

Highlight and Opinion

Managing childhood epilepsy in a resource-limited setting: A pragmatic approach

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ABSTRACT

Epilepsy is a complex neurological disorder. Its burden constitutes a major public health problem in resource-limited countries like Sudan. When it affects children, the challenges surrounding its diagnosis and management are enormous resulting in large numbers of patients missing out on adequate treatments. Epilepsy has the potential of not only adversely affecting the physical health of children but of also impacting negatively on their emotional, cognitive and social well-being. A pragmatic approach based on sound clinical skills of how to accurately diagnose epilepsy, as a priority, coupled with the choice of a cost-effective, wide spectrum and efficient anti-epileptic drug, is recommended.

Key words:

Childhood epilepsy; Resource-limited countries; Management; Anti-epileptic drugs.

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INTRODUCTION

The word epilepsy is derived from a Greek word meaning “a condition of being overcome, seized or attacked”. Interestingly, the Arabic synonymous “الصرع” is translated in English to “to be knocked down” which reflects the ancient name “the falling sickness” so called because the patient suddenly falls to the ground [1].

A seizure is defined as a paroxysmal alteration of neurologic function caused by the abnormal discharge from cortical neurons in the brain. The term ‘epileptic seizure’ is used to distinguish a seizure caused by abnormal neuronal firing from a paroxysmal non-epileptic event such as a psychogenic seizure or syncope and from symptomatic seizures caused by direct causes such as hypoglycaemia or head injury. Epilepsy, in the broader sense, refers to the clinical condition in which there is a tendency to have recurrent epileptic seizures. It is essential to recognize that epilepsy is not a single disorder but rather a group of different syndromes with specific defining features. Many authors thus prefer to use the term ‘epilepsies’ in order to emphasize the heterogeneity of the condition. An epilepsy syndrome is defined as a complex of symptoms and signs (including investigational findings) that define a unique epilepsy condition [2].

In this review, challenges facing the satisfactory management of childhood epilepsy in resource-limited settings, Sudan as an example, along with a practical guide on epilepsy investigation and treatment are presented. Management of neonatal seizures and status epilepticus is not included.

The epilepsy burden: how heavier could it be?

Epilepsy is a major public health problem. Worldwide, more than 50 million people suffer from epilepsy with over 80% of them living in developing countries [3]. In

a report published by the World Health Organization (WHO), epilepsy was considered the second or third neurological reason for hospital admission or to consult a neurologist in Africa [3]. The WHO also estimates that epilepsy affects at least 10 million people in Africa [3]. Inadequate perinatal care and the high rate of central nervous system infections in rural Africa are leading causes. In Uganda, for example, epilepsy incidence is 159 per 100,000 [3] and in Senegal, the prevalence of epilepsy was estimated to be 14.2/1000 in one study [4].

A recent systematic review of the epidemiology of epilepsy in Arab countries (namely, Tunisia, Libya, Saudi Arabia and Sudan) found the median prevalence of epilepsy to be 2.3 per 1000 [5]. Cerebral palsy and infections were reported among the commonest aetiological factors. In this review, only two studies from Sudan were identified. The first study was by Younis in 1983, who conducted a survey among the entire school population in the so called then ‘Khartoum Province’, estimated a prevalence of 0.9 per 1000 [5,6]. A subsequent study conducted in 2004 in South Sudan estimated the prevalence to range between 10.6 to 21.2 per 1000 population [5].

There is a large number of patients with active epilepsy who are not on treatment or are receiving inadequate therapy, a phenomenon known as the ‘treatment gap’. This was estimated in a systematic review to be 49% in Africa and in rural communities to be as high as 73% [7]. Main reasons for treatment gap cited were high cost of treatment, non-availability of anti-epileptic drugs (AEDs) and belief in superstitious explanations and traditional treatments [7].

Epilepsy has the serious potential of negatively impacting on the child’s physical, emotional, cognitive and social well-being. This effect may also extend to the whole family. Not surprisingly, a recent study by Abbas et al [8] showed that the quality of life in a group of Sudanese children with epilepsy and their caregivers was significantly low.

Epilepsy management challenges

Paediatricians treating children with chronic conditions in resource-limited countries are commonly faced with a multitude of challenges. Poverty, illiteracy, social taboos and fragmented healthcare systems are common denominators. Unlike most other childhood chronic diseases, epilepsy has its unique notorious reputation. This is partly due to the fact that it is commonly conceptualized by many as a primarily psychiatric disease. Moreover, symptomatic epilepsy can coexist with 'socially-embarrassing' conditions such as learning disabilities and cerebral palsy. Ironically, many childhood epilepsy syndromes can spontaneously remit whereas no 'cure' as such exists for other more 'socially-acceptable' lifelong conditions like diabetes.

Commonly, there is a negative public attitude towards

epilepsy intermingled with prejudice and myths. In Senegal, for instance, over half of those interviewed in one study agreed that epilepsy is caused by some 'evil spirit' and more than one third believed that epilepsy is contagious [4]. In a study from southern India, 27% of the respondents thought that epilepsy is a mental illness and 11% did not want their children to play with a child with epilepsy [9]. Mohammed and Babikir conducted a cross sectional study in the two largest cities of Sudan (Khartoum and Wad Madani) amongst the caregivers of children with epilepsy. One-third of their sample thought that epilepsy was caused by supernatural powers and more than two-fifths thought that spiritual and / or traditional treatments were effective in the management of epilepsy [10]. A summary of the main treatment challenges of epilepsy is presented in Box 1 below.

Box 1- Main challenges facing paediatricians treating children with epilepsy in a resource-limited setting

- > Widespread poverty and illiteracy
- > Social stigma, misconceptions and potentially harmful traditional practices
- > Lack of public awareness and negative attitudes
- > Diagnostic challenges:
 - Fragmented health system
 - Paucity of specialized epilepsy services
 - Poor knowledge and clinical skills
 - Epilepsy is likely to be confused with other paroxysmal conditions
 - Non-availability (and affordability) of diagnostic investigations
 - Reliability of investigations, when available, is often questionable
- > Anti-epileptic drugs (AEDs) therapy:
 - Not many AEDs to choose from
 - Relatively high cost especially the newer AEDs
 - Inconsistent sustainability of AEDs supply in the market
 - Poor adherence due to side effects (e.g. sleepiness), affordability, length of treatment not explained by doctors, polypharmacy and psychosocial factors (e.g. peer group pressure)
- > Inadequacy of non-drug therapies:
 - Limited availability and efficiency of paediatric epilepsy surgery programmes
 - Unavailability of the ketogenic diet

THE CLINICAL APPROACH

First things first: *is it epilepsy?*

Unfortunately, epilepsy is commonly overdiagnosed and some authors estimated the rates to be as high as 30% even in resource-rich countries [11]. This is mainly due to poor clinical skills and knowledge and the fact that epileptic syndromes have a large differential diagnosis [11,12]. Paroxysmal neurological or non-neurological events in children and adolescents are commoner than epileptic seizures. One of the reasons why epilepsy misdiagnosis is common is the occasional difficulty in recognizing these non-epileptic events.

Therefore, the most helpful approach is of an informative history from an eye witness combined, whenever possible, with a video recording caught on a mobile phone camera for instance. It is commonly advised that where uncertainty exists, delaying treatment whilst adopting a watchful eye policy is probably far less harmful than initiating (or maintaining) treatment on a rushed 'just-in-case' basis.

Role of the EEG

Over-reliance on investigations such as the standard electroencephalogram (EEG) can be contributory to the problem of over diagnosing epilepsy. Non-specific EEG abnormalities can be seen in normal children and a normal inter-ictal EEG does not exclude epilepsy on the other hand. In fact, the commonly asked question 'is it epilepsy?' can rarely be answered by a 20-minute or so EEG recording; making this an inappropriate request on most occasions [2].

Once a diagnosis of an epileptic seizure is established from a good history and/or a video account, an EEG is needed. This is to serve the purpose of making a syndromic classification; a piece of information helpful in deciding the choice of the AED as well as informing prognosis. The EEG may also clarify if

there is doubt from the history whether the seizure onset is focal. For instance, persistent localized EEG discharges may point towards a structural cortical lesion that warrants neuroimaging.

The availability of reliable neurophysiology services where resources are scarce may be a hindrance to managing children with epilepsy effectively. Not uncommonly, paediatricians will rely on their clinical acumen to decide on diagnostic and treatment issues without the help of an EEG. In such circumstances, following a simple basic classification of the predominant seizure type into generalized convulsive seizures (tonic, clonic, atonic- in any combination), focal-onset seizures, myoclonic seizures, absence seizures and epileptic spasms can guide treatment decisions efficiently (Figure 1).

To scan, or not to scan?

Neuroimaging is most helpful in addressing the question of 'what is the cause of this child's epilepsy?' thus aiding the process of making a syndromic diagnosis. For example, in an infant presenting with epileptic spasms and developmental stagnation who is found to have hypsarrhythmia on EEG with his/her brain MRI showing cortical tubers and subependymal nodules, a firm diagnosis of 'West syndrome' secondary to 'tuberous sclerosis' is then made. In other circumstances, imaging is helpful in detecting tumours, cortical and vascular malformations, neuro-infection, hippocampal sclerosis and perinatal or acquired brain injuries.

MRI is more sensitive and specific than CT. Current guidelines recommend imaging children with epilepsy according to the following criteria:

- Onset of seizure under 2 years.
- Either history or EEG suggestive of focal seizures with the exception of benign childhood focal epilepsies.

- Refractory- to – treatment seizures.

Unfortunately, facilities for MRI in Africa are inadequate and only available in 26% of the countries according to one study [13]. It is a costly investigation that needs general anaesthesia in most young children. Furthermore, the standards of specific `epilepsy protocols` for acquisition of MRI images are rarely applied along with the lack of the expertise of a trained paediatric neuroradiologist. Except for the suspicion of treatable neuro-infections such as tuberculomas or neurocysticercosis or of a surgically resectable brain lesion, a selective judgement is to be exercised by the treating paediatrician.

PRINCIPLES OF TREATMENT

Just like in other chronic conditions, management of epilepsy should be holistic aiming at maximizing the physical, emotional, educational and social potentials of the child. Ideally, the ultimate goal of drug therapy is seizure-freedom with no side effects. The rationale behind treating epilepsy is twofold: to prevent injuries and to foster psychosocial and cognitive wellbeing. An adult hospital-based Sudanese study found that nearly 9% of the study group had scars due to repeated convulsions [14]; a figure which is perhaps an underestimate given the limitations of that study. A recent community survey in 5 African countries identified more than 2000 patients with epilepsy, half of whom were children and over two-thirds had their epilepsy onset during childhood [15]. Status epilepticus occurred in 25% of the patients, and up to 16% had burns as a consequence to their active convulsive seizures. Common comorbidities were malnutrition, neurologic deficits, cognitive impairment and lack of education [15]. On the other hand, the child who has daily typical absence seizures is not at risk of injury per se but of school failure.

Anecdotally, controlling seizures leads to an improvement in social participation, self confidence

and cognitive abilities. Any child with epilepsy should be able to go to school and to lead as normal life as possible. Babikar and Abbas [16] surveyed a sample of school teachers in Gezira State, Sudan, and found that 80% believed that parents should not send their children with epilepsy to school and 90% of the respondents said that they would not allow these children to participate in sports. In some regions in Nigeria, paediatricians and community nurses visit the school of the child diagnosed with epilepsy to provide adequate explanation to staff and to ensure that support is provided to the child which is an integral part of the management plan of that particular child (personal communication). Vigorous campaigns aiming to increase the community awareness and demystify myths about epilepsy are desperately needed. Needless to say, community-based epilepsy care programs, when implemented, will increase access to treatment and significantly improve the likelihood of those affected by the disease.

Should epilepsy *always* be treated?

The risk of having a second unprovoked seizure is commonly quoted to be around 50% and consideration for commencing AED treatment is usually given after 2 seizures. Realistically, AEDs offer seizures `control` rather than `cure` and on average two out of three patients will have their seizures controlled with at least one AED.

If the clinician is able to make a syndromic diagnosis based on the clinical and EEG data this decision becomes easier. In children with benign Rolandic epilepsy, the paediatrician and the parents may jointly elect not to start AEDs given the seizure infrequency and the commonly favourable prognosis. On the other hand, in children with symptomatic epilepsy, secondary to a cortical malformation for instance, long-term AED treatment is likely to be needed. Box 2 provides an overview of the practicalities surrounding commencing drug therapy.

Box 2- Practicalities of anti-epileptic drugs (AEDs) treatment

- > Always aim for a high degree of diagnostic accuracy; there is no place for `therapeutic trials`!
- > Ensure chosen AED is the right drug for the right seizure type, right syndrome (if possible) and right patient.
- > Know chosen AED's side effects and counsel parents/ patients accordingly.
- > Be realistic: explain that there may not be an instant response when starting AED treatment.
- > Be `market-aware`: know costs of different AEDs, their current availability and the family's affordability.
- > Prescribe convenient doses; simplify by rounding up or down.
- > Once or twice daily dosing is commonly used.
- > Always start with one AED at a small dose and increase gradually in weekly or two weekly increments to avoid side effects. Give clear instructions.
- > Most patients will need to continue treatment for at least 1-2 years of seizure-freedom. Exceptions to this include juvenile myoclonic epilepsy and symptomatic epilepsies.
- > Adhere to one brand and formulation as much as feasible throughout the treatment course to avoid fluctuating bioavailability.
- > Avoid sudden cessation of AEDs except in cases of hypersensitivity reactions (e.g. skin rash with carbamazepine/ lamotrogine)
- > If asked for (or already initiated), do not antagonize `harmless` spiritual/ traditional treatments besides AED therapy.
- > Only consider adding on another AED if the maximum dose of first AED is reached or unacceptable side effects experienced.
- > If a patient had already failed 2 AEDs, adding a third is unlikely to be beneficial.

Choosing an AED: *is old still as good as gold?*

Broadly speaking, the choice of an AED is dependent on the seizure type (for example, sodium valproate for myoclonic seizures but not carbamazepine as it can exacerbate them), the epilepsy syndrome, concomitant drugs and the age of the patient. Figure 1 below

illustrates a suggested treatment algorithm that aims at cost-effectiveness while maintaining efficiency. Evidence supporting these recommendations is presented in the following paragraphs.

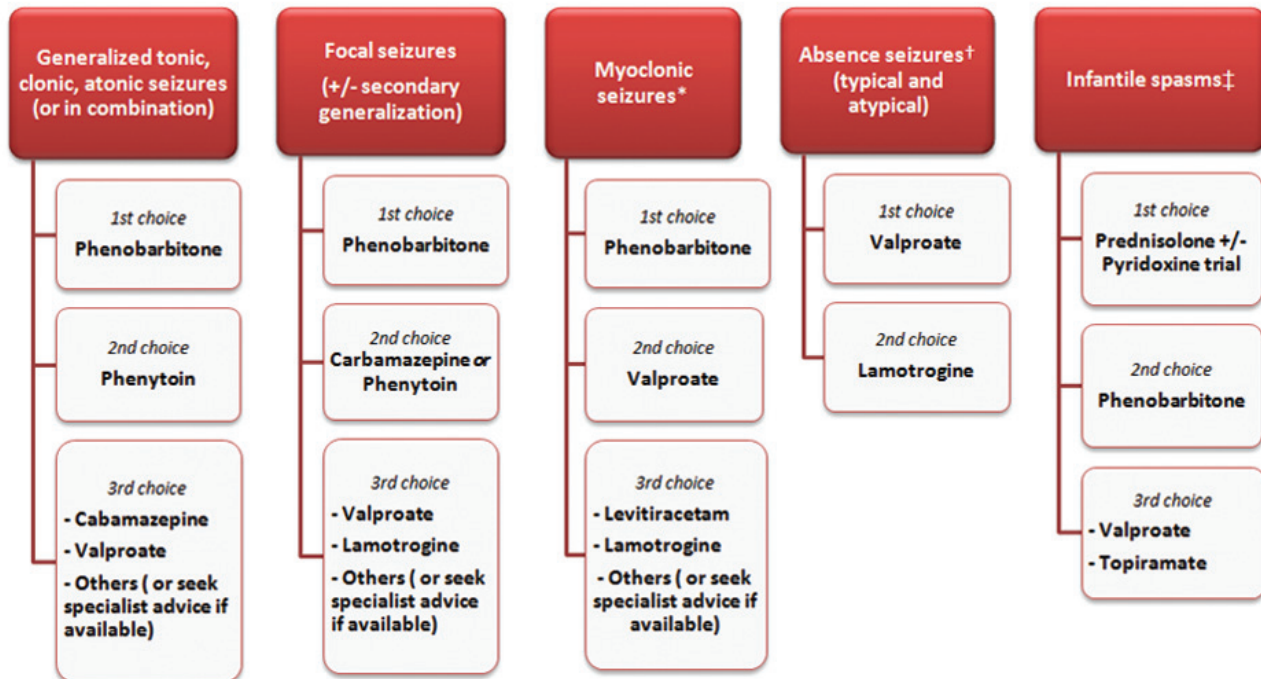


Figure 1 - A suggested algorithm for treating different epileptic seizure types using available and cost-effective anti-epileptic drugs in a resource-limited setting. Different seizures can occur in the same patient and when data is not available regarding a syndromic diagnosis, an approach of targeting the prominent seizure type is recommended.

* Avoid carbamazepine, gabpentin and oxcarbazepine.

† Avoid carbamazepine and phenytoin. Phenobarbitone is ineffective in typical absences but can be used in atypical absences.

‡ Use high-dose oral prednisolone i.e. 10 mg four times a day for 14 days with a gastric protecting agent (e.g. ranitidine). If spasms disappear (or the EEG is normalizing) wean by reducing daily dose by 10 mg every 5 days. Consider a 1-2 week trial of pyridoxine (50-100 mg twice daily) if there is additional seizure type or no apparent aetiology. For further information visit www.iciss.org.uk.

In the developed world, there are currently over 25 licensed AEDs in clinical practice, and the list is expanding with more drugs in trial phases now (e.g. cannabinoids). In contrast, old AEDs are more prevalent in developing countries, so to speak. These

include phenobarbitone, carbamazepine, phenytoin, sodium valproate and benzodiazepines. Registered AEDs in Sudan are listed in Table 1. Table 2 provides a brief guide to using some of the important AEDs individually.

Table 1- Registered anti-epileptic drugs in Sudan (as of December 2014)*

Drug	Registered formulation and strength	
Carbamazepine	Tablets	200mg and 400mg CR prolonged-release
	Liquid	100mg/5ml syrup
	Suppositories	Not registered
Clonazepam	Tablets	0.5mg, 2mg
	Liquid	2.5mg/ml oral drops
Diazepam	Tablets	5mg , 10mg
	Liquid	Not registered
	Injection	10mg/2ml
Gabapentin	Capsules	100mg, 400mg
	Liquid	Not registered
Lamotrigine	Tablets	25mg, 50mg, 100mg
Levetiracetam	Tablets	250mg, 500mg, 750mg , 1000mg
	Liquid	100mg/ml syrup
	Injection	Not registered
Lorazepam	Tablets	1mg, 2mg
	Liquid	Not registered
	Injection	Not registered
Midazolam	Liquid	Buccal form not registered
	Injection	5 mg/ml
Oxcarbazepine	Tablets	150mg, 300mg, 600mg
	Liquid	60mg/ml suspension
Phenobarbitone	Tablets	30mg
	Liquid	Not registered
	Injection	Not registered
Phenytoin sodium	Tablets	100mg
	Liquid	30mg/ 5ml suspension
	Injection	250mg/5ml
Pregabalin	Capsules	50mg, 75mg, 100mg, 150mg, 300mg
Sodium valproate	Tablets	200mg, 500mg
	Liquid	200mg/5ml syrup
	Injection	Not registered
Topiramate	Tablets	25mg, 50mg, 100mg, 200mg

*Note that availability can be variable.

Table 2- A brief guide to the paediatric use of commonly available anti-epileptic drugs in Sudan

Drug	Dose titration	Main side effects	Comments
Phenobarbitone (PHB)	<ul style="list-style-type: none"> Initially 1mg-1.5mg/kg twice daily. Can be increased by 2mg/kg/day weekly until maintenance dose 2.5mg – 4mg/kg once or twice daily if seizures persist. Maximum 8mg/kg or 180mg daily. 	<ul style="list-style-type: none"> Drowsiness, unsteadiness Irritability Behaviour disturbances and hyperactivity 	<ul style="list-style-type: none"> When needed, withdraw slowly over months. Valproate can increase plasma PHB levels. Risk of foetal teratogenicity
Carbamazepine (CBZ)	<ul style="list-style-type: none"> Initially 5mg/kg at night or 2.5mg/kg twice daily. Can be increased (as necessary) by 2.5mg-5mg/kg weekly up to a maximum of 30mg/kg daily in two divided doses. Round dose up to the nearest half tablet or 0.5ml liquid. 	<ul style="list-style-type: none"> Rash – should be seen by doctor and medication discontinued as can cause Stevens–Johnson syndrome. Drowsiness/dizziness/double vision – can sometimes be managed by reducing dose then more gradual titration Leucopenia and hepatitis can rarely occur. 	<ul style="list-style-type: none"> Withdraw routinely at a rate of 5-10mg/ kg every two weeks. Erythromycin can increase the level of CBZ. Exacerbates myoclonic and absence seizures and should be avoided.
Phenytoin (PHT)	<ul style="list-style-type: none"> Start at 1.5- 2.5mg/kg twice daily. Increase to maintenance dose 4mg – 8mg/kg twice daily if seizures persist. Maximum daily dose is 300 mg 	<ul style="list-style-type: none"> Drowsiness, unsteadiness, slurred speech Occasional abnormal movement disorders (choreiform, athetoid) Allergic reactions: rash, swelling of lymph glands, hepatitis, fever, mouth ulcers Chronic use may lead to coarsening facial features, gingival hypertrophy and cerebellar atrophy. 	<ul style="list-style-type: none"> Use with caution in absence and myoclonic seizures Enteral feeding should be stopped for 1-2 hours before and after oral PHT to enable full absorption. Plasma concentration of PHT can be increased or decreased by CBZ.
Sodium valproate (SVP)	<ul style="list-style-type: none"> Begin at a dose of 10 mg/kg/day divided into two daily doses. Increase by 10mg/kg/day weekly until a dose of 20-40mg/kg/day is reached. Maximum 2g daily in teenagers if necessary and tolerated. 	<ul style="list-style-type: none"> Weight gain (affects 30%) Drowsiness, confusion, irritability, Nausea, vomiting Hair loss - thinning or alopecia. If hair grows back on treatment, it may be curly and coarse but will normally grow on discontinuation of treatment, Tremors Thrombocytopenia – warn parents to look out for excess bruising 	<ul style="list-style-type: none"> Given with caution to under 2 years (especially if a metabolic disorder is possible as it may exacerbate the condition). Metabolism of lamotrigine is decreased slightly more than 2 fold by SVP – lamotrigine dose should be decreased by 50% if SVP added.

Despite being fashionable to prescribe newer AEDs because of their theoretical better tolerability, there is emerging evidence suggesting that older ones still have a major role to play. A large head-to-head unblinded trial in the UK found that sodium valproate was more efficacious in controlling generalized and unclassified seizures when compared to the newer AEDs topiramate and lamotrigine [17].

Phenobarbitone (also known as phenobarbital) is the oldest and the cheapest AED in clinical practice today. It is effective in a wide spectrum of seizures (Figure 1). Despite its efficacy, recent decades saw a decline in its use in the Western world due to concerns raised by some studies regarding its cognitive and behavioural side effects [18]. However, those studies used high doses in the phenobarbitone arm [18]. Moreover, systematic reviews of randomized controlled trials provided evidence for its long-term tolerability and efficacy in children in the developing world [18,19]. A series of large prospective population-based studies in rural China demonstrated that more than two-thirds of the patients with convulsive seizures had significantly

benefited from phenobarbital monotherapy [20]. Based on the evidence currently available for its safety and efficacy, the WHO recommends using phenobarbitone as a first line therapy for epilepsy in resource-poor countries [21].

CONCLUSION

Epilepsy in resource-limited countries, Sudan being an example, continues to be a major public health problem with a considerable gap in its treatment. Despite many great challenges hindering its efficient management, paediatricians have a vital role in reducing the burden of epilepsy. Sensible decisions regarding accurate diagnosis, rational utilization of investigations when required and the use of cheap and affordable yet efficient AEDs, such as phenobarbitone, are at the heart of their role. Wide scale health education programmes to improve public knowledge, attitude and practices should be high on the agenda of most child health promoting initiatives. Box 3 summarizes key points regarding these issues.

Box 3- Key points in managing childhood epilepsy in a resource-limited setting

- > A considerable number of children with epilepsy living in resource-poor countries receive inadequate or no treatment.
- > Diagnostic accuracy of epilepsy depends, in most occasions, on good history taking skills thus minimizing the need for costly investigations or unnecessary treatments.
- > Although a syndromic diagnosis is helpful, it is not always feasible, and a pragmatic classification based on seizure type can guide the choice of anti-epileptic drugs.
- > Phenobarbitone offers a cost-effective, efficacious and safe option in treating a wide range of childhood epilepsies.

REFERENCES

1. Noah Webster, Webster's 1828 American Dictionary from Webster's Online Dictionary. Available at <http://websters-online-dictionary.org/>. Accessed 25/12/11.
2. Engel J, Chair JR. Report of the ILAE classification core group. *Epilepsia* 2006; 47:1558–1568.
3. The Global Campaign against Epilepsy "Out of the Shadows", Epilepsy in the WHO African Region: Bridging the gap, WHO Publications; 2004.
4. Ndoye NF, Snow AD, Diop AG et al. Prevalence of epilepsy its treatment gap and knowledge, attitude and practice of its population in sub-urban Senegal an ILAE/IBE/WHO study. *Seizure* 2005; 14:106–111.
5. Benamer H, Grosset D. A systematic review of the epidemiology of epilepsy in Arab countries. *Epilepsia* 2009; 50:2301–2304.
6. Younis YO. Epidemiology of epilepsy among school populations in Khartoum Province, Sudan. *J Trp Med Hyg* 1983; 86:213-216.
7. Mbuba CK, Ngugi AK, Newton CR, Carter JA. The epilepsy treatment gap in developing countries: a systematic review of the magnitude, causes, and intervention strategies. *Epilepsia* 2008; 49:1491–1503.
8. Abbas Z, Elseed MA, Mohammed IN. The quality of life among Sudanese children with epilepsy and their care givers. *Sudan J Paediatr* 2014; 14:51-58.
9. K. Radhakrishnan K, Pandian DJ, Santhoshkumar T, Thomas SV, Deetha TD, Sarma PS, et al. Prevalence, knowledge, attitude, and practice of epilepsy in Kerala, south india. *Epilepsia* 2000; 41:1027–1035.
10. Mohammed IN, Babikir HE. Traditional and Spiritual medicine among Sudanese children with epilepsy. *Sudan J Paediatr* 2013; 13:31-37.
11. Chowdhury FA, Nashef L, Elwes RD. Misdiagnosis in epilepsy: a review and recognition of diagnostic uncertainty. *Eur J Neurol* 2008; 15):1034-1042.
12. Ferrie CD. Preventing misdiagnosis of epilepsy. *Arch Dis Child* 2006; 91:206-209.
13. Dua T, de Boer HM, Prilipko LL, Saxena S. Epilepsy care in the world: results of an ILAE/IBE/WHO global campaign against epilepsy survey. *Epilepsia* 2006; 47:1225–1231.
14. Mohamad AH, Mohmad AE, Omer FY, Abdulgalil AS, Ahmad EM, Aldar MM. Dermatological manifestations of epilepsy among adult Sudanese epileptic patients. *Neurosciences (Riyadh)* 2008; 13:259-262.
15. Kariuki SM, Matuja W, Akpalu A, Kakooza-Mwesige A, Chabi M, Wagner RG, et al. Clinical features, proximate causes, and consequences of active convulsive epilepsy in Africa. *Epilepsia* 2014;55:76-85.
16. Babikar HE, Abbas IM. Knowledge, practice and attitude toward epilepsy among primary and secondary school teachers in South Gezira locality, Gezira State, Sudan. *J Fam Community Med* 2011; 18:17-21.
17. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet*. 2007; 369:1016-1026.
18. Brodie MJ, Kwan P. Current position of phenobarbital in epilepsy and its future. *Epilepsia* 2012; 53: 40–46.
19. Pal DK. Phenobarbital for childhood epilepsy: systematic review. *Paediatr Perinat Drug Ther* 2006; 7:31–42.

20. Kwan P, Wang W, Wu J, Li S, Yang H, Ding D et al. Long-term outcome of phenobarbital treatment for epilepsy in rural China: A prospective cohort study. *Epilepsia* 2013; 54:537–542.
21. Ilangaratne NB, Mannakkara NN, Bell GS .Phenobarbital: missing in action. *Bull World Health Organ.* 2012; 90:871–871A.