EANS/UEMS European examination in neurosurgery

Variants of questions with answers (compilation - Vyacheslav S. Botev, Department of Neurosurgery, M.Gorky Donetsk National Medical University)

CASE HISTORIES IN EPILEPSY

Case 1

Temporal lobe epilepsy

A 28-year-old left-handed woman presents with the diagnosis of epilepsy since childhood. She suffers from two types of seizures.

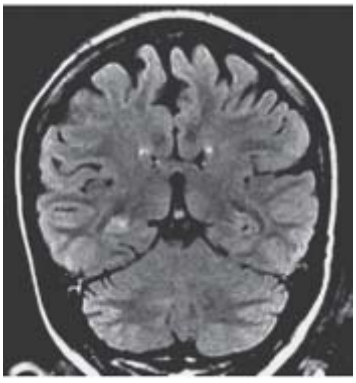
— The first type is described as a diurnal episode preceded by an aura of a rising abdominal sensation and fear followed by loss of awareness associated with lip smacking and fine hand-motor automatisms. This is followed by postictal tiredness (2 to 3 per day).
– The second type consists of nocturnal convulsions (2 to 3 per week).

She was tried on several antiepileptics, and currently her epilepsy is refractory to triple medications.

Questions

1. How do you classify her seizures?
2. Where would you localize her first type of seizures?
3. What would be your presurgical management steps?

She had video electroencephalography (EEG) monitoring that showed ictal and interictal evidence of a right temporal focus.
A magnetic resonance imaging (MRI) scan of the brain is performed:



Fluid-attenuated inversion-recovery coronal magnetic resonance image of the brain.

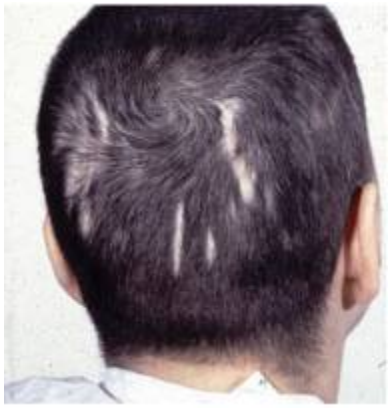
Neuropsychological evaluation reveals normal intelligence, verbal and visuospatial memory. She was shown to be strongly left hemisphere dominant, and Wada test lateralized her verbal functions, memory, and speech to the left side.

4. Describe the finding shown on the MRI.
5. What surgical options are available for this patient?
6. According to current evidence-based studies, what is the expected seizure outcome after temporal lobe surgery compared with best medical management?
7. What is the chance of her becoming completely seizure free (Engel class Ia) after successful surgery? What are the chances of being on monotherapy after surgery? What are the chances of antiepileptic drug freedom after surgery?
8. What are the possible complications associated with temporal lobe epilepsy surgery?
9. Describe the surgical principles in temporal lobe epilepsy surgery.
10. What is the central point? How does it help you during temporal lobe resection?
11. What is Meyer‘s loop and how can it be avoided during temporal lobe surgery?

Case 2

Corpus callosotomy for drop attacks

A 17-year-old right-handed boy was diagnosed with multifocal epilepsy since the age of 4 years. His epilepsy has become progressive with time and was been intractable for the past 3 years. The seizures are described as staring events that occurs 2–4 times a day and atonic drop attack that occur once or twice daily despite compliance with triple therapy. He is on three antiepileptic medications, without which he has frequent generalized tonic clonic seizures. On examination, he is somewhat cognitively subnormal. He has multiple scalp scars of different ages from frequent unprotected falls to the ground:

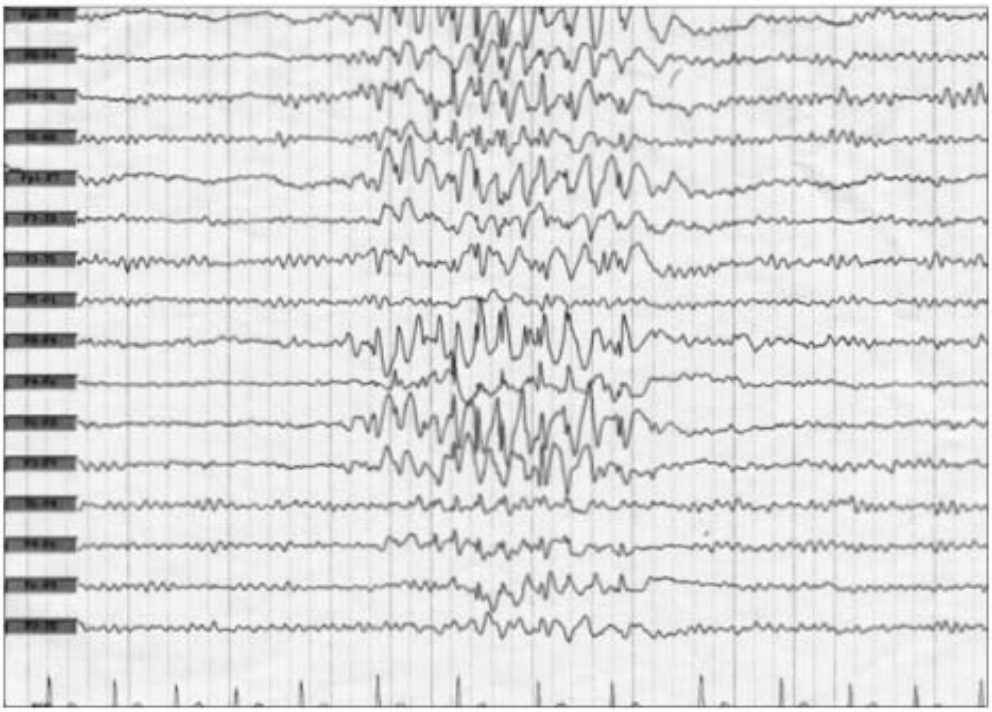


Questions

1. How would you investigate this case?
Magnetic resonance imaging (MRI) of the brain was essentially normal. Electroencephalography (EEG) showed bilateral multifocal epilepsy.
2. What are the surgical options?
3. What would you tell the parents regarding expected seizure outcome after surgery?
4. What are the predictors of a better outcome?
You operate on her and perform an anterior two-thirds corpus callosotomy. Postoperatively she is well and awake but would not interact or speak for the first few days. She returns to her normal self by the end of the week.
5. The parents were concerned; what do you tell them happened?
6. What are the possible complications related to corpus callosotomy?
7. What are the indications for corpus callosotomy?
8. Describe the parts of the corpus callosum.
9. Compare the callosotomy procedure with vagal nerve stimulation.
10. What are the approaches for corpus callosotomy?

Case 3

A 19-year-old male presents with his first tonic–clonic seizure after missing a night's sleep. His previous medical history was unremarkable, but he had noticed over the preceding 2 years that he would have jerks of either arm soon after waking that could result in him spilling his morning tea. An EEG was performed.



1. What does the EEG show, what is the likely diagnosis and what other seizures are associated with this syndrome?
2. What precipitating factors should he avoid?
3. What is the treatment of choice, and for how long will he need to be treated?
4. “I’ve had one seizure. What are the chances I will have another one?”
5. “Can I drive? Can I work?”

Case 4

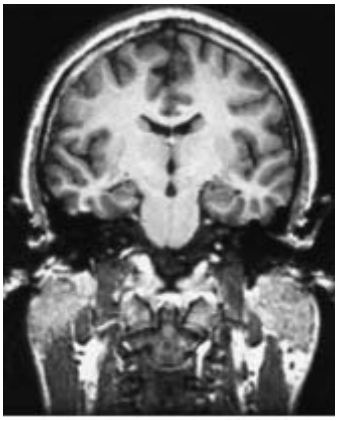
A 20-year-old female first presented with seizures at the age of 18 years. These were of generalized tonic–clonic type. She also complained of brief episodes lasting minutes of experiencing blobs of color masking her vision. In addition, she reported separate episodes of ‘jumpiness’ of her arms and legs with preserved consciousness.

There was no family history of neurologic diseases, although she was born of consanguineous parents. Despite treatment with phenytoin, the seizures worsened and she developed severe flurries of brief random jerks in all four limbs. Two years later, she has continued to deteriorate, with child-like regression and global cognitive decline. On examination, she is deaf and her speech interrupted by choreiform mouth movements. Noises and reflex testing provoke flurries of severe jerking occurring in random patterns separately in all limbs.

1. Was her initial treatment appropriate?
2. Into what subgroup would her jerking disorder be classified?
3. What is the likely diagnosis?

Case 5

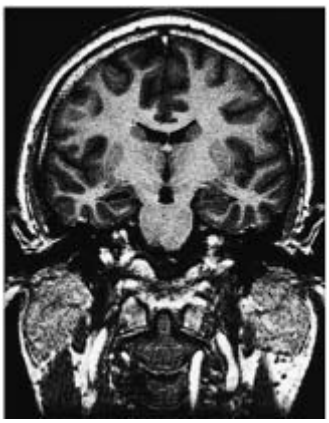
A 22-year-old, right-handed female is referred for the futher management of her epilepsy. She had a prolonged febrile convulsion in infancy. She has frequent complex partial seizures with an aura of fear and a rising epigastric sensation followed by impairment of consciousness. Witnesses describe how she may utter simple phrases during seizures, will fiddle with her right hand, and be confused after attacks, on one occasion burning herself on her gas cooker. She has never had secondarily generalized seizures, but her complex partial seizures have not responded to treatment with phenytoin, valproate, carbamazepine, lamotrigine or topiramate. Her attacks tend to cluster around menses. An MRI was performed.



1. What does the MRI scan show?
2. What is your management strategy?

Case 6

A 31-year-old female has a 20-year history of seizures in which she first has a feeling of fear that rises up from her stomach, and then she occasionally loses touch with her surroundings for approximately 10 minutes. During this period, she walks around as if in a dream and fiddles with her clothes, and after this she is confused for 5–10 minutes. These seizures are resistant to medication. The only past history of note was a series of seizures with fever in the first couple of years of life. An MRI was performed.

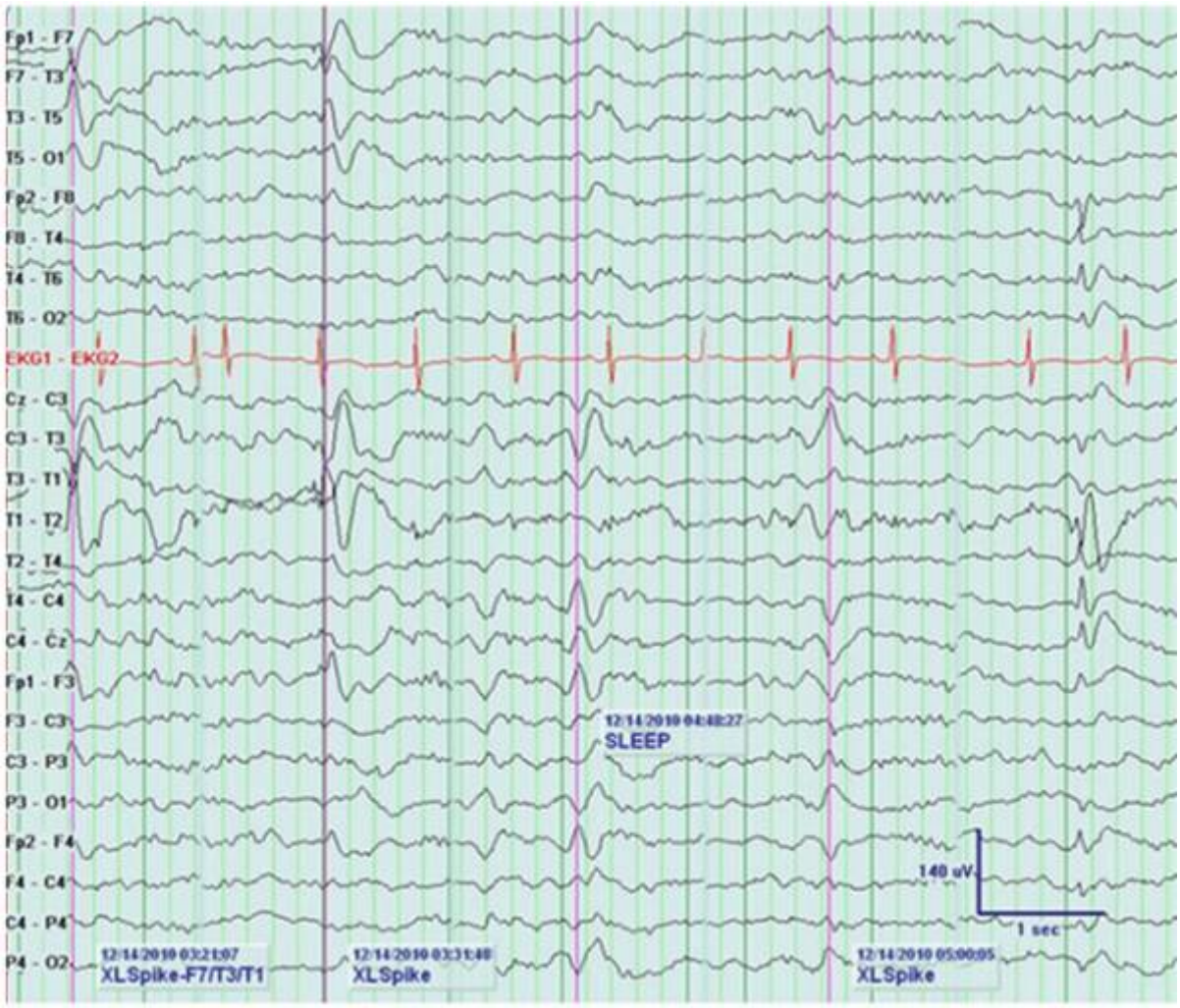


1. What type of seizures does she describe?
2. What does the MRI show?
3. What is the association between this pathology and her past medical history?
4. What is the most common cause of these seizures?

Case 7

Starting antiepileptic drugs

A 44-year-old male experienced a single, unprovoked, generalized tonic–clonic seizure at 5:30 a.m. The seizure duration was approximately 2 min with gradual recovery following a postictal state. There was no prior history of seizures or predisposing neurological conditions or comorbidity. The only risk factor for epilepsy included a concussion as a child while playing sports. Additionally, the patient did have a sibling with childhood absence epilepsy. The patient was not on prescription medication at the time of the seizure. Upon evaluation in the emergency department, a CT of the head was normal. An EEG performed several hours after the seizure showed bitemporal independent sharp waves:



EEG demonstrating independent bitemporal epileptiform discharges. Parameters of recording include sensitivity of 7 μV/mm; display speed 30 mm/s; and filter settings of 1–70 Hz.

Other than complaining of a mild headache, myalgias, and a “sore tongue” the patient appeared to be doing well at the time of dismissal from the emergency department. An MRI head was subsequently performed and was unremarkable.

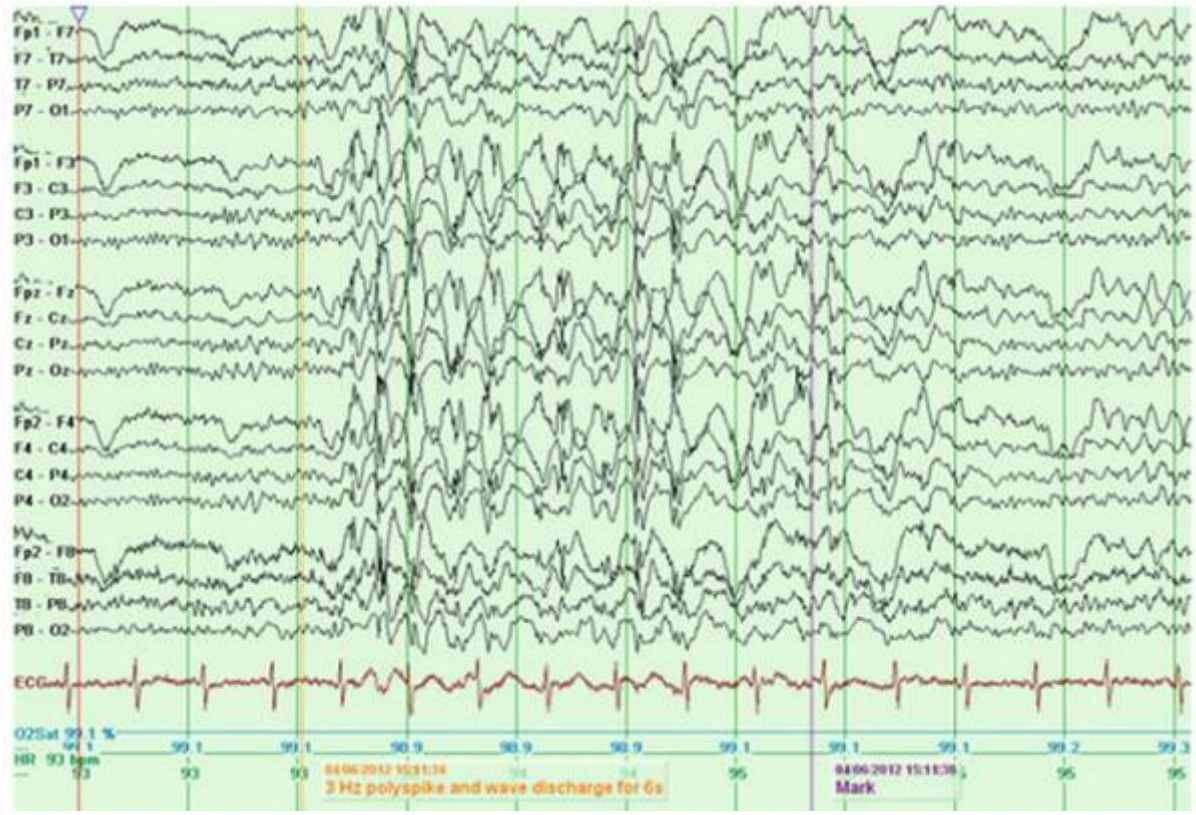
Questions

1. What is the likelihood of seizure recurrence?
2. What clinical risk factors increase the chance of recurrence?
3. What is the anticipated clinical course?
4. What should the patient do about driving?
5. What is the best course of treatment?

Case 8

Pregnancy and epilepsy

A 28-year-old right-handed female came to the clinic 3 days after her first seizure. The seizure occurred out of sleep and was described by her boyfriend as a convulsion. The emergency medical service took her to the nearest hospital where she was diagnosed with new-onset generalized tonic–clonic seizure. The patient was amnestic for the event and was without memory recall until she arrived at the hospital. Her routine and neurological examinations were unrevealing, excepting the post-ictal state. A CT of the head and routine laboratory assessment, including a urine drug screen, were normal. A outpatient EEG was performed and showed bursts of generalized anterior-predominant 3 Hz spike-and-slow-waves, consistent with genetic generalized epilepsy:



EEG demonstrating a burst of generalized anterior-predominant 3 Hz spike-and-slow-waves.

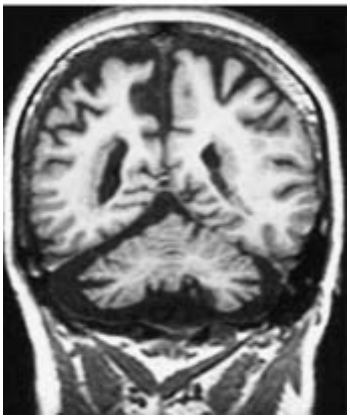
The patient was subsequently started on lamotrigine (LTG) and told to refrain from operating a motor vehicle. During titration of LTG, she experienced a second generalized tonic–clonic seizure 2 weeks later, which occurred at work.

Questions

1. If she does want to start a family, what risks are associated with being on ASDs during pregnancy?
2. Are there ASDs that would be preferred and ones that should be avoided?
3. Is there a risk to the baby if she has seizures during pregnancy?
4. What is the risk of worsening of seizure frequency during pregnancy?
5. Is she at higher risk for pregnancy complications?
6. What are the risks after delivery for women with epilepsy and their babies?

Case 9

A 25-year-old female is referred having had four unprovoked generalized tonic–clonic seizures over the last 6 months She has a mother with epilepsy and she herself is due to be married in a year's time. Examination is unremarkable.

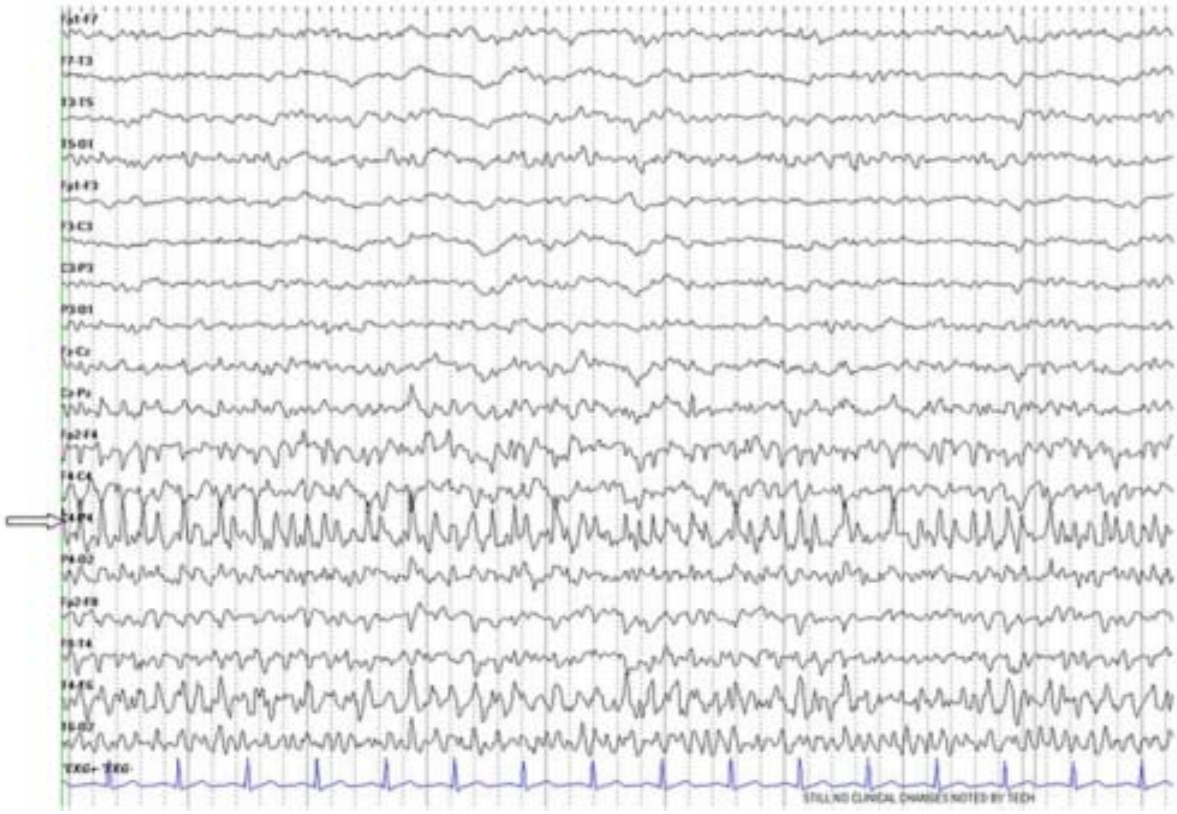


1. What does the MRI show?
2. What other investigations would be appropriate?
3. What would you advise her?

Case 10

Status epilepticus convulsive

A 23-year-old male with a history of localization-related epilepsy was taking Carbamazepine, 400 mg PO BID. His epilepsy would manifest as recurrent focal seizures that intermittently progressed to convulsions. Shortly after midnight he developed a “grand mal” seizure. This repeated two more times and his friends called 911 for help. He was transported to the nearest hospital and had persistent impairment of his consciousness. In the Emergency Department (ED), he did not answer questions and was “just staring at the nurses”. A brain CT was unrevealing. Laboratory evaluation did not demonstrate any abnormalities in his electrolytes or complete blood count with differential. A toxicology screen was negative for illicit substances and alcohol. A carbamazepine level was non-detectable. An EEG was obtained in the ED:



Focal electrographic status epilepticus confined to the right hemisphere.

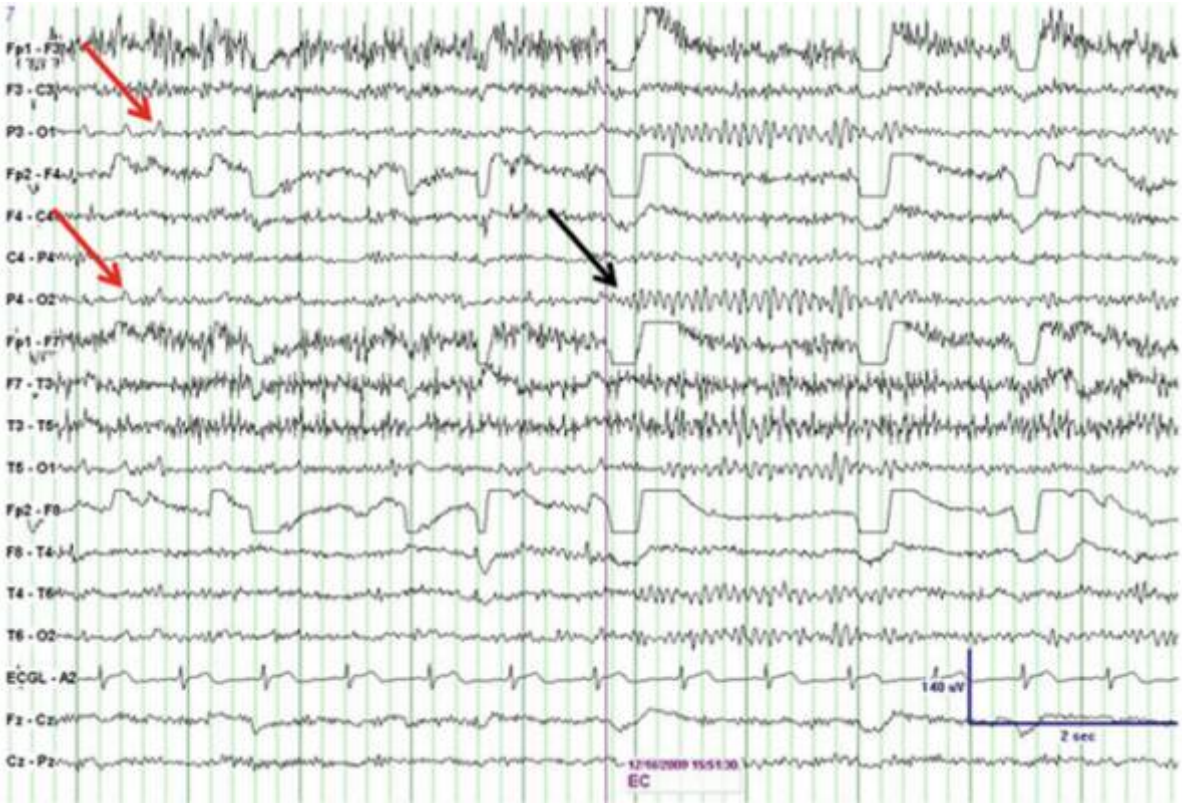
Questions

1. How does the EEG help in making the diagnosis?
2. What is the definition of status epilepticus (SE)?
3. How is status epilepticus classified?
4. What are the most common causes of status epilepticus?
5. What is the rate of mortality of SE?

Case 11

Stopping antiseizure drugs

A 32-year-old, right-handed white male with a history of well-controlled epilepsy is evaluated because he is interested in stopping his antiseizure drug (AED). He developed epilepsy manifested as infrequent focal seizures that evolved into convulsions when he was 28 years of age. He exhibited one type of seizure semiology and became seizure free following initiation of ASDs. The cause for his epilepsy was felt to be due to a motor vehicle accident which resulted in a traumatic brain injury. A brain MRI performed just after the accident showed a small amount of hemosiderin deposition in the right frontal lobe affecting the cortex. His current AED regimen is 1,000 mg of oral levetiracetam twice a day. He had not had a seizure in more than 2 years. He was working full time and was driving a car. While he does not report having any side effects from his medication, he does not like taking it, and is concerned about the cost of continuing use. His last EEG was performed 2 years ago and showed intermittent theta-delta slowing over the right frontal head region, but was otherwise normal (shown below). His neurological examination in the clinic was normal.



EEG demonstrating a normal recording in the awake state with a well-formed 10 Hz alpha rhythm reactive with eye closure (*black arrow*). Note the normal lambda waves (*red arrows*).

Questions

1. What are the positive prognostic factors for seizure freedom upon discontinuation of ASDs?
2. What are the negative prognostic factors for seizure freedom upon discontinuation of ASDs?
3. Is it appropriate to consider discontinuing the AED for this patient?
4. What ancillary procedures may be of help in stratifying his risk of seizure recurrence?
5. How quickly should ASDs be tapered?

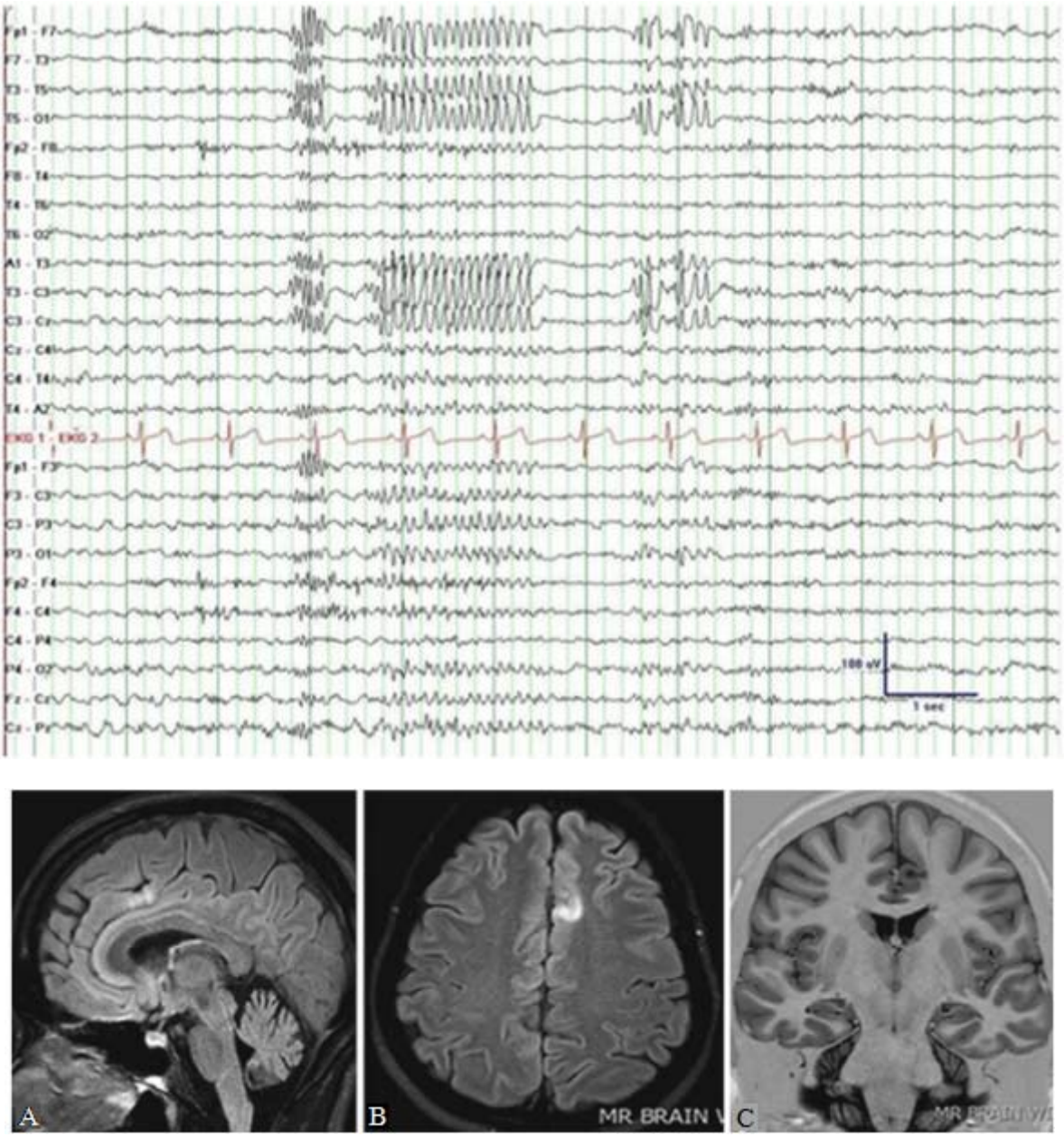
Case 12

Classification of epilepsy

A 20-year-old, right-handed, white female had drug-resistant epilepsy. She had failed several ASDs as single agents due to tolerability issues and had been maintained on Phenytoin for years. She was born via an uncomplicated delivery and was without any known risk factors for epilepsy. Seizure onset began at 9 years of age, manifesting as “petit mal” seizures. These occurred weekly and were worse after menarche. She was initially given Ethosuximide after an EEG demonstrated “petit mal seizure discharges,” though she had incomplete improvement in her episodic staring spells.

Subsequently, “grand mal” seizures developed within the year following puberty, and she was changed to valproate. She continued with intermittent “petit mal” seizures on a weekly basis. Trials of ASDs included VPA, Dilantin, and Ethosuximide were ineffective. TPM and LEV lead to side-effects of “memory problems” and severe anxiety. When she was seen for another opinion regarding pregnancy and driving, she was taking PHT 400 mg PO qHS which had provided her the best control thus far. Her neurological examination was normal. A CT of the brain was normal. A high resolution brain MRI with an epilepsy protocol was performed.

A computer-assisted ambulatory EEG demonstrated a staring spells associated with 2 Hz generalized spike-and-waves with normal background electrocerebral activity.



Interictal EEG demonstrating bilateral left hemispheric temporally predominant polyspikes. Note the temporal predominance despite the mesial frontal location of a lesion identified on brain MRI (**A** –**C**) with sagittal and transverse FLAIR, and coronal T1 images of a left mesial frontal lesion suggestive of cortical dysplasia. Note the cerebellar atrophy on brain MRI. EEG: longitudinal bipolar montage, sensitivity 7 µV, and filters 1–70 Hz.

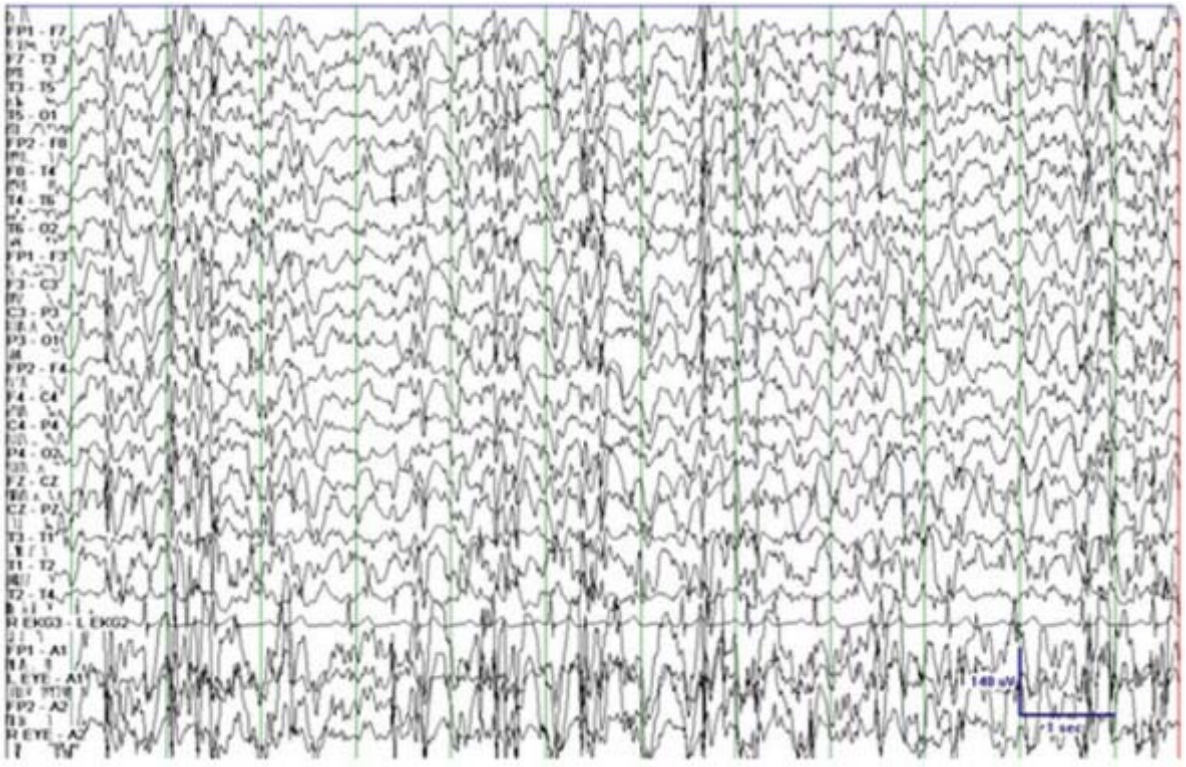
Questions

1. Does this patient have “petit mal” seizures?
2. How do the ancillary tests help classify the staring spells in this patient?
3. What type (classification) of epilepsy does this patient have?
4. What antiseizure drugs are appropriate for the corresponding classes of epilepsy?
5. What is the best course of action?

Case 13

Progressive myoclonic epilepsy

A 19-year-old, right-handed female of mixed Caucasian and Mediterranean decent presented to an epilepsy clinic with a diagnosis of “seizure disorder.” At 14 years of age she experienced her first generalized tonic–clonic seizure. Subsequently, she developed multifocal myoclonus and was diagnosed with the Juvenile Myoclonic Epilepsy (JME) syndrome. However, she gradually worsened with uncontrolled frequent daily generalized myoclonus and monthly convulsions that were resistant to multiple antiseizure drugs. Over the years, her grades fell, and dedicated neuropsychological testing demonstrated a slow reduction in full scale IQ into the 60s. She developed difficulty walking with frequent falls and ultimately became wheel-chair dependent. Seizures became refractory to multiple broad-spectrum ASDs. Neurological examination revealed a young female awake and cooperative but with psychomotor slowing, visual inattention, and dysarthria. She relied on single-word answers and hand gestures. Gait revealed an unsteady ataxic gait. Her brain MRI was unrevealing, and an EEG was abnormal.



EEG showing diffuse slowing of the background activity punctuated by nearly continuous generalized spike and polyspike discharges. Note the occipital predominant sharp waves. EEG
parameters include a bipolar montage, sensitivity of 7 μV/mm, and filters of 1–70.

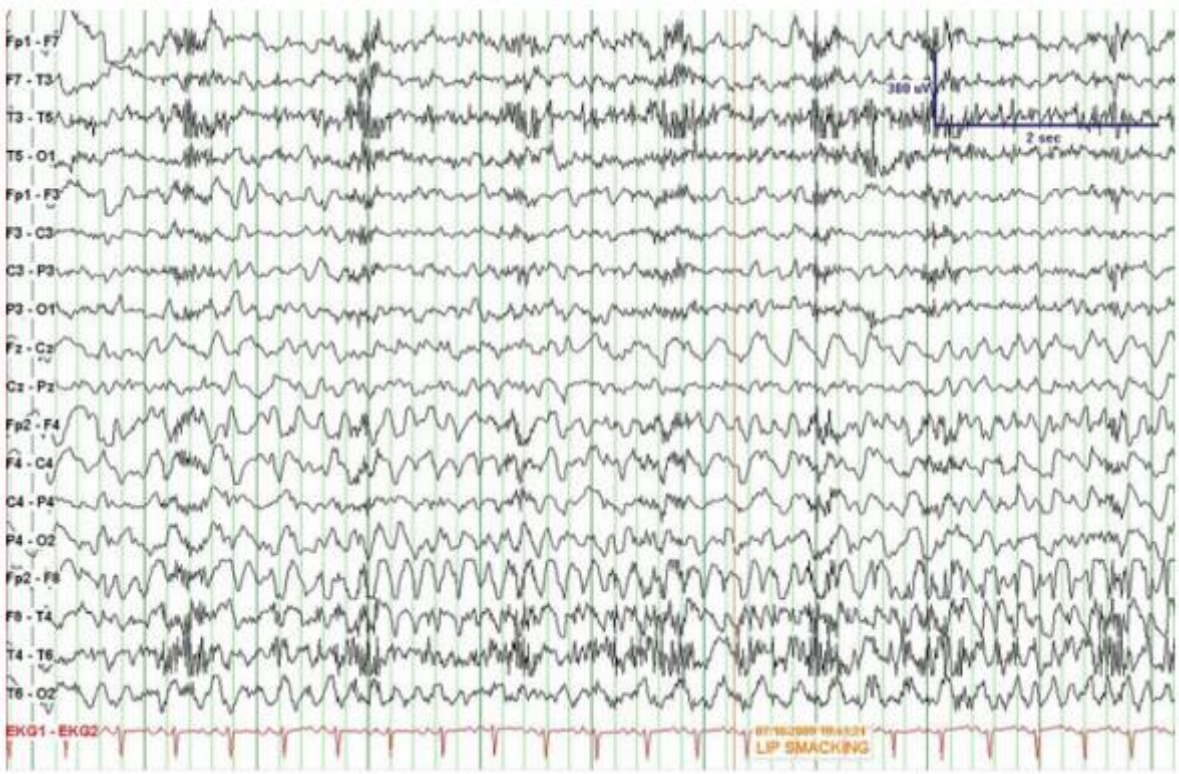
Questions

1. Does this patient have JME?
2. Does this EEG support a particular clinical diagnosis?
3. What are myoclonic epilepsy syndromes to be considered and what are the defining characteristics for them?
4. What diagnostic testing should be considered?
5. What is the anticipated clinical course and prognosis with the expected diagnosis?

Case 14

Driving and epilepsy

A 41-year-old female pilot for a major airline presented with subacute worsening of brief events of involuntary stereotyped motor movements. The episodes began 3 years ago and until recently were sporadic. They consisted of an abrupt onset of left arm posturing with elevation toward her face and "smacking her lips." At the same time she reported that her left face would draw upward associated with a transient inability to verbally respond to questions. The episodes were several seconds in duration and occurred three times daily on average. She reported that they were so brief that they did not impact her cognition or impair her overall ability to function.



EEG demonstrating a brief focal seizure with left arm extension during right frontal 10 Hz activity. Note the arousal from sleep following the evert.

Worsening began following a long airplane flight where she had been sleep-deprived due to a busy and difficult work schedule causing them to occur several times an hour. Her general and neurological examination was normal. An MRI was obtained and was found to be normal. A serum drug screen and laboratory was unrevealing. An EEG was subsequently obtained and captured an episode.

Questions

1. How does the EEG assist in the diagnosis?
2. What implications does the diagnosis of epilepsy have for driving?
3. What implications does the diagnosis of epilepsy have for flying?
4. What implications does the diagnosis of epilepsy have for the patient who is a commercial truck driver or railroad engineer?
5. What are your responsibilities in reporting this information?

Case 15

Hormonal replacement therapy

A 40-year-old woman developed seizures in early adolescence following viral encephalitis. She described her typical seizures as beginning with a feeling of fear and a peculiar sensation rising up from her epigastric region. This was followed by staring and unresponsiveness with repetitive lip smacking. She was diagnosed with localization-related epilepsy and was prescribed numerous ASDs that failed to work for her. She is currently on monotherapy lamotrigine and has a vagus nerve stimulator. She was previously evaluated for epilepsy surgery, but was found to be a limited candidate.

The high-resolution MRI of her brain was normal and bilateral independent focal seizures arising from the left and right temporal regions were present on inpatient video-EEG monitoring. Seizures were occurring once every 4–8 weeks, but in the last 2 years they had increased to 1–3 times per month. Breakthrough seizures always clustered around her menstrual period. She was once treated with acetazolamide begun the week prior to her menses; however, this was discontinued as her periods had become increasingly irregular over the last 2 years. She is now having frequent hot flashes and night sweats that significantly disrupt her sleep. She brings in a diary in which she has charted her

seizures and her menstrual periods. Examples of the months in which a menstrual period occurred with seizures are shown below:

Sun	Mon	Tue	Wed	Thu	Fri	Sat
	SZ		SZ M	M	M	M
M						

Sun	Mon	Tue	Wed	Thu	Fri	Sat
SZ SZ	M	SZ M	M	M		
			SZ			

Sun	Mon	Tue	Wed	Thu	Fri	Sat
	SZ M	M	M			
	SZ		M	M	M	M

Seizure calendars for 3 months demonstrating a catamenial pattern of breakthrough seizures in relationship to the menstrual cycle. ***SZ*** seizure, ***M*** menses.

Questions

1. Does the diary contain information valuable to the management of this patient?
2. How does catamenial epilepsy change during perimenopause and menopause?
3. Could this patient's epilepsy have impacted her menopausal status?
4. Could hormone replacement therapy have any benefits for this patient?
5. Could hormone replacement therapy worsen her epilepsy?

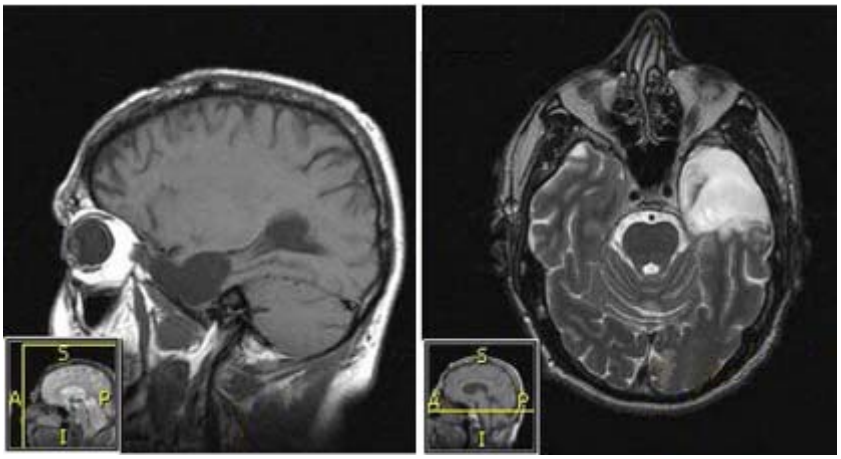
Case 16

Drug-resistant surgical failure

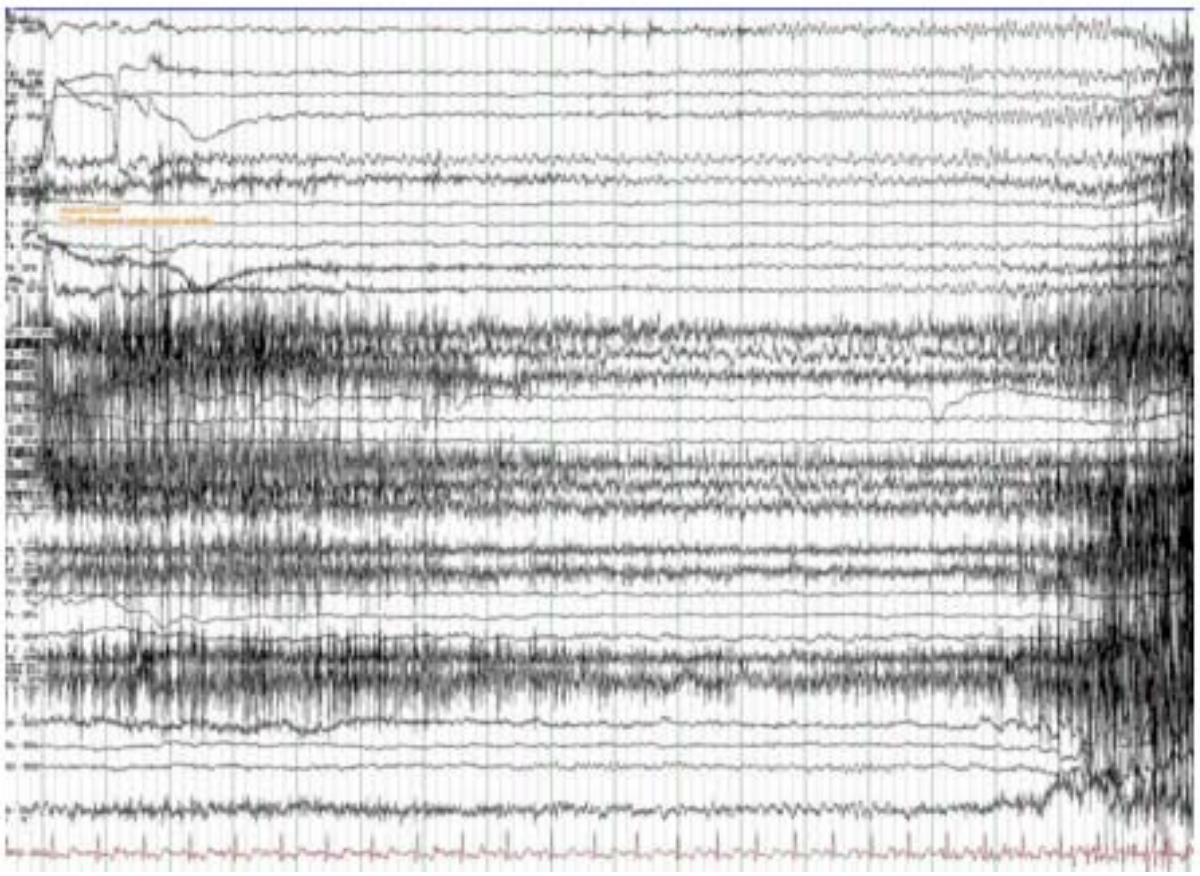
A 45-year-old right-handed Caucasian male was referred for evaluation of drug-resistant localization-related epilepsy. His seizures were characterized by an abrupt onset of staring with behavioral arrest, lip smacking, and transient impairment of consciousness. Occasionally, his focal seizures evolved into generalized seizures. His epilepsy had been refractory to multiple antiepileptic medications, so he underwent a comprehensive evaluation including an MRI of the brain which was normal. Prolonged video-EEG monitoring recorded seizures of left frontotemporal onset. He subsequently underwent surgical placement of intracranial electrodes for intracranial EEG (iEEG) monitoring.

He was implanted with an electrode array providing left frontotemporal coverage for definitive lobar localization and to provide language mapping using electrical cortical stimulation, if necessary. Re-monitoring with iEEG

demonstrated left temporal lobe onset for his typical seizures. He underwent *en bloc* left temporal lobectomy. He was seizures free for 2 months after his resective surgery, though unfortunately his seizures returned and again he manifested drug-resistance. Subsequently, he returned for reevaluation. Brain MRI showed only anticipated postoperative changes. Postoperative scalp video-EEG monitoring again recorded seizures of left temporal onset.



Brain MRI demonstrating expected postoperative changes after *en bloc* left anterior temporal lobectomy.



EEG showing a left temporal lobe seizures.

Questions

1. What are the possible explanations for failed epilepsy surgery?
2. What is the expected outcome for resective surgery in patients with a non-lesional preoperative brain MRI?
3. When should iEEG be considered?
4. Is reoperation in this patient an option?
5. What options are available if reoperation is not possible?

Case 17

Memory loss and seizures

A 22-year-old male underwent a left anterior temporal lobectomy for drug-resistant epilepsy. He presented with complaints of memory and word-finding difficulties. He was first diagnosed with epilepsy at age 21 when he experienced a generalized tonic–clonic seizure. Risk factors for epilepsy included a motor vehicle accident with closed head injury at age 16 and repeated self-asphyxiation “play” during early adolescence.

Plot of composite *z*-scores across representative cognitive domains assessed 1 month prior to surgery (*baseline*) and 7 months post surgery. *VC* verbal comprehension, *PO* perceptual organization, *WM* working memory, *PS* processing speed, *SP* semantic processing, *VerL* verbal learning, *VisL* visual learning, *VerM* verbal memory, *VisMem* visual memory, *Dep* depression screen. *Shaded area* reflects the range of “normal” limits.

Prior to diagnosis, he reported a 9-month history of brief, recurrent, stereotyped spells characterized by sudden-onset “head rush” followed by a lense of “excitement” in his chest and extreme diaphoresis initially misdiagnosed as anxiety. He was unresponsive during his spells and afterwards felt “drained,” with incomplete memory of the event.

He became resistant to ASDs and underwent epilepsy surgery. A preoperative MRI, PET, and neuropsychological testing prior to surgery were normal. Video-EEG monitoring had interictal epileptiform discharges and three typical seizures with ictal onset in the left temporal region corroborated and localized by invasive monitoring with depth electrodes. Wada testing revealed left hemisphere dominance for language and bilateral representation of memory functioning. The patient underwent left anterior temporal neocorticectomy and partial left amygdalohippocampectomy guided by language mapping. Surgery resulted in seizure-free outcome and he returned to college 6 months later to complete an Associate’s degree that he had started prior to the onset of his generalized seizures.

At that time he noticed new-onset cognitive difficulties. He reported that it was taking him longer to learn new information in class and, even after understanding the material, he was less able to process and fully explain it to others or demonstrate his knowledge on tests. He was referred for repeat neuropsychological studies (Fig. above) to evaluate his cognitive change and to offer recommendations to improve functional status.

Questions

1. Does the patient demonstrate any postoperative cognitive impairment to substantiate his subjective complaints?
2. Has there been any change in cognitive function compared with his presurgical status?
3. Does the neuropsychological profile reflect change associated with the neuroanatomical resection?
4. Are there any factors other than surgical resection that could also contribute to cognitive change?
5. What therapies or resources could be recommended to improve cognitive functioning in this patient?

Case 18

A 45-year-old woman with status epilepticus

Patient name: Helen Yarwood
ID number: 100006
Date of birth: 03/12/1969
Age: 45 years
Weight: 69 kg
Admission date: 07/01/2015
Date/time seen: 07/01/2015 02:00

History

PC Helen Yarwood was brought into the emergency department by ambulance with repeated tonic–clonic seizures. You are called to see her because she is having a further seizure, which has lasted 9 minutes so far.

HPC Collateral history is available from her son who heard Mrs Yarwood fall out of bed. He found her having a seizure and called the ambulance. She had two further seizures in the ambulance and has not fully recovered consciousness in between.

PMH Mrs Yarwood has had epilepsy since her mid-teens. She usually has 1–2 seizures per year, each lasting around 3–5 minutes.

DH Carbamazepine 600 mg twice daily.
Intolerances: none known.

SH Mrs Yarwood lives with her son and daughter and is usually independent. She is a non-smoker and does not drink alcohol.

Examination

General She is on her left side and is undergoing a tonic–clonic seizure. The trolley has rails which have been raised and padded. She has a nasal airway and intravenous cannula in situ. There are no contusions.

Obs T 36.4°C, HR 110 beats/min, BP 138/84 mmHg, SpO_2 92% breathing oxygen via non-rebreathe mask at 15 L/minute. Capillary blood glucose 5.9 mmol/L.

Investigations

Blood tests sent on admission, including full blood count, renal and hepatic function and electrolytes were all normal apart from:

Test	Value	Normal range
Serum carbamazepine	1 mg/L	4 – 12 mg/ L

A diagnosis of status epilepticus is made.

Questions

1. What should I consider when deciding what to prescribe?
2. How do I write the prescription?

Case 19

A 31-year-old man with increased seizure frequency

Patient name: Abdul Raffiq
ID number: 100041
Date of birth: 25/02/1983
Age: 31 years
Weight: 68 kg
Admission date: 01/01/2015 10:00
Date/time seen: 07/01/2015 13:00

History

Problem You are asked to review and act on a serum phenytoin concentration result.

History Mr Raffiq was admitted 6 days ago with recurrent complex partial seizures. He has epilepsy and usually experiences 1–2 short-lived seizures per week. On presentation, the type of seizure had not changed, but their frequency had increased to more than 20 per day. He did not always recover to baseline in between. Phenytoin was started with an initial intravenous loading dose and oral maintenance therapy thereafter.
His seizures are now occurring at a frequency of about 5–10 per day, with full recovery in between. No cause for the increased

seizure activity has yet been found. The neurology team have advised that you should 'aim to achieve a serum phenytoin concentration in the upper half of the target range'.

PMH Focal epilepsy due to a cerebral arteriovenous malformation.

DH Phenytoin 300 mg daily, levetiracetam 1.5 g 12-hourly. Intolerances: none known.

SH Non-smoker; no alcohol consumption; independent.

Examination

General Normal.

Obs T 37.0°C, HR 65 beats/min, BP 122/86 mmHg, RR 16 breaths/min, SpO_2 99% breathing air.

Systems Normal.

Investigations

Test	Value	Normal range
Creat	82 µmol/L	60 – 110
eGFR	>60 mL/min/1.73 m^2	>60
Alb	38 g/L	35 – 48
Serum phenytoin:		
02/01/2015 12:00	14.5 µg/mL	10 - 20
07/01/2015 07:30	12.9 µg/mL	10 - 20

Questions

1. What should I consider when deciding what to prescribe?
2. How do I write the prescription?

Answers

Case 1

1.
• The first type is a complex partial seizure.
• The second type is probable secondary generalized tonic-clonic seizure.

2. The semiology localizes these seizures to the temporal lobe.

3.
• Management steps include the following:
– Obtaining a full history and clinical examination
– Verifying antiepileptic medication serum levels
– Obtain EEG followed by video EEG telemetry if the EEG was not conclusive.
– Obtain MRI of the brain
– Neuropsychological evaluation
– Wada testing (Dr. Juhn Wada's intracarotid solium amobarbital procedure to lateralize speech and memory functions)

4. Figure showing a hyperintense signal demonstrates atrophy in the right hippocampus greater than on the left side. These are characteristic features of mesial temporal sclerosis (MTS).

5.
• As all seizures are coming from the right nondominant temporal lobe along with evidence of rightsided MTS the surgical options are as follows:
– Corticoamygdalohippocampectomy (temporal lobectomy)
– Selective amygdalohippocampectomy
▪ Transsylvian (Yaşargil technique)
▪ Transcortical (Olivier technique)

6.
• According to Wiebe et al. (the only randomized controlled trial assessing temporal lobe epilepsy surgery as of 2008), the number of patients needed to treat for one patient to become free of disabling seizures is two.
• 58% of surgical cases compared with 8% of test medical management cases will be free of disabling seizures.
• Long-term favorable seizure outcome (Engel class I and II) ranges between

50–90%.

7.
• According to the McGill group, 40–58% of patients undergoing temporal lobe epilepsy surgery end up in the Engel Ia class — seizure free.
• The chance of becoming antiepileptic drug free according to Téllez-Zenteno et al. is 20%.
• Based on the same study 41% will be on monotherapy.

8. Complications vary among centers and range between 5–10%. They include
– Infections
– Hematoma
– Hemiparesis
– Memory and language deficits
– Contralateral upper quadrantanopia — pie-in-the sky deficit (Some consider it to be an expected finding rather than a complication.)

9. Temporal lobectomy indicates the removal of the entire temporal lobe including the mesial structures. Therefore, this term should be reserved for such a total removal, which is quite rare today. From an anatomical point of view, the term “anterior temporal lobectomy” is also some what misleading. It is preferable to use the term “anterior temporal resection” or corticoamygdalohippocampectomy (CAH) to describe the extent of the cortex and limbic structures that are removed.

• The following summarizes the steps in the temporal lobe surgery and corticoamygdalohippocampectomy:
– Positioning:
▪ The aim here is to have the operative fields (frontotemporal area) almost horizontal
▪ Patient is supine, head in pins, roll under the shoulder.
▪ The head is kept higher than the heart and turned 60 degrees, slightly extended, and exposing the temple.
▪ Make sure the neck veins are not compressed or over stretched to avoid compressing the neck veins.
– Neuronavigation is used to tailor the skin incision and bony opening.
– Craniotomy:
▪ Question mark skin incision from the zygoma just anterior to the ear going back around the pinna and up and parallel to the temporalis line to the hairline (Fig. 1).

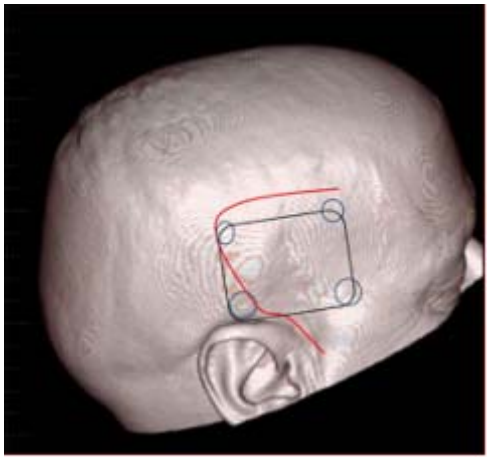


Fig.1 Anterior temporal resection. Position and extent of bone flap in relation to the scalp incision.

▪ Then temporalis fascia incision and muscle opening are done.
▪ Exposure of the pterion, the zygomatic root is performed.
▪ The craniotomy should reach the anteroinferior - most of the temporal base and then taken to the limits of the skin incision, making sure exposure comprises at least 6.5 cm behind the temporal tip.
▪ This is followed by controlling the middle meningeal artery and durotomy.
– Temporal neocorticectomy:
▪ The sylvian vein and especially the vein of Labbé (located 5 to 6 cm behind the temporal tip) need to be protected.
▪ The middle cerebral artery branches must be avoided.
▪ This is achieved via a subpial resection of the first temporal gyrus on the nondominant hemisphere and following the pia of the sylvian fissure.
▪ Posteriorly, the dissection is performed up to the central point or as tailored by functional imaging if the speech area is close by.
▪ More medially the temporal resection should not reach or cross the petrous ridge and the temporal horn roof (Meyer’s loop) should be avoided.
– Amygdalohippocampectomy and parahippocampal gyrectomy:
▪ After opening the lateral wall and the lateral part of the roof of the temporal horn one should identify the collateral eminence and the lateral ventricular sulcus.
▪ Medial to the sulcus is the hippocampus. The fimbria is identified by moving the choroid plexus superiorly and posteriorly.
▪ The fimbria and the stria terminalis join, making the anterior border of the choroid fissura (Fig.2,3).

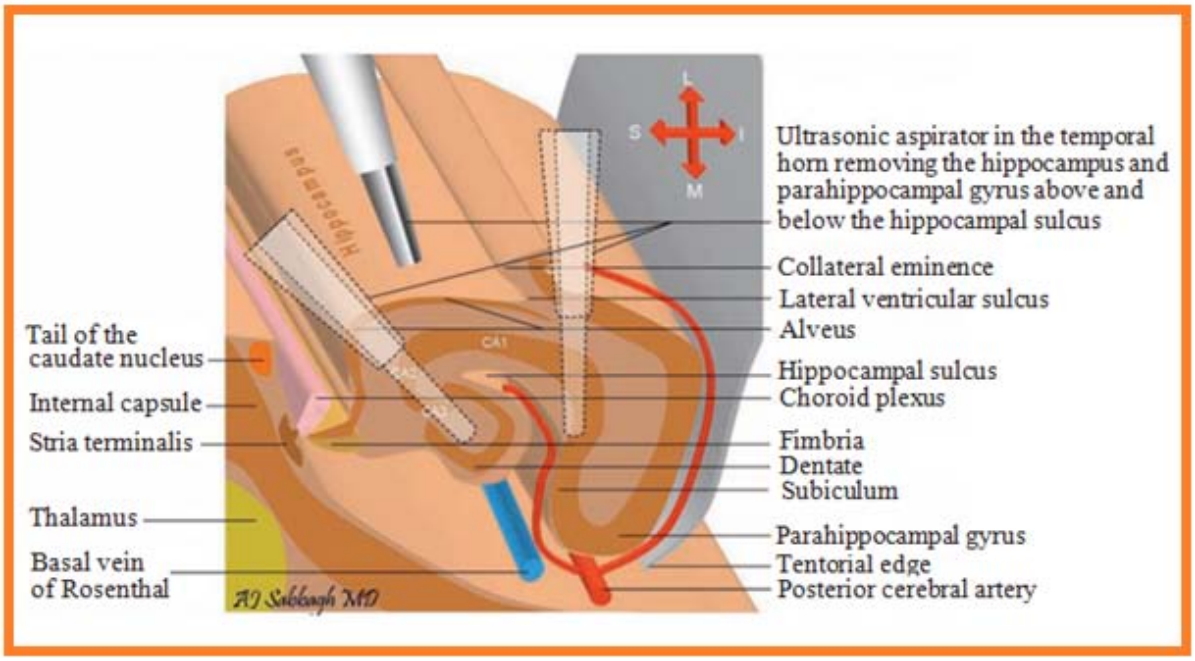


Fig. 2 The hippocampal resection. L, lateral; M, medial; S, superior; I, inferior; CA, cornu ammonis.

▪ The amygdale should be identified anterior and medial through the temporal horn.

▪ Using the ultrasonic aspirator the parahippocampus and then the rest of the hippocampal formation is emptied above and below the hippocampal sulcus while holding it with forceps.

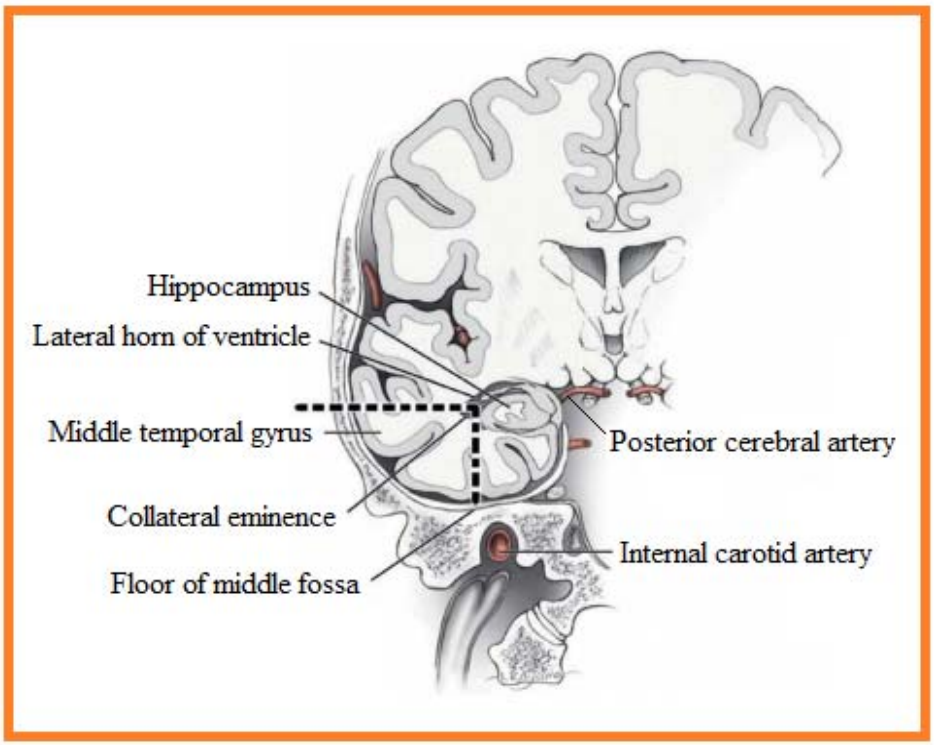


Fig. 3 Coronal section of the brain at the level of the hippocampus demonstrating extent of resection for temporal lobectomy, as well as relationship of resected structures to the ventricle and the middle fossa floor.

▪ The posterior limit of the hippocampal removal should be at the tectal cistern.
▪ Care should be taken not to injure the posterior cerebral artery, the basal vein, or the third cranial nerve and cross cerebri medially.
▪ The dorsomedial limit of removal of the amygdala corresponds to the entorhinal sulcus.
▪ Intraoperative imaging (if available, such as iMRI or iCT) is particularly helpful to confirm completeness of resection or for reregistration after brain shifts.
▪ Microscope magnification is very helpful at this stage.

10.

• The central point is the meeting point between the motor (M) and sensory (S) strips (there may be a connecting sulcus in the hand area of the homunculus at that level referred to as “pli de passage frontopariétal moyen” of Broca 9).
• The dotted line indicates extent of resection (Fig. 2).

11.

• It represents the part of optic radiation that projects from the relay neurons in the lateral geniculate body (thalamus) forward and lateral.

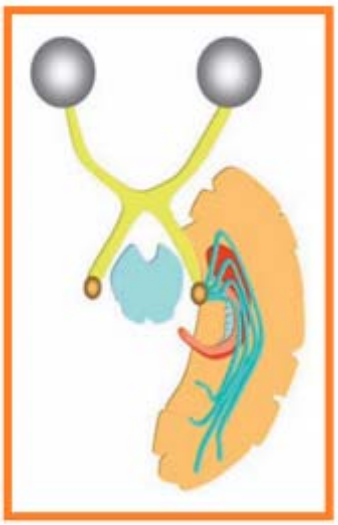


Fig. 4 Meyer’s loop and the visual system. Meyer’s loop is illustrated as the structure in turquoise blue. The optic nerve and chiasm are in bright yellow; the lateral geniculate body is the small darker yellow sphere; the temporal horn and contents are in red and orange.

• These projections loop on the roof of the temporal horns all the way just beyond them, anterosuperiorly, then backward toward the occipital visual cortex along the calcarine fissura (Fig. 4).
• The loop should be protected during surgery by avoiding the roof of the temporal horns.
• For selective amygdalohippocampectomy:

– Transcortical: through the middle temporal gyrus onto the lateral wall of the temporal horn would be a safe pathway.
– Transsylvian: incisions at the level of the limen insulae, or the adjacent 5 mm of the inferior insula sulcus should be a safe pathway.

Case 2

1.
• Investigations include the following:
– Drug levels to check compliance
– Single photon emission tomography (SPECT) scans
▪ Ictal mode
▪ Interictal mode
– MRI brain
– Video electroencephalogram telemetry

2.
• Surgical options for intractable multifocal epilepsy include
– Corpus callosotomy
▪ Anterior two-thirds callosotomy
▪ Complete callosotomy (not recommended for almost normal children)
– Vagal nerve stimulator

3.
• This surgery is palliative.
• It is more effective in treating atonic or drop attacks compared with other epilepsy types.
• A meta-analysis/systematic review of the literature showed that the long term seizure outcome is 35% of patients with callostomy become free of most disabling seizures.

4. Factors predicting better chance of improvement include the following:
– Lateralization
– Frontal origin of seizures
– Extent of corpus callosum resection

5. She has developed the expected postcallosotomy transient mutism.

6.

• Postoperative complications are as follows:
– Mortality risk is less than 1% and morbidity rate are 6–30%.
– The callosal syndrome includes
▪ Inability to name objects presented briefly to the left visual hemifield
▪ Left hemialexia
▪ Left hemianomia
▪ Difficulty imitating the hidden other hand
▪ Unilateral tactile anomia
▪ Unilateral left agraphia
▪ Right-hand constructional apraxia (inability to copy a complex design with the right hand, but ability to outperform this by using the left hand)
– Interhemispheric retraction
▪ Supplementary motor area injury
▪ Cingulate gyrus injury
– Vascular compromise or injury to the following:
▪ Superior sagittal sinus hemorrhage or occlusion
▪ Pericallosal and supramarginal artery injury
– Disconnection syndrome

7.

• Callosotomy is a palliative treatment aimed at seizure reduction rather than seizure cure.
• It is indicated for intractable multifocal epilepsy that is not amenable to resection of an epileptic focus and that is associated with drop attacks.
• Such examples include patients with severe Lennox–Gastaut syndrome.

8. Parts of the corpus callosum are described below (Fig. 5).

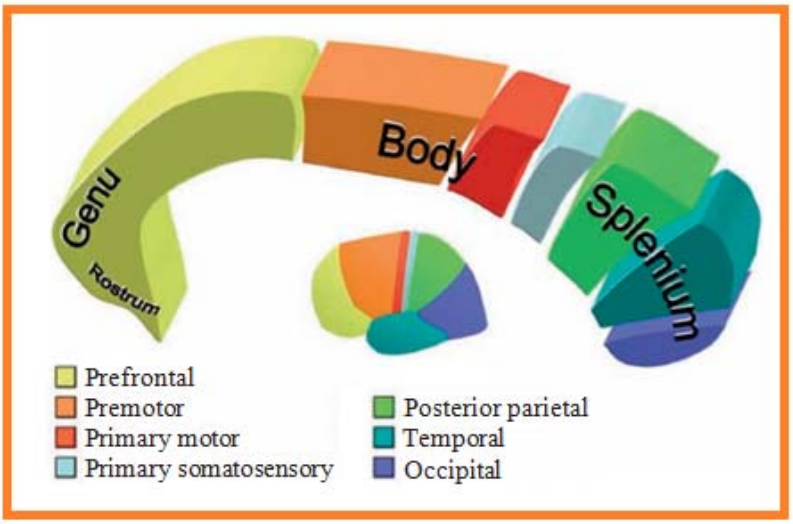


Fig. 5 Parts of the corpus callosum. The approximate locations of connecting fibers of major cortical brain regions are highlighted in the smaller unlabeled image.

Rostrum, Genu, Body, Isthmus, Splenium, Forceps minor and major.

• Figure 5 also shows the approximate locations of connecting fibers of major cortical brain regions.

9.

• Better seizure control can be achieved by callosotomy, especially drop attacks.
• Vagal nerve stimulation is less invasive.
• Vagal nerve stimulation is reversible unlike callosotomy.
• Vagal nerve stimulation has less morbidity.
• Vagal nerve stimulation requires battery change and a closer follow-up.

10.

• Standard anterior two-thirds callosotomy or complete callosotomy (Fig.6)
– Supine position
▪ Slight flexion with placement of the midline of the cranium at a right angle to the floor

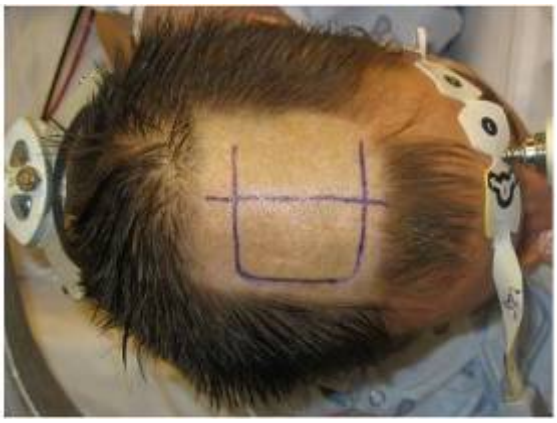


Fig.6 Surgical site preparation for corpus callosotomy. Right hemisphere is inferior, and left hemisphere is superior. In this position, left hemisphere will be held out of field by falx cerebri, and right hemisphere will fall away from field, minimizing need for traction.

▪ Single or double skin openings (anterior and posterior)
▪ Interhemispheric approach by entering the cranium at the nondominant hemisphere and/or the side with the least crossing superior sagittal sinus tributaries obstructing the way (neuronavigation is very helpful in outlining those vessels preoperatively).
– Lateral position (Olivier technique)
▪ Letting the side of entry inferior, so the brain will sag with gravity to help open the interhemispheric fissure without retraction.

• Two-stage approach
– Starting with the two-thirds callosotomy approach and planning for the remaining one-third at a second stage if seizures need better control despite improvement.
• Other techniques
– Endoscopic approach
– Gamma knife or other forms of radiosurgery.

A rectilinear, U-shaped, vertex scalp incision is centered over the junction of the coronal and sagittal sutures (see the image below). A 4-hole bone flap which straddles the sagittal and coronal sutures is elevated. From this point, an operating microscope is used. To provide superior stability, the authors prefer to operate while seated, using a sterile, draped Mayo stand for elbow support.
The dura over the dependent hemisphere is opened to the edge of the sagittal sinus. The dural flap is pulled tight with retention sutures to provide maximum exposure of the interhemispheric fissure. Lysis of midline adhesions between the arachnoid and dura is performed using bipolar cautery. Attempts are made to preserve bridging veins, but 1 or 2 veins (anterior to the coronal suture) can be sacrificed, if necessary.

Moist cottonoid strips are placed over the medial frontal cortex of the dependent frontal lobe, and any additional adhesions between the cortex and falx are cut with bipolar cautery. In this manner, dissection is carried down to the corpus callosum, which is identified only after clear visualization of both pericallosal arteries. Without this verification, an inexperienced surgeon may mistake the cingulate gyrus for the callosum.

After both pericallosal arteries are separated and protected and the callosum has been exposed, the callosum is opened along the midline of the body. This incision is carried deep until the cavum septum pellucidum is entered, with the ventricular ependyma left intact. In rare instances, one major pericallosal artery supplies both hemispheres and makes the dissection more difficult because the artery must be manipulated from side to side without damaging branches to either hemisphere.

A bipolar cautery is used to cut the callosum. Care is taken to stay within the cavum septum pellucidum. The entire rostrum, genu, and body are divided, and dissection is carried posteriorly until only the splenium remains intact.

The lumbar drain is removed, and the partial pressure of carbon dioxide (PCO_2) is allowed to rise to 40 mm Hg. Nitrous oxide anesthesia should be discontinued at this point. The wound is irrigated generously to replace most of the drained CSF. If mannitol was used earlier, intravenous (IV) fluid should replace the volume loss from diuresis.

The dura is closed, dural tack-up sutures are secured, and the craniotomy is closed in layers. Blood loss should not exceed 150 mL. Experience has suggested that patients fare better postoperatively if the net fluid balance for the surgery is positive at the end of the case.

Case 3

1. The EEG shows a generalized epileptiform burst (polyspike and slow-wave) consistent with a generalized epilepsy. The combination of early morning jerks, tonic–clonic seizures and age of onset are typical of JME – one of the idiopathic generalized epilepsies. Absence seizures may also occur. Absences are typically associated with a 3 Hz spike/wave discharge on the EEG. There is often an associated family history of epilepsy.

2. Seizures in idiopathic generalized epilepsies often occur following lack of sleep or alcohol consumption. In addition, photosensitivity is common in JME, occurring in up to 30% of cases. The flicker frequency that usually results in a discharge is 10–25 Hz. Although the flicker frequency of television (50 Hz) is higher, harmonics in this frequency can induce seizures. This risk can be minimized by sitting further from the screen in a well-lit room. Computer screen flicker frequency is much higher and is unlikely to induce a seizure. The content of a game, however, may contain objects that flicker at a frequency liable to induce seizures.

3. Sodium valproate is the treatment of choice. Carbamazepine and phenytoin can worsen both the myoclonus and the absences. Clonazepam can be helpful for the myoclonus, and there have been reports of the effectiveness of some newer antiepileptic drugs in this syndrome (especially lamotrigine). Although JME responds well to treatment, most (90%) will need life-long treatment. This contrasts with other epilepsy syndromes in which overall about 60% of those who become seizure-free can expect to come off medication, and other childhood idiopathic generalized epilepsies that usually spontaneously remit in adulthood.

4. The risk depends on whether the seizure was deemed to be provoked or not. A provoked seizure is one that is caused by an acute brain insult (e.g. hypoglycaemia, alcohol intoxication or withdrawal, subarachnoid hemorrhage, meningitis); if the provoking factor can be identified and withdrawn the risk of further events is low (around 3% for a reversible metabolic insult such as hypoglycaemia). It is higher (around 10%) if the provoking factor results in a

structural brain lesion (e.g. ischemic stroke). Overall the risk of recurrence after an unprovoked first seizure is around 40%, although this varices enormously according to the type of seizure, based on brain imaging and EEG results. The risk is greatest in the first 6 months; after 2 years the risk falls to < 10%.

5. The legal situation in the UK is that after an unprovoked seizure, drivers of cars or motorcycles should not drive for 6 months. It is the patient's duty to inform the relevant authorities and the treating doctor is not obliged to do so, although this is a possible course of action if the doctor believes that the patient is continuing to drive against medical advice. The restriction is longer (at least 10 years) for patients who are drivers of commercial vehicles.

Advice about work and hobbies depends on the patient's occupation; certain jobs would pose risks to the patient if they were to have a seizure whilst at work (e.g. scaffolder, heavy machinery operator). Negotiation should take place between doctor, patient and employer and if necessary the patient should be moved to alternative duties if this is possible.

Case 4

1. No. As well as generalized seizures, her experience of colored blobs in her vision were likely to represent simple focal occipital seizures. Her jerky movements were likely to be myoclonic in type. Myoclonus may be defined as a brief, sometimes as little as 30 ms, contraction of a muscle or group of muscles resulting in a body jerk. It may be repetitive, but is distinguished from tremor on the basis that the movement is unidirectional rather than bidirectional. Phenytoin is not a very effective anti-convulsant for simple partial seizure and may in fact worsen myoclonus. Better choices would have been sodium valproate, lamotrigine or perhaps topiramate. The myoclonic jerks may themselves have been treated with clonazepam and piracetam.

2. Myclonus may be classified according to the likely location of origin or according to etiology. A random pattern of jerking in different limbs with a focal stimulus sensitivity is suggestive of cortical myoclonus. An etiologic classification of myoclonus might include physiologic myoclonus (e.g. hypnopompic jerks), essential myoclonus (idiopathic and occurring in isolation), epileptic myoclonus (part of a characteristic and generally non-progressive epileptic syndrome), progressive myoclonic epilepsy, progressive myoclonic ataxia (progressive inherited diseases with the characteristic combination of

features), and symptomatic myoclonus (other underlying structural diseases, focal lesions or encephalopathies).
This patient's initial presentation with epilepsy and myoclonus and subsequent severe generalized deterioration, together with her susceptibility to recessively inherited disease, would make it most likely that she has a progressive myoclonic epilepsy.

3. Lafora body disease. The autosomal recessive progressive myoclonic epilepsy presents usually in late adolescence or early childhood. Characteristic features are the severe stimulus sensitive myoclonic flurries, behavioral problems, simple visual hallucinations and deafness later on. The disease is relentlessly progressive. It is a storage disease and may be diagnosed from an axilla skin biopsy by polyglycosan accumulation in the duct cells of eccrine sweat glands. It relates to a mutation of protein tyrosine phosphatase gene on chromosome 6.

Case 5

1. The MRI shows loss of volume of the right hippocampus. In this setting, the cause is almost invariably hippocampal sclerosis. This could be further substantiated on T2-weighted or proton-density sequences, which might also show increased signal in the right mesial temporal region.

2. The history is typical of refractory temporal lobe epilepsy due to hippocampal sclerosis, associated with an early prolonged febrile convulsion. Her seizure semiology would be typical for a right temporal lobe seizure in a right-handed individual. The resistance to drug treatment is common in epilepsy due to hippocampal sclerosis (90% of cases are refractory to medical treatment). Her epilepsy is clearly serious –she has burnt herself already. Though she may not have an increased risk of sudden death, in the absence of secondarily generalized seizures and not being male, nevertheless she is at increased risk of morbidity and requires careful counseling about lifestyle issues. She is a potential surgical candidate. She requires referral to an epilepsy center, where she is likely to have at least videotelemetry, which is the first step in determining her suitability for surgery and prognosis therefrom. She may have up to a 70–80% chance at best of becoming seizure free. In the meantime, if there is a true catamenial predominance to seizures, the option of perimenstrual clobazam therapy (e.g. 10 mg/day for 7 days around her menses) would be worth considering, in addition to the option of altering her prophylactic anti-epileptic drugs. As for all women of child-bearing age, the issues of

contraception and teratogenicity must be discussed if this has not already been undertaken.

Case 6

1. Partial seizures in which consciousness is impaired are referred to as complex partial seizures. They may evolve from simple partial seizures (as in this instance), resulting in an aura, or may occur with impairment of consciousness at onset. The nature of the complex partial seizure is determined by the lobar origin. The seizure described is typical for a complex partial seizure originating in the temporal lobe. In temporal lobe seizures the aura commonly consists of: rising epigastric sensation, autonomic symptoms, psychic symptoms (especially déjà vu, depersonalization, memory flashbacks, fear, anger) or hallucinations (especially gustatory and olfactory). Automatisms commonly occur and consist of fumbling, picking clothes, lip smacking and chewing.

2. The MRI demonstrates a smaller hippocampus on the right – typical for hippocampal sclerosis (mesial temporal sclerosis). The hippocampus is an archeo-cortical structure, in the medial part of the temporal lobe. It is part of the limbic system.

3. Febrile convulsions are a common cause of hippocampal sclerosis. Febrile convulsions, however, are usually benign with only 7% of children with febrile convulsions developing epilepsy by the age of 25 years. The greatest risk of developing epilepsy is in those with a prolonged febrile convulsion (longer than 20 minutes), focal features in the convulsion, a family history of epilepsy (non-febrile convulsions), and prior abnormal neurology or development.

4. Mesial temporal lobe epilepsy is the most common cause of complex partial seizures. About 70 to 80% of these seizures arise from the temporal lobe, and more than 65% of these originate in the mesial temporal lobe structures, especially the hippocampus, amygdala, and parahippocampal gyrus.

Case 7

1. Clinical studies have shown that the risk of seizure recurrence is 30–50 % at 2 years after a single unprovoked seizure. The likelihood of a second seizure is greatest in the initial 3 months following the seizure. The risk of a third seizure is approximately 65 % after a second seizure.

2. Clinical factors that may increase the risk of recurrent seizures include a preexisting neurological disorder, a focal neurological deficit, a history of remote symptomatic neurological disease, and a positive family history for epilepsy. An abnormal EEG recording with an epileptiform discharge and a lesion on neuroimaging are risk factors that carry a high likelihood of seizure recurrence.

3. The use of antiepileptic drug (AED) therapy to reduce seizure recurrence after a single unprovoked seizure needs to be individualized. AED medication has been shown in clinical studies to reduce the risk of seizure recurrence during shortterm follow-up. However, there is no evidence that the use of AED therapy after a single seizure improves long-term seizure control in patients who develop a seizure disorder. The potential benefit of AED therapy needs to be contrasted with the potential adverse effects of medication. Important issues in patients who consider AED medication are the duration of therapy and the need for drug level monitoring. Patient compliance with medical therapy should also be considered in making a treatment decision (see response 5).

4. The laws regarding driving and epilepsy are determined by each state. Many of the restrictions are limited to patients with seizure disorders or epilepsy. The “seizure-free” duration period may range from 3 months to 1 year. Most states require self-reporting by patients. Medical forms may need to be completed prior to the individual being permitted to operate a motor vehicle. The patient should discuss the issue with the health care provider and review the individual state laws.

5. The clinical course is variable in patients who present with a single unprovoked seizure. Conditions where treatment may be warranted include a prolonged focal seizure or status epilepticus, the presence of an immediate family history, a neurological deficit, an abnormal MRI or EEG, and a remote seizure. From an individual patient perspective, those with high-risk jobs or an individual inability to accept a second seizure may warrant considering treatment. The occurrence of a second seizure would usually warrant AED therapy and careful monitoring of the patient. Approximately 80 % of patients with a seizure disorder have a favorable outcome with AED medication and nearly two-thirds of patients are rendered seizure free (see response 3).

Case 8

1. Some women with epilepsy (WWE) find it harder to conceive. Gynecological problems including menstrual irregularities, polycystic ovaries, and catamenial seizures may complicate the course of treatment. In addition, WWE may have a greater risk of pregnancy-related problems including vaginal bleeding, risk of prematurity, small-for-gestational-age babies, and other obstetric risks. However, most can safely become pregnant while on ASDs. This does require planning by the patient and physician.

The goal in AED use during pregnancy is monotherapy with the lowest dose required for efficacy. The overall prevalence of major congenital malformations of children born to mothers with epilepsy is 4–10 %. This is two to four times higher than in the general population, and can vary depending on which drugs are used, the number of drugs used, and their doses. Polytherapy has consistently been associated with an increased risk of congenital malformations by comparison to monotherapy.

2. AED selection, in regard to potential for fetal malformations, should be made before the patient becomes pregnant. In general, LTG and levetiracetam appear to have the lowest risk of fetal malformations, though carbamazepine, and perhaps oxcarbazepine, may be relatively safe too. Valproic acid was consistently been associated with an increased risk of major congenital malformations, compared to other ASDs, in multiple large pregnancy registries worldwide. Phenobarbital has also been associated with a greater teratogenesis in those treated in the USA. Phenytoin has an intermediate risk. Valproic acid has also been associated with lower postnatal IQs in children up until 6 years of age when they are exposed in utero within the first trimester. The relative risks of using newer ASDs or requiring VPA when a dose <1,000 mg is compared to polytherapy are not yet established. Risk of major congenital malformations may be decreased by supplementation of at least 0.4 mg of folic acid daily.

3. Generalized tonic–clonic seizures during pregnancy can result in fetal harm due to traumatic injury, resulting in fetal bradycardia and systemic lactic acidosis. The impact of focal seizures, with or without impaired consciousness, and absence seizures on the developing fetus is not known. Still, focal seizures with impaired consciousness have been shown to alter placental blood flow and should be treated. In general, any seizure that could potentially result in harm to the mother is dangerous to the baby during pregnancy.

4. Change in seizure frequency during pregnancy is unpredictable, though seizures freedom in the 9 months prior to pregnancy has been found to be predictive of seizure freedom during pregnancy. Averaging all studies, approximately 50 % of WWE have no change in seizure frequency, 25 % have an increase in seizures frequency, and 25 % have a decrease in seizure frequency. However, these numbers vary with individual studies.

5. Most WWE have uneventful pregnancies. For WWE on ASDs, there is probably no substantially increased risk of bleeding late in pregnancy or Caesarean section, and likely no moderately increased risk of premature contractions, labor, or delivery. There is a higher risk of premature labor and delivery in WWE who smoke, and smoking cessation should be encouraged prior to conception.

6. After delivery, there may be risk of breakthrough seizure due to decreased serum AED levels and sleep deprivation. Children born to WWE carry a higher risk of developing epilepsy later in life, though the risk is related to the underlying etiology for epilepsy.

Case 9

1. BPNH. The extensive bilateral heterotopic masses lining the lateral ventricles are of the same signal intensity as cortical gray matter on all sequences. They are not irregular or ovoid, nor are there any cortical lesions. This is not tuberous sclerosis. BPNH is a relatively common developmental cause of epilepsy; seizures may not begin until the second or third decade and, in females at least, cognitive impairment is unusual.

2. BPNH may be sporadic or familial. Familial cases are most likely to be due to a mutation in the FILAMIN 1 gene (FLN1). The gene is on the long arm of the X chromosome. Inheritance is mainly X-linked dominant with male lethality, though theknown spectrum of inheritance patterns is broadening. The gene is large (>50 exons) and routine genetic analysis is not widely available. However, the likelihood of a genetic cause could be increased by imaging the patient's mother, who also has epilepsy. If she were found to have BPNH, an FLN1 mutation is very likely. The patient herself would require baseline hematology and biochemistry prior to consideration of anti-epileptic drug treatment.

3. Three issues need consideration: (1) counseling for epilepsy and prophylaxis with anti-epileptic drugs for the patient; (2) discussion of the issues of

contraception, conception, and pregnancy in epilepsy and with anti-epileptic drugs; and (3) genetic counseling.

Case 10

1. This EEG shows ongoing status epilepticus with ongoing seizure activity emanating from the right hemisphere (see arrow on Fig.). This patient initially had convulsive status epilepticus that evolved to non-convulsive seizures to explain the impaired consciousness in the ED.

2. Status epilepticus has been defined as 30 min or more of a prolonged seizure or the patient does not return to their baseline state between recurrent seizures. Operational definitions now include any seizure that is greater than 5 min. Status epilepticus is a medical emergency and newer definitions reflect the move toward earlier treatment.

3.
• Convulsive: clear clinical evidence of seizures
• Generalized
• Focal
• Nonconvulsive: no clear physical signs of seizures; evidence of abnormal electrical activity on EEG
• Absence
• Complex partial
• Electromechanical dissociation: lack of muscle activity due to muscle fatigue (present late in the course of SE)

4.
Stroke
Medication changes
Alcohol or drugs
Anoxia
Metabolic disorders
Infection
Trauma
Tumors

5. 20%

Case 11

1. Treatment with ASDs after an initial seizure reduces the risk of seizure recurrence by approximately 50 %. After a patient has remained seizure free for >2 years, favorable prognostic factors for seizure freedom after medication discontinuation include normal neurological exam and IQ, an EEG that normalizes after the initiation of ASDs, special epilepsy syndromes (e.g., childhood absence epilepsy where remission likelihood is high), epilepsy that is readily controlled with AED monotherapy, a short duration of epilepsy, a single seizure type, and successfully undergoing lesionectomy for epilepsy.

2. Negative prognostic factors for seizure freedom after medication discontinuation include the presence of an abnormal neurological examination, epileptiform abnormalities on the EEG, special epilepsy syndromes (e.g., juvenile myoclonic epilepsy), the need for two or more ASDs prior to control, a long duration of uncontrolled epilepsy (i.e., more than 20 seizures), and the presence of a focal lesion on brain MRI.

3. After a patient achieves 2–5 years of seizure freedom on an antiepileptic medication (AED), most neurologists will discuss *a trial* of discontinuing ASDs. In women anticipating pregnancy, this should be first addressed after 2 years. In those that have syndromes that are long-lasting (e.g., JME) ASDs are typically for lifelong. This patient has positive prognostic factors for successful discontinuation of ASDs because his seizures are controlled with monotherapy; he has a single seizure type; he has a relatively short duration of epilepsy; and he has a normal neurological exam. A relatively negative prognostic factor is the presence of an abnormal MRI that may suggest seizure control as opposed to seizures remission where ASDs may be successfully tapered.

4. Further testing should include a repeat EEG. EEG has prognostic value in patients considering a trial of AED taper. In most studies, the presence of epileptiform suggests a higher likelihood of relapse when medication is withdrawn.

5. When the decision to taper ASDs is made, most patients do well. A slow taper schedule has been found to be more successful than regimens that stop medication abruptly. When breakthrough seizures do occur, half of the time it happens within the time period of drug taper and otherwise will occur within the first 3–6 months after patients are no longer taking ASDs. During this time it is

best to continue seizure precautions, including temporarily restricting driving privileges.

Case 12

1. This patient does not have true “petit mal” (aka absence seizures). Episodes of staring may be differentiated by a sudden stare for 10–15 s in absence while focal seizures with impaired consciousness typically last 30–40 s and manifest a warning (aura). Absence seizures begin and end abruptly while focal seizures often exhibit post-ictal disorientation and lethargy. Automatisms may occur in absence seizures that are longer in duration. Our patient is manifesting focal seizures, as supported by a focal lesion on brain MRI. Many patients refer to staring episodes as “petit mal” because they are mean to indicate to the non-convulsive nature of the events.

2. The EEG has left hemispheric predominant polyspikes. Generalized epileptiform discharges may occur in patients such as ours due to secondary bilateral synchrony. This bilateral diffuse epileptiform discharge occurs as a consequence of a localized process such as the left mesial frontal lesion. A generalized EEG pattern is probably due to the proximity of the lesion to the corpus callosum. Mesial frontal lesions have a rapid transit time via the callosum to manifest as bilateral synchronous epileptiform discharges on the EEG. There may be a “lead in” to generalized discharges that can appear, and the generalized spikes (or polyspikes) usually have a repetition rate of <3 Hz when it occurs. In this case, the burst of polyspikes is lateralized to the left and the brain MRI clearly shown an area of FLAIR abnormality that probably reflects focal cortical dysplasia to strengthen the classification of the seizures in this case.

3. This patient has localization-related epilepsy manifest as brief focal seizures with impaired consciousness and focal seizures that evolve to convulsions. Focal seizures that evolve to convulsions are a commonly recognized entity in patients with localization-related epilepsy. In addition, lateralized semiologies and EEG features may occur in patients with generalized seizures associated with genetic epilepsy (i.e., JME) are common. Terminology and concepts for reorganization of the epilepsies have been recently performed dichotomizing common focal and generalized seizures. Overlap between generalized and focal seizures may rarely occur. The clinical onset of absence (“petit mal”) with subsequent convulsions “grand mal” suggests one of the genetic generalized epilepsies. However secondary bilateral synchrony on the EEG (and generalized discharges from a

focal lesion) or focal abnormality on brain MRI suggests focal seizures as the correct classification.

4. Treatment is predicated upon proper seizure and epilepsy classification. Narrow-spectrum ASDs such as carbamazepine and phenytoin may aggravate seizures control or worsen some generalized seizure types (absence and myoclonic seizures). Similarly, some ASDs for generalized seizures (ethosuximide) as in this case may be ineffective for the treatment of focal seizures. EEG is fundamental to seizure classification when semiology is unclear, such as when dealing with staring episodes and convulsions. Even EEG may be challenging when a lack of defining interictal discharges or secondary bilateral synchronous epileptiform discharges are present. Brain MRI may reveal a focal lesion (as in this case) that supports localization-related epilepsy and guide AED choices for focal seizures. Most ASDs have been approved by the US Food and Drug Administration for clinical use in the treatment of focal seizures. Valproate, lamotrigine, topiramate, levetiracetam, and zonisamide have demonstrated efficacy in some patients with both focal and generalized seizures. The barbiturates and benzodiazepines may also demonstrate benefit in both seizure types.

5. The best course of action for this patient is to treat her for drug-resistant seizures. Following the failure of two appropriate AsDs for an adequate time period, the substitution or addition of alternative agents carries a low yield of success. Because our patient has a definable lesion on brain MRI, surgical therapy was recommended, which she refused, noting that her seizures were not a “disability” for her. A change to Lamotrigine as a non-enzyme inducing AED was also recommended given the long-term consequences that were possible on PHT with uncontrolled seizures; however, she felt too comfortable with her treatment to accept a change. Her wishes were respected, and she continues to have infrequent seizures. She has since delivered two healthy children on PHT monotherapy.

Case 13

1. JME is a common genetic generalized epilepsy that manifests in adolescence. It is characterized by repetitive irregular myoclonic jerks predominately involving the upper body. No loss of consciousness is encountered unless the patient manifests generalized (clonic)–tonic–clonic seizures. Nearly all JME patients wave GTC seizures with myoclonic seizures (one-third also have

absence seizures). Seizures occur with morning predominance and require long-term therapy.

Interictal EEG demonstrates 3–5 Hz generalized spike- and polyspike-and-waves and photosensitivity is common. In our patient, the clinical presentation of myoclonic and convulsive seizures early on may suggest JME, but the progressive course and the abnormal EEG background activity suggests otherwise. The progressive course with worsening of mental status, gait, dysarthria, and uncontrolled seizures suggests one of the progressive myoclonus epilepsies (PME).

2. The EEG findings of the frequently intermixed generalized spike- and polyspike-and-waves would suggest generalized epilepsy. However, the diffusely slow background activity would suggest an encephalopathic process as opposed to JME. PME has EEG changes that may precede the clinical symptoms by 6 years. Diffuse slowing and generalized IEDs occur in virtually everyone. Slowing and loss of an alpha rhythm gradually became replaced by generalized IEDs with occipital predominance in addition to focal and multifocal abnormalities. The IEDs wane during sleep unlike genetic generalized epilepsy where the IEDs become more prominent. Giant somatosensory evoked potentials and increase cortical excitation to paired pulse transcranial magnetic stimulation may be seen. The myoclonus of PME is a prominent clinical feature though, in addition, generalized, focal, and atypical absence seizures may also occur.

3. The progressive myoclonus epilepsies (PME) are a rare group of disorders. Unverricht–Lundborg disease, Lafora disease, myoclonic epilepsy with ragged red fibers (MERRF), the adult form of neuronal ceroid lipofuscinosis (Kufs), and sialidosis are the principal PMEs. Our patient presented in early adolescence and at first mimicked JME. The progressive cognitive decline, worsening myoclonus, dysarthria, and gait disorder led to a clinical diagnosis of Lafora Disease (LD). LD presents in early adolescence and may initially mimic IGE though progressively worsening myoclonus after an initial GTC signals a different course. Slow cognitive decline, visual impairment, visual hallucinations, and occipital seizures become evident. Progressive myoclonus, refractory epilepsy, dementia, ataxia, and speech dysfunction occurs. Total care is evident prior to a fatal demise which occurs within 10 years after onset.

4. MRI brain may identify atrophy in the more aggressive PMEs. Basal ganglia signal changes may be seen in MERRF but were absent in our patient. In our

patient, EEG demonstrated a diffusely slow background with frequent GSW and PSW coupled with myoclonic jerks. SSEPs were performed without high amplitudes of the N19 waveform to median nerve stimulation. Genetic testing is helpful to establish the diagnosis. In our patient, EPM1 and EPM2 were normal. A point mutation on tRNALys gene was not recovered. An axillary skin biopsy was without Lafora bodies but did demonstrated intracytoplasmic “fingerprint” inclusions and lipofuscin pigment stored in the lysosomes characteristic of adult NCL (Kuf’s disease).

5. The prognosis for patients with PME is oftentimes poor. Treatment is usually supportive. ASDs chosen should have broad spectrum utility due to the possibility of narrow spectrum ASDs aggravating seizures. Valproate is useful, through needs to be avoided in MERRF. Lamotrigine may worsen myoclonus in some.

Neurostimulation may have a role for some. Unverricht–Lundborg disease has the most favorable prognosis. The epilepsy is usually less refractory to ASDs though phenytoin is contraindicated. Patients may become wheelchair bound, though the cognitive decline may be mild and the course tends to stabilize over time. Our patient with Kuf’s requires complete care and has already become wheelchair bound. Her rapid deterioration refl ects a poor prognosis. Most patients with PME, including adult NCL and Lafora disease, have limited lifespans with the course culminating in death within a decade. Genetic markers are helpful, though biopsy may still be required for confirmation.

Case 14

1. The EEG demonstrates an electrographic seizure manifest as generalized left frontally predominant burst of rhythmic 10 Hz alpha frequencies. This discharge was recorded during one of the individual’s typical events and occurred directly from sleep. As such, given the clinical aspect of the diagnosis, this ictal EEG would confirm the diagnosis of localization-related epilepsy consisting primarily of focal seizures with left-sided motor symptomatology.

2. Individuals who experience an unexplained loss of consciousness, seizures, or epilepsy are subject to state driving laws. The state laws vary and depend upon the individual state of licensure. Most states require a seizure-free interval to maintain driving privileges. State laws vary from a minimum of 3 months to a maximum of 1 year in the USA before legally being able to operate a motor

vehicle.

3. Given that the patient has a diagnosis of epilepsy, the issue of piloting any plane is governed by Codes and Regulations set forth by the Federal Aviation Administration as part of the Department of Transportation. As such, this individual would need to show that they have been seizure free for nearly a decade without a diagnosis of epilepsy to independently operate an airplane. Commercial pilots are subject to even more rigorous restriction. Moreover, for this individual to return to flying airplanes, they need to be completely off of their seizures medications.

4. Commercial interstate trucking licenses as well as railroad engineers also fall under federal regulations by the Department of Transportation. This individual would also need to show that they have been seizure free for a prolonged time period (governed by individual state law) and well controlled by ASDs prior to release to truck driving. Chauffeur class A and B licenses are subject to even tighter control.

5. All 50 states mandate that physicians counsel their patients regarding their individual state driving laws. This should be documented in the patients' clinic chart. Six states including Delaware, New Jersey, Pennsylvania, California, Oregon, and Nevada have additional requirements that mandate physician reporting of all patients presenting with seizures to the state medical bureau. Failure to report individuals with epilepsy to the state bureaus could result in loss of physician licensure. The legal issue of the mandatory reporting of patients who have seizures to the department of motor vehicles or other federal bureaus is controversial. The American Academy of Neurology does not support the position of universal reporting. Under the current laws with the exception of reporting states, unsafe or risky drivers may electively be reported if they are deemed a safety risk without fear of impunity.

Case 15

1. The diary demonstrates a consistent pattern of seizure exacerbation related to the menstrual cycle, known as catamenial epilepsy. When strictly defined as a doubling of seizure frequency during a specific phase of the menstrual cycle, over 30 % of women with refractory partial epilepsy have catamenial epilepsy. The most common pattern, as demonstrated in this patient's diary, is the perimenstrual pattern with increased seizures in the days immediately before (and after) the onset of menses. The influence of the menstrual cycle of seizure

activity is attributed to the pro-convulsant effects of estrogen via enhancement of neuronal sensitivity to glutamate, and to the anticonvulsant effect of progesterone mediated primarily through gamma-aminobutyric acid (GABA) receptors in the brain.

2. Menopause is defined as cessation of menstrual periods for more than 1 year. This is preceded by perimenopause, which consists of several years when the menstrual cycle becomes increasingly irregular and fertility decreases due to increasingly irregular secretion of estrogen and progesterone. An increase in anovulatory cycles is encountered resulting in infertility. This patient's reporting of increasing menstrual irregularity and vasomotor symptoms (hot flashes, night sweats) are clinically consistent with perimenopause. Many women with catamenial epilepsy report worsened seizure control during perimenopause. Although cessation of ovarian production of estrogen and progesterone might be predicted to improve epilepsy after menopause, changes in seizure control after menopause are unpredictable.

3. Women with epilepsy may be at greater risk for premature menopause, defined as menopause that occurs at or before age 40. Increasing number of lifetime seizures has also been correlated with younger age at menopause. This patient's longstanding history of intractable epilepsy may have contributed to development of perimenopausal symptoms at her young age.

4. Hormone replacement therapy (HRT; estrogen or estrogen plus progesterone) is currently used to effectively treat menopause related symptoms and to prevent postmenopausal osteoporosis that may be accelerated by some ASDs placing women with epilepsy at increased risk for fractures. Vasomotor symptoms are the most common indication. Women undergoing premature menopause (age 40 years or less) are at increased risk for bone disease, and may receive greater benefit from HRT than women developing menopause at a later age. For women with epilepsy, vasomotor symptoms that disrupt sleep can adversely impact not only quality of life, but also seizure control. When considering initiation and duration of HRT, the potential benefits to a given individual must be weighed against her personal risk profile for venous thrombosis, vascular disease, and breast cancer associated with treatment.

5. HRT could exacerbate this patient's seizures in two ways. Firstly, the hormones themselves could influence seizure threshold. A randomized, controlled trial of combined estrogen/progesterone HRT in postmenopausal women with epilepsy demonstrated increased seizure frequency in over half of those treated. Furthermore, in those women using lamotrigine, serum drug levels

were lowered 25–30 % by HRT. The patient should be counseled on the potential risks of worsened seizure control related to HRT. However, these risks should be balanced against the severity of the vasomotor symptoms and the risks in an individual patient for osteoporosis. If HRT is started, AED dosing may need to be adjusted to maintain therapeutic serum drug levels.

Case 16

1. Unfortunately, despite a comprehensive presurgical evaluation, 30–40 % of patients undergoing surgical treatment continue to have disabling seizures after surgery. Studies have shown that recurrence of seizures most often occurs within the first year of surgery. The reasons that lead to failed epilepsy surgery can be roughly divided into three groups. Group 1 comprises patients with incorrect localization of the epileptogenic zone (i.e., temporal resection for "pseudotemporal" lobe epilepsy). Group 2 is associated with correct localization but inadequate excision of the epileptogenic zone. This is especially true in cases of insufficient hippocampal resection in mesial temporal lobe epilepsy or when the epileptic zone cannot be removed because it involves eloquent (functional) cortex. Group 3 is due to a second generator that existed preoperatively (i.e., dural pathology) or that developed after the initial resection.

2. After resective epilepsy surgery, rarely would MRI be able to identify potentially epileptogenic lesion. In the absence of a potentially epileptogenic lesion on MRI, localization of the site for epilepsy surgery is more complex and postoperative outcome is generally less favorable than that in lesional epilepsy surgery. Patients who underwent anterior temporal lobectomy have been shown to have an excellent outcome in 62 % of those with no MRI lesion versus 85 % of those with MRI lesion. The outcome in patients with non-lesional frontal lobe surgery is evel less favorable. One study showed that of patients who underwent frontal lobe surgery, only 40 % of those without MRI lesion had an excellent outcome versus 72 % of those with an MRI lesion.

3. iEEG monitoring is considered to be the gold standard for seizures localization. However, due to inherent morbidity and mortality, the use of iEEG has to be judiciously determined. iEEG is especially important for patients with nonlesional MRI in which an epileptogenic focus is poorly defined. Often, functional imaging studies (i.e., single-photon emission computed tomography [SPECT] and positron emission tomography [PET]) are used to guide the implantation of intracranial electrodes. In the absence of an MRI lesion, intracranial electrode implantation tends to be more extensive. It is not unusual

that additional electrodes need to be implanted if initial implantation yields inadequate seizure localization. Unfortunately, studies have shown an increase in complication rates related to longer iEEG monitoring and a greater number of electrodes.

4. Unsuccessful epilepsy surgery can lead to significant frustration on the part of patients, their families, and their health care providers. Sometimes, a repeat surgical evaluation leads to consideration of another epilepsy operation. Approximately 20–50 % of patients are seizure free after reoperation. Repeat surgery carries not only reduced likelihood of seizure freedom but also higher risk of morbidity. Several studies have demonstrated a transient or a permanent complication rate of 20–25 % associated with reoperation, which is not insignificant. Prognostic factors that have been associated with a favorable seizure outcome include (1) completion of a previous partial lesionectomy and (2) extending the previous resection when the prior localization has been validated.

5. Many patients with medically and surgically refractory epilepsy are not suitable for repeat surgery. Electronic neurostimulators and a low-glycemic diet are potential alternatives. Unfortunately, rarely do these therapeutic interventions render patients seizure free. Vagus nerve stimulation (VNS) is an FDA-approved adjunctive therapy for localization-related epilepsy, though it may be effective for other forms as well. It is generally well tolerated. The most common size effects include hoarseness, coughing, or problem swallowing. Studies wave shown 50 % of seizure-reduction in 30–40 % of patients. Deep brain stimulation (DBS) and a responsive neurostimulator (RNS) involve the implantation of a device that sends electrical impulses to specific parts of the brain to provide therapeutic benefits. In the USA, DBS is only approved to treat movement disorders and, like the RNS, is still an experimental procedure in patients with epilepsy. The ketogenic diet is a high-fat, adequate-protein, and low-carbohydrate diet to treat uncontrolled epilepsy and is especially useful in the pediatric population. Due to its stringent requirements, the ketogenic diet is not well tolerated by many patients. Instead, a modified Atkins diet or low-glycemic diet can be considered. Investigational ASDs may also offer hope to a few patients who have found little success with other treatments.

Case 17

1. Cognitive test performances that fall within 1 standard deviation above or below the normative mean ($z = 0$) are typically considered to be within normal

limits (shaded area of figure). Examination of this patient's postoperative test results alone reveals that he performed within the normal range across all cognitive domains assessed.

2. With the benefit of comparing his presurgical data, it can be seen that even though postoperative results are technically within normal limits, verbal learning, verbal memory, and semantic processing abilities (i.e., object naming and semantic verbal fluency) have declined. The longitudinal data support the patient's subjective experience of acquired difficulty learning and expressing knowledge in his college courses.

3. The neuropsychological findings reflect a strong clinical correlation with what is anticipated to occur with surgery involving the left temporal lobe in patients with a normal preoperative brain MRI. Wada testing revealed left hemisphere language dominance and intact left hemisphere memory functioning in this patient. The language-dominant anterior temporal lobe is believed to play an important role in semantic processing, linking together areas of the brain containing semantic information. Together with hippocampus and other medial temporal lobe structures, these systems within the language-dominant hemisphere are also essential to new learning and memory of verbal information.

4. Surgical resection is not the only risk factor for cognitive impairment on postoperative testing in epilepsy patients. Preexisting neurodevelopmental conditions such as learning disability, attention-deficit disorder, or low intellectual junction can cause or enhance functional cognitive deficits, but can often be predicted by preoperative testing or ruled out, as was the case with this patient. Uncontrolled seizures can cause progressive memory decline in individuals with temporal lobe epilepsy due to interruption in the neuronal mechanisms underlying memory encoding (i.e., hippocampal long-term potentiation). In this patient, however, seizures were controlled by surgery and cannot account for the observed memory decline. Use of ASDs, sleep disturbance, and mood disorders can impair memory, often through deficits in attention. This patient is on fewer ASDs at lower doses following his surgery, and he reported no sleep difficulty. He reported depressed mood at the time of postoperative evaluation; however, mood resting at baseline revealed more severe depression prior to his surgery. After excluding potential contributing factors, it appeared that the observed cognitive change could not be accounted for by nonsurgical factors.

5. Enough time had passed for the effect from acute surgical “trauma” to resolve. Therefore, formal cognitive rehabilitation and development of compensatory language and learning strategies were recommended, and a referral for outpatient cognitive rehabilitation was made. He could also benefit from more immediate and direct assistance with his college studies. Although his overall neuropsychological profile falls within normal limits, tasks that were once effortless when his semantic processing/verbal learning were above average are more difficult and require more effort now that these abilities are below average. The Student Services Center at his learning institution was approached to offer a study skills evaluation to help him develop more effective and efficient ways to learn new information. Other services, such as tutoring or note-taking assistance may also facilitate his ability to learn. His cognitive profile suggested that he was likely to experience difficulty and frustration on tests employing open-ended or essay questions. Hence, allowing him to take multiple-choice tests where semantic retrieval demands are minimized was suggested. If he had continued having difficulty pursuing career goals, despite appropriate academic accommodations, vocational counseling could help identify alternate career paths that fit better with his retained cognitive strengths. Finally, providing psychological intervention for his residual depression at this stage may prevent progressive worsening of mood and disability going forward.

Clinical Pearls

1. A single neuropsychological study at one point in time may identify areas of cognitive weakness or impairment as compared to normative standards but may not always be able to determine whether a patient was *declined* from a previously higher level of functioning.

2. Obtaining baseline neuropsychological studies prior to epilepsy surgery can facilitate identification of specific areas of cognitive decline post operation. This is especially relevant when the surgical target will involve functional tissue that could affect cognition.

3. The temporal lobes are the most common location for seizure onset. The medial temporal lobe (i.e., hippocampus) has the lowest threshold for seizure activity in the brain and is also critical for new memory formation. The anterior temporal lobe of the dominant hemisphere is especially important for semantic processing, particularly naming ability. Removing functional tissue from the left temporal lobe may result in a decline in naming, new learning, and memory that is quantifiable on neuropsychological testing.

4. There are many variables, other than surgical resection, that may contribute to memory deficits in patients with epilepsy. These include seizure variables (e.g., frequency, location of seizure focus, location of resection, AED use), mood disorders, sleep disorders, or preexisting neurodevelopmental disorders such as learning disability, attention-deficit disorder, or low intellectual functioning. Comprehensive pre- and postoperative neuropsychological assessment can help guide recovery and rehabilitation plans, contributing to improved outcomes in the functional status of surgical epilepsy patients.

Case 18

1. Status epilepticus is defined as one seizure lasting more than 5 minutes or two or more seizures without a return of consciousness in between. As Mrs Yarwood has had repeated seizures without full recovery of consciousness and her current seizure has lasted 9 minutes, she meets these diagnostic criteria. Status epilepticus is a life-threatening emergency associated with neurological damage and an increased risk of death. Mrs Yarwood therefore needs urgent supportive care and prompt and effective treatment to terminate the seizure.

Using the ABCDE approach for the critically ill patient, you can see that Mrs Yarwood has a nasal airway in place, is being nursed on her side and is oxygenating adequately despite her ongoing seizure. She is maintaining an adequate blood pressure and has a cannula in place for intravenous access. Trolley rails and padding have already been implemented to reduce the risk that Mrs Yarwood will injure herself during her seizure.

Emergency seizure management

The first choice of anti-convulsant for treatment of status epilepticus is a benzodiazepine. Benzodiazepines potentiate the actions of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), which may account for their anti-epileptic activity.

You should only prescribe benzodiazepines for seizures lasting longer than 5 minutes, as seizures usually self-terminate within 3 minutes. Mrs Yarwood's current seizure has now lasted 9 minutes and she has not regained full consciousness between seizures, so benzodiazepine treatment is appropriate. She already has an indwelling intravenous (IV) cannula, so you should prescribe IV lorazepam. Lorazepam is the IV benzodiazepine of choice in status epilepticus, as it has a longer anti-seizure effect and causes less thrombophlebitis than IV

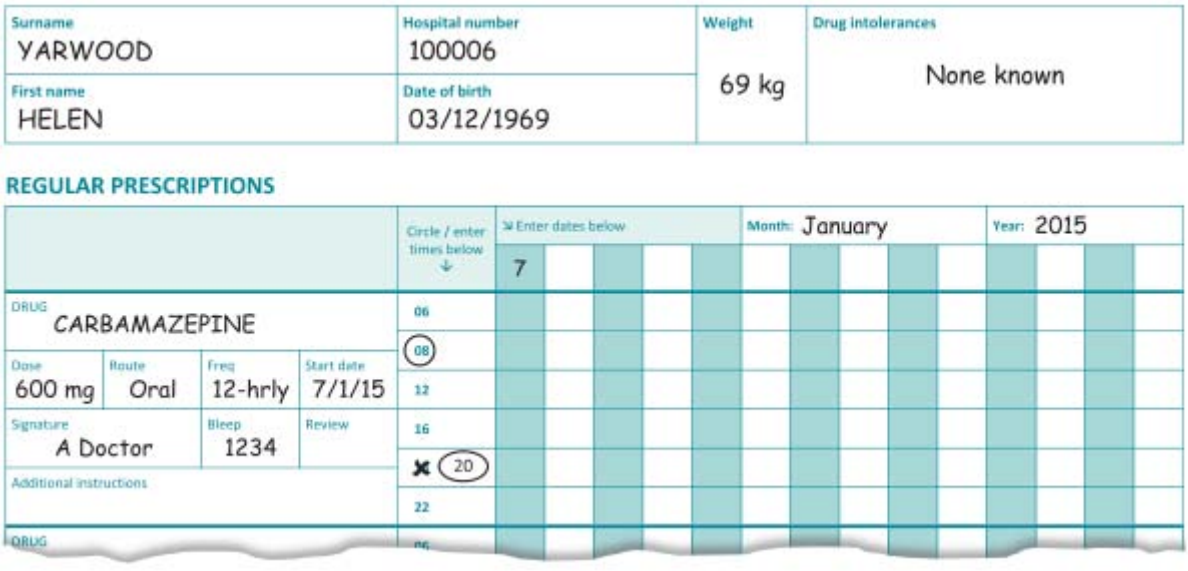
diazepam. Where IV access is not possible, you can prescribe buccal midazolam, administered into the oral cavity, or rectal diazepam.

After benzodiazepine administration, you should monitor Mrs Yarwood for efficacy (seizure termination, recovery of consciousness) and adverse effects (respiratory depression, hypoxia) of treatment. If seizures persist, you can prescribe a second dose of lorazepam. However, lorazepam should not be given more than twice in a 24-hour period. If seizures continue despite benzodiazepines, IV phenytoin should be given. IV phenobarbitone is an alternative if phenytoin is already being taken or is contraindicated. Patients who continue in status epilepticus despite these measures require sedation and ventilation.

Other emergency measures

Metabolic abnormalities. If status epilepticus is caused by a metabolic abnormality, such as hypoglycemia or pyridoxine (vitamin B6) deficiency (malnutrition, isoniazid treatment), you should correct these immediately with IV glucose (20% or 50%) or Pabrinex® (high dose B and C vitamins including pyridoxine and thiamine). In patients at risk of thiamine deficiency (alcohol excess, malnutrition), Pabrinex® should be given before or with intravenous glucose to reduce the risk of glucose precipitating Wernicke's encephalopathy. Mrs Yarwood does not require intravenous glucose or Pabrinex® as she has normal capillary glucose and no risk factors for pyridoxine or thiamine deficiency.

Further management

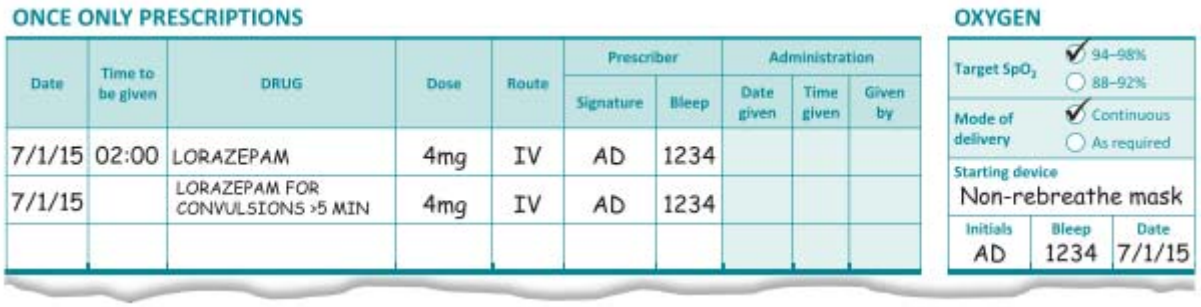


Mrs Yarwood has longstanding epilepsy, usually reasonably well controlled with carbamazepine. However, her blood test currently shows very low plasma

carbamazepine concentrations. When she recovers, discussions should include adherence to treatment, any recent changes in prescription or dose and any other new medicines that could potentially interact with carbamazepine. Review by an epilepsy specialist may also be useful.

You should also check that Mrs Yarwood does not drive. People with epilepsy must be free of daytime seizures for 1 year or have had asleep-only attacks for 3 years before they can drive a motor vehicle. They cannot drive large goods or passenger vehicles.

2. Lorazepam



ONCE ONLY PRESCRIPTIONS

Date	Time to be given	DRUG	Dose	Route	Prescriber		Administration		
					Signature	Bleep	Date given	Time given	Given by
7/1/15	02:00	LORAZEPAM	4mg	IV	AD	1234			
7/1/15		LORAZEPAM FOR CONVULSIONS >5 MIN	4mg	IV	AD	1234			

OXYGEN

Target SpO_2	✓ 94–98%	○ 88–92%	
Mode of delivery	✓ Continuous	○ As required	
Starting device	Non-rebreathe mask		
Initials	Bleep	Date	
AD	1234	7/1/15	

Your most urgent task is to terminate her seizure. You should prescribe lorazepam on the once only section of the drug chart for immediate administration. The usual dose is 4 mg given as a slow IV injection over 2 minutes. A maximum of two doses of lorazepam can be given in 24 hours. As long as no other benzodiazepines have been given, e.g. in the ambulance, you should write a second lorazepam dose on the once only section of the drug chart. Note that in the model prescription we have stated that this second dose of lorazepam is for administration only if the seizure lasts >5 minutes (most self-terminate after 3 minutes). This second advance prescription allows rapid treatment of further seizures if the prescriber is not immediately available. An acceptable alternative would be to prescribe lorazepam in the as required section of the drug chart. However, it must be made clear that Mrs Yarwood should receive a maximum of one further dose today and subsequently should receive no more than two doses in any 24-hour period.

Carbamazepine

You should prescribe her regular anti-convulsant treatment to start as soon as possible. On the model chart, carbamazepine has been prescribed at the dose that appeared to control her seizures in the past. When she has recovered from status epilepticus, further discussions may result in changes to her treatment. However, prescribing regular anti-convulsant therapy at this stage ensures that it is not forgotten and will help prevent further seizures.

Other measures

You should prescribe oxygen to maintain saturations at 94–98%. You should carry out a venous thromboembolism assessment and consider whether prophylaxis is needed. Mrs Yarwood has reduced consciousness and is currently trolley-bound so her mobility is reduced. However, she has fallen out of bed, had several tonic–clonic convulsions and is experiencing unusual seizure activity. At this stage it would be reasonable to withhold low molecular weight heparin and impossible to apply anti-embolism stockings. The need for VTE prophylaxis should be reviewed once the seizures have been terminated and further clinical assessment has been performed.

Further reading:

NICE epilepsy pathway. Available at: http://pathways.nice.org.uk/pathways/epilepsy (accessed 21 January 2014).

Case 19

1. Phenytoin now has a limited role in the management of epilepsy because of the availability of newer drugs that are generally better tolerated. However, it retains a place in the management of status epilepticus. The concentration of phenytoin in the blood has a reasonably good relationship with anti-epileptic efficacy. However, its therapeutic index is narrow (i.e. there is little margin of safety between the dose required for therapeutic effect and the dose that may be toxic). For these reasons, it is important that the plasma concentration of phenytoin is measured to guide its dosage adjustment (therapeutic drug monitoring, TDM).

Understanding phenytoin concentration monitoring

In the context of status epilepticus, you should first take a sample for phenytoin concentration measurement about an hour after administration of the IV loading dose. This is to ensure that a therapeutic concentration has been achieved, as was the case for Mr Raffiq. If maintenance therapy is then prescribed (which may be IV or oral, depending on the circumstances), you should take the next sample once *steady state* has been achieved. Steady state means that the rate of drug administration equals the rate of drug elimination; in other words, that the serum concentration has plateaued (other than for concentration oscillations associated with administration of individual doses).

Measuring the phenytoin concentration before steady state is reached is likely to be misleading and should generally be avoided unless toxicity is suspected. A good general rule is that steady state is achieved after the patient has been taking a stable dose for 5 half-lives of the drug. In the case of phenytoin this is more complicated because the half-life is not constant.

Nevertheless, most authorities would recommend not sampling until the patient has been on a stable dosage for at least 5 days. It is best if the sample is taken just before a dose, but because phenytoin has a long half-life and its absorption is slow, this is not crucial. In Mr Raffiq's case, the latest concentration appears to have been appropriately taken, so can be used to guide dosage adjustment.

Understanding phenytoin dosage adjustment

At low serum phenytoin concentrations, the rate at which phenytoin is eliminated from the body increases in proportion to its serum concentration, such that its half-life is stable (first-order kinetics). However, as the phenytoin concentration approaches the therapeutic range, the body's capacity to eliminate it becomes saturated. Now, the rate of phenytoin elimination is fixed: it does not increase as the serum concentration rises (zero-order kinetics). This means that the half-life will *lengthen* in proportion to the serum concentration. If you increase the dose further, not only will more phenytoin be entering the body, but its half-life within the body increases. The practical implication of this is that phenytoin dosage changes can have a more dramatic effect on the serum concentration than you might expect. You should therefore only make small adjustments to the phenytoin dosage, unless working under specialist advice.

Special circumstances

When interpreting a phenytoin level, you should also check the patient's serum albumin concentration. This is because, under usual conditions, about 90% of the circulating phenytoin is bound to albumin. Only the unbound 10% is pharmacologically active, and yet, when you send a sample for phenytoin concentration it will usually be the 'total' concentration (i.e. bound [inactive] plus free [active] phenytoin) that is measured and reported.

If the amount of albumin in the blood is reduced (as in, for example, liver disease or critical illness), the total phenytoin concentration will fall, because there is less phenytoin bound to albumin. However, the concentration of *free*

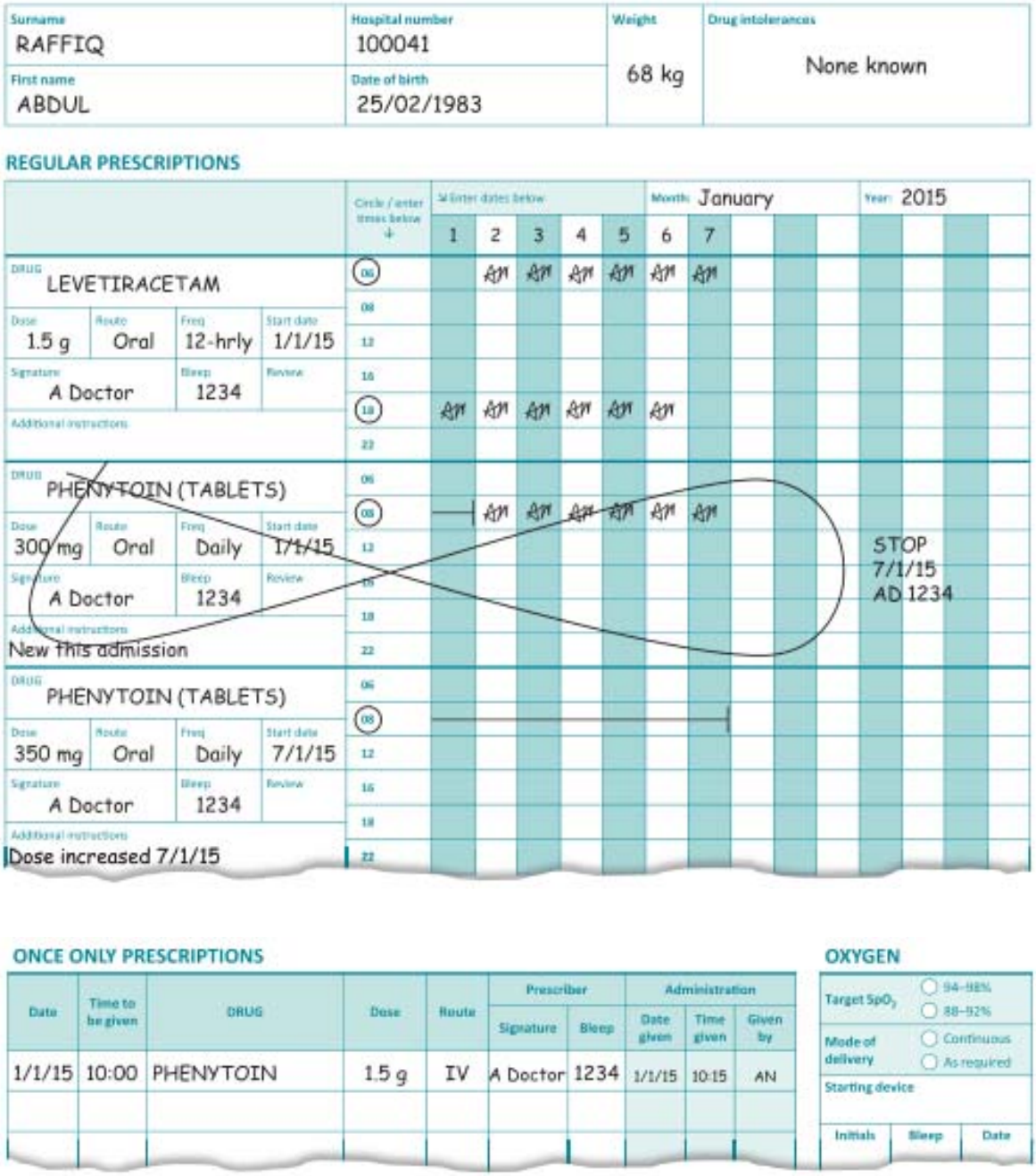
phenytoin may remain constant. This means that the target range is no longer appropriate: the patient may have a therapeutic or toxic concentration of free phenytoin, despite the total serum phenytoin concentration being below the target range.

A similar effect occurs in renal failure, which changes the affinity with which phenytoin binds to albumin. Consequently, you should also check the renal profile when interpreting a serum phenytoin concentration: if there is renal impairment (high serum creatinine concentration or low eGFR), there may be more free (active) phenytoin than would be suggested by the total phenytoin level.

Mr Raffiq's renal function and serum albumin concentration are within normal limits. Had they not been, you would ideally request measurement of the *free* phenytoin concentration. As this facility is not widely available, an alternative is to apply a mathematical correction to the total concentration to take account of renal function and albumin concentration. Some hospital laboratories apply this correction automatically – check the report carefully and seek advice if in any doubt.

2. As the current phenytoin dosage seems to yield a serum phenytoin concentration that is lower than what we are seeking to achieve (the upper half of the target range, i.e. 15–20 μg/mL), the dosage should be increased. This is usually done by stopping the existing prescription and re-prescribing the drug at the new dosage. This has been illustrated on the model chart, with an increase of the daily dose from 300 to 350 mg. The increment of 50 mg has been selected as it is the smallest dosage change that can be made without having to cut tablets or switch to a different formulation (capsules or syrup). A lower increment (25 mg) would be preferable in patients who are elderly, have a low serum albumin concentration or impaired renal function.

Mr Raffiq should now be monitored clinically (both for seizure frequency and signs of phenytoin toxicity, e.g. ataxia, nystagmus) and a further measurement of the serum phenytoin concentration should be performed after about 5 days at the new dosage. An earlier measurement could be made if features of toxicity supervene, but will otherwise just confuse matters.



Surname	Hospital number	Weight	Drug intolerances
RAFFIQ	100041	68 kg	None known
First name: ABDUL	Date of birth: 25/02/1983		

REGULAR PRESCRIPTIONS

Month: January Year: 2015

Drug	Dose	Route	Freq	Start date	Signature	Bleep	Review	Additional instructions
LEVETIRACETAM	1.5 g	Oral	12-hrly	1/1/15	A Doctor	1234		
~~PHENYTOIN (TABLETS)~~	300 mg	Oral	Daily	~~1/1/15~~	A Doctor	1234		New this admission
PHENYTOIN (TABLETS)	350 mg	Oral	Daily	7/1/15	A Doctor	1234		Dose increased 7/1/15

STOP 7/1/15 AD 1234

ONCE ONLY PRESCRIPTIONS

Date	Time to be given	DRUG	Dose	Route	Prescriber: Signature	Prescriber: Bleep	Administration: Date given	Administration: Time given	Administration: Given by
1/1/15	10:00	PHENYTOIN	1.5 g	IV	A Doctor	1234	1/1/15	10:15	AN

OXYGEN

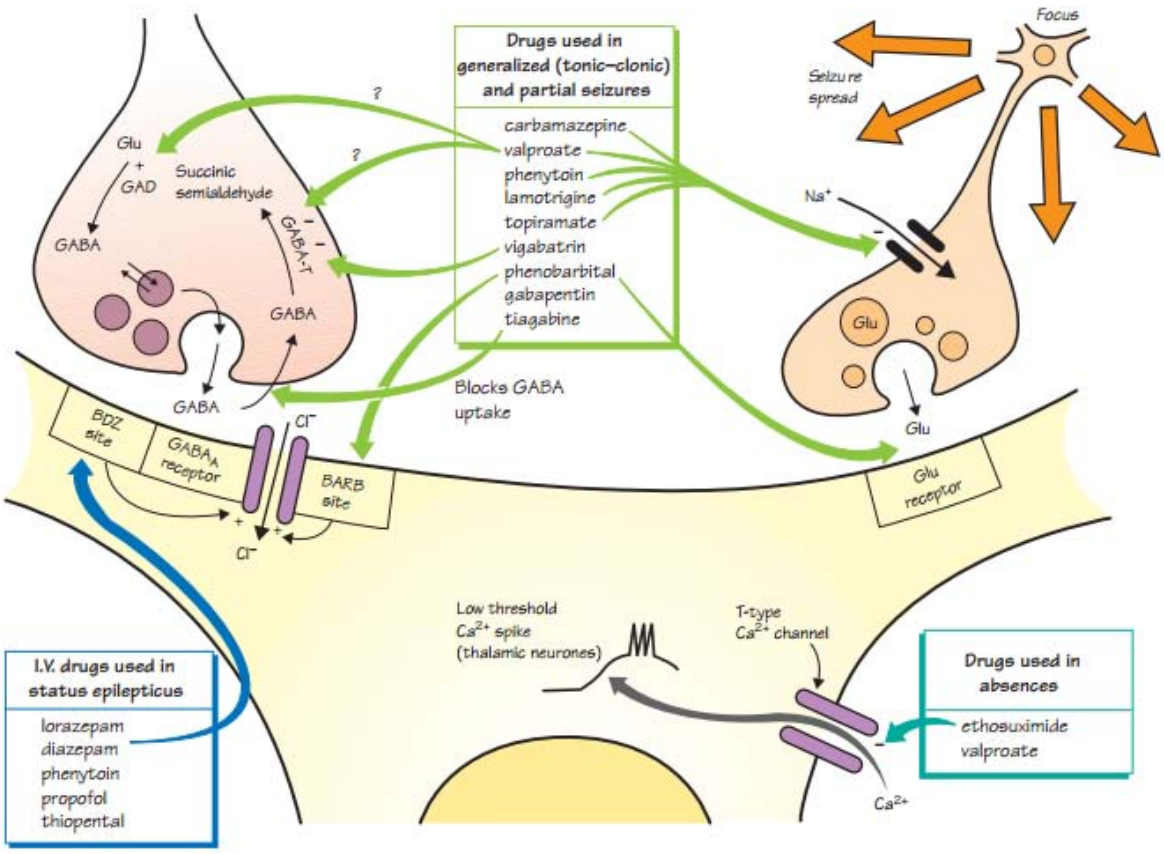
Target SpO_2: ○ 94–98% ○ 88–92%

Mode of delivery: ○ Continuous ○ As required

Starting device

Initials | Bleep | Date

Note that the formulation (tablets) has been specified in the phenytoin prescription. There is little evidence to suggest clinically significant difference between formulations (e.g. different brands; tablets, capsules or syrup). However, because of the drug's narrow therapeutic index, many specialists nevertheless recommend keeping patients on the same formulation.



Causes of epilepsy

The etiology is unknown in 60–70% of cases, but heredity is an important factor. Damage to the brain (e.g. tumors, asphyxia, infections or head injury) may subsequently cause epilepsy. Convulsions may be precipitated in epileptics by several groups of drugs, including *phenothiazines*, *tricyclic antidepressants* and many *antihistamines*.

Mechanisms of action of anticonvulsants

Inhibition of sodium channels

Carbamazepine, **lamotrigine**, **valproate**, **phenytoin** and probably **topiramate** act by producing a use-dependent block of neuronal Na^+ channels. Their anticonvulsant action is a result of their ability to *prevent high-frequency repetitive activity*. The drugs bind preferentially to inactivated (closed) Na^+ channels, stabilizing them in the inactivated state and preventing them from returning to the resting (closed) state, which they must re-enter before they can again open. High-frequency repetitive depolarization increases the proportion of Na^+ channels in the inactivated state and, because these are susceptible to

blockade by the antiepileptics, the Na^+ current is progressively reduced until it is eventually insuffiient to evoke an action potential. Neuronal transmission at normal frequencies is relatively unaffected because a much smaller proportion of the Na^+ channels are in the inactivated state.

Enhancement of GABA action

Vigabatrin is an irreversible inhibitor of GABA-transaminase, which increases brain GABA levels and central GABA release. **Tiagabine** inhibits the reuptake of GABA, and by increasing the amount of GABA in the synaptic cleft, increases central inhibition. The benzodiazepines (e.g. **clobazam**, **clonazepam**) and **phenobarbital** also increase central inhibition, by enhancing the action of synaptically released GABA at the $GABA_A$ receptor–Cl^- channel complex. Phenobarbital may also reduce the effects of glutamate at excitatory synapses. **Valproate** also seems to increase GABAergic central inhibition by mechanisms that may involve stimulation of glutamic acid decarboxylase activity and/or inhibition of GABA-T.

Inhibition of calcium channels

Absence seizures involve oscillatory neuronal activity between the thalamus and cerebral cortex. This oscillation involves (T-type) Ca^{2+} channels in the thalamic neurones, which produce low threshold spikes and allow the cells to fire in bursts. Drugs that control absences (**ethosuximide**, **valproate** and **lamotrigine**) reduce this Ca^{2+} current, dampening the thalamocortical oscillations that are critical in the generation of absence seizures.

Drugs used in partial and generalized tonic–clonic (grand mal) seizures

Treatment with a single drug is preferred because this reduces adverse effects and drug interactions. Furthermore, most patients obtain no extra benefit from multiple drug regimens. **Carbamazepine** and **valproate** are the fist-line drugs in epilepsy because they cause relatively few adverse effects and seem to have least detrimental effects on cognitive function and behaviour. Some anticonvulsants, specially phenytoin, phenobarbital and carbamazepine, are potent *liver enzyme inducers* and stimulate the metabolism of many drugs, e.g. oral contraceptives, warfarin, theophylline.

Carbamazepine is metabolized in the liver to carbamazepine-10,11-epoxide, an active metabolite that partly contributes to both its anticonvulsant action and neurotoxicity. Mild neurotoxic effects are common (nausea, dizziness,

drowsiness, blurred vision and ataxia) and often determine the limit of dosage. Agranulocytosis is a rarer idiosyncratic reaction to carbamazepine.

Phenytoin is hydroxylated in the liver by a saturable enzyme system. Measurement of serum drug levels is extremely valuable because, once the metabolizing enzymes are saturated, a small increase in dose may produce toxic blood levels of the drug. *Adverse effects* include ataxia, nystagmus gum hypertrophy, acne, greasy skin, coarsening of the facial features and hirsutism.

Topiramate blocks sodium channels in cultured neurones. It also enhances the effects of GABA and blocks α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Adverse effects include nausea, abdominal pain and anorexia. Topiramate has been associated with acute myopia and secondary closed-angle glaucoma.

Phenobarbital is probably as effective as carbamazepine and phenytoin in the treatment of tonic–clonic and partial seizures, but it is much more sedative. Tolerance occurs with prolonged use and sudden withdrawal may precipitate status epilepticus.

Vigabatrin, **gabapentin**, **levetiracetam**, **pregabalin** and **tiagabine** are used as ‘add-on’ drugs in patients in whom epilepsy is not satisfactorily controlled by other antiepileptics. Gabapentin (and carbamazepine) are also used to relieve *shooting and stabbing neuropathic pain* that responds poorly to conventional analgesics.

Drugs used to treat absences (petit mal)

Ethosuximide is only effective in the treatment of absences and myoclonic seizures (brief jerky movements without loss of consciousness). It is widely used as an anti-absence drug because it has relatively mild adverse effects (e.g. nausea, vomiting).

Drugs effective in tonic–clonic (grand mal) and absence (petit mal) seizures

Valproate. The advantages of valproate are its relative lack of sedative effects, its wide spectrum of activity and the mild nature of most of its adverse effects (nausea, weight gain, bleeding tendencies and transient hair loss). The main disadvantage is that occasional idiosyncratic responses cause *severe or fatal hepatic toxicity*.

Lamotrigine is used alone or in combination with other agents. Adverse effects include blurred vision, dizziness and drowsiness. Serious skin reactions may occur, especially in children. These includes Stevens–Johnson syndrome and toxic epidermal necrolysis.

Benzodiazepines. **Clonazepam** is a potent anticonvulsant but is very sedative and tolerance occurs with prolonged oral administration.

Drug withdrawal

Abrupt withdrawal of antiepileptic drugs can cause rebound seizures. It is difficult to know when to withdraw antiepileptics but, if a patient has been seizure-free for 3 or 4 years, gradual withdrawal may be tried.

Pregnancy

Anticonvulsant therapy in pregnancy requires care because of the teratogenic potential of many of these drugs, especially valproate and phenytoin. Also there is concern that *in utero* exposure to valproate may damage neuropsychological development even in the absence of physical malformation.

Further reading:

For adjustment of serum phenytoin concentration due to hypoalbuminemia or renal impairment, online calculators are available, two examples of which are given below. These are provided for educational purposes only and are not intended to be taken as a recommendation for use in clinical practice. Take care to ensure that you are working in the same units of measurement, and that you check all results carefully.

1. MDCalc. Phenytoin/dilantin correction for albumin or renal failure. Available at: http://www.mdcalc.com/phenytoin-dilantin-correction-for-albumin-or-renal-failure/ (accessed 24 January 2014).

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2. Carl W. Bazil, Derek J. Chong, Daniel Friedman. Epilepsy. Oxford University Press, Inc., New York, 2011.

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6. Simon Shorvon, Renzo Guerrini, Mark Cook, Samden D. Lhatoo. Oxford Textbook of Epilepsy and Epileptic Seizures. Oxford University Press, UK, 2013.

7. Michael J. Neal. Medical Pharmacology at a Glance. 7th Ed., John Wiley & Sons, Ltd., UK, 2012.