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Testing blood and CSF in people with epilepsy: a practical guide

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ABSTRACT – Laboratory investigations, whilst not essential to the diagnosis of seizures or of epilepsy, can be fundamental to determining the cause and guiding management. Over 50% of first seizures have an acute symptomatic cause, including a range of metabolic, toxic or infectious cause. The same triggers can precipitate status epilepticus, either *de novo* or as part of a deterioration in control in individuals with established epilepsy. Some, such as hypoglycaemia or severe hyponatraemia, can be fatal without prompt identification and treatment. Failure to identify seizures associated with recreational drug or alcohol misuse can lead to inappropriate AED treatment, as well as a missed opportunity for more appropriate intervention. In individuals with established epilepsy on treatment, some laboratory monitoring is desirable at least occasionally, in particular, in relation to bone health, as well as in situations where changes in AED clearance or metabolism are likely (extremes of age, pregnancy, comorbid disorders of renal or hepatic function). For any clinician managing people with epilepsy, awareness of the commoner derangements associated with individual AEDs is essential to guide practice. In this article, we review indications for tests on blood, urine and/or cerebrospinal fluid in patients presenting with new-onset seizures and status epilepticus and in people with established epilepsy presenting acutely or as part of planned monitoring. Important, but rare, neurometabolic and genetic disorders associated with epilepsy are also mentioned.

Key words: epilepsy, seizure, blood, CSF, therapeutic drug monitoring, investigations

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ILAE Curriculum Primary Learning objective: Decide which patients should receive laboratory tests and which types of tests should be ordered
Sub-objectives:
- Blood and cerebrospinal fluid investigations in people with new-onset seizures
- Blood and cerebrospinal fluid investigations in patients with status epilepticus
- Utility of laboratory investigations in differentiating seizures from other events
- The role of blood tests, including therapeutic monitoring in long-term management

The diagnosis and management of epilepsy, including first seizures and status epilepticus, depends largely on thorough history taking, including a forensic approach to obtaining witness accounts and information about the background and circumstances affecting an individual. Investigations, such as EEG and MRI, as will be covered in separate articles in this series, and are of particular value in identifying the type of epilepsy and underlying cause, and contributing to predicting risk of recurrence after a first unprovoked seizure. However, at least 55% of new-onset seizures (Beghi *et al.*, 2010), including around 50% of status epilepticus cases, are provoked (acute symptomatic seizures). In patients with known epilepsy, systemic illnesses may also contribute to deterioration in seizure control. It is in this context that laboratory (blood, urine, cerebrospinal fluid) investigations are especially important. This review summarises the role of laboratory investigations in the diagnosis and management of people presenting with seizures, to provide an educational resource to help the managing clinician decide which patients should receive laboratory tests and which types of tests should be ordered. This is a core competency (Level 1) defined in the ILAE Epileptology Curriculum (Blümcke *et al.*, 2019), which is relevant for all health professionals involved in the diagnosis and management of people with epilepsy.

First seizure

Although not key to the diagnosis of a first seizure, or new-onset seizures, some laboratory investigations performed as soon as possible after the seizure onset can be key to identifying the cause, specifically with respect to determining if the event is provoked (acute symptomatic) or unprovoked. Acute symptomatic seizures occur at the time of, or in close association with, a documented brain insult (Thurman *et al.*, 2011), which likely account for over 50% of all first seizures (Hauser and Beghi, 2008). Importantly, with an acute symptomatic seizure, the key priority in management is addressing the cause. Some untreated are rapidly fatal, but if successfully managed, are associated with full recovery and a recurrence risk of less than 3% (Pohlmann-Eden *et al.*, 2006). In contrast, the five-year risk of recurrence is at least 10-fold higher following a first unprovoked seizure (Marson *et al.*, 2005). Thus, correctly distinguishing between provoked and unprovoked at the outset has important implications for the individual both in the first few hours and also with respect to longer-term management and safety advice including driving. Almost any acute brain insult, including stroke and trauma, can result in an acute symptomatic seizure, but in the context of this article, the most important triggers are metabolic, toxic, infectious and inflammatory.

Metabolic: Metabolic derangements causing seizures can be extremely dangerous and need to be treated urgently, therefore checking (capillary and then serum) glucose, sodium, calcium and magnesium and renal and liver function should be done as soon as possible. These, and other essential initial tests, are summarized in *table 1*. The only exception is children with simple febrile seizures, for which there is consensus that additional investigations are not required unless there are other clinical markers of concern (American Academy of Pediatrics, 2011; Wilmshurst *et al.*, 2015).

– *Glucose:* In patients of any age, including neonates for whom it is especially important (Gataullina *et al.*, 2015), checking that the blood glucose is within normal range should be of the utmost priority, as untreated hypoglycaemia can rapidly lead to irreversible neurological damage and death. In adults, a glucose level below 2 mM/L or above 25 mM/L is usually required to produce seizures, the latter most commonly in older patients with type II diabetes, whereas hyperglycaemia accompanied by ketosis is not usually epileptogenic (Nass *et al.*, 2017; Ohara *et al.*, 2017). Additionally, diabetes mellitus is an independent risk factor for seizures in the elderly, therefore HbA1c (glycosylated haemoglobin) testing should be performed in older patients as a measure of longer-term blood glucose (Baviera *et al.*, 2017).

– *Sodium:* Hyponatraemia is the commonest electrolyte disturbance to provoke seizures in adults. The mechanism for this is cerebral oedema, which is due to the osmotic gradient between the plasma and the brain. The more rapid the fall in sodium, the fewer adaptive responses the brain can produce to protect itself and more severe the resulting cerebral oedema will be. Whilst less common, children are particularly vulnerable to the effects of cerebral oedema as they have relatively large brains compared to their scull size (Nardone *et al.*, 2016). Correction of low sodium must be carefully monitored to avoid the potentially devastating complication of pontine

Table 1. Essential laboratory investigations after a first seizure, ideally within 24 hours*.

Parameter	May provoke acute symptomatic seizure	
METABOLIC TRIGGERS	Lower limit	Upper Limit
Glucose	≤2 mM/l (36 mg/dl)	>25 mM/l (450 mg/dl)
HbA1c		
Sodium	≤115 mM/l (50 mg/dl)	≥160 mM/l (70 mg/dl)
Calcium	≤1.2 mM/l (5.0 mg/dl)	≥3.0 mM/l (12.0 mg/dl)
Magnesium	≤0.3 mM/l (0.73 mg/dl)	
Urea or		≥16.7mM/l (100
Blood urea nitrogen (BUN)		mg/dl)
		>35.7mM/l
Creatinine		>884μM/l (10 mg/dl)
OTHER	Rationale	
Liver function tests	May indicate systemic disease or alcohol abuse	
Full blood count	May indicate infection (raised white blood cell count) or alcohol abuse (raised mean corpuscular volume)	
C-reactive protein	High levels may indicate infection or systemic inflammation	
Serum alcohol level	Detectable levels indicate recent alcohol ingestion	
Urinary drug screen	Detectable levels may indicate recreational drug use	

HbA1c: glycosylated haemoglobin. *All investigations should be requested urgently, as soon as the patient presents. After more than 24 hours following the index event, a causal relationship between any abnormalities and the seizure cannot be definitively established.

myelinolysis. Hypernatraemia is a much less common cause of seizures but may produce them due to brain shrinkage (Castilla-Guerra *et al*., 2006).

– *Calcium and magnesium:* Hypocalcaemia, and less frequently hypercalcaemia, can provoke seizures. When this is identified, further investigations as to the cause, usually in consultation with an endocrinologist, may also be required, which is beyond the scope of this article. Hypomagnesaemia is much less common but can cause seizures in any age group.

– *Potassium:* Derangements in serum potassium are clearly very dangerous from a cardiovascular and neuromuscular perspective, and so important to identify, but do not cause central nervous system (CNS) symptoms or seizures (Riggs, 2002; Castilla-Guerra *et al*., 2006).

– *Urea, nitrogen and creatinine:* Seizures are common in patients with renal failure due to elevated urea. It should be noted that non-convulsive status and status epilepticus may mimic uremic encephalopathy, therefore it is particularly important to consider these as possible diagnoses in renal patients (Titoff *et al*., 2019).

Infective and inflammatory disease: Infective or inflammatory causes should be considered in any one with a history of fever or recent malaise, and untreated can prove fatal. Febrile seizures are particularly common in children up to school age, but seizures can be the presenting feature of infection or inflammatory conditions at any age. All patients should have a full blood count (FBC) and test for C-reactive protein (CRP) as a minimum. Mild leucocytosis and raised CRP are commonly found postictally due to a generalised inflammatory response, with a lack of evidence to define clear levels above which a more aggressive search for infection should follow. Further investigations will depend on the clinical history, examination, observations and sometimes repeated laboratory tests to look for trends. If there are clinical reasons to suspect a central nervous system infection or sepsis (which can itself be associated with an encephalopathy), blood and urine cultures, and cerebrospinal fluid (CSF) samples should be obtained. In any patient with focal signs or who has not completely recovered, brain imaging (typically brain CT) will be needed before CSF can be collected (indications for brain imaging in epilepsy are covered in a separate article). CSF opening pressure should be recorded (for example, venous sinus thrombosis can present with seizures and a high opening pressure), and CSF sent for routine tests including cell count, protein, sugar (with matched blood sugar), bacterial culture and viral PCR. Depending on the clinical history and examination, additional tests for fungal or mycobacterial infections, and oligoclonal bands, might also be appropriate. It is sensible to take more than required for initial tests, with a saved sample for additional tests, should they be required based on initial results, or other information that emerges later.

In persons presenting with behavioural changes, memory problems, a high frequency of new-onset seizures or (as will be covered later) status epilepticus, if other tests have been non-contributory, the possibility of an autoimmune encephalitis needs to be considered. This should be investigated alongside specific serum and CSF antigens (Dalmau and Graus, 2018). If there is any suspicion of multiple sclerosis, then oligoclonal bands may also be important. Clinical treatment decisions usually have to be made before the results of these additional investigations are available (this can take 2-3 weeks, even in well-resourced settings), further discussion of which is beyond the scope of this article, but decision-making algorithms have been created to aid this (Graus *et al*., 2016; Wagner *et al*., 2018).

Intoxication: In parallel with assessing for metabolic and infectious causes of a first seizure, one should consider whether recreational drugs, alcohol or medications may have been precipitants. It is not possible to provide absolute cut-off thresholds for these, as inter-individual differences in seizure susceptibility play a substantial role (Brathen *et al*., 2005), but the detection of substances at all in the appropriate time window may be highly relevant. Importantly, when drug or alcohol-provoked seizures are identified, comorbid epilepsy, sometimes as yet undiagnosed, is not uncommon and the recurrence risk (due to recurrent ingestion or epilepsy) is also higher, therefore additional investigations as for any first unprovoked seizure (EEG and MRI) should still be undertaken at a later date.

– *Alcohol:* Alcohol withdrawal, particularly in combination with sleep deprivation, is a very common cause of seizures. Seizures usually occur 6-48 hours after cessation of drinking (Leach *et al*., 2012). As markers of chronic alcohol consumption, mean corpuscular volume (MCV) and serum gamma glutamyl transferase (GGT) may be useful, although the latter may be elevated due the ingestion of certain drugs, including many antiepileptic drugs (AEDs).

– *Benzodiazepines and recreational drugs:* A broad range of widely available, though mostly illegal, stimulant drugs can cause seizures even at low levels of consumption. Cocaine, crack, normeperidine, meperidine, methaqualone, glutarimide, ethylenedioxymethamphetamine and a range of other synthetic stimulants are considered high risk, along with phencyclidine and quatadine (Beghi *et al*., 2010). Other drugs with narcotic effects, such as benzodiazepines, synthetic cannabinoids, gamma-hydroxybutyrate and opiates including heroin, may trigger seizures during their withdrawal (Leach *et al*., 2012). The use of multiple intoxicants is common, so rather than testing for individual agents, urinary drug screening for metabolites is recommended in the first instance.

– *Prescription medications:* Drugs such as antibiotics, antidepressants and antipsychotics in routine use rarely induce seizures, even in people with epilepsy other than in the context of significant overdoses. Usually patient history is sufficient, but to identify intoxication or slow metabolizers, serum drug monitoring may be useful.

Was it a seizure? Diagnostic uncertainty. A number of laboratory investigations have also been proposed as potentially useful where there is diagnostic uncertainty as to the nature of an event, specifically to discriminate between epileptic seizures, psychogenic non-epileptic seizures (PNES) and syncope. However, whilst of academic interest, none should be considered diagnostic and, in most instances, will not be useful. Many of these markers are only raised in tonic-clonic seizures, and even then, they are not wholly reliable as summarized below. Clinical history and witness accounts remain the mainstay in the diagnosis of epileptic seizures.

– *Prolactin* is the most widely suggested but has substantial limitations: It is only useful when there is a known (pre-event) baseline and taken 20 minutes post-event, which is rarely achievable. It does not always rise after an epileptic seizure; it may rise due to other events such as syncope and its levels depend on many other variables including age, gender, circadian rhythm, medications, pregnancy and even psychological stress. In status epilepticus, prolactin levels may normalise after an initial rise (Abubakr and Wambacq, 2016; Nass *et al*., 2017).

– *Creatinine kinase (CK):* A transitory (sometimes very substantial) increase in creatinine kinase, 24-72 hours after a tonic-clonic seizure (TCS), is a relatively specific but not sensitive marker (*i.e*. raised CK points towards a TCS, but a normal CK does not rule it out). However, it should be noted that CK may be elevated due to other conditions such as a post-syncopal long lie. Nevertheless, a raised CK is important to help identify patients who will be at higher risk of developing acute kidney injury as a result of muscle breakdown due to seizures, and these patients will need careful monitoring and treatment if this develops (Nass *et al*., 2017).

– *Ammonia:* A transitory increase in ammonia, lasting 3-8 hours after an event, is a relatively specific but not sensitive marker of a convulsion. Patients with cirrhosis and no history of convulsions will have persistently elevated ammonia. Valproic acid may also cause elevations in serum ammonia (Nass *et al*., 2017).

– *Lactate:* A raised lactate level above 2.45 mmol/L, taken within two hours of the event, has been postulated to be a useful indicator of a likely TCS. However, this is not very sensitive (Matz *et al*., 2016). Furthermore, simulated seizures can also produce markedly

raised lactate levels (Lou Isenberg *et al*., 2020). There are also numerous other causes of a raised lactate level, such as sepsis, tumour or liver disease, therefore this cannot be considered diagnostic in isolation.

Other parameters in infants: In infants (under one year) with new-onset seizures (also covered below), ideally, the genetic syndrome of pyridoxine-deficiency epilepsy should be excluded (van Karnebeek *et al*., 2016) based on determination of alpha-aminoadipic semialdehyde/pyrroline 6′ carboxylate (in urine, plasma or cerebrospinal fluid) and *ALDH7A1* molecular analysis.

Status epilepticus

In the previous sections we discuss what to test the first time someone presents with seizures, and the limited utility of laboratory testing in the case of diagnostic uncertainty. In this section, we discuss what laboratory tests to perform in the patient who does not stop seizing, *i.e*. presents with status epilepticus (SE). As with any seizure, the diagnosis of status epilepticus is primarily a clinical one, supported, when possible, by neurophysiological (EEG) data (Trinka *et al*., 2015). The role of laboratory testing is, as with first seizures, to identify the cause but also, particularly in convulsive SE, to evaluate the possible consequences of what is a life-threatening medical emergency, to inform on ongoing management. A suggested approach to laboratory testing for SE is summarized in *figure 1*.

For all patients: All patients in SE should have the mandatory blood tests described in *table 1*. In addition, coagulation studies and creatine kinase, an arterial blood gas and toxicology screening should be performed. This is to establish a baseline, as part of investigating the cause, and to identify those who might be at particularly high risk of complications, such as those with acute kidney injury (from rhabdomyolysis) or a coagulopathy.

Patients with known epilepsy: An antiepileptic drug (AED) level must be checked as low AED levels are the most common cause of SE in this group of patients (Trinka *et al*., 2012). Ideally, AED levels should be tested on a sample taken prior to any AED administration. In practice, as relevant background information may not be available at the point of presentation, it is sensible to take an additional 5 mL of serum saved for future testing at the outset, before AEDs given as part of treating the episode confound interpretation. Specific AED levels can then be requested for the original sample at a later date when prescribed drugs are known. AED levels are most useful/reliable if a prescribed drug is not-detected, indicating poor adherence, though beyond that the results should be interpreted with caution, ideally compared to the individual's own therapeutic concentration as this may vary from the standard reference ranges (Lunardi *et al*., 2019). Therapeutic drug monitoring is not routinely recommended during SE treatment as AED concentrations may actually exceed the published target concentrations (NICE, 2012 [Update 2019]), other than in refractory or super-refractory cases in which confirming at least adequate levels before an agent is considered ineffective can be useful.

Infectious disease: Lumbar puncture should be performed in any patient with a suspicion of CNS infection or inflammation or in any patient without another clear cause of SE. A CSF pleocytosis of greater than 5×106/L is not usually caused by SE alone, and so this should prompt careful investigation of any infectious or inflammatory cause (Frank *et al*., 2012; Scramstad and Jackson, 2017; Johnson *et al*., 2014). Testing for HIV is also important to consider if not already known. Common infectious causes of SE are bacterial (*e.g*. meningococcus, pneumococcus and haemophilus), viral (*e.g*. herpes simplex 1 and enteroviruses) or protozoal (Lowenstein *et al*., 2014; He *et al*., 2016). There is considerable regional variation in likely infectious causes of SE, for example Japanese encephalitis is endemic in South-East Asia, malaria in sub-Saharan Africa and Asia, and neurocystericosis in Latin America, India and Africa, therefore the country of origin and travel history will impact on choice of laboratory investigations. HIV-positive patients will need a more comprehensive workup to exclude opportunistic infections (Solomon *et al*., 2012).

Immunological & inflammatory disease: Autoimmune encephalitis (AE) is an uncommon but potentially treatable cause of SE. Identifying it is of vital importance because it may be associated with AED-refractory seizures that will only improve with immunotherapy or, in the case of paraneoplastic encephalitis, with treatment of the underlying cancer. Our knowledge of the autoimmune encephalitides and the antibodies associated with them is relatively recent and continues to evolve (Dalmau and Graus, 2018). Multiple anti-neuronal antibodies may be implicated, including, likely, some yet to be discovered, with a range of presentations. Those most frequently associated with seizures and status epilepticus include: antibodies against the GluN1 subunit of the NMDA (N-methyl-D-aspartate) receptor and anti-GAD, anti-GABA (gammaaminobutyric acid) type A and B receptor, anti-LGI1 receptor (leucine-rich glioma inactivated 1), and anti-Hu antibodies (Jacobs *et al*., 2003; Johnson *et al*., 2010; Lancaster *et al*., 2010; Illingworth *et*

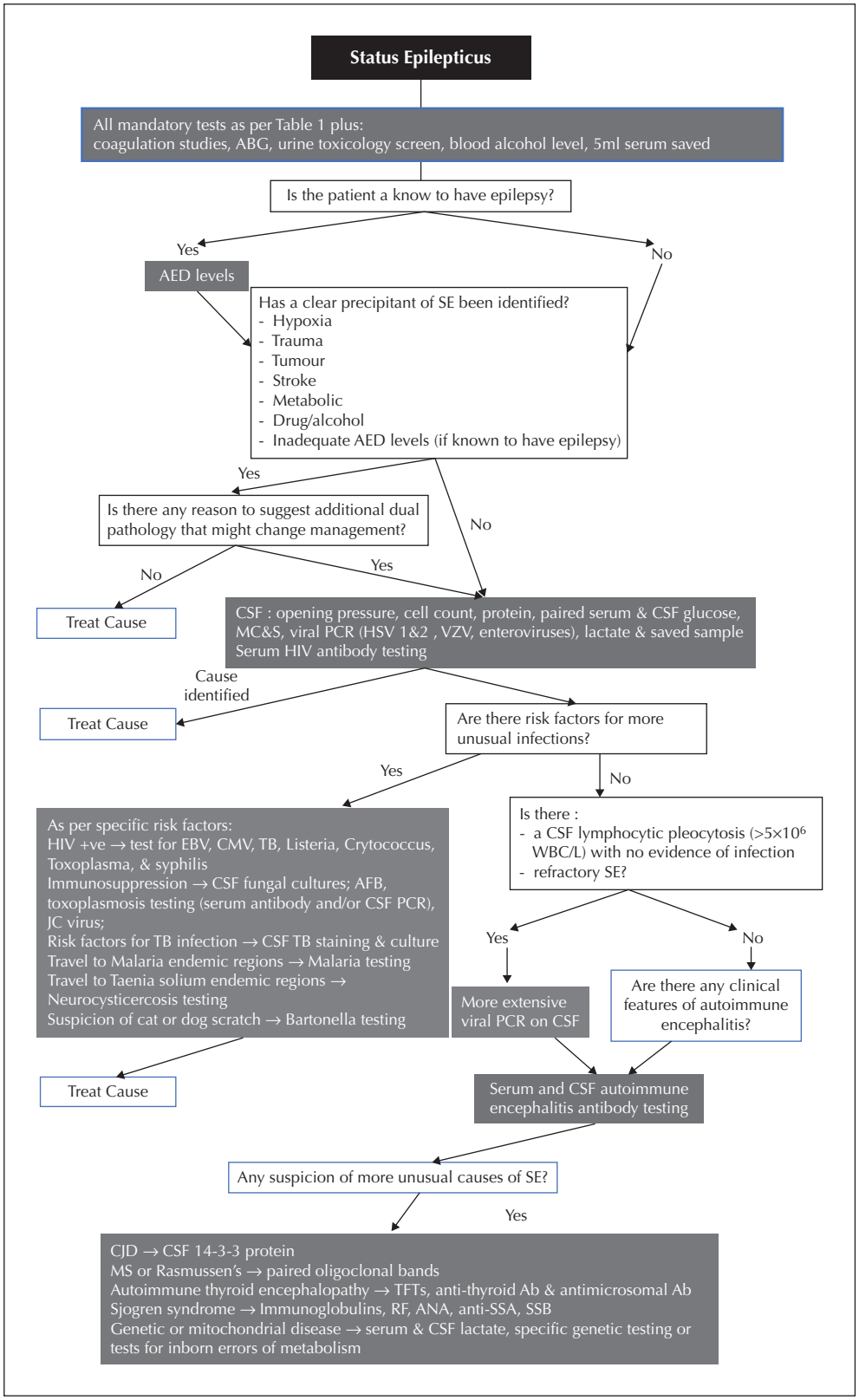

Figure 1. Laboratory testing for status epilepticus.
Ab: antibody; ABG: arterial blood gas; AED: antiepileptic drug; AFB: acid fast bacilli; ANA: antinuclear antibody; CMV: cytomegalovirus; CSF: cerebrospinal fluid; EBV: Epstein Barr virus; HIV: human immunodeficiency virus; HSV: herpes simplex virus; L: litre; MC&S: microscopy, culture and sensitivities; PCR: polymerase chain reaction; RF: rheumatoid factor; SSA, SSB: Sjogren syndrome related antigens types A and B ; TB: tuberculosis; TFT: thyroid function tests; VZV: varicella zola virus; WBC: white blood cells.

al., 2011; Suleiman *et al*., 2011; Bien, 2013; Petit-Pedrol *et al*., 2014). Any patient with a history of new-onset cognitive or memory deficits, speech problems, movement disorder or behavioural changes leading up to the SE, when no other obvious cause is identified, should be investigated for autoimmune encephalitis. In practice, rather than requesting full panels for all patients, discussion with the local laboratory, to agree priorities and understand local techniques and their sensitivity and specificity which can vary, is recommended. Anti-GAD (glutamic acid decarboxylase) antibodies are also not uncommonly identified, but also found in a range of other disorders including diabetes, and of uncertain pathogenicity (Alexopoulos and Dalakas, 2013). CSF will usually show a mild pleocytosis, but it may be normal. Both serum and CSF should be tested for antibodies (Graus *et al*., 2016). For further guidance on when to investigate for AE, see *figure 1*. A diagnosis of Hashimoto's encephalopathy may be considered in patients who have no anti-neuronal antibodies in serum and CSF. These patients should be investigated with thyroid function tests, and serum thyroid peroxidase and thyroglobulin antibodies, in order to assess if they meet the diagnostic criteria. In patients who are negative for anti-neuronal antibodies, and do not meet the criteria for Hashimoto's encephalopathy, further antibody testing in research laboratories for new antibodies may be considered, and the patient may be evaluated for the diagnosis of auto-antibody-negative but probable autoimmune encephalitis (Graus *et al*., 2016). Systemic autoimmune conditions may also cause SE, including Sjogren's and systemic lupus erythematosus, and serum autoantibody testing may be useful in these cases. SE can also occur in the context of multiple sclerosis and Rasmussen's encephalitis, but almost never as the presenting symptom. If there is clinical suspicion of either of these inflammatory conditions, then testing of serum and CSF oligoclonal bands may be supportive in diagnosis.

Cryptogenic new-onset refractory status epilepticus (NORSE) and what may be a subtype of the same condition, febrile infection-related epilepsy syndrome (FIRES), are characterised by the rapidly progressive onset of seizures and encephalopathy that evolve into prolonged super-refractory SE over a few days. In the case of FIRES, this is preceded by a minor febrile infection (Gaspard *et al*., 2018). Both are thought to have an inflammatory/autoimmune basis, possibly involving a post-infection cytokine-medicated mechanism. There are currently no diagnostic laboratory tests for these conditions.

Genetic, mitochondrial and other disorders: There are a number of mitochondrial diseases which, though rare, have SE as a prominent feature. These include: Alpers disease; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); Leigh syndrome; and myoclonic encephalopathy with ragged red fibres (MERRF) (Trinka *et al*., 2012; Myers *et al*., 2019). For these patients' serum and CSF, testing for lactate is recommended, though alone, this neither proves nor excludes a mitochondrial disorder, and where there is a strong clinical suspicion, specialist advice should be sought. Inborn errors of metabolism, such as porphyria, Wilson's disease and Alexander's disease, as well as chromosomal aberrations such as Angelman syndrome, may be investigated with specific genetic and/or laboratory testing. A comprehensive list of all the genetic and mitochondrial disorders which may cause SE is beyond the scope of this article, but covered in Myers *et al* (2019).

Role of blood tests in long-term monitoring

Some authorities suggest laboratory tests should ideally be performed prior to initiation of, and during treatment with, almost any AED (Patsalos and St. Louis, 2018). In most instances, some baseline parameters will nevertheless be available as part of an initial investigation of the presenting seizure or associated illness. Beyond that, the only other recommended pre-treatment test (*table 2*) is when treatment with carbamazepine, oxcarbazepine or eslicarbazepine is considered in individuals of Southeast Asian descent. The human leucocyte antigen (HLA) allele, HLA-B*1502, is highly prevalent in this population (up to 15% in Hong Kong, Thailand and the Philippines), and strongly associated with severe cutaneous hypersensitivity reactions (Stevens Johnson syndrome, toxic epidermal necrolysis). For carbamazepine, hetero- or homozygosity is estimated to show 98.3% sensitivity and 97% specificity for the development of SJS/TEN, with a 100% negative predictive value. Guidelines for screening prior to treatment are now in place in several developed countries (Fowler *et al*., 2019), though simply avoiding these drugs when alternatives are readily available is also of course entirely appropriate. A number of other alleles have also been identified, but none with such a strong association.

According to most practitioners and guidelines, regular (*e.g*. annually or more) blood test monitoring of children or adults with epilepsy is not recommended as routine and should only be performed if clinically indicated (NICE, 2012 [Update 2019]). Infrequent monitoring, *e.g*. at 2-5-year intervals, is almost certainly sufficient. That said, awareness of the more common potential laboratory abnormalities associated with AED use is important. Patients need to be advised to seek medical advice if indicative symptoms occur,

Table 2. Recommended investigations in relation to antiepileptic drug use.

Antiepileptic drug	Essential pre-treatment	To be considered during treatment if there are clinical concerns, or every 2-5 years
Acetazolamide		Bicarbonate[1]
Brivaracetam		
Cannabidiol[2]		Liver function[2]
Carbamazepine	HLA-B*1502 in people of Southeast Asian descent	Full blood count, liver function, renal function
Clobazam		Full blood count, liver function
Clonazepam		Full blood count, liver function
Eslicarbazepine	HLA-B*1502 in people of Southeast Asian descent	Liver function, renal function, sodium
Ethosuximide		Full blood count
Felbamate[3]		Full blood count, liver function[3]
Gabapentin		
Lacosamide		Liver function, renal function
Lamotrigine		Full blood count, liver function
Levetiracetam		
Oxcarbazepine	HLA-B*1502 in people of Southeast Asian descent	Renal function
Perampanel		
Phenobarbital		Liver function
Phenytoin		Liver function, renal function
Pregabalin		Renal function
Rufinamide		Liver function, renal function
Stiripentol		Full blood count, liver function, renal function
Topiramate		Bicarbonate[1]
Valproate		Full blood count, liver function
Vigabatrin		Fll blood count, liver function, renal function
Zonisamide		Bicarbonate[1]

[1]To be considered in all children or cognitively impaired patients who may not be able to describe symptoms. [2]Newly licensed, recommended regular testing pre-initiation, after dose change and during maintenance; see summary of product characteristics. [3]High-risk, sometimes, fatal reactions, recommended within the first month and no less than three-monthly thereafter. Liver function should include aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, alkaline phosphatase, and may include gamma glutaryl transaminase. Renal function should include urea, sodium, potassium, and creatinine and may include bicarbonate and chloride. Also, 25-hydroxy vitamin D should be considered in all patients, as covered in the text.

and non-specialists need to know which specific abnormalities to test for depending on the AED in question, and the clinical situation. It is similarly just as important to know what minor derangements can be safely attributed to AED use, without needing any change in treatment or further investigation. Broad recommendations by drug are summarized in *table 2*.

Haematologic reactions: Many AEDs are associated with a spectrum of haematological side effects. These include aplastic anaemia (carbamazepine, valproate and phenytoin), megaloblastic anaemia (phenytoin, phenobarbital and primidone) and thrombocytopaenia (carbamazepine and valproate). Transient leukopaenia and neutropaenia may also occur, especially in patients with low pre-treatment levels. Clinical indications to test include the development of a sore throat/bacterial infection within a few weeks of starting or a dose increase, new bleeding or bruising, or excessive fatigue. Second and third-generation AEDs tend to be associated with fewer haematological side effects, but for newer drugs, it must not be forgotten that rare but potentially dangerous effects can sometimes only become apparent some years after licensing. For all AED therapy, discontinuation is usually not indicated, unless symptoms are severe. In general, withdrawal should be considered if cell count falls below: 2,000/mL for white blood cells, 1,000/mL for neutrophils, 3.5×106/mL for red blood cells (11 g/dL for haemoglobin concentration) and 80,000/mL for platelets (Verrotti *et al*., 2014). Overwhelmingly, haematological reactions are reversible after withdrawal and do not need any special treatment (Callaghan *et al*., 1985).

Electrolytes and pH changes: Hyponatremia is a common finding with carbamazepine, oxcarbazepine and eslicarbazepine treatment, most likely due to antidiuretic effects. It is usually mild (>130 mmol/L) and asymptomatic, though often causes undue concern if picked up incidentally. Concurrent use of other agents, such as antihypertensives and serotonin re-uptake inhibitors, increases the risk. Levels between 125 and 130 nmol/L (moderate), particularly when chronic, may also appear to be asymptomatic, though can also be associated with subtle symptoms and increased morbidity and mortality in some contexts. Symptoms, when present, range from minor unsteadiness, falls, and reduced concentration through to confusion, nausea, and in severe cases, life-threatening cardiorespiratory distress or coma (Williams *et al*., 2016). Thorough clinical assessment is essential, with management of symptoms (or lack of) being a more important factor than absolute sodium. Additional investigations (including plasma and urine osmolality) are indicated in all but the mildest cases to exclude and address other contributors and inform decisions about the suspect AED. Asymptomatic metabolic (renal tubular) acidosis is common during topiramate treatment (Garris and Oles, 2005), and also seen with other carbonic anhydrase inhibitors, zonisamide (Baulac *et al*., 2014) and acetazolamide (Hamed, 2017). In some, this is likely associated with an increased the risk of nephrolithiasis (Kuo *et al*., 2002; Hamed, 2017) and a crystalline nephropathy, although not all studies support this (Shen *et al*., 2015).

Hepatotoxicity: Use of many AEDs, especially older drugs such as phenytoin, carbamazepine and valproate (Bjornsson, 2008; Hamed, 2017), as well as some of the newer agents including cannabidiol, is associated with abnormalities of liver function. Mild derangements based on liver function tests (<double the normal upper limit of normal) are usually not of concern unless symptomatic or deteriorating on repeat testing. Valproate use also causes raised ammonia levels, sometimes causing a reversible encephalopathy (Chopra *et al*., 2012), though, of note, a non-hyperammonaemic valproate encephalopathy is also recognized. Testing should be considered in any patient presenting with confusion, lethargy or drowsiness after initiation or a dose increase.

Bone health: An increased risk of fracture related to AED use is now well established (Theochari and Cock, 2018). Whilst a broad range of parameters such as markers of bone turnover have been evaluated in research studies, the only laboratory measure independently associated with fracture risk is vitamin D. AED use and epilepsy are both risk factors for hypovitaminosis D, with likely pharmacological and other contributors (*e.g.* reduced sunlight exposure, lower physical activity). Current evidence supports testing serum vitamin D, calcium, albumin and alkaline phosphatase ("bone profile"), 2-5 times yearly in adults and children on AEDs (NICE, 2012 [Update 2019]), with vitamin D supplementation as required, aiming for a yearly average serum level of >50nmol/L (Dobson *et al*., 2018). Most of the evidence relates to enzymes inducing older AEDs, specifically carbamazepine, phenytoin and barbiturates, in whom more frequent monitoring (*e.g.* annually) may be justified (Arora *et al*., 2016). However, there is no doubt that valproate (and enzyme inhibitor) is also implicated (MHRA, 2009), and the paucity of evidence against newer AEDs may just reflect less cumulative exposure and should not be considered to indicate a lack of risk. It is reasonable to assume, unless proven otherwise, that other enzyme inducers carry at least similar risks, and other AEDs may carry some risk, though

some reassuring data with respect to lamotrigine and levetiracetam is emerging (Theochari and Cock, 2018).

Cardiovascular risk factors; Obesity, diabetes and hypercholesterolaemia are all independently associated with cardiovascular disease and premature mortality. These risks apply as much to people with epilepsy as to others in the population. Several antiepileptic drugs can be associated with weight gain, in particular, valproate, pregabalin, gabapentin, and vigabatrin, in whom monitoring of lipid profile and glucose may be appropriate and inform lifestyle change, or in some instances, a change in AED. In recent years, interest in the potential for AEDs to influence other circulatory markers of vascular risk, such as homocysteine, folate, C-reactive protein, and more recently, homoarginine and asymmetric dimethylarginine, has also emerged (Kim *et al*., 2013; Sarecka-Hujar *et al*., 2019). However, the clinical implications of this in practice remain uncertain, with insufficient evidence as yet to guide a monitoring or intervention strategy.

Therapeutic drug monitoring: Therapeutic drug monitoring (TDM) is a tool which, correctly utilized, can be extremely helpful in optimizing treatment for some individuals. Certainly for many drugs, there is a better correlation between serum levels and efficacy than with the oral dose (Patsalos *et al*., 2018). However, for the vast majority of patients, if they are free of seizures and side effects, Class I evidence now supports that knowing the serum level is of little, if any, benefit in routine practice (Aícua-Rapún *et al*., 2020). Thus, taking costs into account, routine monitoring is generally not recommended (NICE, 2012 [Update 2019]). TDM can, however, be critical to support (or refute) a suspicion of non-adherence or for suspected toxicity or seizure persistence despite prescribing of an adequate dose (to identify fast metabolisers or non-compliance), when a formulation change is to occur and when pharmacokinetic variability is expected (*e.g*. in children or the elderly, pregnancy, or for hepatic or renal disease), or drug interactions are anticipated (Patsalos *et al*., 2018). This is particularly so with phenytoin (which exhibits saturation kinetics, meaning even a small change in dose or metabolism can result in substantial changes in level), and in situations where reliance on clinical judgement alone is felt to be insufficient, for example, when even a single, potentially preventable seizure, after a period of remission, might have significant consequences. In this situation, if available, the best comparator is the "individual therapeutic concentration", *i.e*. a plasma AED concentration trough level taken during a time of optimum therapeutic response on an established dose. Individualized therapeutic AED monitoring is accepted as much more meaningful than a comparison to fixed reference ranges (Patsalos *et al*., 2018). Strictly speaking, predicting drug adherence or non-adherence based on AED plasma levels is only possible when the level is compared to that individual's therapeutic concentration (Lunardi *et al*., 2019), though in practice reasonable inferences can be drawn from big fluctuations or undetectable levels despite stable prescribed doses.

Known epilepsy with deterioration of control

A frequent clinical challenge is represented by people with established epilepsy presenting to acute medical services, reporting a deterioration in seizure control. This might be a single unprovoked seizure after a period of remission, a reported increase in seizure frequency, or seizure clusters sometimes escalating and leading to concern about imminent status epilepticus. In this situation, it is important to remember that all the factors discussed earlier that can trigger acute symptomatic seizures, or status epilepticus, can similarly influence seizure frequency in individuals with established epilepsy, therefore a similar approach to laboratory testing is recommended. Excluding intercurrent infection, as well as checking AED levels and alcohol and toxicology screens can be key, yet the latter in our experience are often overlooked in favour of CT or even EEG, which are rarely informative or indicated in this context.

Pregnancy in women with epilepsy

Specific issues pertain to women with epilepsy who might become or who are pregnant:

– Some AEDs are known to have teratogenic effects and so choice and optimization of drug treatment in advance of any potential pregnancy in women of childbearing age is particularly important (Tomson *et al*., 2019).

– Non-adherence rates are increased during pregnancy (likely due to concerns over teratogenicity as well as other factors such as vomiting) (Schmidt *et al*., 1983). Therefore, pre-pregnancy counselling regarding the importance of treatment continuation, because of the maternal and foetal risks of uncontrolled seizures, is extremely important (Pennell, 2003).

– Serum levels of most AEDs fall during pregnancy due to haemodilution, changes in absorption and metabolism and increased excretion.

– Whilst the seizure frequency of most women will remain unchanged or fall during pregnancy, a significant number of them will experience an increase in seizures, likely due to medication non-compliance and reduced serum levels (Harden *et al*., 2009; Pennell, 2003).

In light of the above issues, the question arises as to the utility of therapeutic drug monitoring (TDM) during pregnancy, and to some, identifying a pre-pregnancy individual therapeutic concentration and then monitoring and adjusting the dose during pregnancy may seem like an obvious strategy. However, in the only study to date to formally address this in a prospective and blinded manner, there was no evidence to support "treating the level" over and above standard practice (increasing the dose in response to changes in seizure frequency) (Thangaratinam *et al*., 2018). An exception to this might be lamotrigine which exhibits markedly increased clearance during pregnancy, resulting in a reduction of plasma levels of around 65% in the second and third trimester (Petrenaite *et al*., 2005). There is some evidence that TDM of lamotrigine during pregnancy may be superior to clinical monitoring alone in reducing seizure deterioration (Pennell, 2003; Pirie *et al*., 2014). Both the ILAE and the American Academy of Neurology currently recommend TDM during pregnancy in women on an AED known to undergo substantial clearance changes, including lamotrigine, levetiracetam, oxcarbazepine and phenytoin. When a pre-pregnancy level is unknown, increasing the dose, at least in women with a history of tonic-clonic seizures, should be considered in any case (Tomson *et al*., 2019). When AED doses have been increased during pregnancy, tapering after delivery will usually be required. TDM may also be useful if there is concern about toxicity during this time, although in practice the decision will usually be made on clinical grounds before any level is available. The other important test to do in relation to pregnancy is ensuring adequate vitamin D status ideally before conception, but also during pregnancy. Vitamin D is essential for foetal development, therefore checking 25-hydroxyvitamin D levels at least once early on, and supplementing accordingly, is recommended (Hart *et al*., 2015, Roth *et al*., 2017). Folate supplementation (all, at least 0.4 mg/day) is also recommended but does not require serum monitoring. Similarly, there is no requirement for monitoring vitamin K or clotting parameters in women, including those on enzyme-inducing AEDs. Oral or intramuscular vitamin K administration in neonates is standard care for all women in many countries, and there is no evidence that the historical practice of additionally supplementing the mother during the last trimester is necessary (Sveberg *et al*., 2015; Panchaud *et al*., 2018).

Other considerations in rare or unusual cases

A range of rare but important neurometabolic disorders can cause epilepsy (Lee *et al*., 2018), the detailed discussion of which is beyond the scope of this article and will almost always require specialist assessment in a tertiary centre. Some are particularly important not to miss, as AEDs will often be ineffective, whereas targeted therapy for the underlying disorder, in the form of supplements or dietary modifications, can substantially improve outcomes.

Glutamine transporter type 1 deficiency syndrome (Glut1DS): This classically presents in infancy with seizures that are treatment-resistant or influenced by fasting, associated with developmental delay, acquired microcephaly and a range of movement disorders. However, a much broader phenotype, including later onset and paroxysmal movement disorders, is also now recognized (De Giorgis and Veggiotti, 2013). Glut1 facilitates glucose transport across the blood-brain barrier and the initial diagnostic step, feasible worldwide, is a fasting lumbar puncture which will show relatively low CSF glucose (hypoglycorrhachia) compared to blood glucose and a low-to-normal lactate level. Genetic confirmation by analysis of the solute carrier family 2 (facilitated glucose transporter) member 1 (*SLC2A1*) gene may then be performed. Early diagnosis is critical because it allows prompt initiation of treatment with a ketogenic diet (Klepper and Leiendecker, 2007; De Giorgis and Veggiotti, 2013).

Vitamin B6-dependent epilepsies: The B6 vitamins, in particular pyridoxal-5′-phophate (PLP), are involved in over 70 human pathways, including amino acid and neurotransmitter metabolism (Wilson *et al*., 2019). In any neonate or infant presenting with AED-resistant seizures, often myoclonic in the first days of life, plasma, urine and ideally CSF samples should be collected and frozen at -80°C for biomarkers. Hypoglycaemia and lactic acidosis may be present in the acute phase, but testing should not delay a prompt empirical trial of treatment with pyridoxine in the first instance, with next steps dependent on response. Later-onset cases, including status epilepticus in adults, have also been reported but appear to be extremely rare.

Mitochondrial disorders are another important group, characteristically causing a combination of different types of focal seizures and can pose a significant risk of SE (Bindoff and Engelsen, 2012). Indicators to consider onward referral include seizures developing in association with failure to thrive, developmental delay, ataxia and multiorgan involvement (Rahman, 2012). Whilst none are yet treatable, some are associated with a higher risk of potentially fatal adverse liver reactions with commonly used AEDs, such as valproate. Raised serum and/or CSF lactate may be another clue, but in the acute setting, is non-specific.

Case 1

A lady in her 40s with drug-resistant focal epilepsy due to a cortical dysplasia presented in 2018 to her local hospital with a cluster of seizures. She had undergone epilepsy surgery in childhood, with only partial benefit. She had been on carbamazepine since early childhood, and tried serial add-on therapies including phenobarbitone, valproate, clonazepam, acetazolamide, pregabalin, phenytoin and levetiracetam without benefit. For several years, she would have 5-10 focal seizures/week, and weekly tonic-clonic seizures. On a combination of carbamazepine, lamotrigine and clobazam, she had been relatively stable for four years with typically three focal seizures and one focal-onset bilateral tonic-clonic seizure a month, and occasionally a few weeks seizure-free, and did not wanted to make further changes. Attempts to lower the dose of carbamazepine had been associated with deteriorations the past. On presentation, she was found to have a sodium level of 130 mmol/L without any other new symptoms. The local team, without consulting her regular neurologist, decided to switch her carbamazepine to levetiracetam, and later add lacosamide; her seizures then became more frequent, and her mood substantially deteriorated. There were multiple further acute presentations, culminating in transfer to the regional neurosciences centre for diagnostic clarification and further management. Review of her records, dating between 2011 and 2018, by her regular treating neurologist identified that her sodium level had ranged between 124 mmol/L and 136 nmol/L with stable carbamazepine doses, independent of other drug changes, and without any associated symptoms. Both levetiracetam and lacosamide were withdrawn, and eslicarbazepine introduced with a substantial reduction in her seizures, no further acute presentations since, and the last recorded sodium level at 133 mmol/L.

Case 2

A lady in her 20s presented with two nocturnal tonic-clonic seizures, two months apart. A history of episodic intense sudden-onset anxiety, heightened emotion and *déjà vu* sensations lasting up to a minute was obtained, escalating in frequency in the two weeks before each event. A diagnosis of epilepsy was made clinically and treatment with lamotrigine initiated. MRI was negative, and her EEG showed rhythmic epileptiform discharges in her left temporal lobe. She was appropriately counselled about pregnancy and bone health, became seizure-free without side effects on 50 mg twice a day and was reluctant to increase it any further. A pre-pregnancy trough level was documented at 1.8 mg/L. In 2011, she enquired about withdrawing medication as part of planning pregnancy, and was advised to wait until she had been free of seizures for at least two years. She then represented, several months later, already 24 weeks pregnant, having had another cluster of focal seizures leading to a bilateral tonic seizure, with a trough level of only 0.5 mg/L. Her lamotrigine was increased to 100 mg twice a day, and she went on to deliver a healthy boy without complications or further seizures. A trough serum level on this dose the following year, still seizure-free, was 3.1 mg/L, and she elected to remain on this with advice to let us know if she was planning a further pregnancy. She reported that she was again pregnant six years later, having herself (without advice) reduced the dose to 50 mg, twice a day, the preceding year. A review of events in the previous pregnancy, later supported by a first-trimester trough level of <1 mg/L, persuaded her to increase the dose to 100 mg, twice a day. A second-trimester level was still low at <1 mg/L, and despite being seizure-free, she elected to increase the dose further to 150 mg, twice a day. She remained seizure-free throughout the pregnancy, delivering a healthy baby. Lamotrigine was returned to 100 mg, twice a day, after delivery, in two steps, and to date, she has continued with this amount of drug.

Diagnosis is based on genetic testing, initially using blood to identify common mutations, but not infrequently, a muscle sample is required for genetic and biochemical analysis.

Everolimus for tuberous sclerosis complex (TSC). The mTOR inhibitor (mammalian Target of Rapamycin), everolimus, which has been used for various benign tumours associated with TSC for some years, has more recently been licensed for the treatment of drug-resistant epilepsy associated with TSC (French *et al*., 2016). As well as monitoring of serum levels to determine appropriate dose, adverse events include hyperglycaemia, hypercholesterolaemia, hypertriglyceridemia, and worsening of proteinuria requiring regular monitoring on initiation and throughout treatment, alongside standard haematological, bone health, renal and liver function tests.

Other genetic testing. Epilepsy genetics is a rapidly developing field and has not been covered in this article, but is becoming increasingly relevant in specialist practice both for diagnosis and drug development, and in some instances with respect to informing treatment choices. This has been recently reviewed elsewhere (Myers *et al*., 2019).

Conclusions

Laboratory investigations, whilst not essential to the diagnosis of seizures or epilepsy, can be fundamental to determining the cause and guiding management. Over 50% of first seizures have an acute symptomatic cause, including a range of metabolic, toxic or infectious causes. The same triggers can precipitate status epilepticus, either *de novo* or as part of a deterioration of control in individuals with established epilepsy. Some, such as hypoglycaemia or severe hyponatraemia can be fatal without prompt identification and treatment. Failure to identify seizures associated with recreational drug or alcohol misuse can lead to inappropriate AED treatment, as well as a missed opportunity for more appropriate intervention. In individuals with established epilepsy on treatment, some laboratory monitoring is desirable at least occasionally, in particular, in relation to bone health, as well as in situations where changes in AED clearance or metabolism are likely (extremes of age, pregnancy, comorbid disorders of renal or hepatic function). For any clinician managing people with epilepsy, awareness of the commoner derangements associated with individual AEDs is essential to guide practice. A very broad range of neurometabolic disorders can be associated with epilepsy, which may manifest as a presenting feature. Awareness of suggestive clinical features and onward referral to specialist centres is recommended, though in resource-poor settings, trials of dietary treatments or supplements may be appropriate as a first step. □

Supplementary data

Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures

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TEST YOURSELF

(1) A 63-year-old man presents to hospital at midday having had a first witnessed self-limiting tonic-clonic seizure, 45 minutes before arrival. He has been previously well other than hypertension for which he takes a thiazide diuretic. He had celebrated his 40th wedding anniversary the previous night. His wife says he had about 8 units of alcohol, and usually drinks 3-4 units, two or three times a week. Initial blood tests are normal other than a random glucose level of 14 mM/L, a sodium level of 126 mg/dl and a creatine kinase level of 334 U/L. Serum alcohol is undetectable. How is this event best characterised?

A. Alcohol-withdrawal seizure
B. First unprovoked seizure
C. Seizure provoked by hyperglycaemia
D. Seizure provoked by hyponatraemia

(2) A 27-year-old women with focal epilepsy of unknown cause, with previous focal-onset bilateral tonic-clonic seizures, with onset at age 17, has been in remission on lamotrigine monotherapy for eight years. A pre-pregnancy trough level was documented at 4.2 mcg/ml on 100 mg twice a day. She is newly pregnant and started taking a folate supplement before she conceived. Which of the following blood tests should be repeated now she is pregnant? You may select one or more answers.

A. 25-hydroxyvitamin D
B. Ammonia
C. Folate
D. Trough lamotrigine
E. Vitamin K

(3) A 15-year-old girl is sent to the emergency department having collapsed at school. She had been standing in a longer-than-usual queue for lunch, felt lightheaded and the next thing she remembers is her friends all standing around her looking shocked and calling for help. She felt too weak to get up for about 10 minutes, and was embarrassed at having wet herself, but had no other symptoms. Witnesses say she just collapsed suddenly, had some jerky stiff movements for about 10 seconds, was unconscious for less than a minute and looked pale. Which blood tests will help confirm this was syncope and not a seizure?

A. Calcium
B. Electrolytes
C. Full blood count
D. None
E. Prolactin

(4) A 38-year-old man was found collapsed and convulsing in the street by passers-by. Witness accounts from the paramedics confirm this was a tonic-clonic seizure, which they terminated with intravenous lorazepam. He is still very confused and post-ictal some hours later in hospital. His creatine kinase is elevated at 780 units/L two hours after he was found. Why is knowing his CK is elevated useful for his management?

A. It confirms this must have been an epileptic seizure and not dissociative
B. It indicates an underlying muscle disease that needs investigating further
C. It indicates that this was status epilepticus and not a self-limiting seizure
D. The level might continue to rise and cause kidney injury, thus requiring monitoring

(5) A 73-year-old woman presents with new-onset convulsive status epilepticus with a background of cerebrovascular disease, and having failed to respond to benzodiazepines and intravenous valproate is intubated, sedated and admitted to intensive care. She had convulsed for around 45 minutes in total. The emergency department had already checked full blood count, urea and electrolytes, calcium, magnesium and glucose which were normal. ICU have checked her blood gases. She is afebrile. Which additional blood tests are indicated at this stage? You may select one or more answers.

A. Antineuronal antibodies
B. Coagulation studies
C. Creatine kinase
D. HIV serology
E. Liver function tests

(6) A 41-year-old man is called in for a review with his primary care physician. He has juvenile myoclonic epilepsy which has been in remission for 22 years on valproate at 600 mg/day. He has collected prescriptions regularly, but not attended in person for over four years. He is otherwise entirely healthy. Which laboratory investigations would be important to check? You may select one or more answers.

A. Ammonia
B. Full blood count
C. Liver function tests
D. Valproate levels
E. Vitamin D

(7) A 52-year-old Chinese woman was started on carbamazepine five weeks ago, and is now on 300 mg twice a day, without any baseline blood screening tests. She has a new diagnosis of focal epilepsy attributed to a previous traumatic brain injury. She presents to her primary care physician with a severe sore throat and temperature. Which is the most important blood test to now request urgently? You may select one or more answers.

A. Full blood count
B. Liver function tests
C. Urea and electrolytes
D. HLA-B*1502 status
E. Carbamazepine level

(8) A 22-year-old man with severe intellectual disabilities and drug-resistant epilepsy has been commenced on topiramate at 150 mg/day in addition to his longstanding lamotrigine. His mother reports that he keeps flapping his hands unusually, and seems agitated and distressed but she does not know why. What blood test might indicate that topiramate is causing symptoms in his hands?

A. Ammonia
B. Bicarbonate
C. Full blood count
D. Liver function tests
E. Topiramate levels

(9) A 51-year-old woman is brought in to hospital having had a middle cerebral artery stroke, successfully treated with thrombolysis. She has a background of focal epilepsy of unknown cause which has been well controlled since onset (age 40 years) on carbamazepine at 400 mg twice a day, with no other medication. Her sodium level is low at 129 nmol/L, without any associated symptoms. What would you recommend with respect to her antiepileptic drug treatment when discussing this result with her?

A. Lower the dose of carbamazepine
B. No change, this is common and not of concern
C. Switch her to an alternative drug
D. Withdraw the drug, as she is seizure-free

(10) A 19-year-old man with generalized epilepsy and tonic-clonic seizures on awakening had been seizure-free for two years on lamotrigine at 150 mg/day, but is brought into hospital at 9 a.m. by his girlfriend having had seizures on three consecutive mornings; two only 15 minutes apart that morning. He is otherwise well, reports taking his medication regularly, and does not report any lifestyle changes. You start taking some blood samples, but he withdraws consent and you only get enough for one test serum test. What would you request?

A. Calcium
B. Creatine kinase
C. Lamotrigine levels
D. Liver function tests
E. Urea and electrolytes

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".