epilepsy action

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CURRENT AWARENESS SERVICE

Febrile seizures: the perennial hot potato

Anand Iyer has written a clear and comprehensive review of temporal lobe epilepsy (TLE) in children. One of the most commonly talked about, and, at times, heated issues in TLE, is its uncomfortable association with febrile seizures and specifically the belief that prolonged febrile seizures cause TLE.

I thought it would be useful to write a brief review of febrile seizures (FS) and specifically to focus on what is known and what is perhaps speculation.

Before I begin: probable 'fake news'

Many of the data on the incidence and outcome of FS which originated from the early 1990s were derived from populations in which the diagnosis of FS might now be challenged. This is because the diagnosis was made in the context of no or very limited magnetic resonance imaging (MRI) data, no formal psychological assessments and no clear knowledge of Dravet syndrome and PCDH19. (The latter are two genetically-determined conditions that present between three and 12 months of age with 'febrile seizures'). Consequently, some of the children included in earlier studies may not have had what we would now understand and diagnose as FS. This would have had a knock-on effect on the reported outcomes of children with FS and particularly the reported occurrence of any cognitive impairment and the development of epilepsy.

How common are FS?

Febrile seizures affect 2-5% of the paediatric population in the UK, Europe and the USA. The prevalence is considered to be higher (up to 10%) in other continents and this may reflect the definition of an FS, the underlying genetic predisposition to them, or both. Recurrent febrile seizures occur in 15-70% and usually within two years of the first seizure, and often much sooner. There is no clear explanation for this very wide range in the reported rates of recurrence but in part it may again reflect its definition.

Why are FS so uncommon?

This is unknown and particularly in view of how extremely common febrile illnesses are in young children. The generalised tonic-clonic or focal clonic seizure that is an FS is identical in semiology to an epileptic seizure, but even recurrent febrile seizures are not epilepsy. It is also unknown why the manifestation of an FS is the same as an afebrile seizure. There may be a number of explanations:

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CONTENTS

- Genetic: Children who have one or more FS may have one (or more) genes that are linked with epilepsy but these are only activated by fever – when they will then have what is essentially an epileptic seizure. However, they don't then later develop afebrile seizures (epilepsy) because they do not have the additional facilitatory genes that are required for the epilepsy genes to be activated and the epilepsy expressed. However, this genetic predisposition only operates until the age of six years.

- Maturational: The brain of children who have FS may be genetically programmed so that between six months and six years of age there is a maturational 'window of opportunity' for a seizure to occur in the presence of a raised body temperature. Beyond the age of six years, maturation has occurred and this window (for the development of FS) has been closed. Clearly, this 'window' may be genetically-determined.

- Multi-factorial: Finally, as in any unexplained medical phenomenon, it may be due to a combination of factors.

What are the ages of onset and resolution of FS?

The universally-accepted age of onset is six months and the latest age at which a first febrile seizure may occur is six years. Some early literature cited three months and earlier definitions by the International League Against Epilepsy (ILAE) even gave the age of onset as on month. However, these lower limits are no longer tenable. An age of onset of one month is inappropriate for two main reasons:

- It may 'encourage' doctors to not consider that an infant aged between one and six months might have a serious infection, and specifically meningitis, encephalitis or sepsis. They may therefore not undertake the appropriate investigations to exclude these diagnoses.

- Some genetic epilepsies have an onset before six months of age. This is particularly in PCDH19 and to a lesser extent, Dravet syndrome (although in this latter syndrome, seizure onset is typically after six months of age). Children with either of these two syndromes may present with seizures in association with a febrile illness or when in a very hot environment. However, these would not be defined or classified as being 'FS'. A lower limit of one month may therefore lead to a failure to consider these diagnoses.

When practising, I never accepted a diagnosis of an FS in an infant less than six or even nine months of age. I would always consider and formally exclude meningitis at these ages. I was also very reluctant to accept a diagnosis of a first FS in a five-year-old.

Can children be developmentally delayed and still have FS?

Purists argue that a child must be neurologically and developmentally normal while pragmatists consider that this is unnecessary for a definition of an FS. Purists argue that the only certain way of linking outcome (specifically cognitive and behavioural) of FS is to study those who are 'developmentally pristine' prior to their first FS. Pragmatists might respond by stating that this is unrealistic, in part because it might depend on how 'normal' development is defined in a 12-18-month-old child. Specifically, it might not identify symptoms and signs of autistic spectrum disorder at this age. However, there is general agreement that a child cannot and should not be diagnosed as having an FS with a prior diagnosis of epilepsy, cerebral palsy or a genetically determined disorder (such as tuberous sclerosis, Rett and Angelman syndromes). In these children, it is more likely that the febrile illness has provoked an epileptic seizure.

How are FS manifest?

First, to rebut some more fake news; not everything that shakes or jerks is an epileptic seizure. Rigors are often misdiagnosed as febrile seizures. This is because the child 1) has a fever, and 2) shakes or jerks, and with or without some perioral cyanosis. The shaking in a rigor is much more rapid (more like a coarse tremor) and may be intermittent and stop abruptly, unlike the clonic activity in a tonic-clonic seizure which gradually subsides before stopping. The movements in a rigor are also usually far less violent than the clonic movements of a generalised tonic-clonic seizure and the face is rarely involved.

Most FS are generalised tonic-clonic; less commonly they may be generalised clonic. A minority are focal clonic. This different presentation (generalised versus focal), is currently a key differentiating feature between 'simple' and 'complex' FS. The term 'complex' is problematic as this may cause confusion with 'complex partial seizures', even though this latter term is no longer used. In my opinion, 'complicated' would be a more appropriate word.

The differences between simple and complex (complicated) FS are shown in *Table 1*.

Status epilepticus (SE), both febrile and afebrile, share the same definition: 'A focal or generalised tonic-clonic seizure that has lasted for 30 minutes (or longer), or repeated (serial) and briefer seizures without the recovery of consciousness between each seizure and this cycle persists for 30 minutes'. The ILAE changed the definition of status epilepticus in 2015 [Trinka et al, 2015] and this encompassed both non-febrile and febrile SE:

Table 1. Differences between simple and complex FS.

	Simple FS	Complex FS
Duration	≤10 minutes in UK ≤15 minutes in USA	≥15 minutes
Onset	Generalised (tonic-clonic or clonic)	Focal or generalised
Recurrence within 24h	None	Often: and may be more than one recurrence
Recovery	Rapid; no deficit	• May be rapid or slow • May have a deficit (including Todd's paresis)

- 5 minutes for generalised tonic-clonic seizures
- 10 minutes for focal seizures
- 10-15 minutes for absence seizures

This change was driven by the concern that the old definition of 30 minutes might suggest that emergency anti-seizure medication was not required until the child (or adult) had been seizing for 30 minutes. However, in reality, this was never the case. For almost two decades before 2015, doctors, nurses, paramedics, families and carers had been using anti-seizure medications to try and stop all tonic-clonic seizures (febrile and afebrile) that had lasted for five or more minutes. Consequently, this most recent definition of SE will have no impact on the management of febrile SE.

What is the outcome of children who have had FS?

Mortality: mortality from FS is extremely low (between 0 and <1%) and is likely to be related to the underlying illness and not the seizure itself. The results of one study suggested a possible association between FS and sudden unexpected death in childhood (SUDC) [Crandall et al, 2019]. This was based on a prevalence of almost 30% of FS in children who had died of a SUDC in contrast to the background prevalence rate of 2-5%. There are a number of methodological problems with this study, some of which its authors acknowledged. One was the definition of a FS (e.g. the child may have had meningitis or sepsis) and the second was a highly selective population, both of which could significantly affect the results and the authors' conclusions. No other study published before or subsequently, has replicated these findings. Consequently, it would be inappropriate and unwise to conclude that FS is linked with an increased risk of SUDC.

Epilepsy: The most debated outcome of febrile seizures, and particularly prolonged FS, including febrile SE, is their relationship with later mesial temporal epilepsy caused by mesial temporal sclerosis (MTS). This can be readily identified on MRI or, prior to the introduction of MRI, by histopathological analysis of resected temporal lobes [Waruiru and Appleton, 2004]. The prevalence of MTS as a cause of TLE has shown a large and sustained decrease over the past few decades. It has been suggested that this is because of a much lower incidence of prolonged FS, including febrile SE. This is likely to reflect the introduction of rescue (emergency) medication to stop a FS that has lasted five or more minutes. However, it is possible that there might be other explanations for this reduced prevalence:

- MTS may not have time to develop because children with any identified lesion in the temporal lobe now undergo resective surgery far earlier than in the 1980s and 1990s
- Other aetiologies that may cause temporal lobe epilepsy, and specifically cortical dysplasia, low grade tumours and the consequences of traumatic brain injury or encephalitis have increased in frequency. This may reflect improved identification through the use of higher resolution MRI or a definite increase in the incidence of these diagnoses, or a combination of both
- A revised histopathological diagnosis of MTS
- A combination of the above reasons

Two studies one undertaken in the UK [Pujar et al, 2018] and the other in the US (the 'FEBSTAT' Study) [Lewis et al, 2018], looked at febrile SE and MTS. They reported that 3% and 4% of children, respectively, who had experienced an episode of febrile SE, subsequently showed evidence of MTS on high-resolution magnetic resonance imaging (MRI). The UK study followed patients for up to nine years but in the US study follow-up was only one year. In the US 'FEBSTAT' study, nine of 226 children (4%) had evidence of hippocampal sclerosis (which is very similar to MTS) on MRI following the episode of febrile SE. However, only four of these children had a normal MRI and no developmental delay at the time of their febrile SE. If only these four (and not all nine) children are included

then the prevalence of MTS in the US cohort falls from 4% to 1.8%.

An earlier and much smaller UK study that involved only 35 children (21 with prolonged FS) showed MRI abnormalities suggestive of hippocampal oedema within five days of the episode of febrile and also afebrile SE; however, this finding had completely resolved on a scan done between four and eight months later [Scott et al, 2002].

A further MRI study was undertaken in 80 children (0.18-15.5 years) who had experienced an episode of convulsive status epilepticus (CSE). Thirty-three had prolonged FS (including febrile SE) and 47 had non-febrile CSE [Yoong et al, 2013]. MRI scans were done one month post-CSE; 50 had a repeat MRI at six months and 46 had repeat MRI at 12 months post-CSE. Hippocampal volume loss was found in 20-30% of patients and was not associated with the aetiology or the duration of CSE or likely seizure focus. The authors appropriately concluded that progressive hippocampal damage can occur after CSE of any aetiology and is not limited to febrile SE.

It is important to note that after a mean follow-up period of almost nine years, there was a difference in epilepsy prevalence between non-febrile CSE and prolonged FS. The cumulative prevalence of epilepsy was much lower in patients with prolonged FS, including febrile SE (14·3%), than in those whose episode of CSE was remote symptomatic (45·5%) and unclassified CSE (50%) [Pujar et al, 2018].

Finally, an alternative hypothesis is that complex and prolonged FS are caused by a pre-existing and previously undetected hippocampal or temporal abnormality. This could include from an earlier insult, subtle cortical dysplasia or genetic predisposition [Cendes, 2004; Koepp, 2000]. The theory is that any pre-existing abnormality has, through an unclear mechanism, lowered the threshold for both recurrent and prolonged FS and also the development of later TLE.

In summary, all of these results indicate that the association between prolonged FS, including febrile SE and later epilepsy (and specifically TLE), is very weak.

What are the long-term neurological and cognitive (including memory) outcomes of children with FS?

There are no long-term adverse neurological and cognitive sequelae following 'simple' FS. The evidence for cognitive consequences following complex FS, including febrile SE, is less clear. A UK population-based study analysed 381 children with FS (287 simple; 94 complex). It reported that those with previous FS performed as well as other children academically (using British Ability Scales) and behaviourally when assessed at 10 years of age [Verity et al, 1998]. However, a Dutch cohort-based study showed that children with recurrent FS demonstrated an increased risk of delayed language development [Visser et al, 2012]. Surprisingly, this study did not specify whether the FS were simple or complex. Finally, a very small study of only 26 children with prolonged FS, 15 of whom were followed for an average of one year after their seizure, showed an increased risk of "some" visual memory impairment [Martinos et al, 2012]. Perhaps predictably, the authors concluded: "The present study cannot conclude whether the prolonged febrile seizures have caused the observed impairments or not". The debate continues…

To summarise, current evidence indicates that the association between prolonged FS and later cognitive impairment is weak.

Can recurrent FS and particularly later epilepsy be prevented?

This previously hotly-debated topic has now run out of steam and is resolved.

In summary, and as emphasised in one of the ubiquitous Cochrane Reviews there is no evidence that the regular and prophylactic use of either antipyretics or anti-seizure medications will prevent further febrile seizures or the development of epilepsy [Offringa et al, 2012]. The Cochrane review, and one of many studies, has assessed prophylactic rescue medications (rectal and oral diazepam, oral clobazam but not buccal midazolam) and oral anti-seizure medications (phenobarbital, phenytoin and sodium valproate). Perhaps predictably, the review found that there was a high frequency (30%) of adverse side-effects in the participants that received oral prophylactic anti-seizure medications in the included studies that comprised the review.

However, wisdom and pragmatism would suggest that rescue medication (buccal midazolam or rectal diazepam) should be prescribed for those children who are likely to be at high risk of experiencing recurrent and prolonged FS. This is particularly important if they live in very rural postcodes that are difficult to access by the emergency services.

Conclusion

FS remain somewhat of an enigma in terms of how uncommon they are within a paediatric population that very commonly experiences febrile illnesses. Why they occur in the first place and their identical semiology with epileptic tonic-clonic or clonic seizures is also still to be fully understood. Fortunately, most FS are brief, although their occurrence certainly does upset or frighten the child's family and carers – and this must

never be under-estimated or dismissed lightly. Most children with simple FS will not develop long-term adverse cognitive outcomes and the development of later epilepsy, including temporal lobe epilepsy seems very rare. It is more likely that the very rare occurrence of any cognitive impairment or epilepsy reflects the underlying cause and not the FS itself. Finally, there is no indication to use long-term, oral anti-seizure medication to prevent recurrent febrile seizures or late epilepsy because they are not effective and may be associated with significant adverse side-effects.

Professor Richard Appleton
Co-Editor

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Temporal lobe epilepsy in children: an overview

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Introduction

The temporal lobe is a common source of epilepsy in all age groups. In children, extra-temporal lobe epilepsies are more common, but temporal lobe epilepsies (TLE) can present with extra-temporal clinical features in younger children. Unlike adults, where TLE is a relatively homogenous syndrome with stereotyped clinical features, children may have different presentations at different ages. In addition, the effect of seizures on other aspects of the immature brain, particularly development and learning, may be profound. Structural causes, including cortical dysplasias and developmental tumours, are more common in children and often result in early drug-resistance. Clearly, this requires prompt recognition and early assessments for potential epilepsy surgery which is likely to lead to an improvement in overall outcome in many cases.

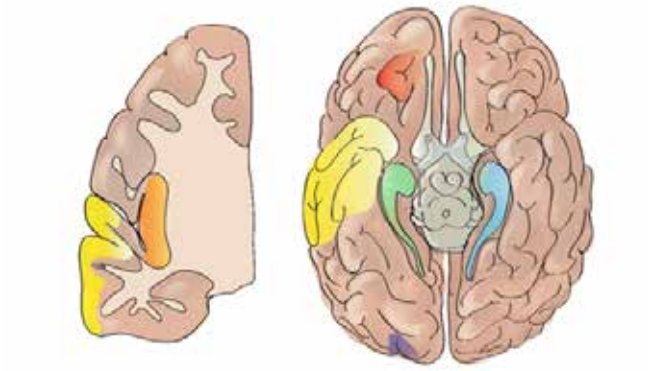
Temporal lobe and predisposition to epilepsy

The temporal lobe carries out many essential functions including language, processing of memory and emotion. Unlike other areas of the brain, most areas of the temporal lobe are involved in some function and are therefore indispensable. The temporal lobe is broadly divided into the lateral temporal lobe and the mesial (medial) temporal lobe. The Human Connectome Project, based on advances in technology and functional studies, has been able to subdivide the temporal lobe into four main areas considering its functional connectivity (*Figure 1*):

1. Lateral for semantic processing
2. Polar for emotional processing
3. Inferior for visual processing
4. Mesial for memory and visuo-spatial processing

Anatomically, the posterior aspect of the superior temporal gyrus is responsible for receptive language function and is known as the Wernicke's area, in the dominant temporal lobe [Catani et al, 2017]. The hippocampus and amygdala are located deep within the mesial temporal lobe. The hippocampus is responsible for creating declarative memories (long term memory of previous fact or event), which can be episodic or semantic (language related). The amygdala is responsible for fear and other emotional functions, including anxiety processing, and is involved in drug addiction. It is also implicated in basic behaviours such as eating, drinking, and sexual and aggressive behaviour, as well as in some psychiatric disorders and autism. In addition, several important connections, also termed fasciculi, connect parts of the temporal lobe to other areas of the brain and specifically the frontal and occipital cortex. This thereby allows the spread of the seizures to other areas of the brain.

Figure 1. The area marked in yellow is the lateral temporal lobe, the orange is the insula, and the green and blue are the hippocampi [Harroud et al, 2012]



Epidemiology

Approximately half of all children with new-onset epilepsy will have focal seizures. Very few large cohort studies have analysed focal epilepsies in childhood. In one such study, 63 children were identified with new-onset TLE over a four-year period [Harvey et al, 1997]. A review of 468 children with new-onset focal epilepsy that had presented over a 30-year period to the Mayo Clinic in the USA, showed that TLE was responsible for 8% of all paediatric epilepsy, and for 13% of all focal seizures [Nickels et al, 2012].

Temporal lobe epilepsy in adults

Mesial temporal lobe epilepsy has been very well researched in adults and constitutes almost 30% of all cases presenting with focal seizures and epilepsies. Adults are better able to describe different aspects of the seizures, unlike children, where one relies heavily on description by their parents or others. Older children may be able to describe different features – but they need to be asked specifically about these. The typical temporal lobe seizure description starts with an epigastric aura associated with fear, followed by loss of awareness. There can be associated oroalimentary automatisms and ipsilateral (on the same side) hand automatisms. Some of the seizures can progress to contralateral (on the opposite side) limb dystonic posturing, but bilateral convulsive seizures are rare [Blair et al, 2012]. There can be associated memory problems, particularly with left temporal lobe involvement. The MRI features are characteristic and show increased signal in the hippocampus on FLAIR and T2 weighted images with loss of hippocampal volume on T1 images, as well as loss of grey-white matter differentiation (*Figure 2*).

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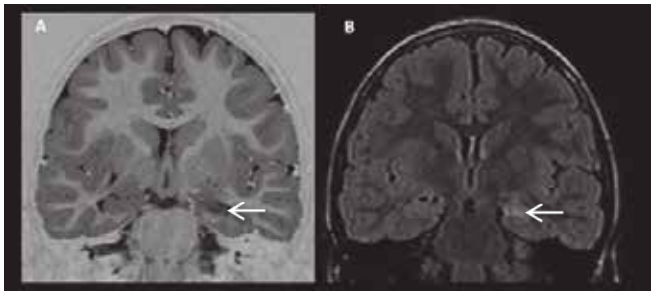
Figure 2. Left sided mesial temporal sclerosis, A: Coronal T1 and B: Coronal FLAIR showing loss of hippocampal volume (A) with increased signal intensity (B) (arrows) [Terra et al, 2010]



Semiology of TLE in detail and salient features in children

Prodrome

Some children experience preictal events, or prodromes, and these may occasionally help in predicting an imminent seizure. Prodromes may last several minutes, hours, or, occasionally, even days. Examples include headache, personality change, irritability, excitement, anxiety, or nervousness. It is important that these symptoms should not be confused with seizure onset. Often, prodromes are recognised by family and school, but not by the child or young person. They may or may not then develop into a clear seizure [Blair et al, 2012].

Auras

Auras (derived from the Latin for breeze and the Greek for air) are seizures with retained awareness (previously termed 'simple partial seizures'). They may occur in isolation, but in most patients, they will then evolve into a more recognised seizure including loss of awareness. Auras can last from a few seconds to as long as 1-2 minutes before awareness is lost. They are experienced by most adults and older children with TLE.

The types of auras reported may correlate with the site of seizure onset within the temporal lobe. Examples include viscerosensory symptoms such as a rising epigastric (in the stomach) sensation and experiential phenomena, such as fear, déjà vu and jamais vu, visceral and auditory illusions, and complex auditory or visual hallucinations. Gustatory and olfactory hallucinations are also relatively specific for TLE. Although auras often have localising value, they do not always have lateralising significance. For example, epigastric aura and fear are commonly reported in mesial temporal lobe epilepsies, whereas auditory hallucinations are seen in lateral temporal lobe epilepsies [Fohlen et al, 2021; Harvey et al, 1997; Ray et al, 2005].

Epigastric (in the stomach) aura is the most common symptom of mesial temporal lobe seizures. It is often reported, even by young children, as a rising sensation that is felt in the upper half of the abdomen. Some children find it difficult to describe the sensation and may simply report it as pain or 'hurting'. Older children may describe it as fluttering, butterflies, bubbling, whirling and squeezing. Fear is the next most commonly reported aura and is a subjective symptom. However, fear may also be felt and manifest by seizures that arise from the frontal lobes. However, the fear in frontal lobe seizures is usually far more expressive and even dramatic than that seen in temporal lobe seizures. This, in part, explains why frontal lobe seizures are occasionally misdiagnosed as night terrors.

Déjà vu (already seen) is another symptom which is experienced and reported mainly by older children and adults. This can include deja entendu (already heard) and deja vecu (already experienced) as a false sense of experiences which occur at that time. This includes a feeling of intense familiarity with visual, auditory or other physical events which patients experience at that moment. An example includes an older child who reported that he felt as if he was with his school friends, although he was in hospital for an appointment. On the contrary, jamais vu (never seen) or jamais entendu (never heard) are experiences where even though the surroundings are familiar they are perceived as no longer known by the patient. These are much rarer than déjà vu. An example includes a teenager, who reported that during the seizure, he would feel that the woman standing in front of him was not his mother, although he knew that she was [Blair et al, 2012].

Auditory hallucinations and illusions are mostly reported in lateral temporal lobe seizures and are less common. They can be elementary (crude) and comprise of ringing, buzzing, humming or clicking sound when they are usually high pitched. They can also present as a brief popping sound. These types tend to arise from the superior temporal gyrus in the auditory cortex. They can also be more complex, consisting of voices, sections of music and other sounds, which may or may not be familiar or comprehensible. Auditory illusions are different and represent altered perceptions of sounds, or voices in the actual environment during the seizure. For example, the conversation may sound muffled or very loud. Olfactory hallucinations are rare and likely to originate from the amygdala, whereas gustatory (taste) hallucinations usually originate from the insula; both are typically unpleasant and brief. Visual hallucinations depict spreading of the ictal discharge to the occipital area or the occipito-parieto-temporal junction [Nickels et al, 2012].

Ictal urinary urge (a sudden need to urinate) is felt by some children and represents origin in the insula of the non-dominant temporal lobe in most cases [Yilmaz et al, 2015].

Awareness and amnesia

Temporal lobe seizures are associated with altered or impaired awareness and amnesia for the event. Typically,

this is a behavioural arrest and staring, which lasts seconds to a couple of minutes, sometimes longer. Awareness has several facets, including cognition, perception, affect, memory and voluntary movement. Impaired awareness should be distinguished from a temporary block of verbal or motor output (seen in absence seizures) or of verbal comprehension with preserved awareness (seen in the self-limiting focal epilepsies). Children may be unaware that they had a seizure minutes earlier. They may also be unable to recall events which occurred before seizure onset. The degree of retrograde and anterograde amnesia is variable. For example, patients may experience an aura which prompted them to signal the onset of a seizure but subsequently are not able to recall having done so. Postictal amnesia probably likely results from bilateral impairment of hippocampal function [Nickels et al, 2012].

Automatisms

Automatisms represent coordinated involuntary motor activity that is stereotyped and virtually always accompanied by altered awareness (consciousness) and subsequent amnesia. They can be de novo or preservative. De novo automatisms are said to occur spontaneously at, or after, seizure onset. They might be classified as 'release' phenomena, which include actions that are normally socially inhibited, or 'reactive' phenomena when they appear to be reactions to external stimuli. For example, the patient may drink from a cup placed in his hand or chew gum placed in his mouth. Preservative automatisms might represent continuation of complex motor acts initiated prior to seizure onset, for example, opening and closing a door repeatedly.

Automatisms are further described as either simple or complex. Simple automatisms include oroalimentary automatisms, such as lip smacking, lip pursing, chewing, licking, teeth grinding or swallowing. They can be vocal noises, including single or repetitive utterances of sounds (grunts or shrieks), or can be words or sentences which are stereotyped, which may be spoken, shouted or sung. Simple gestural automatisms include fumbling, unilateral exploratory movements with the hand, like fiddling, picking, tapping, patting, plucking, rubbing and scratching. Complex automatisms include complex acts performed without awareness. For example, chewing an object and repeatedly saying that it is disgusting. Oroalimentary automatisms often followed by simple gestural automatisms are characteristic of mesial temporal lobe epilepsy, particularly if they are preceded by a rising epigastric aura. Verbal automatisms with coherent speech localise to the non-dominant hemisphere. Ictal vocalisation has no lateralising value. Unilateral limb automatisms are believed to be ipsilateral to the ictal onset, however, this is not always the case [Blair et al, 2012].

Other behavioural automatisms, such as crying (dacrystic), laughing (gelastic), and so-called 'leaving behaviours', for example, running out of the house or down the street during a seizure (cursive) have been reported. Whistling, a very rare automatism, has also been recently reported to occur during a temporal lobe seizure.

Motor features

These are typically the most recognisable feature and are often noticed and described by the parents or family. They are more common in younger infants and children. They may include head and eye deviation and limb posturing, or jerking; this implies some ictal spread to other regions and particularly the frontal lobe. Early gradual, subtle deviation of the head and eyes is considered to be ipsilateral to the epileptogenic focus. Conversely, if it occurs during the progression of the seizure and is more versive and forceful, then it is more likely to be contralateral to the epileptogenic focus. It also suggests involvement of the frontal eye field and supplementary motor area in the frontal cortex.

Unilateral dystonic or tonic posturing of face, arms and legs is reliably always contralateral to the epileptogenic focus. Unilateral ictal eye-lid blinking is ipsilateral, whereas ictal clonic jerking or paresis is contralateral to the epileptogenic focus [Dupont et al, 2015; Kamida et al, 2001].

Autonomic features

Another potentially useful marker of TLE is autonomic (primarily cardiac and respiratory) change. The most commonly observed autonomic change in temporal lobe seizures is ictal tachycardia. This occurs in roughly equal frequency in children and adults. It can be seen in up to 98% of all temporal lobe seizures that occur in children [Mayer et al, 2004; Nickels et al, 2012].

This is particularly true if seizures arise from the right temporal lobe. In contrast, ictal bradycardia is rare in children, occurring in less than 4% of monitored seizures.

One of the most dramatic autonomic disturbances that can occur during temporal lobe seizures in children is hypoxaemia or apnoea. Nearly half of all children and one-quarter of their seizures captured in inpatient monitoring units are accompanied by oxygen desaturations of < 90%. Such desaturations are not insignificant, with nearly one-third (32.1%) falling to < 60%. Ictal hypoxaemia in children is not specific for TLE and is more likely to be observed when focal seizures become secondarily generalised. However, in children aged between two and six years, apnoeic attacks may be the sole manifestation of TLE. Such hypoxaemia/apnoea could theoretically exacerbate bradycardia induced by carotid chemoreceptors, causing further respiratory suppression [Nickels et al, 2012].

Vomiting can also accompany temporal lobe seizures and may overshadow any reported auras. Repetitive retching is also noted in some children, particularly when seizure-onset is in the mesial temporal lobe [Pietrafusa et al, 2015].

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Speech

Speech and its involvement play an important role in the localisation of TLE. Language disturbance can include receptive, expressive or global aphasia. Speech arrest at seizure onset (before loss of awareness), or ictal or postictal aphasia, implies seizure onset in the dominant hemisphere. Speech arrest is usually tested in most epilepsy monitoring units while undertaking video telemetry. Its mechanism is either involvement of Wernicke area, Broca's area or the basal temporal region. Paraphasia is a sound substitution or rearrangement made in a word but the uttered word still resembles the intended word, such as saying 'tephelone' instead of 'telephone'. Paraphasia and alexia (an inability to read or understand the written word) occur in a seizure that originates from the dominant hemisphere. Speech preservation during a seizure is likely to imply origin in the non-dominant hemisphere.

Ictal and postictal mannerisms

Certain unusual behaviour may help localise the origin of the TLE. Ictal spitting or drinking may suggest origin in the right temporal lobe. Postictal nose wiping is occasionally seen and implies origin in the temporal lobe ipsilateral to the hand used for wiping. Postictal cough similarly suggests involvement of the non-dominant temporal lobe.

Table 1. Key semiological features and their localisation

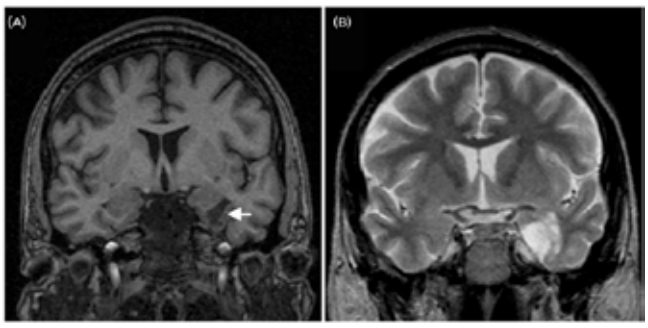
Semiology	Localisation
Auras	
Epigastric rising sensation and fear	Mesial
Auditory hallucination	Lateral
Urinary urge	Non-dominant insula
Automatisms	
Unilateral limb	Ipsilateral
Oral	Mesial
Postictal nose wipe	Ipsilateral
Postictal cough	Non-dominant
Ictal spitting	Non-dominant
Motor	
Early non-forced head turn	Ipsilateral
Late and often forced versive head turn	Contralateral
Eye deviation	Contralateral
Focal clonic jerking	Contralateral
Dystonic or tonic posturing	Contralateral
Postictal paresis	Contralateral
Speech	
Ictal speech arrest	Dominant
Ictal speech	Non-dominant
Postictal aphasia	Dominant

Aetiology of TLE

In children, the most frequent aetiologies of TLE are low grade tumours, cortical dysplasia, mesial temporal (hippocampal) sclerosis (MTS) (Figure 2) and dual pathology (presence of mesial temporal sclerosis and extra-hippocampal lesion). Although MTS is the most common cause of TLE in adults, accounting for nearly 40% of cases, the actual incidence in children varies [Sztriha et al, 2002]. Some studies have indicated that 10-20% of children that undergo evaluation for epilepsy surgery have MTS. This is more common in older children and adolescents, and is rare in children younger than five years of age. MTS has been linked with complex febrile seizures with one report suggesting that 43% of patients with MTS had a previous history of complex febrile seizures [Franzon et al, 2006]. However, it is uncertain whether the febrile seizures have caused the MTS, are a contributory factor or are a coincidence. The association between febrile seizures and TLE has been discussed in the introductory editorial by Richard Appleton (page 1).

The low grade tumours most frequently found in childhood TLE are neuronal or glioneural tumours like ganglioglioma, gangliocytoma, dysembryoplastic neuroepithelial tumours (DNET) (*Figure 3*) and low grade astrocytoma. Pleomorphic xanthoastrocytoma is rare and oligodendrogliomas are more infiltrative tumours. Focal cortical dysplasias are more common in the extra-temporal region, but can occur in the temporal lobe, particularly when there may be dual pathology. Some studies have found cortical dysplasia in the temporal neocortex associated with MTS in 67% of cases who underwent anterior temporal lobe resection [Bartolini et al, 2017; Mitchell et al, 2003]. Other lesions associated with TLE include vascular malformations (cavernomas and arterio-venous malformations), and gliosis following herpes and autoimmune encephalitides. In developing

Figure 3. Dysembryoplastic neuroepithelial tumour (DNET) in the left mesial temporal lobe. (A) Coronal T1 shows a mass with relatively homogenous hypointense signal (arrow). (B) Coronal T2 reveals a more extensive area of hyperintense signal in this area [Wehner and Lüders, 2008]



countries, neurocysticercosis is a relatively more common cause and, particularly in neuroimaging, shows a ring enhancing lesion in the temporal lobe.

There are some non-structural temporal lobe epilepsy syndromes that need to be considered in the differential diagnosis. Autosomal dominant lateral TLE, also known as autosomal dominant partial epilepsy with auditory features, is caused by mutations in the leucine-rich, glioma inactivated 1 (LGI1) gene in approximately 50% of cases. The median age at onset is late adolescence, and the seizures are characterised by simple auditory auras. Neuroimaging is usually normal, and the epilepsy responds well to anti-seizure medications (ASMs). Reading epilepsy presents with ictal alexia provoked by reading and is accompanied by dominant (usually left) temporal ictal discharges. Other well-known paediatric epilepsy syndromes may involve the temporal lobes with consequent temporal seizure semiology. These include the self-limiting focal epilepsies of childhood, previously termed 'benign rolandic epilepsy with centro-temporal spikes', or BRECTS. They also include the much rarer and more encephalopathic syndromes, continuous spike and wave during slow wave sleep (CSWS) and Landau-Kleffner syndrome (auditory agnosia).

Certain genetic conditions may also be characterised by seizures that involve the temporal lobe. Recurrent and prolonged febrile status epilepticus and mesial temporal lobe sclerosis have been noted in Dravet syndrome [Tiefes et al, 2019]. 12q22 duplication syndromes are also known to be associated with temporal lobe seizures [Stella Vari et al, 2018].

The EEG in TLE

The scalp EEG in patients with TLE is important in establishing the initial diagnosis of epilepsy, as well as localising seizure onset. The value of scalp EEG is improved by ensuring a sleep recording during routine EEG. Furthermore, localisation of seizure onset is improved through the use of additional EEG electrodes, either sphenoidal or inferolateral temporal, as well as closely placed electrodes. However, these techniques are more frequently used during surgical evaluation rather than in routine clinical practice.

The interictal EEG in TLE is typically characterised by temporal spike or sharp wave discharges and temporal intermittent rhythmic delta activity (TIRDA). Temporal spike or sharp-wave discharges are highly epileptogenic discharges that are maximal over the anterior temporal region and may predominantly involve the ear leads (*Figure 4*). There is often increased activation of spike and sharp-wave discharges during drowsiness and sleep, with nearly 90% of patients with temporal lobe seizures showing spikes during sleep. The spike-wave discharges may occur independently or synchronously over both bilateral temporal regions.

However, most patients with bi-temporal interictal EEG patterns are found to have unilateral temporal lobe seizures [Nickels et al, 2012].

TIRDA has also been seen in patients with TLE and becomes more prominent during drowsiness and NREM sleep (*Figure 5*). It is characterised by rhythmic trains of low- to moderate-amplitude monomorphic theta-delta frequency slow waves over one or both temporal regions. The monomorphic (similar appearance, see *Figure 6*) slow waves do not have any clinical correlate and must be differentiated from the polymorphic (subtle variation in size and appearance) delta activity that would be seen with a structural lesion within the temporal region [Mani 2014].

However, it is important to note that scalp ictal and interictal EEG recordings in infants and young children (5-6 years) may be poorly localising, even in TLE, due to incomplete or abnormal brain maturation. A focal lesion can present with generalised or multi-focal epileptiform discharges in these age groups. Similarly, the ictal EEG in a focal seizure of anterior temporal lobe origin may initially demonstrate bilateral or generalised scalp EEG changes at this age.

Typically, the ictal scalp EEG during a temporal lobe seizure will demonstrate moderate- to high-amplitude rhythmic paroxysmal activity which is maximal over a unilateral temporal region (*Figure 6*). This may then progress to generalised rhythmic slowing that is maximal ipsilateral to seizure onset [Barba et al, 2007]. Prior to seizure-onset and postictally, there may be increased interictal temporal or bi-temporal spike wave activity. Postictally there may also be focal temporal or generalised arrhythmic slow wave activity. This must be distinguished from continuing seizure activity.

Figure 4. Interictal EEG showing runs of spikes in the right temporal region (arrows). Reproduced from [Mani, 2014]

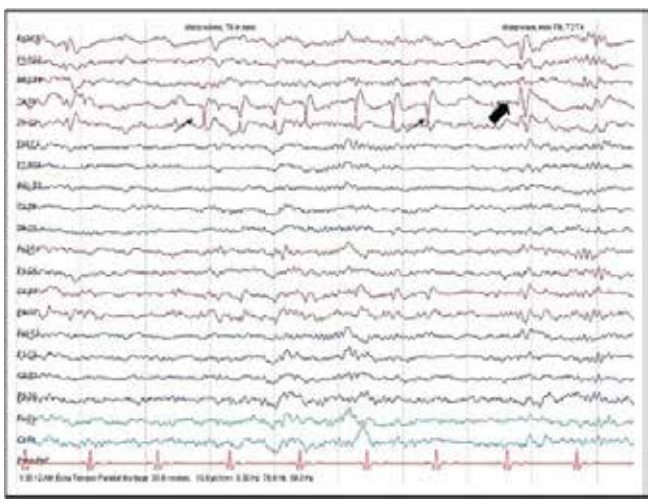


Figure 5. Interictal EEG showing runs of temporal intermittent rythmic theta-delta activity (TIRDA) over the left side (stars). Reproduced from [Mani, 2014]

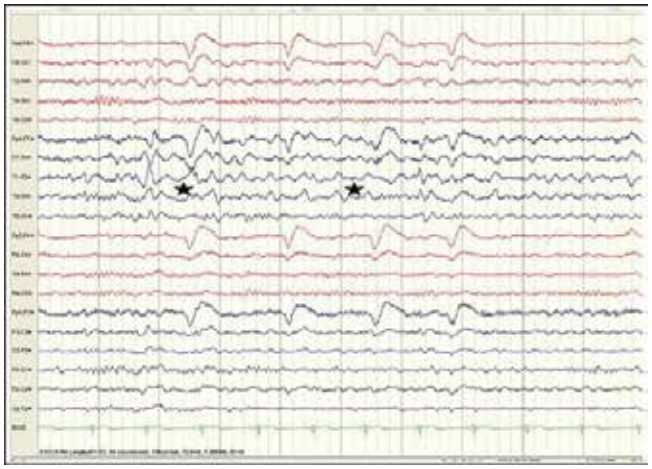
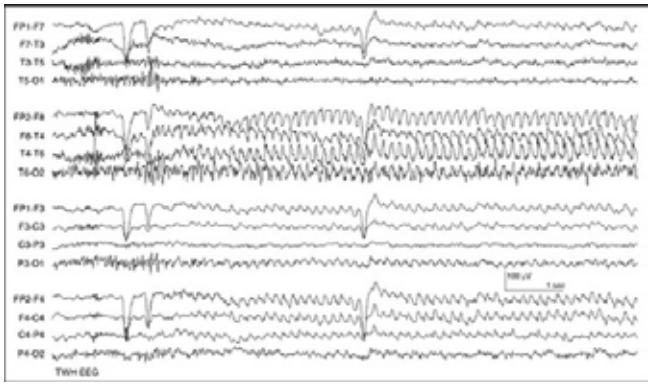


Figure 6. Ictal EEG showing built up of rhythmic monomorphic theta activity over the right temporal region (arrow). Reproduced from [Mani, 2014]



Management of TLE

Medical management remains the mainstay of treatment in TLE, similar to the management of other focal epilepsies in childhood. However, the risk of developing drug-resistant epilepsy is high. It is interesting that early on in the evolution of TLE, seizure control may be reasonable, but is then lost. This may even occur in the presence of a structural lesion within the temporal lobe. Any child with a focal epilepsy that has not responded to two ASMs in appropriate doses, or with an identified lesion on MRI, should always be referred for surgical evaluation. This would be to one of the Children's Epilepsy Surgery Service (CESS) centres in England or the epilepsy surgery centre in Scotland. Epilepsy surgery provides an important management option and must be considered and undertaken early for optimal outcomes.

Medical management

The goal of epilepsy treatment is long-term seizure freedom with minimal or no side-effects with ASMs. Over the past 30 years, despite the availability of many new ASMs, no single drug has been shown to be significantly more effective than any other. However, generally, the newer medications licensed over the past decade are associated with fewer and less severe adverse side-effects and are better tolerated. The choice of medication depends on the individual case: the age of the child, the range of available preparations (capsule, flavoured liquid etc.), the need for initial intravenous administration and side-effect profile. Carbamazepine (CBZ) and lamotrigine (LTG) are the two first choice medications in the treatment of focal epilepsies [Marson et al, 2007]. However, their slow titration and risk of allergic rash (particularly with LTG) does pose some practical difficulties. This is particularly relevant for those children who present with a high initial seizure frequency. Levetiracetam (LEV) has proven to be effective, with the advantage of a smooth transition from intravenous to oral preparation, favourable side-effect profile and better tolerability. Limited data suggest that CBZ and LEV show similar efficacy in treating focal seizures in children [Perry et al, 2008] and in adults following a stroke [Consoli et al, 2012]. However, adult data suggest that LEV may not be as effective as LTG in the treatment of focal seizures [Marson et al, 2021]. Usual add-on therapies to these medications include topiramate (TPM), clobazam or zonisamide (ZON). However, TPM and ZON are associated with potentially serious side-effects, including anorexia and weight loss, cognitive difficulties (particularly affecting language), renal stones and behaviour problems. A recent study also showed that ZON was not as effective as LTG or LEV in suppressing focal seizures [Marson et al, 2021]. Sodium valproate and vigabatrin may be appropriate medications to use for a brief period and possibly during the process of surgical evaluation. However, both must be used cautiously because of their potential serious adverse side-effects.

If children continue to experience seizures despite trying two or more appropriate medications in adequate doses and duration, then they are defined as having drug-resistant epilepsy. Carpay et al [1998] found that 51% of children whose first medication failed for lack of efficacy had a good response to a second agent. However, the likelihood of achieving a seizure remission of more than one year with subsequent drug regimens was only 29% after the failure of two medications and 10% after the failure of three medications [Berg et al, 2012]. In a separate study reported by Berg et al [2006], among children whose seizures persisted despite trials of two ASMs, only 38% achieved a one-year remission and 23% achieved a three-year remission at their last follow-up. It is this group of patients that must be referred for a formal surgical evaluation.

Surgical management

Early referral for consideration of epilepsy surgery should be undertaken in children with drug-resistant epilepsy, or structural lesions. Hippocampal sclerosis and dual pathologies are generally associated with less chance of seizure-freedom with medical management alone. In addition, long-term medications carry the risk of compliance, drug-interactions, menstrual irregularities, teratogenicity, osteopenia and sexual dysfunction (in males and females). Early surgery may allow significant improvements in other areas, specifically memory and learning, as well as seizure freedom, with a consequent improvement in a person's quality of life.

Every child who undergoes epilepsy surgery evaluation needs video telemetry to capture their usual (habitual) seizures and to ensure that the findings are concordant with the lesion or likely site of origin. In addition, telemetry is useful in differentiating patterns between mesial and neocortical temporal lobe epilepsies, although this is often difficult in young children (<5-6 years of age). A 3Tesla MRI brain scan with an epilepsy protocol is essential and this includes images in the oblique coronal plane, perpendicular to the long axis of the hippocampus. Quantitative volumetric studies are helpful in the assessment of hippocampal atrophy, particularly if there are bilateral changes or hippocampal mal-rotation. Detailed neuropsychology assessments are important in trying to lateralise speech and language function and identify any memory impairment. These include detailed evaluation of multiple domains such as intelligence, language, memory, attention, problem-solving, visuo-spatial and academic skills, motor and sensory function, and adaptive functioning. Studies have shown that verbal memory dysfunction exists in right-handed children with drug-resistant TLE, whereas non-verbal dysfunction was more commonly seen in children with a right temporal focus. In addition, atypical language reorganisation is seen in early-onset TLE with structural lesions, or insults to the left hemisphere before the age of six years. In some cases, functional MRI is a non-invasive but cumbersome option to determine language lateralisation. Occasionally and only in older children (usually >14 years) it may be necessary to perform the intracarotid sodium amobarbital (Wada) test. This is where sodium amobarbital is injected into one carotid artery while children are woken up and asked to perform a series of neuropsychology tests, to determine memory and language function or impairment. Neuropsychiatry assessments are important to exclude any unrecognised comorbid problems, such as depression or a pervasive developmental disorder. Following an initial discussion in the epilepsy surgery multidisciplinary meeting, further tests may be required including PET (positron emission tomography), SPECT (single photon emission computed tomography) or MEG (magneto-electroencephalography) to further identify the site of origin of the seizures.

Once all the investigations and specialist reports have been completed, the child is discussed in the epilepsy surgery meeting and a decision is made on the surgical approach. This may include the decision that surgery is not a feasible or safe option. Classically, resective surgery is offered in which the lesion is resected (removed). However, in some cases the option will be non-resective. There are two resective surgical options for mesial TLE. The first is a 'standard' anterior temporal lobe resection and the second is a selective amydalo-hippocampectomy. The anterior temporal lobe resection is preferred in younger children where seizure onset occurs in the lateral neocortical temporal structures or where there is dual pathology. The primary objective in choosing the more selective mesial resection mainly is to preserve neuropsychological outcome, but the evidence for this in children is equivocal [Elliott et al, 2018]. Seizure outcome following a selective resection is poorer in children than in adults, due to the higher frequency of pathologies outside the hippocampus [Dallas et al, 2020]. When the epileptogenic focus is due to a structural tumour, then a lesionectomy, with or without hippocampectomy, is usually the preferred option [Benifla et al, 2017].

In some cases, where there is dual pathology, or to better delineate the area for surgical resection, invasive EEG recordings are used. These can be intraoperative as in electrocorticography (ECoG). This technique involves the application of a set of electrodes embedded on a silicon mat directly on to the brain surface. It records electrical activity during surgery and is used to guide the extent and limits of surgical resection. This is unlikely to be useful or needed in standard anterior temporal lobe resection or resection of the hippocampus, but is more relevant and beneficial in lesionectomies, or resection of tubers in tuberous sclerosis complex. There are limitations of ECoG because the epileptiform activity recorded is exclusively interictal and not ictal. In addition, there is limited time during surgery to come at a definitive decision with this procedure. In bilateral hippocampal sclerosis, bilateral hippocampal depth electrodes are inserted along with some grid electrodes applied over the neocortical temporal lobe. This is also done when there is uncertainty from standard EEG recordings about the lateralisation of epileptogenic network. This technique has now been largely replaced by stereo-electroencephalography (SEEG). In this technique, under robotic guidance and with meticulous planning, a number of invasive electrodes are inserted through small burr holes into the temporal region. SEEG aims to determine the exact extent of any putative resection and to avoid damaging eloquent areas. This also allows preoperative cortical stimulation to map out eloquent areas and also to stimulate the person's habitual seizure(s). In some cases, thermo-coagulation of selected brain tissue before removal of the electrodes may allow the clinician to ensure that removal of the selected area is likely to result in seizure improvement. Trials are underway to assess whether stereotactic EEG-guided

radiofrequency thermo-coagulation is as effective as standard anterior temporal lobe resection in hippocampal sclerosis [Wang et al, 2021]. Complications of dominant temporal lobe resection are potentially multiple and serious. They include language and memory impairments, with naming and fluency of speech [Danguecan et al, 2019], transient diplopia due to trochlear nerve injury (rare) and significant contralateral visual field deficits. The visual field deficits may occur in up to one-third of cases, but usually improve one year after surgery. The most commonly reported complications are psychiatric, but these are usually transient. However, this emphasises the importance of a neuropsychiatric assessment as part of the formal surgical evaluation process and certainly before surgery [Brotis et al, 2019].

Outcomes in TLE

The long-term seizure outcome is mainly dependent on the underlying aetiology. Children with no identifiable aetiology tend to have better seizure control than those with a structural abnormality. A recent review on outcomes in children who had undergone anterior temporal resection quoted seizure-free rates of 58-78% with mesial temporal sclerosis, and 60-90% in neocortical temporal resections [Nickels et al, 2012]. Children with dual pathology do not seem to have unfavourable outcomes, providing both pathologies are adequately resected. Consequently, it would seem that selective amygdalo-hippocampectomy is less successful in achieving seizure freedom in children [de Souza et al, 2020; Elliott et al, 2018]. Long-term cohort studies suggest that there is a risk of late relapse and loss of seizure control. Unlike adults, children with TLE have more significant general cognitive problems rather than selective problems with verbal or visual memory. However, it is also important to note that cognitive improvement has been seen in children following temporal lobe resection [Lee et al, 2013]. Predictors of cognitive decline following surgery include older age at the time of surgery, structural lesions other than mesial temporal sclerosis and left-sided surgery [Farooque et al, 2017; Meguins et al, 2015; Shin et al, 2018]. Psychiatric comorbidities are also commonly associated with TLE, specifically pervasive developmental disorder (including autism spectrum disorder), ADHD, oppositional defiant disorder and disruptive behavioural disorder. Postoperative depression has been reported in some adolescents following temporal lobe surgery [Brotis et al, 2019]. Finally, a recent study from Sweden described the long-term employment of 203 children (aged <19 years) who had undergone surgery (45% of whom had undergone a temporal resection). This showed that the overall employment rates were higher compared to most previous studies that had assessed employment when surgery had been undertaken in adulthood. It was of interest that seizure free patients with a preoperative IQ ≥70 showed rates of full-time employment that were similar to the background, reference population [Reinholdson et al, 2020].

These outcome data again clearly emphasise the importance of early consideration of surgery and any subsequent surgical procedure.

Conclusion

Although TLE is less common in children, it still comprises a significant proportion of all cases of focal epilepsy in children. It can be difficult to identify with absolute certainty in children under the age of six years, because the traditional semiology with auras and automatisms may be absent. Prolonged EEG or even video-EEG telemetry may be needed, but the characteristic electrical signatures of temporal spike or sharp waves or TIRDA may be seen only in older children. It is clearly important to identify a structural lesion, but TLE may also occur in the absence of any structural lesion. It is essential to differentiate TLE from the more common paediatric self-limiting epilepsy syndromes. A minority of children, particularly those with lesions, may prove to be drug resistant and an early and formal evaluation for possible epilepsy surgery is important. In view of the high prevalence of pathology outside the hippocampus, a standard anterior temporal lobe resection provides better outcome. Seizure free rates of between 50-90% can be observed, as well as improved neurodevelopmental and cognitive outcomes. In those who may not be surgically resectable, further research into efficacy of neuromodulation is warranted, including deep brain stimulation and other developing techniques.

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The Epilepsy Space

The mobile friendly website is a helping hand for 16-25 year olds to live their best life with epilepsy

The Epilepsy Space will help young people to:

- Manage their epilepsy
- Feel less alone
- Increase their confidence
- Get the support they need

There's lots of epilepsy facts, tips and stories from young people sharing their experience.

The content is short and interactive. It's not all reading, there's video and young people can share their own quotes, stories and videos too.

It's been created with young people and reviewed by epilepsy nurses.

Take a look at:
epilepsyspace.org.uk

Leaflets about The Epilepsy Space to give to young people can be requested by emailing:
nurseorders@epilepsy.org.uk

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Recently published papers

This section highlights recently published papers. Hopefully this will be very useful to all, helping to keep everyone up to date with the latest developments. It will certainly save you research and reading time, not having to search so many journals.

There are many (often over 300) epilepsy papers published every three months, so what follows has been edited. All animal papers have been excluded and as many review papers as possible have been included. We hope you find the papers of interest in your pursuit to keep abreast of the very latest knowledge.

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