For the use of
Registered Medical Practitioners only

For private circulation

QUARTERLY MEDICAL REVIEW

Vol. 59, No. 4 October - December 2008

Review:

Paediatric Seizure Disorders

Published and issued by **RAPTAKOS, BRETT & CO. LTD., WORLI, MUMBAI 400 030.**

FOR PRIVATE CIRCULATION For the use of a Registered Medical Practitioner only

QUARTERLY MEDICAL REVIEW

Vol. 59, No. 4 **Oct. - Dec. 2008**

PAEDIATRIC SEIZURE DISORDERS

CONTENTS

Published and Issued by

RAPTAKOS, BRETT & CO. LTD., WORLI, MUMBAI 400 030.

QUARTERLY MEDICAL REVIEW

Vol. 59, No. 4 **Oct. - Dec. 2008**

PAEDIATRIC SEIZURE DISORDERS

Dr. Sushma Nangia,
Professor, Department of Pediatrics, Kalawati Saran Children's Hospital &
Lady Hardinge Medical College, New Delhi.

Dr. S. Aneja,
Professor, Dept. of Pediatrics & Division of Pediatric Neurology,
Lady Hardinge Medical College
& Associate, Kalawati Saran Children's Hospital, New Delhi.

MANAGEMENT OF CHILDREN WITH EPILEPSY

Prof. S. Aneja,
Dept. of Pediatrics & Division of Pediatric Neurology, Lady Hardinge Medical College
& Associate, Kalawati Saran Children's Hospital, New Delhi.
&
Dr. Nidhi Chopra

Introduction

Epilepsy is a common neurological disorder. The prevalence is 4-10/1000 persons with higher incidence in infants. An epileptic seizure is the manifestation of an abnormal and excessive synchronized discharge of a set of cerebral neurons. The clinical manifestations are sudden and transient and include a wide variety of motor, sensory, or psychic phenomenon with or without loss of awareness. The symptoms depend on the part of brain involved and in some cases may be very subtle. Epilepsy is defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition.

Seizures that are the result of an acute reversible systemic or neurological condition - for example due to metabolic disturbance or CNS infection - are not considered to be epilepsy because they usually abate once the underlying condition has resolved. Similarly febrile seizures are not considered as epilepsy.

Seizure vs non -seizure

The paroxysmal nature of epilepsy can be mimicked by a variety of events. Because these events may be associated with altered levels of consciousness, tonic or clonic movements, or cyanosis, they are often confused with epilepsy. Affected children may be inappropriately placed on many anticonvulsants with no response. The first step in approaching a child with seizure disorder is to determine whether the event is truly a seizure or not. Benign sleep myoclonus in neonates, breath holding spells in infants and syncopal attacks, night terrors, hysterical seizures, complicated migraine, hyperventilation attacks, tics are commonly seen in children and adolescents.

Breath Holding spells are commonly misdiagnosed as epileptic fits in infancy.

A syncope is defined as a transient loss of "consciousness" usually leading to loss of postural tone. The onset is relatively rapid, and the subsequent recovery is spontaneous, complete, and relatively prompt. The underlying mechanism is transient global cerebral hypoperfusion. A psychogenic seizure is a transient behavioral disturbance without any organic basis.

CLASSIFICATION OF SEIZURES: The seizures which are a symptom of the underlying CNS disorder need to be classified according to clinical semiology whereas the epilepsy or epileptic disorder is classified according to etiology as well as electro-clinical features.

ILAE separates seizure into 2 main groups, partial and generalized. The partial seizures are further classified into simple partial and complex partial depending upon whether consciousness is preserved or impaired (Table I). The classification of seizure tries to locate the origin of seizure by its initial

symptom. However often seizure originating from frontal or temporal lobes may be clinically indistinguishable.

In clinical situations it is not always possible to classify seizures primarily because in children the patient may not be able to give an accurate report and the parents may have missed the initial onset of seizures. Seizure classification is particularly difficult in infants . The younger the age the more the difficult it is to interpret the history and classify the type of seizure due to immature CNS.

Table I

ILAE Classification of epileptic seizures(1981)

I Partial (focal seizures)

A Simple partial seizures (consciousness not impaired)

1 *With motor signs*- Focal motor with march; focal motor without march; versive; postural; phonatory

2 *With somatosensory or special sensory symptoms:*

3 *With autonomic symptoms or signs* (epigastric sensation; pallor; piloerection; sweating; flushing

4 *With psychic symptoms* (disturbance of higher motor function usually seen with loss of consciousness) dysphasia; affective symptoms

B Complex partial seizures (with impairment of consciousness; may sometimes begin with simple symptomatology)

1 *Simple partial onset followed by impairment of consciousness*

2. *With impaired consciousness at onset*

3. *Partial seizures evolving to secondarily generalized*- generalized tonic clonic/ tonic/ clonic

II Generalized seizures (convulsive or non-convulsive)

A Absence seizures

B Atypical absence

C Myoclonic seizures

D Clonic seizures

E Tonic seizures

F Tonic clonic seizures

G Atonic seizures

(combinations of above may occur)

III Unclassified epileptic seizures: neonatal seizures; incomplete data

Partial seizures

Simple partial seizures: (SPS)

Their clinical form depends upon the area of the cortex involved in the origin. Motor manifestations are mainly clonus or spasm and usually occur in epilepsies originating from frontal or central regions. Sensory symptoms such as tingling, numbness, shock like sensation are the usual manifestations of epilepsy originating from parietal or central area. If the focus is in calcarine cortex visual phenomenon such as flashing lights may be reported. In SPS arising from mesial temporal lobe a rising epigastric sensation is often reported.

Complex Partial Seizures:(CPS)

CPS may be preceded by an aura or SPS. The alteration of consciousness takes the form of motionless stare which is often associated with spasm or posturing or mild tonic jerking. This state may be followed by automatism in a full blown CPS. The common automatism may be a) oro-alimentary -e.g. lip-smacking; chewing or swallowing b) gestural fiddling with hands; patting; rubbing etc c) Ambulatory- walking, circling d) Verbal - grunting, humming, meaningless words e) violent behavior or f) mimicry

Complex partial seizure may arise from temporal lobe or from frontal lobe.

Partial seizures evolving to secondary generalized seizures:

SPS or CPS may spread and become secondarily generalized. The generalized seizure is usually tonic-clonic or tonic or atonic. The SPS may be experienced as an aura just before the generalized seizure.

Generalized Seizures:

Generalized seizures have loss of consciousness at the beginning because of bilateral and extensive involvement of both hemispheres and motor changes if present are bilateral and more or less symmetrical.

Typical Absence:

The seizure consists of abrupt cessation of all activity and LOC. Tone is preserved and there is no fall though patient appears glazed with vacant stare. The attack stops as abruptly as it started with the patient resuming his activity as if nothing has happened. Most seizures last for fewer than 10 seconds and occur frequently in clusters and the patient may experience hundreds of such seizures in a day. These seizure are a hallmark of idiopathic generalized epilepsies such as childhood absence and juvenile absence epilepsy. The EEG during a typical absence is characteristic comprising of 3hz spike and wave paroxysm. Absences should be distinguished from CPS with which it can be confused.

Myoclonic Seizures:

Myoclonic seizure is a brief contraction of a group of muscles or several groups of muscles caused by a cortical discharge. It can be single or repetitive and there is no LOC. Myoclonic seizures can

occur in idiopathic juvenile myoclonic epilepsy or as a spectrum of LGS; or in symptomatic epilepsies such as SSPE.

Atonic seizures:

The most severe form is the drop attack in which patient loses all postural tone and collapses like a rag doll. In less severe seizures only a part of body is affected causing head nodding or sagging of knees etc. These types of seizures are seen in patient with underlying diffuse cerebral damage and are associated with other neurological signs such as learning disability.

Clonic Seizures:

These comprise of bilateral clonic jerking and are commonly seen in young infants.

Tonic seizures:

Tonic seizures are seen as tonic muscle contraction of a large part of body - neck, face and trunk along with LOC. If the arms are involved arms may be held up and the legs are extended. These generally last for less than a minute and may be accompanied with apnea.

Tonic - clonic seizures:

Tonic clonic seizure can occur at any age and in a variety of epileptic syndromes. The seizure starts with LOC making the patient fall if he is standing. This is followed by tonic flexion which later gives way to rigidity and axial extension, uprolling of eyes and clenching of teeth. After this tonic phase which may last for seconds the patient has clonic movements of all four limbs, jaw and facial muscles. The patient may bite his tongue and become cyanosed and have drooling of saliva. Confusion or post-ictal sleep is invariable.

CLASSIFICATION OF EPILEPSY AND EPILEPTIC SYNDROMES:

The Classification of epileptic seizure can only tell the physician the seizure semiology. Since similar seizure can occur in a wide variety of disorders this classification gives only a limited information. Classification of epilepsies and epileptic syndromes combines etiologic and localization information obtained from clinical, neuroimaging and EEG data This classification makes a primary distinction between partial or localization related epilepsy in which seizure semiology and investigations reveal a localized seizure origin and generalized epilepsies in which history and electro-clinical data suggest bilaterally synchronous onset of seizure. The ILAE classification defines an epileptic syndrome as a disorder with a cluster of signs and symptoms that customarily occur together. Epilepsy syndromes are subclassified depending upon the etiology into ***symptomatic*** which are caused by a known abnormality of CNS; ***cryptogenic*** - which have a presumed underlying cause though not apparent; and ***idiopathic*** epilepsies which have no underlying cause other than genetic predisposition.

Table-II

Classification of epilepsy and epileptic syndromes proposed by ILAE

1. Localisation related epilepsies and syndromes

1.1 Idiopathic (with age related onset)
- Benign childhood epilepsy with centritemporal spike
- Childhood epilepsy with occipital paroxysms
- Primary reading epilepsy

1.2 Symptomatic
- Chronic progressive epilepsia partialis continua of childhood
- Syndromes characterized by seizures with specific modes of precipitation
- Temporal/frontal/parietal/occipital lobe epilepsies

1-3 Cryptogenic

2. Generalized epilepsies and syndromes

2.1 Idiopathic (with age related onset- listed in order of age)
- Benign myoclonic epilepsy of infancy
- Childhood absence epilepsy
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Epilepsy with grand mal seizures on awakening

2.2 Cryptogenic or symptomatic (in order of age)
- West syndrome(infantile spasms)
- Lennox Gastaut syndrome
- Epilepsy with myoclonic astatic seizures
- Epilepsy with myoclonic absences

2-3 Symptomatic

2.3.1 Non specific etiology
- Early myoclonic encephalopathy
- Early infantile epileptic encephalopathy with suppression burst

3. Epilepsies and syndromes undetermined whether focal or generalized
- Neonatal seizures
- Severe myoclonic epilepsy of infancy
- Epilepsy with continuous spike waves during slow wave sleep
- Acquired epileptic aphasia

4. Situation related seizures
- Febrile convulsions
- Isolated seizures or isolated status epilepticus
- Seizures accompanying an acute toxic or metabolic event.

In pediatric epilepsy centers nearly 50% of cases are symptomatic. It is likely that in population based studies idiopathic variety will be commoner. Symptomatic epilepsies are more common in developing countries because of the higher incidence of CNS infections and Neurocysticercosis and perinatal insult to brain.

The syndromic classification helps to decide which AED to be used. The ILAE classification has been shown in Table II.

COMMON EPILEPTIC SYNDROMES OF CHILDHOOD

West Syndrome: West syndrome is a triad of infantile spasms, hypsarrythmia on EEG and developmental delay. Age of onset ranges from 3 to 12 months. Seizures are brief bilaterally symmetrical contractions of neck and trunk musculature which occur in clusters especially on awakening. West syndrome can be symptomatic or cryptogenic. Nearly 2/3 are symptomatic following a known insult to the brain e.g. hypoxic -ischemic encephalopathy, neonatal meningitis, IU infection, tuberous sclerosis or CNS malformation.

Lennox Gastaut Syndrome: The Lennox-Gastaut syndrome may result from a variety of diffuse encephalopathies. It is characterized by the clinical triad of diffuse slow spike-and-waves on EEG, mental retardation, and multiple types of generalized seizures, including atypical absences and tonic and atonic seizures .The age of onset is between 2 and 8 years in most cases. Symptoms can appear de novo without apparent cause (cryptogenic LGS) or result from obvious brain insult (symptomatic LGS). In young children, the Lennox-Gastaut syndrome usually begins with episodes of sudden falls. This is soon followed by frequent seizures, progressively deteriorating intellectual functions, personality disturbances. Myoclonic, myoclonic-atonic, and atonic seizures, as well as tonic seizures, all cause falls (drop attacks) which result in recurrent injury.

Childhood absence epilepsy: (CAE). CAE is an idiopathic primary generalized epilepsy which occurs in neurologically normal children. Age of onset is in childhood with peak manifestation at 6-7 years. CAE is more common in females. 80% absences are of <10sec and the patient has total amnesia of the event. The patient has very frequent absences throughout the day. The seizure can be precipitated at bedside by asking the patient to hyperventilate for 3 minutes. Mild motor accompaniments may be seen in nearly 50% of the patients. The EEG shows a typical 3Hz generalized spike and wave discharge which is bilaterally synchronous and is precipitated by hyperventilation.

Benign childhood epilepsy with centrotemporal spikes (BECTS) This is an idiopathic localization-related epilepsy characterized by childhood onset and centrotemporal spikes on EEG. BECTS begins between 2 and 13 years of age and remits by 16 years. The patient is normal with no neurologic or intellectual deficit. Partial seizures with motor signs, frequently associated with somatosensory symptoms occur mostly in sleep. Interictal EEG is characterized by a spike focus located in the centrotemporal area with normal background activity. There is spontaneous remission during adolescence.

Juvenile Myoclonic epilepsy (JME): This is an idiopathic generalized epileptic syndrome which is inherited. The seizures have an age related onset often appearing around puberty. Family history of epilepsy is present in 25% of patients. Seizures which are single or repetitive, bilateral, arrhythmic irregular myoclonic jerks predominantly in the arms with no loss of awareness are the predominant seizure type. These occur more often in the morning and are of variable intensity. GTC seizure and absences are also seen in this syndrome. Patients are otherwise normal with normal neuroimaging. The EEG is nearly always abnormal and shows multiple spikes mainly 3-5Hz with a characteristic or 'W" appearance. Lifelong treatment is usually necessary.

INVESTIGATION:

EEG - EEG is a valuable tool in the diagnostic evaluation of children presenting with seizures. EEG is essential for characterizing the seizure type and the epilepsy syndrome. Epileptiform abnormalities strongly support a clinical diagnosis of epilepsy though normal EEG does not exclude epilepsy. In a suspected case of non-epileptic events a synchronized video EEG is useful. Video-EEG is also essential before surgical evaluation.

Neuroimaging: Neuroimaging has revolutionized the diagnosis of etiology of epilepsy. Neuroimaging is needed in all cases where the epilepsy is presumed to be symptomatic. In developing countries where Neurocysticercosis is endemic contrast enhanced CT is recommended for all children with recurrent seizures except those which are clearly idiopathic e.g. childhood absence epilepsy. In children with intractable epilepsy MRI should be done using standard epilepsy protocol to get optimal spatial resolution and 1-2 mm partitions. The yield of neuroimaging is highest in children with focal seizures, neurological deficits, focal changes on EEG and in infants.

TREATMENT :

Principles of Anti-epileptic drug therapy:

AEDs are the mainstay of treatment of epilepsy. The primary goal of anti-epileptic treatment is to achieve complete freedom from seizures without any adverse effect, reduce morbidity and to improve quality of life.

Prerequisites to starting treatment

Confirm epilepsy : The first step in treatment is to make sure that the child has "epilepsy". Non-epileptic conditions must be excluded. This is done by taking a detailed history from a reliable witness of the event. Epilepsy is diagnosed if there is history of recurrent unprovoked seizures. Febrile seizures are provoked seizures and do not need AED therapy continuously.

Classify seizure & epilepsy : The next step consists of delineation of the type of seizure. The epilepsy syndrome refers to collating information on seizure type and semiology, age at onset, associated symptoms and EEG picture. This helps in delineating etiology, need for further investigations, choice of drugs and prognosis. The syndromic diagnosis may not be possible in initial visit but may be evident as the patient is followed.

Determine Etiology : The etiological diagnosis should be rigorously attempted in all cases. This may be evident in some cases e.g. neurocutaneous syndromes but in a large majority of cases will need sophisticated imaging techniques. Biochemical investigations are required in selected patients.

Decide if AED is needed : After determining the seizure type, epileptic syndrome and etiology the physician should decide whether drug therapy is necessary. A single seizure does not warrant the initiation of AEDs. The benefit of seizure control should be weighed against the cost and adverse effects of drugs. Thus infrequent brief seizures e.g. 2 episodes of brief seizures occurring 12 months apart may not merit drug therapy. Similarly acute symptomatic seizures (seizures occurring due to acute insult to brain e.g. head trauma, CNS infection) require only short-term treatment and should get prolonged treatment with AEDs.

Give 1st line AED

The selection of AED is based on its efficacy, tolerability, cost and ease of use. The efficacy depends upon the type of seizures and epilepsy syndrome while tolerability may be affected by age, sex, comorbidity and comedication besides many other host factors.

The common first line AEDs and alternative drugs for specific seizure type is given in table III. Although the evidence from randomized controlled trials is inconclusive, carbamazepine is probably the most effective drug for partial onset seizures and sodium valproate is accepted as the drug with greatest efficacy for generalized epilepsies.

Age & sex considerations:

Since childhood is a period of brain growth and cognitive development as well as physical growth; the treatment of epilepsy requires special consideration for growth and development. Carbamazepine (CBZ) is not used in infants as there is a risk of inducing generalized seizures in this age group. Phenobarbitone (PB) is the drug of choice for neonatal seizures and is also useful for seizures in young infants. PHT is better avoided in girls because of cosmetic side effects.

Associated morbidity should be considered before prescribing AEDs. Drugs which affect behavior are best avoided in children with learning difficulties. The benzodiazepines (BZD) can worsen the co-ordination and motor problems in children who have pre-existing motor difficulties. BZD also increase oral secretions and worsen the problem of drooling in children with cerebral palsy.

Cost:

This is an important determinant of the choice of drug. Conventional AEDs are cheaper than newer drugs and phenobarbitone and phenytoin are cheap and widely available. Since the duration of therapy is fairly long, a cheap and easily available drug is better than an expensive therapy with poor compliance. The cost of the therapy should be discussed with the family before starting any expensive treatment.

Choice of AEDs for various seizure/epileptic syndromes

Seizure Type	First Line	Second line
Partial Seizures		Valproate
- Simple partial	Carbamazepine	Oxcarbazepine
- Complex partial	Phenytoin	Phenobarbitone
- Secondarily generalised		Lamotrigine
		Topiramate
		Clobazam
Generalized Tonic -clonic seizures	Carbamazepine	Phenobarbitone
Tonic, clonic seizures	Phenytoin	Clobazam
	Valproate	Oxcarbazepin
Childhood Absence Epilepsy	Valproate	Lamotrigine
	Ethosuximide	clonazepam
Atypical Absence	Valproate	lamotrigine
		Clonazepam
		Clobazam
Juvenile Myoclonic Epilepsy	Valproate	Lamotrigine
		Phenobarbitone
Infantile spasms	ACTH/	Valproate
	prednisolone	Clonazepam
	VGB	Topiramate
Lennox-Gastaut Syndrome	Valproate	Lamotrigine
		Topiramate
		Clonazepam
		Felbamate
Neonatal seziures	Phenobarbitone	Phenytoin
		Clonazepam
		valproate

Using AEDs

Monotherapy with an effective drug is a rule. When maximal doses of first drug are ineffective or associated with unacceptable side effects another should be introduced and the ineffective drug slowly withdrawn. Monotherapy is the best therapeutic option and it is recommended that a trial of monotherapy with the 2 first line drugs be given before opting for polypharmacy.

It is advisable to start the AED at a low dose and increase slowly to the target dose and further titrate it to lowest effective dose to get seizure control. Slow introduction reduces the neurotoxic side effects which are commonly seen with most AEDs. The loading dose of AEDs is required only in special situations e.g. after status epilepticus where therapeutic blood levels are required immediately.

It should be remembered that steady state plasma concentrations will be achieved after about 5

elimination half lives and these vary between different AEDs. Compliance is best if the drug is given 1-2 times a day. Extended release formulations are better as less fluctuations are seen with such formulations. The bioavalability of drugs may vary across different brands therefore the patients should be advised not to switch from one brand to another.

Clinical monitoring is essential for all patients. It includes keeping a diary of seizures, drugs taken and other important events e.g. fever. The physician should be aware of side effects and monitor for these during follow up. Monitoring of liver function and blood counts routinely have no role. Therapeutic drug levels are not routinely indicated. It should be done in patients in whom there is suspicion of compliance, in patients receiving multiple AEDs and taking drugs with nonlinear kinetics e.g. Phenytoin.

Breakthrough seizure may occur if there is poor compliance or be triggered by fever etc. A new antilepileptic should not be added every time child has a seizure. A detailed history regarding compliance of therapy, change in seizure type, change of available preparation should be taken to determine the cause of breakthrough seizure.

Nearly 70- 80% of patients may have control of seizures but in the remaining epilepsy may not respond to the initial treatment. If seizure control is poor in spite of appropriate drugs in proper doses child should be re-evaluated and expert opinion sought if necessary.

When to stop therapy-

As AEDs are associated with significant side effects, particularly subtle effects on cognition, it is advisable to withdraw AEDs in patients who have a prolonged period of remission. After 2-3 years of seizure free period drugs should be tapered over a period of 2-3 months. Average risk of relapse after discontinuation of therapy is 20-30%. Family should be counseled regarding the risk of relapse and should be allowed to make an informed choice. The greatest chance of successful drug withdrawal is in patients who had a single type of seizure, normal neurological examination, Normal EEG and who have been seizure free for > 2 years. Prognosis is excellent in some benign childhood epilepsies.

Adverse Effects

The adverse effects of AEDs can be acute dose related, idiosycratic reactions and chronic toxicity. The acute neurotoxic symptoms are common with most AEDs and are nonspecific and characterized by ataxia, giddiness, diplopia, nystagmus and are related to the increase in drug levels. These usually resolve by reducing the dose of AEDs. Acute idiosyncratic reactions are rare, unpredictable, and necessitate immediate withdrawal of the causative drug. Allergic reactions, manifested by rash with or without fever and other multi-organ involvement, occur in 2-4% of patients exposed to carbamazepine, phenytoin, phenobarbitone or lamotrigine. Chronic toxicity is seen after a prolonged use of AEDs.

Management of refractory epilepsy

Treatment of refractory epilepsy requires an evaluation by an epilepsy specialist to confirm "epilepsy" and delineate seizure type by video-EEG; review the type of epileptic syndrome and rigorously

look for any structural pathology. Besides the above mentioned AEDs, other new drugs have been marketed in several countries and have been used in children. These new drugs provide a wider choice to clinicians who would like to tailor AED therapy depending upon host factors such as underlying medical disorders, type of epilepsy and concurrent medication. They help in treatment of refractory epilepsy if the conventional therapy fails or becomes intolerable due to side effects of drugs. Newer antiepileptic drugs have provided clinicians with more options for optimizing the treatment of epilepsy to provide better seizure control. Current approach to treatment is to tailor the therapy as far as possible to epilepsy syndrome, etiology and comorbidities.

The therapeutic option besides drug therapy are - **epilepsy surgery, ketogenic diet, vagal nerve stimulation**. The patients with partial seizures particularly of temporal lobe origin must be evaluated for surgery. Patients who have respectable lesion and are prepared to accept risks of investigation and surgery, should be evaluated at the earliest opportunity.

Some patients who are unsuitable for respective surgery may benefit from ***vagus nerve stimulation***. Clinical trials indicate that this procedure is well tolerated, has no serious side effects, and reduces seizure frequency by 50% or more in a third of patients. ***Ketogenic diet***, in which the fat: Carbohydrate + protein ratio ranges from 2:1 to 5:1 has been shown to be effective in both children as well as adults. The diet is not palatable making compliance a major issue.

For the majority of patients medical treatment remains the only option. The aims are minimization of the number of tonic-clonic seizures and side effects, and limiting disability associated with the psychosocial consequences of the chronic disorder. Newer AEDs should be tried in patients with refractory epilepsy. As a group they produce sustained benefit, in terms of reduced seizure frequency or severity, in a minority of patients. If monotherapy fails and a combination of drugs is used then agents effective for the type of epilepsy with different modes of action and low risk of pharmacokinetic interaction are preferred because of the theoretical possibility of synergy and, more importantly, a lower chance of side effects.

However, despite the continued development and release of new antiepileptic drugs, many patients have intractable epilepsy or epilepsy with intolerable side effects. Even when seizures are controlled, current antiepileptic drugs do not seem to affect the progression or underlying natural history of epilepsy. Better understanding of processes leading to epilepsy is required to create therapies aimed at the prevention of epilepsy in patients at risk. Further there is need to develop disease-modifying therapies which could halt the progression of epilepsy. Advances in pharmacogenomics will perhaps in near future provide information which will help to predict susceptibility of patients to serious adverse effects and provide a better quality of life through an improved safety profile.

References

1. Commission on Classification and Terminology of the International League Against Epilepsy. (1981). Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia1981;22,489-501.
2. Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE Task Force on Classification and Terminology. Epilepsia 2001;42(6): 796-803.

3. 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.
4. Aicardi J, Levy Gomes A. Clinical and electroencephalographic symptomatology of the 'genuine' Lennox-Gastaut syndrome and its differentiation from other forms of epilepsy of early childhood. Epilepsy Res 1992;6(Suppl):185-93.
5. Michelucci R, Tassinari CA. Childhood asbsence epilepsy Chap In Epilepsy in children Ed Wallace SJ chapman & Hall. London 1996 pp277-286.
6. Wolf P. Juvenile absence epilepsy. In: Roger J, Bureau M, Dravet C, Dreifuss FE, Perret A, Wolf P, editors. Epileptic syndromes in infancy, childhood and adolescence. 2nd ed. London: John Libbey, 1992:307-12.
7. Panayiotopoulos CP, Obeid T, Tahan AR. Juvenile Myoclonic epilepsy : a 5 year prospective study. Epilepsia 1994;35:285-96.

Neonatal seizures

Dr. Sushma Nangia, M.D., D.M.
Professor, (Neonatology)

Dr Anu Gulati
Senior Resident

Department of Pediatrics, Kalawati Saran Children's Hospital &
Lady Hardinge Medical College, New Delhi

Neonatal seizures

Introduction

Neonatal seizures or electroconvulsive activity are usually the sign of neuronal compromise and the prognosis in large part will depend on any one of the many underlying causes of the seizure activity. There is increasing evidence that neonatal seizures have an adverse effect on neuro-developmental progression and may predispose to cognitive, behavioral, or epileptic complications later in life. However, given the uncertainty about the efficacy and toxicity of the commonly used anticonvulsants, when and how aggressively to treat such seizures is a difficult decision. Population based studies utilizing the clinical definition of seizures indicate sharp differences in incidence as function of birth weight with values as high as 57.5 per 1000 in infants < 1500gm but only 2.8 per 1000 for those with birth weight of 2500 to 3999 gm.[1]

Pathophysiology

The incidence of seizures in the neonatal period is considerably higher than at any other time of life. Animal studies have shown that the immature brain is more prone to seizure activity than the mature brain, but paradoxically the immature brain appears to be less vulnerable than the adult brain to neuronal damage. The reason for the increased susceptibility of the immature brain to seizure activity is because in the developmental stage of a neonate's brain the GABAergic synapses are functionally more active than NMDA-AMPA ones and provide a net excitatory drive in the developing brain. In early life, GABA receptors have a mainly excitatory effect unlike its function in the mature brain. This propensity changes with progressive development when the sensitivity of the brain to seizures reduces. An important concept of seizure susceptibility in the brain is kindling, and it is considered to be a more important factor in the immature than in the adult brain. Kindling refers to the effect of repeated but brief stimulation on a susceptible area of the brain, which produces an accelerating and prolonged effect resulting in seizures. In a clinical context it has been suggested that kindling due to repeated sub clinical stimuli may render a region of neurons epileptic. Repetitive seizures result in both a progressive increase in the duration of seizures and a decrease in the latency between seizures, and it has been shown in animal studies that kindling in the neonatal period results in an increased susceptibility to seizures later in life. Immature hippocampal and cortical neurons are more susceptible to seizure activity. Additionally only the proconvulsant projection network of the substantia nigra is functional in the early brain development.

Seizure phenomenon in neonates varies considerably from those in older children. The preterm infant has an altogether different process than term baby. Neonates rarely have the well organized, generalizes tonic- clonic seizures. This is related with the status of neuroanatomical and neurophysiological development in the perinatal period. The critical neuroanatomical developmental processes that take place in perinatal period are attainment of proper orientation, alignment and layering, i.e., lamination of cortical neurons, the elaboration of axonal and dendritic ramifications, and establishment of synaptic connection. This is incomplete in newborn baby and explains the inability to propogate and sustain generalized seizures. The relatively advanced cortical development apparent in human limbic system and their connection to the diencephalon and brain stem underlie the predominant oral- buccal- lingual movements, such as sucking, chewing, or drooling; oculomotor phenomena as clinical manifestation of seizures. The hippocampus of the neonatal brain generates electrical discharges that do not propagate sufficiently to be detected by surface

electroencephalogram (EEG).[2,3,4] Even when the synchronous discharges do appear at the surface near the end of the seizure, behavioral phenomena may not correlate due to deficient myelination of the cerebral efferent pathways.

Do recurrent seizures or prolonged seizures cause harm to the immature brain?

Animal studies document that the consequences of seizures in the immature brain are different from those in the adult brain. Following a single prolonged seizure in the developing rat brain, there is less neuronal cell death, limited mossy fiber sprouting, and fewer cognitive deficits than typically seen in the adult rat.[5,6] The reasons for this are not fully understood, but may involve developmental differences in glutamate-induced damage at the cellular level, and differences in the intracellular calcium-buffering capabilities in the immature brain.[5,6] On the other hand, there is an increasing body of animal research that documents long-term physiologic and developmental consequences to brief, recurrent seizures in the immature brain, including: (1) permanent reduction in seizure threshold, and (2) significant deficits in learning and memory.[7]

What is the mechanism of action for the changes that are seen with neonatal seizures?

The most significant biochemical effects of neonatal seizures are the changes in energy metabolism.[8,9] Within 5 minutes after the onset of a seizure, there are significant changes: (1) decline in ATP; (2) decline in the storage form of ATP, phosphocreatine; (3) substantial increase in adenosine diphosphate (ADP); (4) increase in glycolysis, with concomitant increase in pyruvate and lactate; and (5) significant decline in central nervous system (CNS) glucose concentration.[8,9] Although the elevation in lactate does result in local vasodilation, with an increase in delivery of substrate supply, it is not enough to compensate for the decline in ATP. With the shift in ADP:ATP ratio, there is a shift in reduction-oxidation state toward reduction, with an increase in nicotinamide adenine dinucleotide (NADH) and a shunting of pyruvate to lactate. Subsequently, lactate is shunted to anaerobic metabolism resulting in the production of just 2 ATPs instead of 38 as would have occurred with oxidative phosphorylation.

There are other changes in metabolism that can occur with recurrent seizures. These include significant declines in DNA, RNA, and protein metabolism.[10] There is a significant decline in DNA synthesis during a seizure, as well as impairment of neuronal differentiation and myelination. Magnetic resonance spectroscopy (MRS) has also demonstrated significant biochemical changes.[11] Neonatal seizures result in decreases in phosphocreatine concentration and pH, similar to the changes that are measured in infants with hypoxic-ischemic encephalopathy.

There is impairment of cerebrovascular autoregulation and increased cerebral blood flow (CBF) with seizures in the newborn. Although this can be seen as a adaptive mechanism to improve substrate delivery (particularly glucose) in a preterm infant or asphyxiated infant, the increase in blood flow could potentially rupture blood vessels in highly vulnerable areas of the brain, such as the germinal matrix in premature infants or the penumbra of an infarction in an asphyxiated infant. These physiologic changes undoubtedly contribute to the neuronal cell injury and death. Excitatory amino acids may play a major role as the mechanism of neuronal cell death with prolonged seizures. Prolonged seizures cause excessive release of glutamate and aspartate. The topography of seizure-related neuronal damage corresponds to the topography of the postsynaptic sites innervated by the glutamate and aspartate neurotransmitters, particularly the limbic structures and distant sites intimately connected with the limbic structures. When energy

reserves fall and eventually fail, the energy-dependent reuptake systems for these excitatory amino acids in the presynaptic nerve clefts and astrocytes are impaired, with concomitant local accumulation. The cytopathological features of seizure-related neuronal death are indistinguishable from those of glutamate-induced neuronal cell death. The vulnerability of the developing brain of the newborn to this particular form of injury may be related to the rich expression of glutamate receptors in the developing brain-glutamate being an important neurotransmitter in neuronal differentiation and plasticity.

In summary, neonatal seizures adversely affect a wide range of phenomena in the developing brain, including cell division and migration, formation of receptors, sequential expression of receptors, synaptogenesis, and apoptosis. These changes appear to have long-term detrimental consequences with respect to seizure threshold, cognition, and learning. The mechanism of action is probably related to the rich network of excitatory glutamate receptors in the developing brain, the lack of an inhibitory neurocircuitry, and the rapid failure of energy reserves with repeated or prolonged seizures, resulting in an excessive glutamate release with concomitant neuronal cell injury or death. Aberrant neurogenesis and mossy fiber sprouting may also play roles in the increased risk for further seizures and abnormal cognitive outcomes.

Classification of neonatal seizures

A seizure is defined as paroxysmal alteration of neurological function, i.e., behavioral, motor, or autonomic function. These may or may not be associated temporally with surface recorded EEG. Four essential seizure types are: subtle, clonic, tonic and myoclonic. Multifocal seizures are those that involve more than one site, are asynchronous and usually migratory whereas generalized seizures are diffusely bilateral, synchronous and nonmigratory. Jitteriness must be differentiated from seizures in neonates. Jitteriness is not associated with ocular deviation. It is stimulus sensitive (eg, easily stopped with passive movement/restraint of the limb). The movement resembles a tremor, and no autonomic changes are associated with it. Seizures often are associated with ocular deviation and are not stimulus sensitive. Autonomic changes frequently accompany them. The movements are clonic, unlike the tremor like movements of jitteriness. The classification of clinical seizures along with their EEG correlation is depicted in *table 1*.

Table 1: Classification of neonatal seizures

Clinical seizure	**EEG correlation**
Subtle	Variable
Clonic	
Focal	Common
Generalized	Common
Tonic	
Focal	Common
Generalized	Uncommon
Myoclonic	
Focal, multifocal	Uncommon
Generalized	Common

Subtle seizures:

These are more common in preterm than in full term babies. Some subtle clinical phenomena in full term babies are not consistently accompanied by EEG seizure activity. The clinical activity seen commonly with these seizures is eye opening, ocular movements, and peculiar extremity movement (eg. Boxing, hooking or pedaling), mouth movements and apnea. Term babies usually have horizontal deviation of eyes while preterm more commonly show sustained eye opening with ocular fixation. Apnea as manifestation of seizure activity is seen mainly in term babies and is accompanied by other subtle manifestation and importantly tachycardia. Other rarer clinical phenomena observed in babies with apneic seizure are episodic vertical deviation of eyeballs with or without eye jerking, hyperapnea, vasomotor phenomena and abnormal cardiac rhythm. There is an ongoing debate as to whether or not these movements represent clinical subcortical seizures or are "brainstem release phenomena".[12] Animal research strongly suggests that these seizures may represent subcortical seizures. In animal models, stimulation of the midbrain can result in complex motor automatisms, similar to what is observed in newborn infants. In addition, stimulation of the inferior colliculus in a newborn rat often results in an electrographic seizure, with clinical manifestations similar to subtle seizures in human newborns.[13] Finally, the inferior colliculus is very sensitive to hypoxic ischemic injury in the newborn, which may explain why infants with hypoxic-ischemic encephalopathy often exhibit subtle seizure activity in addition to multifocal clonic activity. In research in infants with hypoxic-ischemic encephalopathy, video EEG monitoring has demonstrated that infants with subtle seizures can have variable cortical EEG patterns with subtle seizures - sometimes exhibiting cortical rhythmic electrographic seizure activity, and at other times, no discrete EEG correlate. The emerging hypothesis is that subtle seizures are primarily subcortical and sometimes spread to involve the cortical neurons.

Clonic seizures:

This variant is most consistently associated with time synchronized EEG seizure activity. Clonic movements in newborns are rhythmic and slow (1-3 jerks/ sec). Focal clonic seizures involve face, upper or lower extremity of one side or axial structures (neck or trunk) unilaterally. Loss of consciousness is an inconsistent finding. The pathology is usually focal but metabolic encephalopathies should also be close differential especially hypocalcemia. Multifocal clonic seizures involve several body parts in non ordered (non- Jacksonian) migrating fashion.

Tonic seizures:

They are usually not associated with time synchronized EEG discharges. Focal tonic seizures consist of sustained posturing of a limb or asymmetric posturing of trunk or neck. They are usually accompanied by EEG changes. Generalized tonic seizures are accompanied by tonic extension of upper and lower limbs (mimicking decerebrate posturing) or tonic flexion of upper limbs with extension of lower limbs (mimicking decorticate posturing). They are not associated with EEG changes. If EEG discharges are present, then autonomic phenomena are prominent clinical features.

Myoclonic seizures:

These are clinical episodes that are infrequently associated with time synchronized EEG changes. Focal myoclonic seizures typically involve the flexor muscles of upper limbs. Multifocal myoclonic seizure is characterized by asynchronous twitching of several parts of the body.

Generalized myoclonic seizures are bilateral jerks of flexion of upper limbs and occasionally lower limbs. They are more commonly associated with EEG changes as compared to focal of multifocal variant. Myoclonic seizures are seen in both preterm and term infants. They may or may not have EEG correlate. If the myoclonus is related to sleep or hypoxic-ischemic injury, there is usually no EEG correlate. Specifically, some newborns will have exaggerated physiologic myoclonus of sleep. Infants with hypoxic-ischemic injury may suffer from anoxic myoclonus, which probably reflects brain stem injury. On the other hand, there are special newborn syndromes in which the presence of myoclonus may signify a catastrophic epilepsy of infancy, such as Ohtahara's syndrome or early myoclonic epileptic encephalopathy. These two syndromes are associated with a burst suppression pattern on EEG and portend a poor prognosis.

Etiology of newborn seizures

The most common etiology of neonatal seizures is **perinatal hypoxia-ischemia**. With hypoxic-ischemic encephalopathy, the seizures usually begin within the first 24 hours after birth and are associated with altered sensorium. With more severe hypoxia-ischemia, there is concomitant cardiomyopathy and acute renal tubular necrosis. Hypoxic-ischemic encephalopathy probably accounts for approximately 50% to 60% of all patients with neonatal seizures. In one study, 60% of these infants developed seizures within the first 12 hours. The seizures may become increasingly severe and frequent and may be very difficult to treat. They typically last 48-72 hours and are quite intense, thereafter, they subside over the next day or two. The seizure types include subtle seizures, multifocal clonic seizures, and focal clonic seizures.

Other common etiologies include **intracranial infections and intracranial hemorrhage**. Lethargy, vomiting, temperature instability, or subtle changes in physiologic homeostasis usually identify sepsis. Any infant with these symptoms should have a septic work-up, including blood, urine, and cerebrospinal fluid (CSF). Intracranial infections probably account for 5% to 10% of all causes for neonatal seizures. The most common etiologies for nonbacterial infections include toxoplasmosis (Toxo), cytomegalovirus (CMV), herpes simplex, and less likely, rubella. These infections are usually congenital, transplacentally acquired (CMV and Toxo), or acquired during passage through an infected birth canal (herpes). Seizures are usually present in the first 3 days of life. Herpes simplex-1 (HSV) encephalitis usually presents in the second week of life. Cytomegalovirus infection is the most common and serious congenital infection. It is often associated with intrauterine growth retardation, microcephaly, meningoencephalitis, hepatosplenomegaly, hyperbilirubinemia, and thrombocytopenia. Periventricular calcifications are common but not pathognomonic for this infection. The clinical features of symptomatic congenital toxoplasmosis include intrauterine growth retardation, meningoencephalitis, seizures, intracranial calcifications, microcephaly, chorioretinitis, hepatosplenomegaly, hyperbilirubinemia, and anemia. Neonatal herpes simplex infections are often associated with severe neurological sequelae, presenting with seizures, irritability, and coma. In these infants, in addition to meningoencephalitis, there is usually multifocal parenchymal necrosis, occasionally hemorrhagic, which typically results in diffuse encephalomalacia with concomitant severe developmental delays and epilepsy.

Bacterial infections that produce neonatal seizures include Group B Streptococcus, Listeria, Escherichia coli and almost any gram negative pathogen which can cause sepsis. These infections usually occur slightly later than the congenital viral infections, usually toward the end of the first

week or even later, up to 3 months of age. The most common symptoms of these bacterial infections include fever, lethargy, irritability and seizures which may progress to coma.

Intracranial hemorrhage as the sole etiology for neonatal seizures is estimated to account for approximately 10% of all neonatal seizures. Germinal matrix-intraventicular hemorrhages account for the majority of these seizures. In the premature infant, small germinal matrix hemorrhages do not result in seizures. In general, these hemorrhages present clinically with lethargy and a sudden drop in hematocrit, usually within the first 3 days of life. Seizures occur less frequently as the initial presentation in this subgroup of premature infants. When the hemorrhage also involves the surrounding parenchyma or is extensive, seizures are often a common correlate. Generalized tonic seizures are the most typical seizures, although subtle seizures have also been documented. In the subgroup of premature infants with germinal matrix hemorrhage who also have parenchymal infarctions, seizures are also prominently seen, typically later in the first week of life. Subarachnoid hemorrhages can also produce seizures. Classically, these seizures occur on the second day of life in an otherwise healthy looking infant-these seizures have been nicknamed "well-baby with seizures". They resolve quickly with no known sequelae. Subdural hemorrhages can also occur in the newborn infant, usually associated with trauma. There is commonly an associated cerebral contusion. Seizures in this clinical context are often focal and not multifocal. One large retrospective study found that 50% of newborns with subdural hemorrhages had seizures, usually within the first 48 hours after the traumatic event.

Metabolic disturbances can also cause neonatal seizures. The most common metabolic etiologies for neonatal seizures include hypoglycemia, hypocalcemia, and hypomagnesemia. Hypernatremia and hyponatremia can also produce seizures in the neonatal period but are less common. Infants of diabetic mothers (IDM) or infants who are small for gestational age (SGA) are at the greatest risk for hypoglycemia, hypocalcemia, and hypomagnesemia. The most common presenting symptoms of hypoglycemia in SGA infants are neurological and include seizures, hypotonia, jitteriness, stupor, and apnea. Onset is usually in the first 2 or 3 days of life. The hypoglycemia rarely occurs in isolation and is commonly associated with perinatal asphyxia, intracranial hemorrhage, and infection. In contrast, IDM who present with hypoglycemia are often minimally symptomatic, possibly related to the short duration of the hypoglycemia. Hypocalcaemia most often occurs in SGA infants, but can occur in IDM. As with hypoglycemia, hypocalcemia rarely presents alone and is often associated with perinatal asphyxia. In the past decade, these metabolic disturbances are often anticipated, recognized early, and treated effectively and quickly. The severity of the neurological symptoms is directly correlated with the duration of the metabolic disturbance.

Inborn errors of metabolism are relatively rare causes of seizures in the neonatal population; however, if there is no evidence of hypoxic ischemic injury, sepsis, or hemorrhage, metabolic diseases must then be considered. Metabolic disorders that can result in neonatal seizures include aminoacidopathies, urea cycle disorders, biotinidase deficiency, mitochondrial disorders, glucose transporter deficiency, peroxisomal disorders and defects in beta-oxidation. Metabolic evaluation should include: (1) Blood-lactate, pyruvate, ammonia, biotinidase, quantitative amino acids, and very long-chain fatty acids; (2) urine - quantitative organic acids; (3) cerebrospinal fluid - cell count, pyruvate, lactate, glucose (with simultaneous plasma glucose), and quantitative amino acids.

Disturbances of amino acid or organic acid metabolism are often the most common inborn errors of metabolism that present with neonatal seizures.

Pyridoxine dependency, a defect in pyridoxine metabolism, is a rare disorder, but produces severe seizures in the neonatal period that are resistant to antiepileptic drug therapy.[14,15] This inborn error of metabolism can produce intrauterine seizures or seizure onset in the first days after birth. One recent study found that there were low levels of pyridoxal-5-phosphate in the cerebrospinal fluid of affected infants. The probable molecular defect is a disturbance in the binding of pyridoxal-5-phosphate to the apoprotein of glutamic acid decarboxylase, which is an essential factor in the synthesis of gamma-amino-butyric acid, the primary inhibitory neurotransmitter of the brain. This hypothesis is further supported by the finding of low GABA levels and elevated glutamate levels in the CSF in these patients. Glutamate, an excitatory neurotransmitter, can be neurotoxic (as discussed above) and may produce neuronal cell injury or death. Clinical evidence suggests that the prognosis for these infants depends on the duration of the seizures, recognition of the etiology, and initiation of therapy within the first month of life. Infants with prolonged and repetitive seizures have been reported to have cortical atrophy, deficient cerebral myelination, and intellectual impairment. The seizures are usually multifocal clonic seizures. Diagnosis is empiric. Intravenous infusion of 50 mg to 100 mg of pyridoxine during EEG monitoring will classically demonstrate a cessation of clinical seizures and normalization of the EEG within minutes after the infusion is given. Subsequently, the infant must be started on maintenance pyridoxine at 50 mg to 100 mg twice a day to maintain freedom from seizures. In some infants, though, the response is not immediate. Therefore, in any infant with medically refractory seizures, it is always a wise decision to treat with pyridoxine for 1 to 2 months to determine if pyridoxine dependency is the etiology for the seizures.

There is also a small group of infants with glucose transporter deficiency. In these infants, there is a defect in the facilitated transport of glucose across the blood-brain barrier, resulting in hypoglycorrhachia and impaired cerebral energy metabolism. The CSF lactate in these infants is also low, implying impaired glucose transport, rather than a disturbance in mitochondrial function. It is imperative to obtain a simultaneous sample of serum glucose compared with the CSF glucose. The ratio of CSF glucose to serum glucose should be at least two to three. Early treatment with the ketogenic diet can be protective to the brain, because the brain can use fat as its sole source of energy. Without appropriate treatment, these infants have microcephaly, developmental delays, and medically refractory seizures.

Genetic neonatal epilepsy syndromes: There are a small group of infants who have idiopathic, genetically determined neonatal convulsions. There, seizures may be partial or generalized. These infants have a family history of other relatives with this disorder.

Familial neonatal convulsions

Familial neonatal convulsions [15,16] begin in the second or third day of life and can be either partial or generalized. Typically they are associated with behavioral arrest, eye deviation to one side, and tonic stiffening, sometimes myoclonic jerks. The seizures can occur 15 to 20 times per day. Interictal EEGs can be normal, but ictal findings typically consist of an initial electrodecremental event (flattening of the EEG) followed by bilateral spike and slow-wave discharges, often accompanied by rhythmic clonic activity. The seizures are outgrown in the first year of life and are considered benign. The diagnosis is made by obtaining a good family history for similar seizures in

the newborn period. Diagnostic studies, including EEG, MRI scan of the brain, and blood work, are all normal. Many of these infants receive an infusion of pyridoxine without response. Therapeutically, these seizures may be unresponsive to antiepileptic medication. Small minority of these children (10%) develop nonfebrile seizures and require antiepileptic medication. Two genes have been identified for this disorder. One is located on chromosome 20 and the other on chromosome 8. Both code for a potassium channel.

Fifth-day fits

Fifth-day fits occur in full-term infants and can appear to be quite fulminant, with seizures occurring up to 15 to 20 times per day. Typical onset is in the first week of life. The infants are otherwise healthy appearing. The seizures are usually clonic and fluctuate between the right and left side. Sometimes the seizures are associated with apnea and cyanosis. Duration of the seizures is usually less than 24 hours. The etiology remains undetermined, but may be linked to acute zinc deficiency.[17] These seizures may account for as many as 5% of seizures in full-term infants. It is uncertain that antiepileptic medication makes any difference with respect to seizure control.

Severe catastrophic epilepsy syndromes

There are also two severe, catastrophic epilepsy syndromes identified during the neonatal period. Although not officially recognized by the International Classification System, Ohtahara's syndrome and early myoclonic encephalopathy fit easily into the category of neonatal generalized epileptic syndromes. These two syndromes have many similarities. Both begin in the neonatal period, usually in the first 10 days after birth. The children with these encephalopathies have severe neurological disease, with developmental delays and intractable seizures.[18,19,20]

Ohtahara's syndrome

In Ohtahara's syndrome, the seizures consist of brief, repetitive "tonic spasms" that can be difficult to distinguish clinically from infantile spasms. The seizures can be isolated or can occur in clusters. The interictal EEG shows a persistent burst suppression pattern with an electrodecremental response during the ictal phase. The etiologies for Ohtahara's syndrome are usually malformations of cortical development.[18,19] The prognosis is poor for cognitive and motor development. Successful treatment of this condition is very difficult, but adrenocorticotropic hormone (ACTH), prednisone, valproic acid (Valproate), topiramate, and felbamate have been tried. In the Ohtahara's series, one third of the patients died in infancy.

Early myoclonic encephalopathy

In early myoclonic encephalopathy, the seizures are characterized either by fragmentary myoclonic jerks or violent myoclonic spasms. As with Ohtahara's syndrome, the interictal EEG also demonstrates a burst-suppression pattern. The ictal event, however, is associated with bursts of generalized polyspike, spike, and slow-wave discharges, followed by an electrodecremental pattern. Also as with Ohtahara's syndrome, these infants are severely neurologically impaired. Many die in early infancy. The most common identified etiologies are the inborn errors of metabolism, especially propionic acidemia, nonketotic hyperglycinemia, and D-glyceric acidemia.[19,20]

Table 2: Etiologies of neonatal seizures

Disorder	24 Hours	24-72 Hours	3-7 Days	7-28 Days
Cerebrovascular	Hypoxic ischemic encephalopathy	Intraventricular hemorrhage (preemies)	Cerebral infarction	
	Subarachnoid hemorrhage	Cerebral infarction	Intracerebral Hemorrhage	
	Intraventricular hemorrhage	Intraventricular hemorrhage		
		Subdural hemorrhage		
		Subarachnoid hemorrhage		
Traumatic	Laceration of tentorium or falx	Cerebral contusion		
	Bacterial meningitis	Bacterial meningitis	Bacterial meningitis	Bacterial meningitis
Infectious	Sepsis	Sepsis	Sepsis	
	Intrauterine infection	Intrauterine infection		Herpes simplex encephalitis
Iatrogenic	Anesthetic toxicity	Drug withdrawal		
Nutritional	Pyridoxine dependency	Pyridoxine dependency		
	Hypoglycemia	Hypoglycemia	Hypocalcemia	
Developmental	Congenital malformations	Congenital malformations		Congenital malformations
	Neurocutaneous disorders	Neurocutaneous disorders	Neurocutaneous disorders	
Metabolic		Hypoparathyroidism	Hypoparathyroidism	Adrenoleukodystrophy
		Hypocalcemia	Kernicterus	Fructose dysmetabolism
		Glycine encephalopathy	Ketotic hyperglycinemia	Gaucher's disease type II
		Glycogen synthase deficiency		GM_1 gangliosidosis
		Urea cycle disorders	Urea cycle disorders	Ketotic hyperglycinemia
		Nonketotic hyperglycinemia		Maple syrup urine disease
				Urea cycle disorders

Adapted from Fenichel G: Paroxysmal disorders. In Fenichel GM(ed): Clinical Pediatric Neurology: A Signs and Symptoms Approach. Philadelphia, Saunders, 1988, pp 1-41.

Investigations

Lab Studies:

- Serum glucose and electrolytes, including calcium: Transient neonatal hypocalcemia is a cause of neonatal seizures during the first 3 weeks of life.
- CSF analysis: This should include tests checking for pleocytosis, xanthochromia (suggestive of blood breakdown products, particularly if jaundice is not present), lactic acid and pyruvate (for evidence of mitochondrial cytopathies), polymerase chain reaction (PCR) for herpes virus, and glucose concentration (low glucose concentration is suggestive of bacterial meningitis). In the absence of bacterial meningitis, persistently low CSF glucose concentrations may suggest a glucose transporter defect.
- TORCH (toxoplasmosis, rubella, CMV, herpes) and infection studies
- Urine organic acids
- Serum amino acid assay
- Renal function tests: These tests rule out post hypoxic renal dysfunction.

Imaging Studies:

- Cranial ultrasound
  - Cranial ultrasound is performed readily at the bedside; it is a valuable tool to quickly ascertain whether intracranial hemorrhage, particularly intraventricular hemorrhage, has occurred.
  - A limitation of this study is the poor detection rate of cortical lesions or subarachnoid blood.
- Cranial CT scan
  - Cranial CT scan is a much more sensitive tool than ultrasound in detecting parenchymal abnormalities.
  - The disadvantage is that the sick neonate must be transported to the imaging site.
  - A distinct advantage is that with modern CT techniques, a study can be obtained in approximately 10 minutes.
  - Cranial CT scan can delineate congenital malformations. Subtle malformations may be missed on CT scan, requiring an MRI study.
- MRI
  - Cranial MRI is the most sensitive test in determining the etiology of neonatal seizures, particularly when electrolyte imbalance has been excluded as a cause for seizures.
  - A major disadvantage is that it cannot be performed quickly and, in an unstable infant, it is best deferred until the acute clinical situation resolves.

Other Tests:

- EEG plays a vital role in properly identifying and differentiating neonatal seizures from nonepileptic events but continuous 12 lead EEG is very cumbersome, time consuming and labour intensive. Amplitude integrated EEG (aEEG) or cerebral function monitor is

being used extensively in some units for clinical bedside monitoring of the asphyxiated and sick neonates to detect seizure episodes as well as changes in the baseline voltage and its recovery or deterioration with passage of time helping in prognostication.

- ❖ Video EEG monitoring may be helpful to resolve the dilemma regarding electroclinical seizures vs. electrical or purely clinical seizure phenomena.

Newer perspectives

Premature neonates represent a fragile patient population, often subjected to intensive clinical care and multiple drug therapy, which must be monitored carefully and continuously. The difficult and painful nature of repetitive blood sampling, particularly in this population, has provided considerable impetus for the development of noninvasive methods for monitoring blood analytes. Reverse iontophoresis, a relatively new technology already used for the transdermal monitoring of blood glucose levels in adults, may be particularly well-suited to exploit the unique properties of preterm neonatal skin. The underdevelopment of the premature infant's epidermis, and more specifically the stratum corneum (SC), results in an increased permeability to molecular transport.

Treatment of neonatal seizures

Initial Medical Management

There are three phases of acute therapy that are typically individualized for each infant: initial medical management, etiology-specific therapy, and acute AED therapy. During initial medical management of neonates with seizures, the usual principles of general medical management and cardiovascular-respiratory stabilization apply. These supporting measures are particularly important when seizures occur in critically ill neonates; when the seizures are frequent or prolonged; or, when the seizures are associated with clinically significant changes in respiration, heart rate, and blood pressure as a consequence of the seizures themselves or of vigorous AED therapy. Although all neonates may not require aggressive measures to support respiration and circulatory perfusion, the early anticipation of these clinical problems may minimize potential difficulties later. When neonatal seizures occur, blood sugar by dextrostix should be obtained immediately. Clinical studies in newborn animals have shown that glucose administration just before seizures prevents the decrease in brain glucose levels that occurs with status epilepticus and markedly reduces mortality and neuronal cell loss. The glucose appeared to serve as a carbon source, because DNA, RNA, and protein concentrations were maintained in these animals, despite the fact that brain ATP and phosphocreatine concentrations dropped. If there is hypoglycemia, 10% dextrose solution should be administered intravenously, followed by intravenous continuous glucose solution. Hyperglycemia should be avoided.

If seizures persist and are recurrent, 20 mg/kg of phenobarbital should be administered intravenously, followed by additional 10 mg/kg boluses to a total maximum of 40 mg/kg, preferably until all electrographic and clinical seizure activity is stopped. If respiratory depression is a concern, or in infants with hypoxic ischemic injury (who may not tolerate high-dose phenobarbital), the infant could be given 20 mg/kg of intravenous fosphenytoin. Fosphenytoin is the salt ester of phenytoin. Fosphenytoin has major advantages for a newborn, because it is an aqueous solution that is soluble in glucose-containing solutions, it can be administered more quickly than phenytoin, and it will not cause "purple glove syndrome." Purple glove syndrome represents the soft-tissue

necrosis and injury that can occur when intravenous phenytoin, which is highly alkaline, is given.

If a neonate is in status epilepticus, lorazepam is probably the treatment of choice. It has a rapid onset of action and a long half-life. The long half-life is very different from diazepam, which is rapidly redistributed in fat. Lorazepam has a much smaller volume of distribution, accounting for its prolonged retention at high levels in the brain. The dosage should be 0.05 to 0.1 mg/kg. The 0.1 mg/kg dosage is the preferred dosage. If seizures do not stop, phenobarbital should be given 20 mg/kg intravenously. The level may be pushed up to 40 if necessary, using repetitive dosages. Phenytoin may be used subsequently at 20 mg/kg.

Topiramate and zonisamide are emerging therapies that deserve further clinical study. Topiramate is rapidly metabolized in young infants. Due to their rapid hepatic metabolism, neonates require dosages of up to 30 to 40 mg/kg/day divided three times per day. Efficacy and safety in neonates have not been determined. There is Food and Drug Administration (FDA) approval for topiramate in children aged 2 and older. Zonisamide has been used in Japan for over 15 years and has demonstrated safety in this population in the neonatal period. Clinical studies for both AEDs are in process, but no definitive results have been released. Valproate has also been used in neonates for status epilepticus; however, the risk of hepatotoxicity in this age group is a valid concern. In some neonates, it may approach a 1:500 risk. The infants at highest risk have underlying neurologic conditions, are less than 2 years old, and are on multiple antiepileptic drugs. Felbamate, levetiracetam, and lamotrigine may also be effective in the treatment of neonatal seizures. Felbamate should be reserved for the some recalcitrant seizures, given its risk of aplastic anemia and liver failure. There is little pediatric experience on the use of levetiracetam in the newborn infant. The use of lamotrigine in the newborn may be limited, due to the requirement for a slow titration. Rapid titration of lamotrigine places an infant or child at greater risk for a life-threatening allergic rash.

Etiology-Specific Therapy

When potentially treatable causes of seizures are identified, etiology-specific therapy should be initiated as soon as possible to limit ongoing CNS injury. Etiology-specific therapy may also contribute to the control of seizures, because some seizures may not be responsive to AED therapy unless the underlying causes are successfully treated. In some cases, etiology-specific therapy may be the only treatment needed, such as the correction of hypocalcemia, hypomagnesemia, or hypoglycemia (Table 3). In other cases, however, AEDs must be administered for seizure control when brain injury has been caused by the primary process.

First-Line AED Therapy

There is no evidence from randomised controlled trials that either supports or fails to support the use of anticonvulsant therapy for the treatment of seizures in neonates. Data from randomised controlled trials to support the choice of anticonvulsant too are limited. The AEDs typically used in the acute treatment of neonatal seizures are phenobarbital, phenytoin, and a benzodiazepine (Clonazepam or lorazepam) given intravenously. The dosages administered are phenobarbital 20 mg/kg as a loading dose, followed by additional increments of 10 mg/kg as required to achieve serum levels between 20 and 40 micrograms/ml; phenytoin, 20 mg/kg as a loading dose to achieve serum levels between 15 and 20 micrograms/ml; diazepam, 0.1 to 0.3 mg/kg in repeated dosages; and, lorazepam, 0.05 mg/kg in repeated dosages (Table 4). Acute administration of each of these

AEDs may carry some risk of adverse reactions, such as CNS depression, hypotension, bradycardia, and respiratory depression (all of which may be associated with phenobarbital, diazepam, and lorazepam) and cardiac arrhythmia (associated with phenytoin). Thus, appropriate monitoring of infant's vital signs during therapy is needed.

Table 3. Etiology-specific therapy for neonatal seizures of metabolic origin

	Acute Therapy	Maintenance Therapy
Glucose, 10% solution	2 mL/kg, IV	up to 8 mg/kg/minutes, IV
Calcium gluconate, 10% solution (9.4 mg of elemental Ca/ml)	2 mL/kg IV over 10 minutes (18 mg of elemental Ca/kg)	8 m/kg/d IV† (75 mg of elemental Ca/kg/d)
Magnesium sulfate, 50% solution (50 mg of elemental mg/mL)	0.25 mL/kg, IM	0.25 mL/kg IM repeated every 12 hours until normomagnesemia
Pyridoxine	100 mg, IV	

After restoration of normocalcemia, tapering dosage may help in preventing rebound hypocalcemia. Diagnosis of hypoglycemia, hypocalcemia and hypomagnesemia may vary between laboratories and is dependent on neonate's gestational age (with preterm infants tending to tolerate lower physiologic levels). Administration of metabolic-correcting solutions requires careful monitoring of infant's systemic homeostasis, including EKG monitoring during administration of calcium.
IM--intramuscular;
IV--intravenous.

Table 4. Dosages of first-line and second-line AEDs in the treatment of neonatal seizures

	Dose		Average Therapeutic Range	Apparent Half-life
Drug	**Loading**	**Maintenance**		
Phenobarbital	20 mg/kg IV; up to 40 mg/kg	3-4 mg/kg in two doses	20-40 mcg/L	100 h after day 5-7
Phenytoin	20 mg/kg IV; over 30-45	3-4 mg/kg in 2 to 4 doses	15-25 mcg/L	100 h (40-200)
Lorazepam	0.05 mg/kg (IV); over 2-5	May be repeated	31-54 h	
Diazepam	0.25 mg/IV, bolus	May be repeated 1-2 times	Not known and hence used very sparingly	31-54 h

AED--antiepileptic drug.
From Mizrahi and Kellaway, 1998

There is a relative consensus as to which AEDs are first- and second-line drugs. Phenobarbital is almost universally accepted as the first-line AED and phenytoin as the second-line AED.[21,22] There is less of a consensus, however, as to the use of additional AEDs if the initial drugs fail to control the seizures. Typically, a benzodiazepine (e.g., clonazepam or lorazepam) is given in this situation. There is also emerging discussion regarding the effectiveness of initial benzodiazepine treatment prior to administration of first-line, longer-acting AEDs, particularly if the seizures to be treated are brief and infrequent.

There have been few controlled studies as to the relative efficacy of various AEDs in the initial treatment of neonatal seizures; however, the effectiveness of a loading dose of phenobarbital to achieve therapeutic serum levels in previously untreated neonates has been reported but confounded by discrepancies in seizure definition and dosing schedules between studies. Overall, the studies suggest that verification of a loading dose alone does not assure adequate therapeutic serum levels, with rates of achieving this goal ranging from 32% to 86%. A double-blind prospective study by Painter[23,24] et al has documented that if phenobarbital is used as the initial therapy for neonatal seizures, 42% of seizures stop after administration. If phenytoin is combined with phenobarbital, the efficacy increases to 62%. If phenytoin is used as the first drug, 43% of seizures will stop. If phenobarbital is subsequently combined with phenytoin, the efficacy is 63%. Clearly, there is a need for additional treatments.

It should be noted that the use of fosphenytoin in neonates with seizures has been recently investigated. Findings indicate the conversion half-life of fosphenytoin and resultant plasma total and free (unbound) phenytoin concentration-time profiles following intravenous administration in neonates to be similar to older children and adults, although the range of values was greater in neonates and that the drug may be as efficacious as phenytoin in this age group with potentially fewer potential risks compared with the intravenous administration of phenytoin.

Regardless of the initial AED used, monotherapy is most appropriate. Dosages of the initial AED may be increased to a level when seizures cease or when there is evidence of clinical toxicity, such as excessive sedation. Only when seizures have not been controlled by the maximum tolerated dose of the initial AED should a second AED be added.

Adjuvant and alternative therapies for Refractory seizures

Because neonatal seizures may be resistant to traditional AEDs, other medications have been tried with varying success;[25,26,27] however, the true efficacy of these agents is difficult to assess because some trials have not been well controlled. In addition, reports of the effectiveness of these medications have included a limited number of patients and involve infants who have already received and failed other AEDs or who were receiving other AEDs concurrently. In addition, some AEDs were given orally rather than parenterally, limiting assessment of the immediate effect of these medications on seizure control. Because of the preliminary nature and limitations of these trials, little safety data are available. Adjuvant and alternative AEDs reported to be useful in neonatal seizure therapy are listed in *Table 5 and 6.*

Table 5. Dosages of adjuvant and alternative AEDs in the treatment of neonatal seizures that are given intravenously

	Dose		Range of Therapeutic Serum Levels	Comments and References
AED	**Loading**	**Maintenance**		
Clonazepam	0.1 mg/kg IV; infusion over 5		28-117 mg/mL	Higher doses may be less effective
Lidocaine	4 mg/kg/hr IV; first day or 2 mg/kg IV	reduction by 1 mg/kg/h/d on subsequent days or 6 mg/kg/h	2.8-10.5 mg/l	Narrow therapeutic range, can be a convulsant at higher levels
Midazolam	0.15 mg/kg IV	0.1-0.4 mg/kg/h IV		Water-soluble, without polyethylene glycol and sodium benzoate as additives Short half-life (0.8 h)[
Paraldehyde	400 mg/kg IV or 200 mg/kg IV	200 mg/kg IV or 16 mg/kg/h	>10 mug/l	Clearance decreased by phenobarbital and in asphyxia Efficacy linearly dependent on serum levels

IM--intramuscular; IV--intravenous.
AED--antiepileptic drug.
From Mizrahi and Kellaway, 1998

Table 6. Dosages of adjuvant and alternative AEDs in the treatment of neonatal seizures that are given orally

	Dose		Range of Therapeutic Serum Levels	Comments and References
AED	**Loading**	**Maintenance**		
Carbamazepine	5 mg/kg q 12 h, by mouth	5 mg/kg q 12 h by mouth	10-40 mumol/l	Investigated as alternative maintenance AED No data on efficacy
Primidone	15-25 mg/kg	12-20 mg/kg/d	3-18 mug/l	Elevation of phenobarbital levels if given concurrently Difficult to achieve initial high primidone levels
Valproate	20-26 mg/kg by	5-10 mg/kg q 12 mouth	40-50 mug/l h by mouth	Use associated with hyperammonemia Used with caution as adjunctive agent in polytherapy[
Vigabatrin	50 mg/kg by mouth	50 mg/kg/d by mouth	Incomplete data in the neonate	Greater experience in infantile spasms

AED--antiepileptic drug.
From Mizrahi and Kellaway, 1998

Focal Clonic or Focal Tonic Seizures: Prolonged and Recurrent

Focal clonic seizures are repetitive and rhythmic muscle contractions. Focal tonic seizures, are characterized as sustained posturing of a limb. Both types cannot be arrested by restraint or limb repositioning. The focal tonic seizures characterized by eye deviation can be differentiated from the random eye movements of nonepileptic motor automatisms, because the epileptic tonic eye deviation is sustained and cannot be evoked by stimulation. These clinical features help to designate them as epileptic in origin. Once the clinical focal clonic or focal tonic seizures are

considered epileptic, their duration and severity must be considered. When sustained and prolonged, they are treated vigorously with AEDs.

Focal Clonic or Focal Tonic Seizures: Brief and Infrequent

The specific features of seizures of epileptic origin are the same as those just described. Although AEDs may be used in attempts to control them, because these seizures may be brief, occur infrequently, and have a short natural history with relatively rapid spontaneous resolution, their use may not always be required. In these circumstances, the potential adverse effects of AEDs may be greater than the potential risk of these brief and infrequent seizures on the developing brain. There are no quantitative criteria for the differentiation of brief and infrequent seizures from prolonged and recurrent seizures. In addition, the issues of whether AEDs or seizures adversely affect the immature brain remain unresolved.

Generalized Tonic Posturing and Motor Automatisms: Provoked or Intensified by Stimulation and Suppressed by Restraint

Generalized tonic posturing and motor automatisms [more traditionally referred to as subtle seizures] may be presumed to be of nonepileptic origin. These include ocular signs, oral-buccal-lingual movements, movements of progression and complex purposeless movements. This non-epileptic designation is based on clinical features of the seizures and their response to stimulation and restraint. The differentiation from epileptic seizures can be made at the bedside based on the features of the spontaneous events and the response of the infant to clinical maneuvers. The spontaneous events can be suppressed by restraint or repositioning of the limbs or trunk, and events can be evoked or intensified by tactile or proprioceptive stimulation that is similar in character to spontaneous events. Traditionally, these clinical events have been treated with AEDs, often in high doses. In some instances, the seizure frequency and severity have diminished, most likely not the result of specific antiepileptic properties, but because the drugs used are also CNS depressants. Overall, if generalized tonic posturing and motor automatisms demonstrate characteristic clinical features, they can be presumed to be of nonepileptic origin and do not require AED therapy. Although the clinical events may be initially quite dramatic, their natural course is one of gradual and spontaneous resolution without AED therapy.

Generalized Tonic Posturing and Motor Automatisms: Not Responsive to Stimulation or Suppressed by Restraint

For some infants, the clinical features of spontaneous generalized tonic posturing and motor automatisms may be typical of nonepileptic events but they may not respond in a characteristic way to restraint, repositioning, or stimulation. This may be because of techniques of stimulation or restraint or to other undefined factors. In these instances, the decision to initiate AED is more difficult. Some clinicians may withhold AEDs with the understanding that the clinical features of the spontaneous events are evidence enough of the nonepileptic origin of the events. Other clinicians, however, may initiate AED treatment with the belief that clinical observation and maneuvers alone cannot provide data to indicate underlying pathophysiology. Bedside EEG and EEG/video monitoring are invaluable tools in the diagnosis of neonatal seizures and, when available and appropriately applied, provide additional data in assessing whether AED therapy should be initiated.

Clinical Seizures in the Absence of EEG Seizure Activity

These clinical seizure types include generalized tonic posturing and motor automatisms. As discussed earlier, the clinical features of the spontaneous events and the response of the events to clinical maneuvers suggest they are nonepileptic in origin. The lack of EEG seizure activity at the time of the clinical seizures provides additional supportive data. These clinical events are not treated with AEDs.

EEG Seizure Activity in the Absence of Clinical Seizures

Electrical seizure activity without accompanying clinical seizures may occur in neonates who are pharmacologically paralyzed, in neonates with encephalopathy seizure discharges of the depressed brain type, or in neonates with epileptic seizures already being treated with AEDs (see discussion below). Although electrical seizures occurring in the absence of any clinical seizure activity are treated with AEDs, these electrical seizures may be highly resistant to therapy despite high dosages of several AEDs. High-dose polypharmacy may be used in attempts to abolish EEG seizure activity, however, at the risk of adverse effects of these medications. This raises the question of the relative value of AED therapy compared with the potential for respiratory, cardiac, cardiovascular, or CNS depression.

Response of Clinical and EEG Seizures to Acute AED Therapy

In untreated infants, clinical epileptic seizures occur in a time-locked relationship to EEG seizure activity. A characteristic with the persistence of initial response to AED administration is the cessation of clinical seizures; however, the EEG seizure activity may persist. This initial response to AED treatment has been referred to as decoupling of the clinical from the electrical seizure. The response of the electrical seizures to either increasing dosages of an AED or the addition of other AEDs is variable and may prove to be highly resistant to additional AED therapy.

This decoupling response to AEDs raises an important clinical question: What is the endpoint of AED therapy, the cessation of clinical or electrical seizure activity? Vigorous attempts to eliminate electrical seizure activity may require the administration of high dosages or multiple AEDs. Regardless of the degree of success in seizure control (which is often incomplete) high-dosage or polypharmacy may be associated with CNS depression, systemic hypotension, and respiratory depression. Thus, the clinician must consider several factors: the potential risks of aggressive AED treatment, the potential benefits of therapy, the likelihood of success, and whether or not electrical seizure activity is harmful to the developing brain.

Efficacy and Safety of Acute AED Therapy

There is no clear consensus as to what, if any, sequelae may be associated with the occurrence of epileptic seizures in the developing brain. Some animal studies indicate that there are changes in the CNS at a cellular or molecular level or even of brain circuitry. These may be transient or their influence may be limited when animal performance is tested. Recently, performance testing has revealed some abnormalities of post-neonatal behavior adding new data to the argument. In addition recent reports suggest (in animal studies), that early seizures may increase chances for seizure-induced injury later in life.

There are few conclusive clinical investigations of the adverse systemic effects of seizures.

Infants with prolonged seizures, however, may experience changes in respiration, heart rate, or blood pressure, and may also have increased metabolic requirements during seizures. These findings may contribute to further compromise in an already ill infant.

There is also an equal lack of consensus concerning the possible adverse effects of AEDs on the developing brain. Although experimental data suggest some alterations in cell growth and energy substrate used with AEDs, it is unknown whether these findings are applicable to human neonates. In addition, some consider any potential risk small compared with the overall potential gain. There have also been few studies of adverse effects of acute AED therapy, although it has been noted that aggressive treatment may result in CNS depression, hypotension, bradycardia, and respiratory depression with resultant potential for secondary CNS hypoxia or ischemia.

Proposed Regimens for Acute Therapy

A balanced AED acute treatment regimen is needed that may minimize perceived risks and maximize therapeutic effectiveness, despite the lack of definitive supporting data. The following has been proposed:[28] acute therapy is initiated to eliminate clinical seizures with the first-line AED phenobarbital. If clinical or EEG seizures persist, phenobarbital dosage is increased, then, if necessary, phenytoin is added. If required, a benzodiazepine is also added. If clinical seizures are controlled, but electrical seizures persist, phenobarbital and then phenytoin dosages are increased to obtain high-therapeutic serum levels; however, it is acknowledged that there may be a point of diminishing therapeutic returns. If these high levels do not control electrical seizure activity, it is likely further therapy may provide only the potential for control at the risk of systemic physiologic and CNS depression. Often, in these circumstances, further AED therapy is not pursued.

Chronic Therapy

Not all neonates require chronic therapy after acute seizures have been controlled. Specific regimens of maintenance therapy and their application remain controversial. When a therapeutic effect is obtained acutely, infants are typically placed on maintenance doses of the AEDs that control seizures, phenobarbital alone or with phenytoin if it had been required to control the clinical seizures acutely (the maintenance dosage of each is 3 to 4 mg/kg/d). Serum levels are monitored; however, the presence of clinical toxicity rather than elevated serum drug levels should determine adjustment of dosages.

The maintenance of stable chronic levels of either phenobarbital or phenytoin may not always be straightforward and warrant special mention. When maintenance dosages of phenobarbital of 5 mg/kg/d are used, there may be drug accumulation within the first 5 to 10 days of life. This is because of the relatively slow elimination rate of phenobarbital during this period, and this effect may be enhanced in asphyxiated infants who may have concomitant hepatic or renal dysfunction. This may lead to unintended AED toxicity while administering stable dosing. Eventually, however, elimination rates increase and may lead to the potential for subtherapeutic levels on the same stable dosing. Thus, maintenance-dosing requirements are relatively lower early in the course of therapy and increase later. There also may be problems in maintenance of therapeutic levels of phenytoin because of its nonlinear kinetics and the rapid decrease in elimination rates during the first weeks of life. In general, careful monitoring of serum AED levels is needed during the first few weeks of maintenance therapy to avoid unwanted fluctuations and variability in seizure control.

Discontinuation of AED Therapy

The discontinuation of AEDs after a period of clinical seizure control is individualized. No specific practice guidelines have been widely accepted, and specific clinical and EEG predictors of recurrent seizures following AED withdrawal have not been identified. Most clinicians use personal judgement and clinical experience. Maintenance schedules range from 1 week up to 12 months after the last seizure; however, there has been increasing clinical interest in, and the application of, a short-term therapy regimen, with AED withdrawal 2 weeks following the infant's last clinical seizure and initiated after an EEG showing no ictal activity. Currently, quite a few units have started to follow tapering of anticonvulsants after about 96 hours of seizure free interval and stoppage of each drug over the next 48 hours in cases of hypoxic ischemic encephalopathy, permitting the clinicians to stop AEDs during the neonatal hospital stay. Most babies go home without maintenance AED therapy and are evaluated during the follow up with clinical neurologic examination, subsequent EEGs and recurrence of seizures.

The natural history of the specific neonatal seizure disorder may be the best determinant of the timing of AED discontinuation. For example, seizures that are the consequences of acute disorders, such as hypocalcemia, may not require AEDs after the disorder has been successfully treated. On the other hand, seizures associated with structural CNS injury (e.g., hemorrhage, infarction, or malformation) may raise clinical suspicion of the potential for further seizures. Overall, the decision to withdraw AEDs is primarily based on the clinical course of individual infants, the neurologic examination, the presence or absence of clinical seizures, and the absence of electrical seizures recorded by the EEG performed before the initiation of AED tapering.

Prognosis

Neonatal seizures are almost always symptomatic, with an underlying neurological condition. As a result, the prognosis for these infants is usually poor. In a study by MacBride et al, continuous EEG monitoring and outcome data were reviewed in 40 patients with documented electrographic seizures.[29] These infants were identified as having electrographic seizures (with or without clinical manifestations) from a group who met at-risk criteria for neonatal seizures, such as hypoxia-ischemia, intraventricular hemorrhage, sepsis, meningitis, and hyponatremia. Of the 68 selected infants, 40 were having electrographic seizures. Forty three percent of infants had episodes of status epilepticus, ranging from 38 minutes to 32 hours. Thirty percent of infants had refractory electrical status epilepticus that did not respond to 40 mg/kg of phenobarbital and 20 mg/kg of phenytoin. Furthermore, the occurrence of electrographic seizures was correlated with microcephaly, severe cerebral palsy, and failure to thrive. In the subgroup of patients with hypoxic ischemic encephalopathy (approximately 55% of the group), those with electrographic seizures were more likely to die of neurologic causes, have microcephaly, and have severe cerebral palsy. Forty percent of the infants with electrographic seizures either died from their neurologic insults or suffered from severe encephalopathy, in contrast to only 11% of the at-risk infants with no electrographic seizure suffering from death or severe encephalopathy.

In another study by Legido et al, 40 infants in whom neonatal seizures were confirmed by randomly recorded ictal EEG recordings were retrospectively studied to determine their neurologic outcome-developmental status, epilepsy, and cerebral palsy. There were 27 survivors, a mortality rate of 33%. Of those survivors, 70% had an unfavorable outcome. The rate of epilepsy was 56%,

63% had cerebral palsy, and 67% had significant developmental delays. The prognosis was related to the etiology. Specifically, in patients with hypoxic-ischemic encephalopathy, 100% of patients with a seizure frequency of greater than five per hour had developmental delay, and 100% of infants with hypoxic-ischemic encephalopathy who had severely abnormal neurologic evaluations developed epilepsy and had cerebral palsy. Eighty six percent of all patients with hypoxic ischemic injury developed epilepsy, higher than previous reports.

Infants with late-onset hypocalcemia or subarachnoid hemorrhage, on the other hand, will almost always recover without sequelae. The same can be said for the hereditary neonatal convulsions.

Neonates with metabolic disorders can have significant morbidity, particularly if they are not recognized. In a patient with a disorder in amino acid metabolism, alteration of the diet can have important therapeutic consequences. If an infant has pyridoxine dependent seizures, pyridoxine can successfully abort seizures and promote normal development (as discussed above).

The infants with malformations of cortical development can have catastrophic epilepsy syndromes, often presenting with medically refractory seizures in the first few weeks of life. Specifically, those infants with hemimegalencephaly, Sturge-Weber syndrome, or encephalomalacia due to perinatal infarctions may have fulminant, intractable seizures. These infants should be evaluated for epilepsy surgery in the initial few months of life. Preliminary clinical studies indicate that early intervention results in an improvement in prognosis, probably related to the great plasticity of the brain in this age group.[30,31,32,33] Clearly, there is a close relationship between neonatal seizures, the etiology for the neonatal seizures, and permanent neurologic sequelae in infants. Experimental animal studies have shown that seizures in immature animals, even if brief and recurrent, can cause neuronal lesions and clinical, long-term behavioral and cognitive impairments.

References

1) Lanska MJ, Lanska DJ: Neonatal seizures in United States: results of the national hospital discharge survey, 1980- 1991. Neuroepidemiology 1996;15: 117- 125.

2) Aicardi J, Sabril IS, Mumford JP, et al: Vigabatrin as initial therapy for infantile spasms: A European retrospective survey. Epilepsia 1996;37: 638-642.

3) Aicardi J: Neonatal seizures. In: Epilepsy in Children. 2nd edition. International Review of Child Neurology Series. New York, Raven Press, 1994, pp 217-252

4) Aicardi J: Early myoclonic encephalopathy (neonatal myoclonic encephalopathy). In: Roger J, Bureau M, Dravet C, et al. (eds): Epileptic Syndromes in Infancy, Childhood, and Adolescence. London, John Libbey & Company, Ltd, 1992, pp 13-23

5) Sankar P, Shin DH, Liu HT, et al. Patterns of status epilepticus induced neuronal injury during development and long-term consequences. J Neurosci 1998;18: 8382-93.

6) Sankar R, Shin DH, Wasterlain CG. Serum neuron-specific enolase is a marker for neuronal damage following status epilepticus in the rat. Epilepsy Res 1997;28: 129-36.

7) Holmes GL, Gairsa JL, Chevassus-Au-Louis N, et al. Consequences of neonatal seizures in the rat: morphological and behavioral effects. Ann Neurol 1998;44: 845-57.

8) Fujikawa DG, Dwyer BE, Lake RR, et al. Local cerebral glucose utilization during status epilepticus in newborn primates. Am J Physiol 1989; 256: C1160-7.

9) Wasterlain CG, Shirasaka Y. Seizures, brain damage and brain development. BrainDev 1994; 16:279-95.

10) Jorgensen OS, Dwyer B, Wasterlain CG. Synaptic proteins after electroconvulsive seizures in immature rats. J Neurochem 1980;35: 1235-7.

11) Young RS, Petroff OA, Chen B, et al. Brain energy state and lactate metabolism during status epilepticus in neonatal dog: in vivo P and H nuclear magnetic resonance study. Pediatr Res 1991;29:191-5.

12) Mizrahi EM. Neonatal seizures: problems in diagnosis and classification. Epilepsia 1987;28(Suppl 1):S46-55.

13) McCown TJ, Breese GR. The developmental profile of seizure genesis in the inferior collicular cortex of the rat: relevance to human neonatal seizures. Epilepsia 1992;33:2-10.

14) Mikati MA, Trevathan E, Krishnamoorthy KS, et al. Pyridoxine-dependent epilepsy: EEG investigations and long-term follow-up. Electroencephalogr Clin Neurophysiol 1991;78:215-21.

15) Clarke TA, Saunders BS, Feldman B. Pyridoxine-dependent seizures requiring high doses of pyridoxine for control. Am J Dis Child 1979;133:963-5.

16) Pettit RE, Fenichel GM. Benign familial neonatal seizures. Arch Neurol 1980;37:47-8. [51]. Miles DK, Holmes GL. Benign neonatal seizures. J Clin Neurophysiol 1990; 7:369-79.

17) Goldberg HJ, Sheehy EM. Fifth day fits: an acute zinc deficiency syndrome? Arch Dis Child 1982;57:633-5.

18) Aicardi J. Early myoclonic encephalopathy. In: RogerJ, DravetC, BureauM, editors. Epileptic syndromes in infancy, childhood, and adolescence London: John Libbey Eurotext; 1985. p. 12-22.

19) Ohtahara S, Ohtsuka Y, Yarnatogi Y, et al. The early infantile epileptic encephalopathy with suppression burst: developmental aspects. Brain Dev 1987;9:371-6.

20) Lombroso CT. Early myoclonic encephalopathy, early infantile epileptic encephalopathy, and benign and severe infantile myoclonic epilepsies: a critical review and personal contributions. J Clin Neurophysiol 1990;7:380-408.

21) Andre M, Vert P, Wasterlain CG: To treat or not to treat: A survey of current medical practice toward neonatal seizures. In: CG Wasterlain and P Vert (eds) Neonatal Seizures. New York, Raven Press, 1990, pp 303-307

22) Massingale TW, Buttross S: Survey of treatment practices for neonatal seizures. J Perinatol 13:107-110, 1993

23) Painter MJ, Minnigh MB, Gaus L, et al: Neonatal phenobarbital and phenytoin binding profiles. J Clin Pharmacol 34:312-317, 1994

24) Painter MJ, Scher MS, Stein AD, et al: Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med 341:485-489, 1999

25) Hellstrom-Westas L, Svenningsen NW, Westgren U, et al: Lidocaine for treatment of severe seizures in newborn infants. II. Blood concentrations of lidocaine and metabolites during intravenous infusion. Acta Paediatr Scand 81:35-39, 1992

26) Painter MJ, Alvin J: Choice of anticonvulsants in the treatment of neonatal seizures, in CG Wasterlain and P Vert (eds), Neonatal Seizures. New York, Raven Press, 1990, pp 243-256

27) Painter MJ, Gaus LM: Neonatal seizures: Diagnosis and treatment. J Child Neurol 6:101-108, 1991

28) Mizrahi EM, Kellaway P: Diagnosis and Management of Neonatal Seizures. New York, Lippincott-Raven, 1998, p 181

29) Gal P, Toback J, Boer HR, et al: Efficacy of phenobarbital monotherapy in treatment of neonatal seizures--relationship to blood levels. Neurology 32:1401-1404, 1982

30) Grigonis AM, Murphy EH: The effects of epileptic cortical activity on the development of callosal projections. Dev Brain Res 77:251-255, 1994

31) Haagerup A, Andersen JB, Blichfeldt S, Christensen MF: Biotinidase deficiency: two cases of very early presentation. Dev Med Child Neurol 39:832-835, 1997

32) Hahn JS, Tharp BR: Neonatal and pediatric electroencephalography. In: Aminoff MJ (ed) Electrodiagnosis in Clinical Neurology. New York, Churchill Livingstone, 1992, pp 93-142

33) Harris R, Tizard JPM: The electroencephalogram in neonatal convulsions. J Pediatr 57:501-520, 1960.

Dear Doctor,

It has been our endeavour to provide the medical fraternity, the latest thinking on a variety of medical topics, a tradition that we have been following for over 58 years through out Quarterly Medical Reviews.

This booklet is presented to you by Raptakos Brett, & Co. Ltd.

We would very much like to have your valuable suggestions and comments to make our future issues more meaningful to you.

We will appreciate if you could spend a few minutes to fill in your comments and mail the same to us.

Thanking You,

General Manager (Medical)

FEED BACK Oct. - Dec. 2008

1. Your comments on this issue of the Q.M.R.

   .....

   .....

2. Please suggest medical topics for our QMRs which could be printed in future.

   .....

   .....

3. Any other suggestions / comments.

   .....

   .....

Name: Dr. ..... M / F

Clinic Address: .....

.....

City: ..... State: .....Pin: .....

Tel: .....E-mail: .....

Qualifications: .....

Please mail this form to:

General Manager (Medical)
RAPTAKOS, BRETT & CO. LTD.
Dr. Annie Besant Road, Worli,
Munbai 400 030.