Review Article

EPILEPSY: A FAMILY PHYSICIAN' PERSPECTIVE

Rahila Ali[1], Hemna Siddiqui[2], M. Ishaq Lohar[3]

SUMMARY

Epilepsy is characterized by the occurrence of at least two unprovoked seizures. Seizures occur due to abnormal hypersynchronous discharges of cortical neurons and the clinical features depend upon the location and extent of the propagation of the discharging neurons. Family physician should be able to initiate management, alleviate misunderstandings and refer appropriately when required.

For this review, literature search was done on PubMed. Only those articles which were related to the family physicians need were selected. They were further reviewed by the authors and data concerning common problems faced by family physicians was extracted and synthesized.

This article reviews the definition of common terminology to describe seizures, classifications, clinical manifestations and complications along with the evaluation and management of epileptic seizures.

KEY WORDS: Epilepsy, Seizures and Family practice.

Pak J Med Sci July - September 2006 Vol. 22 No. 3 356-362

INTRODUCTION

Seizures occur due to abnormal hypersynchronous discharges of cortical neurons and the clinical features depend upon the location and extent of the propagation of the discharging neurons.[1] Epilepsy is a common disorder with a worldwide incidence of 0.3–0.5%. It is characterized by occurrence of recurrent seizures secondary to disease or dysfunction of the central nervous system.[2] The understanding of epilepsy has been made difficult by terminologies used synonymously or concurrently, which are:

1. Dr. Rahila Ali MCPS
Senior Registrar
2. Dr. Hemna Siddiqui MCPS, FCPS
Asssitant Professor
3. Dr. M. Ishaq Lohar MCPS
Senior Registrar
1-3: Department of Family Medicine,
Ziauddin Medical University, Karachi.

Correspondence:

Dr. Rahila Ali
66/2, 12th Street, Khayaban-e-Badban,
Phase-V, Defence Housing Authority,
Karachi.
E-Mail: drrahali@hotmail.com

* Received for Publication: August 27, 2005

* Accepted: January 28, 2006

Seizure: It results from an excessive discharge of neurons characterized by abnormal electrical discharge/activity as measured by the electroencephalogram (EEG).[3,4] It results due to the shift in the normal balance of excitation and inhibition within the CNS and is an observable phenomenon that is finite in time.[5]

Convulsion: It is defined as violent, involuntary contractions or series of contractions of the voluntary muscles. Epilepsy can occur with or without convulsions.[4]

Status epilepticus: Multiple epileptic seizure occurring without complete recovery.[4]

Incidence: Epilepsy is the most common serious neurological disorder affecting an estimated 50 million people worldwide.[6] The lifetime likelihood of experiencing at least one seizure (febrile/non-febrile) is about 9%,[1] and being diagnosed as having epilepsy is almost 3%.[1,7,8]

Etiology: Epilepsy in many cases is hereditary and many forms of generalized epilepsy have a strong genetic component.[9] Seizures can result from multiple etiologies ranging from hereditary, vascular, traumatic and neoplastic causes.[3] In majority of cases, no cause is identifiable. Primary or idiopathic epilepsy is the most common cause in the young while after the age of thirty years secondary epilepsy

is more common.[3] Head trauma is significant when associated with unconsciousness lasting longer than 30 minutes.[2,10] The etiology according to age group is presented in Table-I.

RECURRENT SEIZURES OTHER THAN EPILEPSY:

Epilepsy is onset of recurrent seizures, but non-epileptic seizures may occur due to precipitating factors like:[2,3]

Organ failure, electrolyte imbalance, medication, missed doses or drug withdrawal encephalopathy, opportunistic infections, immunosuppressive therapy, Metabolic isorders (hypoxia, hypoglycemia, alcohol withdrawal, stimulant drugs and ionic imbalances), sleep deprivation, irregular eating patterns, hyperventilation, menses (catamenial) and sensory stimuli e.g. photosensitivity.

CLASSIFICATION OF EPILEPTIC SEIZURES

In 1981, the International League against Epilepsy (ILAE) developed an International Classification of Epileptic Seizures. Specific seizures are classified according to their clinical features (e.g. complex partial seizures and generalized tonic–clonic seizures).[11] Epilepsy syndromes can also be classified according to the type of seizure, the presence or absence of neurological or developmental abnormalities, and electroencephalographic (EEG) findings.[12]

Table-I: Etiology of Epilepsy according to age group[2]

Neonates	*Infants & Children*
Prenatal hypoxia and ischemia	Idiopathic
Intracranial hemorrhage and trauma	Genetic disorders
CNS infection	CNS infection
Metabolic disorders	Trauma
Genetic disorders	Developmental disorders
Drug withdrawal	Fever
Adolescents and YoungAdults	*Older Adults*
Trauma	Trauma, CVD
Genetic disorders	Brain tumor
Infection	Alcohol withdrawal
Brain tumor	Metabolic disorders
Drug use	Alzheimer's disease / degenerative CNS disease
Idiopathic	Idiopathic

ILAE (International classification of epileptic seizures)

1. Partial (focal) seizures:

A. Simple Partial Seizures (consciousness not impaired)

1. With motor signs (including jacksonian, versify, postural).
2. With sensory symptoms (including visual, somtosensory, auditory, olfactory, gustatory and vertiginous).
3. With psychic symptoms (including dysphasia, dysmnesic, hallucinatory and affective changes).
4. With autonomic symptoms (including epigastric sensation, pallor, flushing and papillary changes).

B. Complex partial seizures (consciousness is impaired)

1. Simple partial onset followed by impaired consciousness.
2. With impairment of consciousness at onset.
3. With automatism.

C. Partial seizures evolving to secondarily generalized seizures

2. Generalized seizures of nonfocal origin (conclusive or nonconclusive):

A. Absence seizures

1. With impaired consciousness only.
2. With one or more of the following: atonic components, tonic components, automatism and autonomic components.

B. Myoclonic seizures

1. Myoclonic jerks (single or multiple).
2. Tonic-clonic seizures (may include clonic-tonic-clonic seizures).
3. Tonic seizures.
4. Atonic seizures.

3. Unclassified epileptic seizures:

The characteristic features of Generalized and Partial seizures types is given in Table-II

FEBRILE SEIZURES

Febrile seizure although not epilepsy[3] is the commonest paediatric neurological symptom. Febrile convulsions are provoked by fever of

Table-II: Seizure type and characteristics[5]

Seizure type	*Characteristics*
Generalized	
Grand mal	Unconsciousness, convulsions, muscle rigidity
Absence	Brief loss of consciousness
Myoclonic	Sporadic (isolated) jerking movements
Clonic	Repetitive, rhythmic jerking movements
Tonic	Muscle stiffness, rigidity
Atonic	Loss of muscle tone
Partial	
Simple (awareness is retained)	
Motor symptoms	Jerking, muscle rigidity, spasms, head-turning
Sensory symptoms	Unusual sensations affecting vision, hearing, smell, taste or touch
Autonomic symptoms	Stomach sensation
Psychologic symptoms	Memory or emotional disturbances (e.g., déjà vu, fear)
Complex (impairment of awareness)	Automatism such as lip smacking, chewing, fidgeting, walking and other repetitive, stereotyped movements
Partial seizure that becomes generalized seizure	Begins as partial (simple or complex) and evolves into grand mal seizure

extracranial infective origin that occur in at least 3–4%[2,13-15] of children, febrile seizures are age dependent, and rare before 9 months and after 5 years, peak age is between 14-18 months.[15] Data from large cohorts of children with febrile seizures indicate that in 2% to 10% of children who have febrile seizures, unprovoked seizures or epilepsy will subsequently develop. In most studies, the risk of developing epilepsy after simple febrile seizures is only mildly elevated compared with the risk for the general population. On the contrary, complex febrile seizures are clearly associated with an increased risk of subsequent epilepsy. Prolonged febrile seizures, particularly very prolonged febrile seizures and febrile status epilepticus (SE), are associated with a substantially elevated risk for future epilepsy.[2,14,16]

The seizures are usually Simple, brief (<10–15 minutes), bilateral clonic, or tonic-clonic attacks.[14] Commonly a single episode of generalized variety occurs. There is a history of fever of less than 24 hours duration. About 10% of children have complex seizures, lasting longer than 10 to 15 minutes, are of partial type and are usually multiple. Fever is also prolonged (>24 hours).

In all seizures intracranial infection must be excluded. In a simple febrile seizure, a focus is identifiable like otitis media or respiratory infection. Further workup is not required and it is not associated with a future risk of epilepsy. In a complex febrile seizure, further work up is essential and it is associated with 2 to 5 % risk of epilepsy.[2]

Complications: The complications which can be encountered include: Status Epilepticus, Injury from fall, bumps, self-inflicted injury like tongue bites, injury if a seizure happens while driving, operating machinery, working at height or near water, fractures, evulsions, injuries due to violent contractions, seizing person may inhale fluid leading to aspiration pneumonia, permanent brain damage, depression, learning difficulties, behavior disorders interference with cognitive and social development particularly in children,[15] Side effects of medications and Social stigma.

EVALUATION AND MANGEMENT

Management includes first aid, psychosocial aspect, alleviating the misunderstandings and reassurance. Diagnosis is both essential and difficult, there is no diagnostic test and yet there are numerous possible reasons for the loss of, or impairment of consciousness.

An incorrect diagnosis of a seizure disorder can have many negative consequences including expensive and potentially toxic medication regimens, loss of driving privileges, and loss of work.[17]

History: The key questions to answer during evaluation are:

* Was it a seizure? If so which type? Is it likely to recur?
* Is it primary or secondary with underlying pathology?[1,3]

The following suggested set of questions both from witness and patient would help answering these key questions.[1]

* Was there any warning just before the attack?
* Did anyone close witness the event?
* What happened during the attack? (Tongue biting, incontinence)
* How long did it last?
* Was there one kind of attack or were there more? (Differentiate a partial onset becoming generalized).
* Have there been any recent symptoms of illness?
* Family history of epilepsy or blackouts?
* Identify risk factors & predisposing events.
* History of febrile seizures, trauma, stroke, tumor, vascular malformation.
* Precipitating factors like sleep deprivation, acute infections, metabolic and electrolyte derangement.
* In children, a detailed birth history is to be noted including instrumental delivery, history of birth asphyxia, maternal illness or drug intake. Note the developmental milestones. Enquire if the schoolwork is affected?

Physical Examination: A vigilant general physical examination should include vital signs, signs of infection & systemic illness, neurocutaneous disorders, chronic liver disease, renal disease, organomegaly (metabolic storage disease), limb asymmetry (brain injury), signs of head trauma, and use of illicit drugs.[2]

A neurological examination should include:[2] Mental status (memory, language) - lesions of anterior frontal, parietal and temporal lobes, cranial nerves, cerebellar signs, balance, coordination and gait, reflexes, eye-vision and examination of the optic nerve – lesion of optic pathway & occipital lobe, hearing tests, sense of touch & smell and Head movements. In absence seizures voluntary hyperventilation may trigger an episode, which may be witnessed.

Laboratory Evaluation: Basic laboratory evaluation[2,7] is carried with the aim to focus on detecting systemic disturbances i.e. Complete blood count, serum electrolytes, calcium, magnesium, phosphorus, glucose, and toxicology screen, evaluating hepatic and renal function blood urea, nitrogen, creatinine, tests for infectious disease and Lumbar puncture if meningitis, encephalitis or HIV if suspected.

Electroencephalograph (EEG): An EEG remains the standard for diagnosis and localization to confirm the presence of and classify seizure. It may also indicate the location of the lesion.[2] EEGs can often be normal in between seizures, hence the need for prolonged EEG monitoring. Obtaining a sleep deprived EEG increases the likelihood of detecting an abnormality in partial complex seizures.[3]

Imaging: Computed Tomography (CT) plays a significant role in the evaluation of patients with partial epilepsy, demonstrates cerebral lesions particularly abnormality in the medial temporal region.[3]

Magnetic Resonance Imaging (MRI) is useful in diagnosing patients with partial epilepsy. MRI will identify lesions such as brain tumors, vascular lesions and other pathologies that need immediate surgery.[2] Skull radiograph is indicated with history of trauma. Newer investigations have lead to better diagnosis of epilepsy. Although a family physician will not be initiating these but he should be aware of the newer diagnostic methods, which aid in early diagnosis of conditions treatable by surgery.[3] Positron emission tomography (PET) and single-photon emission tomography (SPECT) examine cerebral function, confirm presence of organic abnormality, and give outline of an abnormal region for surgery.[3] Fluid attenuated inversion recovery (FLAIR) a newer MRI method, aids detection of abnormalities of cortical architecture.[2]

Differental Diagnosis: Important differentials are:[1,4] syncope, hypoglycemia, transient ischemic attack, migraine, sleep disorder, cardiac arrhythmia, vertigo, movement disorders e.g. tics and choreoethitosis and psychogenic. An investigation to differentiate psychogenic from generalized & complex partial seizure is serum prolactin level, which rises in seizures but not in psychogenic attacks.[2,18]

MANAGEMENT

Management should be initiated with first aid and non-pharmacological education,

followed on by initiation of drug therapy.

The key instructions are:

* Keep calm and reassure other people nearby.
* Do not hold the person down or try to stop his movements as it may lead to muscular injury or even fractures.
* Time the seizure with watch, an attack usually lasts for less then five minutes.
* Clear the area around the person of anything hard or sharp to minimize risk of injury.
* Loosen ties, scarf, dupattas or anything around the neck that may make breathing difficult.
* Put something flat and soft under the head like folded jacket, dupatta, turban, scarf etc.
* Turn patient gently onto one side to keep the airways clear.
* Do not try to force the mouth open with any hard implement like wooden spoons or with fingers, a seizing patient cannot swallow his tongue. Efforts to hold the tongue down can injure teeth or jaw.

The goal of pharmacological treatment is to control seizures completely without causing unacceptable side effects.[2,5,19] Before initiating therapy, establish an epilepsy syndrome diagnosis for each patient. Select medications appropriate for that epilepsy syndrome and choose the drug best suited for the patient. Initiate and titrate up the medication at appropriate dosages, and rates to enhance tolerability. Increase the medication, regardless of serum levels, until complete control is achieved or until persistent, unacceptable side effects occur. If satisfactory control is not achieved, change to another drug appropriate for the epilepsy syndrome being treated, the goal should be monotherapy in each patient, when possible.[6,20,21] To change drug, new drug is introduced in stages, as previous drug is being withdrawn.[7]

If trials with one or two agents fail to achieve acceptable results, refer the patient to an epilepsy specialist.[7] In case of serious side effect stop drug abruptly and use Diazepam I/V as a control drug Diazepam can be given rectally but should not be given I/M because of poor & incomplete absorption. A study of epileptic patients undergoing therapy shows that in 70% control is achieved with monotherapy. More than 30 percent of patients with epilepsy have inadequate control of seizures with drug therapy[20,22] but why this happens and whether it can be predicted are unknown.[20] In 15-20%, a combination regimen is required and another 10% are those who are refractory to treatment and will be referred for surgery or experimental drug therapy.[3] Patients who have many seizures before therapy or who have an inadequate response to initial treatment with antiepileptic drugs are likely to have refractory epilepsy.[20]

The preferred drugs for children are Phenobarbitone in neonatal febrile seizures, Ethsuxamide, Valproic acid and Lamotrigine in Absence seizures. Valproic Acid, Phenytoin, Carbamazapine and Lamotrigine in Tonic clonic seizures while Valproic acid and Clonazepam are drug of choice in myoclonic seizures. In adults Phenytoin and Carbamazapine remain drug of choice in partial, and generalized tonic clonic seizures. The preferred choice for absence and myoclonic remains the same as for children.[2,21] Status epilepticus may be controlled with Diazepam or Phenytoin.[22] Many new drugs for the treatment of epilepsy have become available in the past few years. Effective or promising results predominate for provoked (acute, symptomatic) seizures. For unprovoked (epileptic) seizures, no drug has been shown to be effective.[23] Eight new antiepileptic drugs were licensed in the 1990s with more to come. These new drugs along with earlier resective surgery have led to a better outcome for many patients.[24]

The new drugs in the order of their release since 1993 are Felbamate (Felbatol), Gabapentin (Neurontin), Lamotrigine (Lamictal), Topiramate (Topamax), Tiagabine (Gabitril), Levetiracetam (Keppra) and Zonisamide (Zonegran). Each of these drugs was initially approved as adjunct treatment to a classic drug for refractory partial epilepsy. However, indications for these drugs are gradually broadening.[5]

Phenobarbital, is now in disfavor because of its side effects and lack of efficacy in febrile seizures. Diazepam, administered only during

episodes of fever, may be a safe and effective agent to prevent the recurrence of febrile seizures.[25] Intranasal Midazolam is also effective in the management of febrile seizures in children although rapid control is achieved with intravenous diazepam than with intranasal midazolam,. Intranasal midazolam may be used in general practice and, with appropriate instructions, by the parents of children with recurrent febrile seizures at home.[25]

SPECIAL ISSUES RELATED TO PREGNANCY & BREAST-FEEDING

Sex hormone fluctuations during maturation may exacerbate seizures at particular points during the life of women, eg. during menarche, menses, pregnancy, or later in the perimenopausal years.[26]

American Academy of Neurology recommends monotherapy during reproductive years. There is a teratogenic potential of anti epileptic drugs. Ideally, in well-controlled seizures, taper and discontinue anti epileptic drugs before conception.[1] Risk of continuing must be weighed against the benefits. Post partum adjustment of the anti epileptic drugs dose will be necessary if the dose was increased during pregnancy, and usually can be reduced by eight weeks after delivery.

In utero exposure to antiepileptic drugs (AEDs) can cause intrauterine growth retardation, congenital malformations, and cognitive dysfunction. The most common major malformations are cleft lip/palate, heart defects, neural tube defects, and urogenital defects. Current treatment guidelines advise use of AED monotherapy and folate supplementation beginning before and continuing throughout pregnancy. Prenatal screening for major malformations should be offered.[27,28]

Guidelines recommend that the ideal AED concentration should be established for each patient before conception and that monitoring of AED concentrations should be performed during each trimester and in the last month of pregnancy. Free concentrations should be measured for phenobarbital, phenytoin, carbamazepine, valproic acid, and primidone.[29]

Studies during and after birth in mothers taking the older AEDs indicate extensive transplacental transfer and low to moderate excretion into breast milk. Limited studies of the newer AEDs indicate similar extensive transplacental transfer.[29]

Safety while breast-feeding is a common concern. Authorities recommend that it is safe with no risk of hematological or hepatotoxicity, although some sedation may occur with phenytoin, carbamazapine and phenobarbitone.[3] The efficacy of birth control pills is decreased by the use of enzyme-inducing anticonvulsants.[29] Some prescribe estrogen/progesterone pill with higher hormonal doses or an alternative and preferred approach, is to use a second method of contraception.[1]

PREVENTION

There is no known way to prevent epilepsy. Even in patients in whom pharmacotherapy is efficacious, current antiepileptic drugs do not affect the progression or underlying natural history of the condition.[22] None of the available anticonvulsant agents appear to have a prophylactic effect in patients who are at risk for the development of a seizure disorder.[20,22] All epileptic patients are advised to avoid precipitating factors. Abstain from driving, swimming etc until seizure free for a minimum of 6- 12 months.[1] An early response to drug therapy confers a favorable prognosis.[20]

REFERRAL

As the number of available treatment options for epilepsy increases, the optimal goal for Primary care physicians is collaborative work with neurologist, obstetricians and gynecologists.[28] Physicians must be attuned to making an accurate diagnosis of epilepsy syndrome and promptly referring patients who do not completely respond to treatment to a comprehensive epilepsy center.[7]

CONCLUSION

Epilepsy has multiple causes and history is still most important in establishing diagnosis. Counseling may prevent complications and stress on preventable and precipitating factors

should be laid. Correct diagnosis is essential before starting treatment. Treatment should not be started on first attack (unless evidence for cerebral lesions is present). Patient should be counseled regarding importance of regular treatment as well as the objective and purpose of treatment. Dose should be increased gradually and maintenance dose should be low. Aim should be monotherapy in all cases.

Treatment may be stopped after two to five years of a seizure free period in which case the drug should be withdrawn slowly.[1] There is risk of relapse on withdrawal, greatest in those with a long history of active epilepsy, those with structural disease and who suffer from complex partial seizures with secondary generalization. In such patients with increased risk of recurrence the treatment is continued for many years. All patients with epilepsy should have an annual review.

REFERENCES

1. Cavazos JE, Lum F, Spitz M. Seizures and epilepsy: Overview and classification. Available at http://www.emedicine.com/neuro/topic415.htm
2. Lowenstein DH. Seizures and Epilepsy. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL (ed) Harrisons principals of Internal Medicine . 15th ed Mcgraw-Hill 2001; 2354 – 69.
3. Pruit AM. Approach to patient with seizure in Primary care medicine. In Gorrol AH, Mullay AG, Jr.(ed) Office evaluation and. management of the adult patient 4th ed Lippincott William and Wilkins 1995; 962 –9.
4. Ayuk PB, Management of Epilepsy. Available at secure.lf.com drug ce ce00_epilepsy_lesson.htm
5. Benbadis S R, Tatium IV WO, Advances in the treatment of epilepsy. Am Fam Physician 2001; 64: 105-6.
6. Brodie MJ, French JA Management of epilepsy in adolescents and adults. Lancet. 2000; 356: 323-9.
7. Marks WJ, Garcia AP. Management of seizures and epilepsy. Am Fam Physician 1998. Available at http://www.aafp.org/afp/980401ap/marks.html
8. Annegers JF. The epidemiology of epilepsy. Wyllie E, (ed). The treatment of epilepsy. In: principles and practice. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001: 131-8.
9. Nowack WJ. First seizure in adulthood: Diagnosis and Treatment. available at http://www.emedicine.com/neuro/topic595.htm
10. Chang BS, Lowenstein DH. Epilepsy N Eng J Med 2003; 349: 1257-66.
11. Commission on Classification and Terminology of the International League against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981; 22:489-501.
12. Commission on Classification and Terminology of the International League against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989; 30: 389-99.
13. Neville BGR. Epilepsy in childhood. Br Med J 1997; 315: 924-30.
14. Johnston MV. Childhood Seizures In: Behrman RE, Kleiegman RM, Jenson BH (ed) Nelson Text Book of Pediatrics, 17th edition Elsevier 2004,1993-2005.
15. Camfield P, Camfield C. Epileptic syndromes in childhood: clinical features, outcomes, and treatment. Epilepsia. 2002; 43(3): 27-32.
16. Shinnar S. Febrile seizures and mesial temporal sclerosis. Amer Epilepsy Soc Epilepsy Curr 2003; 3(4): 115–8.
17. Schachter SC. Epilepsy. Neurol Clin 2001; 19:57-78.
18. Kapoor OP. G.Ps can do Better Differential Diagnosis between Syncope and Epileptic seizure Bombay Hosp J 2004; 46: 4.
19. Rosman P, Labazzo CT , Gilbert PL, Gardella NB, Kaye EM, Bennekom CV, et al. A controlled trial of diazepam administered during febrile illnesses to prevent recurrence of febrile seizures. N Eng J Med 1993; 329: 79-84.
20. Kwan PM, Brodie MJ. Early Identification of Refractory Epilepsy. N Eng J Med 2000; 342: 314-9.
21. Mycek MJ, Harvey RA, Champe PC. Drugs used to treat Epilepsy in Lippincott Illustrated Reviews Pharmacology. 2nd ed Lippincott-Raven 1997; 143-50.
22. Locsher W. Current status and future directions in the pharmacotherapy of epilepsy. Trends Pharmacol Sci 2002; 23:113-8.
23. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. Epilepsia 2001; 42: 515.
24. Gidal BE, Baltes E, Otoul C, Perucca E. Effect of levetiracetam on the pharmacokinetics of adjunctive antiepileptic drugs: a pooled analysis of data from randomized clinical trials Epilepsy Res 2005. [Epub ahead of print]
25. Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch M. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children Br Med J 2000; 321: 83–6.
26. Willium O, Tatum IV, Liporace J, Benbadis SR, Kaplan PW. Updates on the treatment of epilepsy in women Arch Intern Med. 2004; 164:137-45.
27. Pennell BP. The importance of monotherapy in pregnancy, Neurology 2003; 60: S31-S38.
28. Kaaja E, Kaaja R, Hiilesmaa V, Major malformations in offspring of women with epilepsy. Neurology 2003;60:575-9.
29. Pennell PB. Antiepileptic drug pharmacokinetics during pregnancy and lactation, Neurology 2003; 61: S35-S42.