Managing first-time seizures and epilepsy in children

A first seizure is a relatively common problem in paediatric general practice.

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An estimated 8% of the population will have a seizure at some point in their lifetime.[1] Half of these occur during childhood, making a first-time seizure a commonly encountered problem in general paediatric practice.[2] It is estimated that 1 in every 100 South Africans suffer from epilepsy; a small rural study in the Northern Province demonstrated an active prevalence of 6.7/1 000 children.[3] The true burden of epilepsy in South African children is unknown but likely to be large. It is one of the most common chronic disorders managed by general practitioners, paediatricians and paediatric neurologists.

A stepwise approach to a suspected first-time seizure ensures a correct diagnosis and minimises unnecessary investigations and treatment.[1] Epilepsy is defined as 2 or more unprovoked seizures and also requires a logical approach to management.

Stepwise approach to a child with a suspected first-time seizure
- Is this a true seizure?
- If so, what type of seizure is it?
- Is this the first seizure?
- Was the seizure provoked or unprovoked?
- What investigations are necessary?
- Is drug treatment necessary?

First-time seizures

Is this a true seizure?

A detailed eye witness account is essential but often not available. An incomplete history is the principal reason for misdiagnosis of epilepsy.[4] There are many seizure mimics and paradoxically some subtle seizure types are easy to miss. Parents should be encouraged to capture the event on their cell phone or via video camera when there is doubt about true epileptic seizures. A few of the more common seizure mimics are detailed in Table I.

What type of seizure is it?

The International League Against Epilepsy (ILAE) has recently revised its classification of seizures.[8] However, the most practical classification remains:
- **generalised seizures** including tonic, clonic, tonic-clonic, absence, myoclonic and atonic seizures and infantile spasms
- **focal/partial seizures** including simple partial seizures (during which awareness is retained), complex partial and secondary generalised seizures.

A seizure which cannot be categorised should remain unclassified until further witnessed events provide more information in order to avoid inappropriate investigations or therapy choices.

Is this the first seizure?

Directed questioning is essential to reveal unreported or unrecognised seizures such as myoclonic jerks and absences. It is important to ask leading questions about these features and to remember that seizures such as infantile spasms may be as subtle as a head nod followed by a cry. The mother will often not volunteer this information, particularly if she has previously been falsely reassured that her baby has colic.

Was the seizure provoked or unprovoked?

This is an important distinction to make. In many children, a thorough history and careful neurological examination will allow a diagnosis without the need for further evaluation.

- **Provoked seizures** are those occurring in temporal relation to an acute systemic or central nervous system (CNS) event, e.g. hypoglycaemia, fever, acute ischaemic stroke, CNS infections and toxins.
- **Unprovoked seizures** occur spontaneously without any known proximate precipitant or relation to an antecedent event.
- **'Remote symptomatic' seizures** are sequelae of a static or progressive CNS disorder, e.g. congenital brain malformation, previous stroke or sequelae of perinatal asphyxia but without any apparent immediate precipitant.

The distinction has implications for future prognosis and management dealt with below.

What investigations are necessary?

Laboratory tests

Investigations should be performed based on the individual clinical history and examination findings.
- Blood pressure and fundoscopy are an essential part of the clinical examination in any child with a seizure.
- Routine blood tests, apart from serum glucose, are not recommended in children older than 6 months with a first unprovoked seizure provided there is cause no apparent, no neurological abnormality and the child returns to baseline alertness and functioning.[5] Serum urea and electrolytes are important in children with a history of diarrhoea or vomiting.
- A toxicology screen should be performed if there is any question of drug or substance exposure evident from the history.
- Recommendations for lumbar puncture (LP) in the child with an unprovoked seizure are not based on strong evidence but include the child below 6 months of age and those with meningeal signs or persistently altered mental state without obvious cause.[7]
- In the child with fever an LP is indicated whenever meningeal signs are present or in young children (under 18 months) in whom signs of meningeal irritation may be absent, provided there are no contraindications.

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When to perform an electroencephalogram (EEG)(Fig. 1)

An EEG should be requested after 2 or more seizures but may be performed after the first event if it will specifically alter management. Examples include children with a suspected benign focal seizure

Table I. Seizure mimics

Breath-holding attacks
- Typically begin before 18 months of age and cease by age 6 years
- Involuntary events, brought about by anger or fright and usually preceded by crying
- Child stops breathing in expiration, becomes rapidly cyanosed, then limp and subsequently loses consciousness
- May have subsequent brief tonic posturing of the limbs – easily confused with seizures
- Rapid recovery is the rule if short lived; more prolonged episodes may lead to sleepiness but the child always rouses before going to sleep

Syncope
- Provoked by circumstances such as pain or prolonged standing
- Premonitory symptoms: nausea, light-headedness, blurred vision
- Observed pallor and sweating, myoclonic jerks are common
- Incontinence is unusual but no tongue biting, loss of consciousness is brief and recovery rapid; may progress to reflex anoxic seizure if held upright
- Cardiac syncope is rare, usually related to aortic stenosis or prolonged QT interval

Night terrors
- The child typically wakes after a few hours of sleep with intense confusion and fear, is inconsolable and then goes back to sleep
- There is no recollection of the event in the morning

Sleep myoclonus
- Hypnagogic jerks, typically occur during the onset of sleep
- Abrupt cessation on awakening

Day dreaming
- Sometimes difficult to distinguish from absence seizures on history alone
- The day-dreaming child may not respond to voice but will respond when touched; so-called 'touch test'

Infantile self-gratification
- More frequently observed in girls in late infancy or early childhood, commonly misdiagnosed as epilepsy on history
- Episodes of rhythmic contractions of the lower limbs often involving flexion of the hips, eye staring and withdrawal, may occur in prone position
- Movements can be stopped if the child is distracted, may cry or become agitated when interrupted

Pseudo-seizures
- Often triggered by emotional factors and usually witnessed by family or friends
- The child may have been exposed to epilepsy previously, whether in the family or community
- Often occurs in dramatic circumstances and movements are not stereotyped
- May have random, semi-purposeful limb movements and display resistance to examination
- Incontinence may occur, tongue biting is rare, events are often prolonged with surprisingly rapid recovery
- Invariably psychological or scholastic problems – be very alert to the likelihood of sexual abuse, especially in the female child (events may be sub-conscious and are always a 'cry for help')

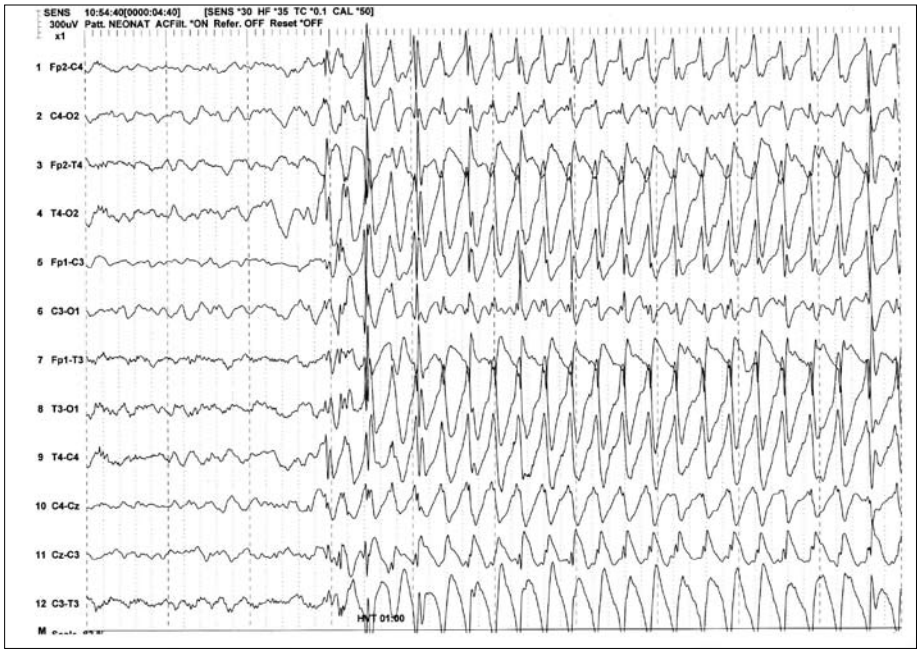

Fig. 1. EEG showing 3 per second (3Hz) spike and wave discharges typical of absence epilepsy.

disorder and unusual syncopal events. A EEG can be performed on an outpatient basis. The clinician should be aware that an EEG abnormality alone is not sufficient to make a diagnosis of seizures and the absence of an abnormality does not exclude seizures.[6] An estimated 5 - 8% of healthy children will have interictal EEG abnormalities.[6]

The EEG technologist should be informed about which seizure type is suspected as this may influence the way in which the study is performed. Sleep enhances the yield of a positive test by 30%, especially in certain seizure types, e.g. temporal lobe epilepsy. It is worth considering a drowsy or a sleep study in the child with a normal awake EEG but a convincing history of seizures.[6] Sleep deprivation prior to the test is useful in the older child. Younger children may require sedation. Children with suspected infantile spasms should have an initial awake EEG as the pathognomonic finding of hypsarrhythmia may be attenuated in the sleeping infant. Infantile spasms are a medical emergency and an EEG should not be delayed as these children need urgent intervention.

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Table II. Important epilepsy syndromes encountered in general practice

FOCAL EPILEPSIES

Benign focal epilepsy of childhood (BFEC, rolandic epilepsy)

- Commonest form of genetic (idiopathic) childhood focal epilepsy
- Presenting age: typically 8 - 12 years, may present as young as 3 - 4 years
- Onset often from sleep, facial grimacing and/or twitching with speech arrest; consciousness is preserved, events usually brief
- May rarely evolve into a generalised tonic-clonic seizure (GTCS)
- Normal neurological examination; EEG demonstrates uni- or bilateral centrotemporal spikes activated by sleep
- Many do not require therapy if seizures infrequent; if necessary, good response to carbamazepine

Benign epilepsy with occipital paroxysms (BEOP)

- Presenting age: 3 - 6 years
- Events infrequent, may occur once only, typically from sleep, may be prolonged
- Visual manifestations or temporary blindness with headache and vomiting, may progress to GTCS
- Normal neurological examination; EEG shows typical occipital paroxysms
- Many do not require therapy; if necessary carbamazepine or sodium valproate

GENERALISED EPILEPSIES

Childhood absence epilepsy

- Commonest form of genetic (idiopathic) generalised childhood epilepsy
- Age of onset: 4 - 8 years
- Typical absences last 5 - 10 seconds with gross motor arrest
- May have associated simple automatisms
- No post-ictal confusion or drowsiness
- Approximately 50% of children will have at least one GTCS
- Pathognomonic EEG: 3 per second spike and wave discharges usually activated by hyperventilation
- First-line therapy sodium valproate; lamotrigine effective add-on therapy; failure to control on valproate alone requires specialist referral

Infantile spasms

- Neurological emergency: ***delayed treatment worsens neurological sequelae***
- Age of onset: 3 - 6 months but may present later
- Often misdiagnosed as colic, clusters of head and/or trunk flexion held for 1 - 2 seconds, limbs may flex or extend with the contraction
- Distressing, usually associated with a cry
- Urgent EEG essential to allow prompt treatment
- Warrants neuroimaging and neurometabolic evaluation to elucidate cause
- First-line treatment in South Africa: steroids (ACTH) or vigabatrin, long-term therapy usually sodium valproate or benzodiazepines (clonazepam)

Genetic epilepsy with febrile seizures plus (GEFS+)

- Age of onset: infancy
- Initial seizures febrile but continue beyond age 6 years
- Thereafter develop non-febrile seizures, may include GTCS, myoclonic, atonic drops, etc.
- Family history of epilepsy often present
- Usually easily controlled with monotherapy; sodium valproate drug of choice

Severe myoclonic epilepsy of infancy

- Age of onset: infancy
- First seizures usually associated with fever and prolonged
- Febrile and non-febrile seizures recur sometimes as status epilepticus
- Generalised myoclonus appears after the age of 1 year which coincides with slowing of development
- Interictal EEG may initially be normal
- Invariably intractable, levetiracetam may be effective in combination with sodium valproate, clobazam or topiramate
- Requires referral to a paediatric neurologist

Lennox-Gastaut syndrome

- Age of onset: 2 - 5 years
- Multiple seizure types: tonic seizures predominantly during sleep, GTCS, atypical absences and atonic drops
- Commonly structural-metabolic (symptomatic) and up to 20% evolve from infantile spasms; commonly associated with preceding neurological abnormality
- Invariably intractable, sodium valproate and clobazam or clonazepam are usually effective agents; lamotrigine and topiramate effective add-on therapies
- Referral to a paediatric neurologist advised

Juvenile myoclonic epilepsy

- Commonest adolescent form of genetic (idiopathic) generalised epilepsy
- Age of onset: 8 - 14 years
- GTCS usually preceded by myoclonus which may be subtle and go unrecognised prior to presentation
- Myoclonic jerks primarily occur within first few hours after awakening
- Photosensitivity common
- Sleep EEG always abnormal
- First-line agent of choice: sodium valproate, usually lifelong treatment

Landau-Kleffner syndrome

- Age of onset: age 2 - 7 years
- Subacute acquired aphasia with associated EEG abnormalities
- Up to 80% have seizures which often precede the aphasia
- No proven anti-epileptic drug of choice; corticosteroids and ACTH commonly used despite a lack of controlled trials
- Early referral to a paediatric neurologist advised

Table III. Epilepsy categorisation according to prognosis[5]

- **Benign epilepsies** (approximately one-third of patients), e.g. benign rolandic epilepsy: remission occurs after a few years, treatment can potentially be avoided
- **Pharmacosensitive epilepsies** (approximately one-third of patients), e.g. majority of absence epilepsy: seizure control easily achieved with monotherapy; spontaneous remission usually occurs after a few years
- **Pharmacodependent epilepsies** (approximately 20% of patients), e.g. juvenile myoclonic epilepsy, many structural-metabolic (symptomatic) focal epilepsies: relapse occurs with attempted drug withdrawal, treatment usually lifelong
- **Refractory/pharmacoresistant epilepsies** (approximately 15 - 20% of patients), e.g. Lennox-Gastaut syndrome: poor prognosis, inadequate response to maximum doses of at least two appropriate drugs

Table IV. Predictors of prognosis: 'good' v. 'bad' epilepsies

'Good' epilepsy' predictors

- Genetic (idiopathic) and unknown (cryptogenic) epilepsies without any poor prognostic factors are three times more likely to achieve remission of seizures compared with structural-metabolic (symptomatic) epilepsies[5]
- Early response to drugs (75 - 100% seizure reduction within the first 3 months of adequate therapy) is a good prognostic predictor of long-term remission, irrespective of underlying aetiology[5]
- Simple partial seizures are the least likely to result in later intellectual disability[9]

'Bad' epilepsy predictors

- Children with multiple seizure types
- Children who fail to respond to 2 appropriately chosen drugs at therapeutic doses, i.e. intractable or refractory epilepsy
- Children with structural abnormalities and the presence of additional neurological impairment are more likely to be refractory to treatment[8]
- Intractable epilepsy in children under the age of 2 is often associated with later intellectual disability (ID); seizure types with the greatest probability of ID are myoclonic seizures

Neuroimaging

If neuroimaging is indicated, MRI is the preferred modality but a CT scan is usually sufficient. Urgent neuroimaging should be performed in the following settings:

- status epilepticus without obvious cause[7]
- postictal focal neurological deficit which does not quickly resolve[7]
- a child who does not return to neurological baseline within a few hours after the seizure – the effects of emergency medication used to terminate the seizure should be taken into consideration[7]
- the child with suspected raised intracranial pressure.

Parents should be encouraged to capture the event on their cell phone or via video camera when there is doubt about true epileptic seizures.

Routine imaging should be performed in the following settings:

- a child who is stable and has had a focal seizure of unknown cause[7]
- a child with other unexplained abnormal neurological findings[7]
- a child with significant developmental delay of unknown cause[7]
- children under 1 year of age with an unprovoked seizure.[7]

There is no evidence to support routine imaging after an unprovoked first-time generalised seizure as the sole indication.[4,7]

Is seizure prophylaxis necessary?

The majority of first-time seizures do not need drug treatment. The indiscriminate use of drug therapy may lead to unnecessary side-effects and loss of parental trust. Watchful waiting is usually the most sensible option in the case of an unprovoked first-time seizure, provided the risks of another seizure do not outweigh the risks of treatment. These include cognitive, behavioural, pharmacological and psychosocial risks of long-term therapy to the child. Certain provoked seizures may warrant short-term prophylaxis (approximately 3 months), e.g. neurocysticercosis with multiple lesions and a prolonged first seizure.

Recurrence risks of first-time seizures

The cumulative risk of having a second seizure increases to 42% after 8 years' follow-up. However, data suggest that the majority of recurrences occur within the first 1 - 2 years with only 3% occurring after 5 years.[6]

According to ILAE criteria a 'first seizure' includes multiple seizures within 24 hours but with recovery of consciousness between seizures. Approximately 10% of first-time, unprovoked seizures will present with status epilepticus.[5] Potential risks resulting from a second seizure are a concern but data from studies in children indicate that even prolonged seizures rarely cause discernable brain damage provided there is no underlying neurological insult.[5] Sudden unexpected death in children with epilepsy is uncommon. Sudden unexpected death in children is often related to an underlying neurological handicap rather than epilepsy itself.[5]

An EEG should be requested after 2 or more seizures but may be performed after the first event if it will specifically alter management.

Factors increasing the likelihood of a second seizure include a remote symptomatic cause, younger age at presentation (under 2 years) and focal seizures or focal neurological findings on examination. This correlates with a higher incidence of symptomatic epilepsy. Recurrence rates are lowest in children with no clear aetiology or suspected genetic aetiology (approximately 30%). The overall recurrence risk following a first prolonged seizure appears to be no different to that following a brief seizure; however, any recurrence is also likely to be prolonged.[5]

Early anti-epileptic drug (AED) treatment, i.e. after the first seizure, may reduce the risk of seizure recurrence but has not been shown to improve the prognosis for long-term remission and does not prevent epilepsy.[2,5]

Epilepsy

Diagnosis of epilepsy

- Differentiation of seizures from seizure mimics and classification of seizure types as detailed above
- Determination of the underlying aetiology
- Classification of the epilepsy syndrome
- Selection of anti-epileptic agent if treatment warranted

Determination of the underlying aetiology

Instead of the aetiological terms idiopathic, symptomatic and cryptogenic, the following three categories have been recommended by the ILAE:[8]

- **Genetic:** epilepsy in which no underlying structural brain lesion or other neurological symptoms or signs are present. The epilepsy is due to a presumed or known genetic defect in which seizures

are the core symptom of the disorder and are usually age dependent, e.g. childhood absence epilepsy.

- **Structural-metabolic:** the presence of a distinct structural or metabolic condition that has been demonstrated to be associated with a substantially increased risk of epilepsy. Structural lesions may be acquired, e.g. stroke or trauma; or genetic, e.g. tuberous sclerosis or malformations of cortical development.

- **Unknown cause:** the nature of the underlying cause is unknown; the cause is believed to be symptomatic but no aetiology is as yet identified.

Classification of the epilepsy syndrome

Up to two-thirds of cases can be assigned to specific syndromes at initial diagnosis. Of those remaining about a third will be assigned to more specific categories within the following 2 years.[6] Common or important syndromes that should be recognised early are highlighted in Table II.

Classification and categorisation may assist one in predicting prognosis and response to treatment. In many cases, however, this is only possible in retrospect. See Tables III and IV.

Selection of anti-epileptic agent

Points to consider when deciding on initiation of therapy:

- The decision to treat should be tailored to the individual child.
- Treatment may not be needed in some of the 'benign' epilepsy syndromes such as benign rolandic epilepsy.
- Treatment goals vary according to the epilepsy syndrome; seizure control without adverse drug effects may not be achievable in all and inappropriate polytherapy may lead to unacceptable side-effects without added benefit.
- Approximately 60 - 70% of newly diagnosed epileptics will become seizure free with first or second choice monotherapy.[10]
- New drugs should be trialled for 3 - 6 months and then gradually discontinued if there is poor response. The likelihood of response to each new agent dramatically decreases with each drug failure. Intractability implies epilepsy that is uncontrolled despite the use of 2 appropriately chosen agents at therapeutic dosages.
- Parents should be warned of potentially life-threatening side-effects as well as the more common ones, e.g. Stevens-Johnson syndrome with use of carbamazepine and lamotrigine, both of which should be titrated slowly to lessen this risk.
- Certain drugs should be avoided with specific seizure types, e.g. carbamazepine may exacerbate myoclonus, absences and drops; lamotrigine may exacerbate myoclonus.
- Drug levels are only useful in certain situations, e.g. sodium valproate levels are useful only for determining non-adherence and drug toxicity and should not be used for dose titration.

Who to refer for tertiary opinion

- Children who have atypical features of the traditionally 'benign' epilepsy syndromes, e.g. absences which start before age 4 years
- Any epilepsy patient who does not achieve adequate control on monotherapy, provided the drug is trialled at an adequate dose and compliance is established
- Multiple seizure types
- Children with epilepsy and unexplained developmental delay or intellectual disability

The majority of first-time seizures do not need drug treatment.

Withdrawal of therapy

The belief that all children should be seizure free for at least 2 years has been challenged in recent years. There is evidence that in children with 'benign epilepsies' AEDs may be withdrawn if they have been free of seizures for a period of between 6 and 12 months.[12] However, as a general rule a seizure-free period of 2 years should be attained before considering drug therapy withdrawal (exceptions include the child with a focal lesion such as neurocysticercosis who has been started on short-term prophylaxis, as discussed above).

The relapse rate after AED withdrawal is approximately 30% at 2 years overall, with 50% of these occurring during the period of drug withdrawal.[12] Aetiology and syndromic diagnosis are the main predictive factors.[9] Recurrence risk is lowest in children with childhood absence epilepsy and benign focal epilepsy of childhood and highest in those with symptomatic seizures or history of Todd's paresis following seizures.[12]

If the child is on multiple AEDs, they should be withdrawn sequentially, i.e. one at a time. Withdrawal of medication should occur gently over a period of 6 weeks. If seizures recur during this period the dose of the AED being withdrawn should be stepped up to the dose prior to the current stepped-down dose.

References available at www.cmej.org.za

IN A NUTSHELL

- Seizures in childhood are one of the most frequently encountered problems in general paediatric practice.
- Epilepsy is the commonest condition managed in paediatric neurology clinics.
- There are a number of seizure mimics.
- The diagnosis and management require a stepwise approach to avoid unnecessary investigations and an incorrect label of epilepsy.
- A thorough neurological examination is essential in any child with a first-time seizure.
- An EEG is usually only warranted after the second seizure.
- Infantile spasms are a neurological emergency and should be managed promptly to avoid severe neurological sequelae.
- Patients with complex or intractable epilepsy should be referred for specialist management.