, ignorance of surgical options, negative views on chances of achieving seizure-freedom, fear of risks and of surgery-related personality changes). [126–129] Lack of resources or expertise is also a barrier in less wealthy countries and may be counteracted by raising public awareness and the establishment of regional epilepsy centres.[130]

The selection of appropriate candidates requires comprehensive evaluation aiming at delineating the epileptogenic zone, estimating risks of postsurgical deficits and predicting outcomes.[131–132] A specialised structural MRI can help identifying the underlying aetiology and to localize the epileptogenic zone. Examinations of *interictal brain function* may identify affected regions pointing towards the putative epileptogenic zone and contribute to the prediction of postsurgical deficits. These usually include neuropsychological testing, functional MRI (fMRI), 2-[18F] Fluro-2-deoxy-D-glucose positron emission tomography (FDG-PET) imaging, tractography, magnetoencephalography (MEG) and a combination of f MRI and EEG.[131,133] fMRI, based on blood-oxygen-level dependent (BOLD) contrast imaging signal approaches, are increasingly being used to localise or lateralize language and other eloquent

cortex, and in have mainly replaced the traditional intracarotid sodium amobarbital "Wada" test.[134] fMRI or Wada tests, along with neuropsychological examinations, can help lateralize memory function in mesial temporal lobe epilepsy. In other epilepsies, the utility of fMRI for memory lateralization is yet unclear.[135] FDG-PET scans performed in the interictal period may show hypometabolism in the epileptogenic area and can be helpful if MRI does not reveal a clear-cut epileptogenic lesion and can also be predictive of outcome.[136–140] The detection of unilateral temporal hypometabolism in an individual with focal epilepsy has been shown to be independently predictive of a good surgical outcome.[138–141] MEG has been reported to be sensitive and specific in the localisation of the epileptogenic focus in people with focal epilepsy, including those with a normal MRI.[142-144] The limited availability and expense of MEG has, however, restricted its widespread use. *Ictal brain dysfunction* is evaluated by video-EEG recordings which help to identify the seizure-onset zone through analysis of seizure semiology and ictal EEG patterns. Single Positron Emission Computed Tomography is performed in selected cases and involves intravenous injection of a radiotracer, allowing imaging of cerebral blood flow patterns during, following or between seizures.[136,145] Co-registration with a MRI scan provides anatomical localization of the regional perfusion change.[146–148] In up to a quarter of pre-surgical candidates, additional invasive video-EEG recordings using intracranial depths, strip or grid electrodes are required if MRI lesions and findings of non-invasive video-EEG recordings are discordant, MRI does not show a clear epileptogenic lesion or the seizure-onset zone may overlap with eloquent brain regions (e.g. motor cortex).[131,149–151] Neuropathological examination after resective surgery helps to characterize the underlying aetiology and may refine the prognosis of long-term seizure outcome.[152]

The effectiveness of surgery in terms of seizure freedom depend on the underlying pathology, epileptogenic zone location as well as the accurate delineation of the zone and the performance of the neurosurgical intervention.[121] Risks and complications include those inherent to neurosurgical interventions (i.e. unintended brain damage due to haemorrhage or infections) as well as calculated risks related to the specific brain tissue removal (e.g. memory deficits due to partial temporal lobe resection). People with a MRI lesion away from eloquent areas and clinical symptoms and an ictal EEG-pattern consistent with this lesion have the best chances of getting seizure free without significant postsurgical deficits. Individual chances of postsurgical seizure-freedom can be estimated with recently developed nomograms.[153] The prototype candidate is a person with temporal lobe epilepsy due to unilateral hippocampal sclerosis.[151] Long-term seizure-freedom rates 8-10 years after surgery are around 50-60%[154,155] apparently with no major differences between those who underwent anterior temporal lobectomy or a selective amygdalohippocampectomy.[156] Reasons for seizure recurrence after surgery are manifold and include false localization or incomplete removal of the epileptogenic zone, presence of additional distant seizure generators or progression of the underlying disease.[157] A second operation after thorough re-evaluation leads to sustained seizure-freedom in some.[157,158] Palliative surgery with the primary goal to reduce severity or frequency of seizures may be performed in some, i.e. by callosotomy or removal of leading seizure generator to reduce disabling seizures with recurrent falls.

Neuromodulation

Neurostimulatory techniques are palliative options when surgery is not possible or if surgery failed. The efficacy of neurostimulatory devices has been shown in

randomized controlled trials, but the actual benefits may be overestimated due to inherent study limitations and methodical weaknesses.[159] Electrical pulses are applied to peripheral nerves or specific brain areas in response to enhanced rhythmicity to counteract potentially seizure generation or propagation. The stimulatory pulses can be delivered in a scheduled manner (open-loop) or in response to seizures (closed-loop). Scheduled stimulation of the vagus nerve reduces seizure frequency by 50% or more in about one third,[159,160] improves quality of life[161] and may decrease SUDEP-risk.[162] A more advanced technology allows application of additional pulses triggered by seizure-related increases of heart rate, which may alleviate seizure severity.[163,164] Deep brain stimulation of the thalamus reduces seizures by more than 50% in about half and may decrease SUDEP-risk.[165] A new approach is to deliver electrical pulses directly to a seizure focus in response to enhanced rhythmicity, changes in frequency or amplitude of the EEG signals related to seizure generation (responsive neurostimulation, RNS) using implanted intracranial electrodes placed according to the results of preceding invasive pre-surgical evaluation. This improves seizure control by more than 50% in about half, and may decrease SUDEP-risk.[166,167] Of note, antiseizure efficacy appears to increase over time in all neurostimulatory techniques, but this has not been properly accessed.

New diagnostic and treatment prospects

An interesting prospect is the rapid development of various wearable non-EEG based seizure detection devices which may alert carers to seizures which may otherwise go unnoticed. Reliable seizure detection could also improve detection of nocturnal seizures which may go unrecognised thus resulting in under-reporting.[168–170]

Automatic detection, especially of convulsions seems feasible, while detection of other seizure types is still unreliable.[168,171] These devices could help timely interventions, such as repositioning or administrating emergency medication, which may prevent SUDEP or status epilepticus. Most devices have been validated in a clinical setting with short term follow-up. Long-term home-based trials are needed to explore added value.

Epilepsy surgery with craniotomy may be associated with variable damage of surrounding brain tissue, possibly worsening postsurgical neurological and neuropsychological outcome.[172] Less invasive techniques with a more circumscribed abolition of the epileptogenic zone could reduce risks. Stereotactic radiosurgery, radiofrequency thermocoagulation and laser interstitial thermal therapy (LITT) damage the target tissue by focally applied irradiation or heat have been shown to lead to a favorable seizure outcome in a reasonable proportion of people with drug-resistant focal epilepsy.[173–175] In a prospective trial the proportion of seizure-free people, however, was higher after anterior temporal lobectomy as compared to stereotactic radiosurgery.[176] LITT may be an alternative to open surgery or radiosurgery, as it has prompt effects on seizure control (as compared to radiosurgery) and rates of those seizure-free comparable to those of resective epilepsy surgery.[177] The antiseizure efficacy and safety of MR-guided ultrasounds is currently under investigation.[178]

Only a minority of people are suitable for surgical therapies, thus novel epilepsy treatments are an unmet need. The gut microbioma could be a promising target to improve the efficacy of the ketogenic diet.[179] Cannabis products have attracted media

attention as a new epilepsy treatment and are often requested in the clinic. Adjuvant use of pharmaceutical-grade cannabidiol has shown some efficacy for people with Dravet and Lennox-Gastaut syndrome.[180–182] Evidence supporting the use of cannabidiol in other refractory epilepsy syndromes is yet still lacking.[183] Fenfluramine may also exhibit some efficacy in Dravet and Lennox Gastaut syndrome.[184,185] In those with tuberous sclerosis complex the model-disease of a deregulated mTOR pathway, the mTOR-inhibitor everolimus appeared to have a similar but slightly delayed antiseizure efficacy as compared to antiseizure medication, suggesting that disease-modifying drugs may improve seizure control.[186] Gene therapy for epilepsy is still experimental. Current basic research focuses on molecules interfering with expression of endogenous neuropeptides and microRNA activity or optogenetic tools to modulate the activity of specific neuronal population by local light application with the ultimate goal of preventing or interrupting seizures.[187–189]

Conclusion

Epilepsy is a symptom-complex with multiple risk factors and in many case a strong genetic predisposition, rather than a condition with a single expression and a single cause. Recent advances in genomic technology are beginning to reveal the complex genetic architecture of the epilepsies. Comorbidities are increasingly recognised as important aetiological and prognostic markers. Antiseizure medications suppress seizures in up to two thirds, if not more, of all individuals but do not alter long-term prognosis. Epilepsy poses a major burden in quality of life, morbidity, and risk of premature mortality especially in those who continue to have seizures. Epilepsy surgery is the most effective way to achieve long term seizure freedom but is only an option in minority of people with drug-resistant epilepsy. With improved

understanding of epileptogenesis, epigenetic determinants and pharmacogenomics comes the hope for better, disease-modifying and curative pharmacological and non-pharmacological treatments.

Conflict of interest statement

RDT has received research grants from Medtronic and fees for lectures from Medtronic, UCB, and GSK. RS has received fees as speaker or consultant from Bial, Cyberonics, Desitin, Eisai, LivaNova, Novartis and UCB. TJO'B has been consulted by and received research grants and fees for lectures and advisory boards from Eisai, UCB and Sanofi. JWS has been consulted by and received research grants and fees for lectures from Eisai, UCB, Bial and Janssen Cilag.

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Panel 1. Key points to diagnosis and management of epilepsy [adapted from[78]]

- Diagnosis should be promptly made by a specialist with an interest in epilepsy (if available)
- The clinical decision as to whether an epileptic seizure has occurred should be based on the combination of the description of the events and a review of symptoms
- EEG should only be performed to support diagnosis when the clinical history suggests it
- MRI should be used to identify structural abnormalities in people who develop epilepsy, in whom a focal onset is presumed
- Seizure types and epilepsy syndromes, causes, and comorbidities should be determined, as incorrect classification can lead to inappropriate treatment and persistence of seizures
- Initiation of appropriate treatment recommended by a specialist with an interest in epilepsy (if available)
- Treatment should be individualised according to seizure type, epilepsy syndrome, comedication and comorbidity, individual's lifestyle, and personal preferences
- Individuals with epilepsy and their family, carers, or both, participate in all decisions about their care, taking into account any specific need
- Epilepsy diagnosis needs to be critically evaluated if events continue despite an optimal dose of a first-line antiseizure medication
- All adults with epilepsy should have a comprehensive care plan including lifestyle as well as medical issues
- Comprehensive provision of information about all aspects of condition
- Regular structured review at least once a year

1

2

3

4

Table 1. List of antiseizure medications by spectrum of efficacy (adapted from [78,110]). All medications are listed in alphabetical order. Selecting of antiseizure medication should take into account seizure type, epilepsy syndrome, comorbidities, tolerability risks and individual characteristics. For information on indications, dosage and side effects consult latest national guidelines and information provided by the licence holder.

Focal and most generalised seizures	Focal seizures only	Absence seizures only	Special encephalopathies only
Benzodiazepines	Brivaracetam[2]	Ethosuximide[4]	Cannabidiol[5]
Lamotrigine[1]	Carbamazepine		Everolimus[6]
Levetiracetam	Eslicarbazepine acetate		Felbamate[7]
Perampanel	Gabapentin		Rufinamide[7]
Phenobarbital	Lacosamide[2]		Stiripentol[8]
Topiramate	Oxcarbazepine		
Sodium valproate	Phenytoin		
Zonisamide	Pregabalin		
	Tiagabine		
	Vigabatrin[3]		

[1] May aggravate myoclonic seizures

[2] Effects on generalised seizures yet unknown

[3] Also effective in infantile spasms

[4] Also effective in myoclonic seizures

[5] Only in the context of Lennox Gastaut spectrum and Dravet syndrome

[6] Only in the context of tuberous sclerosis complex

[7] Only in the context of Lennox Gastaut spectrum

[8] Only in the context of Dravet syndrome

Legend figure 1. ILAE Framework for the classification of epilepsies.[18] Reproduced with permission from *Epilepsia* © ILAE.

* Denotes seizure onset.

Legend figure 2. ILAE Framework for the classification of epileptic seizures.[17]

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Legend figure 3. Epilepsy protocol MRI on a 45-year old woman who had had two failed right temporal resective surgeries two decades ago. Several pre-operative and post-operative MRIs on 1.5T scanners had been performed, all of which had been reported to show no epileptogenic lesions. As part of a recent re-evaluation for consideration of further surgery a repeat, epilepsy protocol MRI on a 3T reveal the features of bilateral perisylvian polymicrogyria (arrowed). The images on the left of the figure are coronal FLAIR sequences, and those on the right volumetric MR-RAGE sequences.

Legend Figure 4. Key decisions in the pharmacological treatment of epilepsy (adapted from [78,109,110]).

Fast facts.

- The clinical decision as to whether an epileptic seizure has occurred should be based on the combination of the description of the events and a review of symptoms
- EEG should only be performed to support diagnosis when the clinical history suggests it
- MRI should be used to identify structural abnormalities in people who develop epilepsy, in whom a focal onset is presumed
- Seizure types and epilepsy syndromes, causes, and comorbidities should be determined, as incorrect classification can lead to inappropriate treatment and persistence of seizures
- Treatment should be individualised according to seizure type, epilepsy syndrome, comedication and comorbidity, individual's lifestyle, and personal preferences
- Epilepsy diagnosis needs to be critically evaluated if events continue despite an optimal dose of a first-line antiseizure medication

Search strategy and selection criteria

We have searched PubMed and SCOPUS for publications in English language from Jan 1, 2008 to May 1, 2018, with the keywords “epilep*”, “antiepileptic drug”, “EEG”, “MRI”, “immunology”, “seizure detection”, “seizure prediction”, “SUDEP”, ”mortality”, “gene*”, “surgery”, and “mechanisms”. We have also quote some earlier articles and reviews, if particularly pertinent to the discussion.

Contributors

All authors planned the manuscript, did the literature search, contributed to the figures, and wrote, edited and approved the manuscript.

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