The adolescent or adult with generalized tonic–clonic seizures

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Abstract

Primary and secondary generalized tonic–clonic seizures (GTCs) together constitute up to 50% of adolescent and adult patients with epilepsy as diagnosed by history and EEG. Syncope and psychogenic nonepileptic seizures are major differential diagnoses and must be carefully excluded in therapy-resistant cases. Individual episodes can have up to seven phases in secondarily generalized GTCs. The distinction between primary and secondary GTCs depends mainly on history and EEG, and yield can be improved with sleep deprivation or overnight recording. Epilepsies with primary or unclassified GTCs can respond to any one of the five broad-spectrum antiepileptic drugs (AEDs): valproate, lamotrigine, levetiracetam, topiramate and zonisamide. Unless a focal onset is clearly confirmed, a sodium-channel blocking AED should not be used in the initial treatment of these conditions.

Key Words

Antiepileptic drugs, generalized epilepsy, tonic–clonic seizure

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History

The early history of epilepsy is largely the history of generalized tonic–clonic seizures (GTCs). The earliest medical reference to epilepsy is in a pair of clay tablets, dated to just before 1000 BCE, which also describes partial motor and gelastic seizures among other details of GTCs.[1] In Ayurveda, the earliest references to epilepsy are attributed to Atreya, in about 900 BCE, whilst the 6th century Charaka Samhita discusses it as "apasmara." Both describe what seem to be secondarily generalized seizures. Focal motor seizures, absences and myoclonic jerks were explicitly identified as distinct phenomena in the repertoire of epilepsy only toward the end of the 19th century.

Pathophysiology

The GTC is recognized as the final common pathway of expression in seizure evolution. It requires adequate myelination and hence does not occur in neonates and is rare under the age of 2 years.[2] The corpus callosum is the main pathway for interhemispheric spread of seizure activity, but other routes may involve the basal ganglia, thalami and the brainstem reticular formation.[3] Impaired consciousness in epilepsy including GTCs is now thought to be due to active inhibition of the default mode network (DMN). The DMN consists of the posterior cingulate/precuneus, lateral parietal and medial prefrontal regions of association cortex, which together are thought to govern spontaneous, self-referential and social cognitive functions, and underlies attention. The motor components have been correlated with increased metabolic activity in the subcortical structures (cerebellum, basal ganglia, brainstem and thalamus).[4,5]

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Epidemiology

GTCs are also arguably the most common seizure type witnessed by laypeople who usually find it terrifying. In 1990, the UK National General Practice Study of newly diagnosed epilepsy found that of 564 incident cases, 29% had primary and 28% secondary GTCs.[6] In 1993, Hauser *et al.* reporting on the Rochester study for the years 1935–1984 found that secondarily generalized seizures and GTCs constituted figures of 15 and 10, respectively, of their total age-adjusted incidence of 44 per 100,000 patient-years.[7] Murthy *et al.* analyzed a hospital-based cohort of 2531 patients and found that 162 (6.4%) had idiopathic generalized epilepsies (IGE), but 503 (19.9%) were unclassified.[8] The SANAD A and B studies recruited a total of 2437 patients, of which 559 (23%) had either generalized (excluding childhood absence epilepsy) or unclassified seizures. Because it is difficult to tease age-specific figures out of these studies, we can only

roughly estimate that between 25 and 50% of adolescent and adult epilepsy patients coming in to our outpatient departments will have either primary or secondary generalized seizures.

Implications

Because of its dramatic occurrence, the GTC seizure is both easily identified and perhaps overdiagnosed by medical practitioners and paramedical personnel who may not be aware of the other causes of transient loss of consciousness when accompanied by bilateral movements. Conventional epileptology as typified by the ILAE Classification of Epileptic Seizures[9,10] recognizes only the primary GTC seizure as a component of an IGE syndrome. In practice, however, probably the more common form is the secondary generalized type, originating from a focal brain abnormality. Frontal lobe seizures are known to generalize very rapidly. Focal epilepsies arising from other sites may also generalize frequently, but this often changes with antiepileptic therapy, and a focal signature may become apparent later in the course of the illness. Nevertheless, the distinction between these two entities is often difficult, and has real therapeutic and prognostic significance. Most neurologists understand the difficulty of delineating the origins of GTCs and deciding treatment in the presence of diagnostic uncertainty. Unfortunately, epileptologists do not consider it important enough to devote significant intellectual resources: none of the published guidelines[11] deal with an approach to the GTCs that are not otherwise classified, except for the special situation of the initial or isolated GTCs. This review focuses on the diagnostic and therapeutic dilemmas of managing an adolescent or adult patient who presents with possible GTCs, with an emphasis on the limited resource setting.

Diagnosis

The diagnostic process begins by excluding other causes of transient alteration in consciousness or loss of awareness together with bilateral motor activity. These include syncope, psychogenic nonepileptic seizures (PNES) and sleep-related phenomena. If there is reasonable evidence that the episodes are GTC seizures, the next priority is to classify them as primary or IGE versus secondary generalized seizures. An overlapping distinction is made between acute and remote symptomatic epilepsy. These diagnoses depend on the history and EEG findings and, partly, on neuroimaging. Facilities available for these investigations vary widely in technological sophistication as well the skill levels available for interpretation. Acquiring and analyzing this information is not easy for nonneurologists, and the UK NICE guidelines clearly recommend referring patients to a neurologist for confirming the diagnosis of epilepsy.[12] Of 232 adults seen at a First Seizure Clinic, only 52% were confirmed to have had an epileptic seizure, of which 56% were provoked by alcohol, recreational drugs or sleep deprivation.[13] If it is not possible to make these distinctions, it is important to acknowledge diagnostic uncertainty by using the label of unclassified paroxysmal events to avoid an incorrect diagnosis of epilepsy with all its implications.[14] Similarly, using the term unclassified epilepsy can help avoid an incorrect diagnosis of focal epilepsy as the consequent application of a sodium-channel blocking antiepileptic drug (AED) can make an IGE appear refractory.[15]

History

The patient, eye witnesses and carer/s all have to be questioned. Details of the seizure will include (1) the first event in the seizure such as the aura and initial movement or sensation, (2) subsequent evolution of the seizure (eye and head version, asymmetrical limb involvement or movements, especially toward the end of the seizure) and (3) postictal manifestations whether focal (Todd paresis) or diffuse and nonspecific.[16] Although these details are of crucial importance, it may often be difficult for even an expert observer to specify details of an event that usually lasts about a minute and video-EEG telemetry is then required to fill in the gaps. The patient may be having or may have had in the past other seizure type/s. Minor seizures are often ignored by patients and carers and must be specifically enquired for, if need be, by mimicking seizure manifestations such as myoclonic jerks or the oromotor and hand automatisms of mesial temporal seizures.[17] Neonatal and febrile seizures and a history of early life brain injury often need corroboration from parents. The age of onset and circumstances of the first attack together with subsequent precipitating or triggering factors can point to etiology. The average frequency of attacks in the past month/s or year should be systematically correlated with the longest seizure-free interval and the response to previous medications. A personal or family history of febrile seizures, epilepsy and other neurologic illnesses may help identify a genetic predisposition. Much of this questioning can be systematized with a questionnaire and can even be delegated to paramedical personnel as is done through the Epilepsy Specialist Nurse system in the UK.[18]

Self-reported episodes

In individuals with the first or with few episodes, a careful reconstruction of the circumstances in which the event occurred together with symptoms immediately preceding and following can provide valuable clues. Presyncopal features and a feeling of coldness or sweating are often ignored. Most physicians tend to forget that syncope is far more common than seizures in the population at large. In an analysis of three studies of causes of blackout presenting to primary care or emergency departments, only 8% (67 of 807 patients) had epilepsy, while syncope constituted 51%.[19] Injuries, if any sustained during the episode, should be noted. A lateral tongue bite is a marker of trismus during the tonic phase of GTCs, with 100% specificity in one study.[20] Post ictal headache, muscle pain and mental clouding are also more suggestive of a seizure. Some patients may have had earlier minor seizures, and unless specifically enquired for, these may not even be mentioned. Less than a third of patients with simple and complex partial seizures present with their first episode and absence and myoclonic almost never do.[21] In a pediatric First Seizure Clinic, 38% of cases had suffered prior epileptic events.[22]

With recurrent episodes, the likelihood of witnesses rises. Eye witnesses tend to blur features of multiple events together with the patients subjective complaints, but important information can often be gleaned by "walking" the witness through a single defined episode, preferably the most recent personally witnessed attack. In addition, companions and family members can be trained to pay attention to the sequence of events and should be urged to obtain a video with a mobile phone camera, and this information can be retrieved at subsequent visits.

Thus, initial bilateral clonic jerks can be markers for a clonic–tonic–clonic seizure, while asymmetrical upper limb abduction can identify a frontal lobe epilepsy. The frequently seen but few clonic jerks in the later part of a syncopal fall[23] can be separated from the vibratory clonic jerks of GTCs. The greatest difficulty arises with PNES, especially when they appear on a background of epilepsy that may have been largely controlled earlier. PNES can be quite heterogeneous, and Senveviratne *et al*. identified six types of events on video-EEG monitoring.[24] However, those misdiagnosed as GTCs usually display rhythmic tremor or rigor-like movements. A smaller number may have complex movements with clonic-like elements, and some may have violent, hypermotor behavior. Most patients tend to be consistent as regards semiology between attacks. Some features can be identified on the initial history, and may be highly suggestive of PNES. These pointers include longer duration as GTCs usually last less than 2 min,[3] onset in the awake state only, resistance to eye opening and precipitation by stressful events. Nevertheless, this is not a diagnosis that can be based on clinical phenomena alone.[25] Sleep-related phenomena that may cause diagnostic confusion (sleep starts, parasomnias) are most common in adolescents and are unlikely to be mistaken for GTCs.[26]

Neurological Examination

Lateralizing features should be sought in the post ictal phase if a detailed examination is possible. During the interictal period, "soft signs" such as mirror movements are of questionable significance. "Hard" signs, even if subtle, point to focal brain abnormalities. Neurocutaneous findings are very important in epilepsies that have their onset in childhood and, if ambiguous, can be confirmed with a dermatologic opinion.

Basic Investigations

Routine labs

Blood glucose and serum sodium must always be checked in a previously neurologically normal adult presenting to the Emergency Department after a first generalized seizure.[27] With the first seizure, it may also be prudent to do a drug screen for recreational substances. In patients with breakthrough seizures, AED levels should be checked to confirm compliance where possible. Patients with seizures due to metabolic disorders usually have an ongoing encephalopathy, and their episodes may not always be generalized. To term these as acute symptomatic seizures, cut-off values have been proposed for hypoglycemia (<36 mg/dL), hyperglycemia (>450 mg/dL), hyponatremia (<115 mg/dL), hypocalcemia (<5.0 mg/dL), hypomagnesemia (<0.8 mg/dL) and azotemia (urea nitrogen >100 mg/dL or creatinine >10.0 mg/dL).[28]

ECG and other cardiac investigations

Patients presenting with a transient loss of consciousness should have an ECG and lying and standing blood pressure measurements to rule out postural hypotension. If the ECG shows any abnormality, an echocardiogram is recommended.[19] This is particularly important in older individuals, but is also significant at younger ages. Zaidi *et al.* investigated 74 patients (ages 18–77) diagnosed with epilepsy by a head-up tilt test with carotid sinus massage during continuous EEG, ECG and BP monitoring. In addition, 10 patients also underwent long-term ECG monitoring using an implantable loop recorder. An alternative diagnosis was found in 31, including 13 patients who were receiving an AED. In all, 11 patients could stop AEDs because of the changed diagnosis.[29]

In a recent study, Surges *et al*. suggest an imbalance in autonomic function with prevailing sympathetic influence following GTCs.[30] Postictal heart rate variability was reduced and heart rate recovery was significantly slower than after complex partial seizures. QT shortening, out of proportion to the heart rate, was seen immediately or 1 min after seizure cessation. The significance of these findings is unknown but the periictal occurrence of pathologic cardiac repolarization resulting in sudden onset of ventricular tachyarrhythmia could be one explanation for SUDEP.

EEG

Although the history is preeminent, the EEG is probably the most important investigation[31] for making the diagnosis of epilepsy and its classification. The presence of epileptiform discharges increases the recurrence risk of seizures by 1.7-times.[32] However, only a third of routine interictal EEGs (20–30-min recording with photic stimulation and 3 min hyperventilation) pick up significant abnormalities.[33] A repeat study probably adds another 20% but, if negative, further routine EEG would add at best about 10% by the 4th recording. The yield improves to 51–70% by doing the study within 24–48 h of a clinical seizure.[33-35] Sleep, especially NREM stage II, is probably the most useful tool to improve yield. This can be drug-induced sleep, but this has the disadvantage of often increasing fast beta activity, which may obscure subtle abnormalities. Sleep deprivation is more physiological and shows discharges in about 50% of the patients with initial normal routine EEG.[36,37] This is because of the added effect of sleep deprivation in enhancing cortical excitability.[38] The yield is highest in younger individuals and in the IGE. In our protocol, the patient/caregivers are instructed to restrict sleep on the night preceding the recording to not more than 3 h, and preferably only 2 h. The patient comes in after breakfast or lunch and the recording is for at least 2 h with a target of obtaining at least 20 min of NREM stage II sleep. The recording must be continued for about 10 min after waking the patient up toward the end of the study. If sleep-deprived EEG is negative, the last option, short of admission for video-EEG telemetry, is to obtain an overnight record. This, in addition to giving a longer NREM sleep exposure, also has the advantage of picking up the early morning increase in cortical excitability that has been demonstrated in the IGEs, particularly Juvenile myoclonic epilepsy.[39]

EEG findings

Interictal epileptiform discharges (IEDs) are essential to the EEG diagnosis of epilepsy as EEG findings may well be obscured by movement artefact during the seizure itself. IEDs are rapid changes in polarity, with a definite physiologic field and voltage gradient across scalp electrodes that occur paroxysmally (distinct from the background).[40] This rapid change in polarity must produce a sharp wave form with duration under 200 ms, and if this is less than 70 ms, it is termed

a spike. Most IEDs have a negative polarity and are followed by an after-going slow wave.

The IEDs of focal epilepsy are usually, but not necessarily, in the sharp wave range (70–200 ms). They are commonly solitary, but can occasionally occur in short runs. Their distribution defines the irritative zone of cortex, which ordinarily overlaps but may be distinct from the ictal onset and/or epileptogenic zone (cortical area that must be resected for seizure freedom). Anterior temporal IEDs are most commonly identified. These are typical of medial temporal lobe epilepsy but may also be seen in secondary generalized epilepsies arising from the orbitofrontal cortex. Other extratemporal focal epilepsies have a rather lower yield of IEDs and may only be marked by focal slowing.[41]

The primary or IGE are marked by IEDs in the spike range (under 70 ms). These may occur as rhythmic generalized spike-and-wave (GSW) complexes at 3 Hz in younger patients. In older individuals, these tend to be faster, up to 4–5 Hz, and less regular. In JME, the wave component may be less prominent and multiple spikes (polyspikes) may be seen in bursts. These discharges typically have a generalized distribution, but sometimes may be obvious only in both frontal areas. Symmetry is the norm, but, within a given recording, some discharges may be asymmetrical and focal fragments are often seen, especially during sleep. In a small number of patients, focal evolution of both clinical and EEG patterns have been reported.[42,43]

The overlap of focal and generalized patterns can occur and must be clearly recognized. A symptomatic focal epilepsy and IGE can coexist, and this has been reported in surgically treated temporal lobe epilepsy.[44] Secondary bilateral synchrony refers to rapid generalization from a structural focal lesion mimicking primary generalized epilepsy. Here, focal IEDs are seen that are distinct in morphology from the generalized discharge and these clearly and consistently precede and initiate the generalized discharges.[40] A third scenario was described recently by Williamson *et al*.[43] identifying six patients in whom the beginning of the ictal discharge consisted of GSW activity but subsequent EEG activity had a focal predominance. Interictal epileptiform discharges were also generalized, but the semiology consisted of prolonged behavioral arrest with mild automatisms, simulating complex partial seizures. All six patients responded only to treatment with broad-spectrum AEDs, similar to IGE syndromes.

Structural Neuroimaging

Most adult patients with epilepsy will have at least one neuroimaging study. The only exception is when a generalized epilepsy syndrome such as Janz's can be clearly identified. The choices available vary widely, and in most parts of India the study will be self-financed. Interpreting skills are important and may not match the technologic capability available locally. In a resource-limited setting, it is the treating neurologist's responsibility to assess the level of sophistication required in a given situation. It may be sensible to defer more expensive investigations until the need is clearly manifest.

In acute situations like head trauma, acute stroke and status epilepticus, noncontrast computed tomography (CT) may be performed,[45] but most patients will also get a contrast-enhanced study. This is particularly useful in diagnosis and subsequent follow-up of the most common cause of acute epilepsy in the Indian setting: the central nervous system (CNS) granuloma. Typically, this is due to neurocysticercosis and two recent reports from Uttarakhand and Vellore suggest that this entity accounts for about a third of active epilepsy in these widely separated parts of India.[46,47] An expert group consensus on the active solitary cysticercus granuloma identified this as a rounded enhancing CT lesion measuring under 20 mm that does not need further evaluation with magnetic resonance imaging (MRI).[48] Calcified lesions are often missed on MRI, and these accounted for 14 of the 49 cases identified in the community-based Uttarakhand study. However, CT alone may miss ischemic and other evolving lesions causing acute symptomatic seizures. If CT is combined with diffusion weighted imaging MR sequences, the diagnostic sensitivity is substantial for almost all acute neurologic situations. and this combination is often offered as a competitively priced package by commercial neuroimaging centers in Western India.

For chronic epilepsy, MRI is the neuroimaging modality of choice. It has been averred that a basic MRI study now has the same status as the EEG in the assessment of a patient with epilepsy.[49] For the optimum yield, this study needs to be performed on equipment with at least a 1.5 T field strength. The epilepsy protocol[50] is designed to identify and delineate the five epileptogenic substrates of focal epilepsy: (1) hippocampal sclerosis; (2) malformations of cortical development; (3) neoplasms (astrocytomas, oligodendrogliomas, dysembryoplastic neuroepithelial tumors, gangliogliomas, pleomorphic xanthoastrocytomas); (3) vascular abnormalities (arteriovenous and cavernous malformations) and (5) gliosis and miscellaneous other abnormalities. Optimal imaging parameters (image orientation, slice thickness and pulse sequences) need to be set on individual MR machines. The ideal plane for identifying the typical changes of hippocampal sclerosis (atrophy, signal change and disruptions of internal architecture) is the oblique coronal, perpendicular to the long axis of the hippocampus. In addition to FLAIR, T1-weighted gradient volume acquisition sequences (SPGR or MPRAGE) are essential for evaluation of and for malformations of cortical development. But, the most important requirement is a radiologist who is trained and experienced in the systematic interpretation of these lesions.

Functional Imaging

BOLD fMRI, positron emission tomography (PET), single photon emission computed tomography (SPECT) and transcranial Doppler studies of cerebral blood flow have been used to look at changes in cerebral blood flow thus inferring changes in cerebral metabolism. Of these, SPECT is the only method capable of capturing cerebral blood flow and metabolic changes as a seizure takes place. This is because the tracer binds immediately as it passes through the brain, without significant redistribution. Imaging can be performed 1 h later so that acquisition of images is not affected by movement artefact. This ictal image can be coregistered and subtracted with interictal (baseline) SPECT and MRI to provide useful localizing information.

In the IGEs,[51] typical absences have been studied by the above methods. Cerebral blood flow changes in generalized spike-and-wave discharges have been captured by EEG-linked fMRI. The main conclusions are that there is an increase in CBF in the thalami and broad decreases in the cerebral cortex corresponding to the EEG discharges. Focal areas of neuronal activation are also occasionally seen, but these are not consistent.

Varghese *et al*. studied 59 secondary GTCs in 53 patients during Video EEG monitoring . In the pregeneralization phase itself, significantly more regions showed CBF increases than in partial seizures without generalization, and a single unambiguous region of seizure onset could not be identified in about 50% of the episodes. However lateralization (identification of the hemisphere of seizure onset) was accomplished correctly in 84% of the cases. These authors also noted that CBF hypoperfusion during the generalization phase was greater on the side opposite to seizure onset in 90%.[52]

Video-EEG Telemetry

Our knowledge of clinical semiology in epilepsy is largely based on ictal video-EEG recordings. This is a crucial part of the investigation of refractory epilepsy, especially for epilepsy surgery. The presurgical evaluation begins with an attempt to define the site of origin of the seizure (ictal onset zone), and this may well be distinct from the cortical area whose activation produces the clinical manifestations of the seizure (symptomatogenic zone). Ictal and interictal EEG activity can also be analyzed during this process and, sometimes, IGE may be identified only during long-term monitoring. The focus in presurgical evaluation is on localization-related epilepsy and hence primary GTC seizures rarely get much attention. The most complete description of the semiology of GTCs is from Theodore *et al*.[3] who analyzed secondary generalized seizures in their presurgical population. To some extent, this now supersedes the classic description of Gastaut and Broughton.[53] Theodore *et al.* were able to identify up to six phases in primary GTC seizures and up to seven in secondary GTC seizures.

The initial part of the seizure was quite variable, and they termed this the antecedent seizure. Of this, Phase 1 is the simple partial seizure with preserved consciousness marking the initial cortical activation. When the description is purely subjective (from the patient), this is termed the aura and, if consistent, this can often have localizing value. For instance, simple visual hallucinations (flashing lights or dots) in one visual field suggest involvement of the contralateral primary visual cortex. It is not often realized that the generalized seizures of the IGEs too can have auras, and one study found them in 70% of the cases studied.[54] This has been correlated with the focal hyperexcitability that is often noted in these disorders. Phase 2 according to Theodore could consist of any one of four alternative semiologies (depending on whether the syndrome was localization related or primary generalized): a complex partial pattern or tonic or clonic or absence. These two phases together had a highly variable duration, from under 10 s to over 4 min. Antecedent seizures could be identified in 115 of 120 seizures, and 100 of these were either simple or complex partial, reflecting this presurgical evaluation population.

The main generalized seizure begins with Phase 3, which is the brief period between the antecedent seizure and full generalization, and is marked by vocalization and/or head turning. This head version can be seen in the IGEs as well, but is usually not consistent between seizures.[55] If eye and head version occur consistently to one side, this marker of frontal eye field activation has considerable lateralizing value and suggests focal onset. Theodore *et al.* identified a brief interlude of early clonic jerking, which may be irregular and asymmetric, and they termed this Phase 4. Phase 5 consists of sustained contraction of all voluntary musculature in the tonic posture with minimal clonic jerking. In Phase 6, decreases in muscle tone interrupt the tonic contraction in a rapid fashion to produce an appearance of tremulousness. This has also been called the "vibratory" clonic phase. Phase 7 is the main clonic phase, and distinct jerks can be counted. In localization-related epilepsies, it has been seen that clonic jerking often ends asynchronously, ipsilateral to the hemisphere of seizure origin, in up to 80% of the patients with temporal lobe epilepsy.[56,57] The mean durations of these phases were: Phase 3, 9.5 s; Phase 4, 8.5 s; Phase 5, 18.5 s; and Phase 6 and 7 together, 43.5 s. No GTCs lasted longer than 2 min. Only 27% of the seizures had all five phases of the main seizure, but tonic Phase 5 and clonic Phases 6–7 were present in 95 and 98%, respectively.

Management

As discussed earlier, after confirming that the patient indeed has epilepsy, the next crucial step is the distinction between GTCs as a manifestation of an IGE syndrome and GTCs that are secondarily generalized as part of a localization-related epilepsy syndrome. Diagnosing the specific IGE syndrome is important for prognosis, but not necessarily so for treatment.[58] Here, the term idiopathic is confusing and it should be explained to patients and carers that this does not mean "unknown cause" and instead implies a genetically determined low threshold for seizure expression. Another source of confusion is the traditionally taught concept that adult-onset epilepsy is partial or focal in origin unless proved otherwise. The majority of patients with IGE syndromes have their onset in childhood and adolescence. However, the initial seizure types may be absences and myoclonus and may not have been recognized or recalled until the GTCs occurs. In addition, adult-onset IGEs are now well recognized. Berkovic's group has shown that 28% of their IGE cases began after the age of 20 years, and the majority of these had GTCs as the predominant seizure type.[59,33] Clinicians are often faced with the situation of an adolescent or adult with infrequent but disabling GTCs and normal EEG and imaging. Instead of presuming this to be localization related, this must be treated as an IGE unless proved otherwise. It has been known for more than a decade now that IGEs can actually worsen to the point of appearing refractory when treated with sodium-channel blocking AEDs.[15] Even worse, these patients can develop iatrogenic status epilepticus.[60] The situation is simpler as regards partial epilepsy as with the exception of ethosuximide (effective only in absence seizures), theoretically all available drugs can be used for these cases. Currently, there is a choice of 10 drugs for use as initial monotherapy and another five that can be used as add-on therapy for the treatment of partial epilepsy.[61]

AED choices for idiopathic generalized and unclassified epilepsies

In contrast to partial epilepsy, only five drugs are effective in the treatment of GTCs in the IGEs: valproate, lamotrigine, topiramate, levetiracetam and zonisamide. Benbadis (2005) and, more recently, Nicholson and Marson (2010) have reviewed these choices. A head-to-head prospective comparison for valproate, lamotrigine and topiramate is available from Arm B of the SANAD study,[62] which included generalized and unclassified seizures. Retrospective data for valproate and lamotrigine are also available from Mohanraj and Brodie (2007). Overall, valproate is accepted as the first-line AED for the IGEs,[58,63] and the main concerns with its use are teratogenesis in women of reproductive age and weight gain. If it is effective, use of a lower dose, preferably in an extended release formulation, may partly address both these issues. Valproate can worsen seizures in mitochondrial disease.[64] Levetiracetam is probably the most commonly used alternative to valproate, and has been shown to be effective against myoclonic seizures as well.[65] CNS adverse effects, especially psychiatric, may limit its use. Lamotrigine is effective against GTCs and absence seizures and has a positive psychotropic effect. However, it may exacerbate myoclonus and is thus probably not a drug of choice for JME.[63] Topiramate is another possible alternative but is not as effective and is distinctly less well tolerated than valproate.[62] Zonisamide has been available for several years and has been shown to be effective in all three seizure types of the IGEs, but in small numbers of patients in retrospective studies.[66-68]

Over 30% of patients with the IGEs may be refractory to treatment.[69] If the patient is on a newer AED, it may be useful to try valproate at maximal doses even if it has been used earlier at conventional levels. In patients who are responsive to valproate but have significant adverse effects, a possible strategy is to titrate the dose downwards to the minimum effective dose. Adverse metabolic effects are probably related to high peak levels of valproate and can be minimized by using multiple doses or avoiding high peak levels by using extended release tablets. If monotherapy fails, duotherapy can be tried. The combination of lamotrigine and valproate is probably the best documented,[69,70] but others can be tried. The only known exception is the combination of topiramate and valproate, which can produce hyperammonemia.[71]

Because these disorders are often prone to external provocations such as sleep deprivation, alcohol and stress, it is important to counsel patients about lifestyle management. Women in their 20s and 30s may have to juggle demands of child rearing and family duties often together with career responsibilities, and sleep deprivation is inevitable. Another source of concern is the irregular sleeping hours of younger individuals working on shift duties in the BPO industries. In both these situations, choice and duration of AED therapy must be tailored to the needs of the individual.

Conclusions

The diagnosis of GTCs requires careful attention to history supported by EEG. In refractory patients, alternative diagnosis such as PNES and syncope must be carefully excluded. Unless a focal onset is clearly established, drug treatment should begin with a broad-spectrum AED. In refractory patients with IGEs, lifestyle factors should also be given attention.

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