NEUROLOGY

DIAGNOSTIC NEUROPHYSIOLOGY IN CHILDREN

Lakshminarayanan Kannan

Abstract: *Neurophysiological tests are an extension of the clinical examination and should be interpreted in the overall clinical context. In children they are often misinterpreted due to lack of experience. Normal EEG does not rule out epilepsy and an abnormal EEG per se is not diagnostic of epilepsy. EEG is not a confirmatory test but rather supports clinical diagnosis of epilepsy. Routine interictal EEG does not distinguish between epilepsy and epilepsy mimics. Nerve conduction study and needle electromyography are performed infrequently in the current era of genetic diagnosis.*

Keywords: *Pediatric electroencephalogram, Video-electroencephalogram, Electroencephalogram in pediatric intensive care unit, Electromyography.*

Commonly performed neurophysiological investigations in children are Electroencephalogram (EEG), nerve conduction study (NCS), needle electromyography (EMG), brainstem evoked response audiometry (BERA) and visual evoked potential (VEP). It is essential for the practicing pediatrician to understand the common indications, clinical use, interpretation of findings and appropriate management. Though neurophysiology tests are performed similarly across age groups, it is technically challenging to perform these investigations in young and uncooperative children who may need sedation.

Electroencephalogram

Electroencephalogram (EEG) is the most common clinical investigation ordered in children with neurological diseases. In this article the common indications, myths about EEG, technicality of EEG recording, pitfalls in interpretation, common EEG findings and clinical utility will be discussed.

* Pediatric Neurologist and Epileptologist, Rainbow Children's Hospital, Chennai.
email: dr_kln@yahoo.co.in

Indications for EEG[1]

Common indications for ordering EEGs are enumerated in Box 1. Judicious use of EEGs avoids unnecessary sedation, undue anxiety for the family and avoids overtreatment with antiepileptic medications. Clinical condition of the child as a whole should be taken into consideration for treatment decisions rather than just an abnormal EEG report.

Most important indication for EEG is to support the clinical diagnosis of epilepsy. EEG is not a confirmatory test. Thus, the diagnosis of seizures and epilepsy is purely clinical, based on detailed history of the reported episodes from first hand witnesses and review of home videos.

The next common indication is to classify epilepsy into focal or generalized. This dichotomous classification of epilepsy has crucial implications for the diagnostic and treatment approach. Interictal EEG epileptiform patterns often guide in choosing the most appropriate and effective antiepileptic drug (AED) for the given patient.

EEG provides crucial prognostic information. In cases of childhood absence epilepsy or benign Rolandic epilepsy, the electroclinical syndromic diagnosis allays parental

Box 1. Indications for EEG[1]

- Support of clinical diagnosis of epilepsy
- Classification of epilepsy into focal or generalized epilepsy
- Diagnosis of specific electro-clinical epilepsy syndrome (e.g., West syndrome)
- Prognostication (recurrence risk, remission rate, etc.)
- Ascertaining recurrence risk before AED withdrawal
- Evaluation of first afebrile seizure
- Exclusion of non-convulsive status epilepticus in cases of coma
- Investigation of acute febrile encephalopathy
- Unexplained encephalopathy, global development delay, language regression / acquired aphasia / auditory agnosia

anxiety as well as avoids investigations such as MRI brain, metabolic work up, CSF analysis and muscle biopsy.

There is no role for serial follow-up EEGs to monitor epilepsy. Exceptions include childhood or juvenile absence epilepsy, continuous spike-wave in slow wave sleep (CSWS) syndrome or Landau-Kleffner syndrome where complete resolution or significant improvement in EEG abnormalities mark the treatment endpoint. In these conditions it is desirable to get an EEG before withdrawal of AEDs, as the EEG patterns predict recurrence risk.

There is no role for EEG in febrile seizures including both simple and complex febrile seizures (Box 2). This is because, febrile seizures are benign and self-limiting in the long run, risks of prophylactic AED treatment far outweigh the perceived benefits and the long-term risk of epilepsy is not altered by the prophylactic AEDs. Even though EEGs may show transient or persistent epileptiform abnormalities in some patients with febrile seizures, there is no evidence to support that the prophylactic AED prevents future epilepsy. Many patients undergoing EEGs after complex febrile seizures are treated with continuous sodium valproate prophylaxis because of EEG abnormalities. This practice exposes the developing brain to the deleterious effects of sodium valproate without added benefits.

Diagnosis of common seizure mimics like breath-holding spells, shuddering attacks, hypnic jerks and infantile self-stimulation behavior is purely clinical. Home video recordings of the habitual episodes will clinch the diagnosis. EEG should be avoided in these cases as these are not diagnosis of exclusion. Many infants with breath holding spells are treated with diazepam, levetiracetam or clobazam because their EEGs have been reported as abnormal. In children with autism who never had seizures, EEG is not indicated as the role of prophylactic AED treatment is unclear and debatable.

Box 2. EEGs are NOT indicated and should be avoided in the following situations

- Febrile seizures (simple and complex)
- Breath holding spells, shuddering attacks, infantile masturbation behavior
- Sleep myoclonus / Hypnic jerks (sleep start)*
- Autism without seizures
- Syncope, headache, dizziness, vertigo

**Benign myoclonic jerks, which occurs usually on falling asleep.*

Role of EEG in pediatric ICU[2]

The most common indication for EEG in PICU is to rule out non-convulsive status epilepticus especially in patients who do not regain consciousness after status epilepticus (Box 3). Continuous bedside EEG monitoring (with simultaneous video recording) is indicated in cases of super-refractory status epilepticus and to induce and monitor burst-suppression pattern in cases of therapeutic coma.[2] Though EEG is not required in all cases, it is used as an ancillary test in brain death, especially when apnea test could not be completed.

Most ICU EEGs show diffuse slowing. This diffuse slowing pattern is non-specific and is not helpful in etiological diagnosis. On the other hand, certain specific EEG patterns denote specific etiology (e.g., delta-brush pattern in autoimmune encephalitis, periodic lateralized epileptiform discharges (PLEDs) in focal encephalitis or focal infarct, etc.)

Role of EEG in neonatal ICU

Continuous bedside EEG monitoring is increasingly being used in neonatal ICUs to manage patients with hypoxic ischemic encephalopathy, patients on therapeutic hypothermia and patients with recurrent seizures and metabolic encephalopathy (Box 4). Electro clinical dissociation is a common feature in neonatal seizures. This means that electrographic seizures could be silent clinically or clinical seizures may not show ictal EEG correlates. Only a third of neonatal EEG seizures manifest clinically. There is emerging evidence to show that treating subclinical seizures might improve long term neurodevelopmental outcome. In neonatal seizures, normal EEG predicts normal long term outcome whereas burst suppression pattern denotes poor long term outcome.

Box 3. Role of EEG in Pediatric ICU[2]

To

- rule out non convulsive status epilepticus
- detect electrographic seizures in cases of super refractory status epilepticus
- induce burst suppression and to monitor therapeutic (thiopentone or midazolam) coma
- investigate encephalopathy (febrile or afebrile) of uncertain etiology
- use as an ancillary test in brain death when apnea test could not be completed

Box 4. Role of EEG in neonatal ICU

To

- assess the severity of neonatal encephalopathy
- provide prognostic information in neonatal encephalopathy
- monitor moderate to severe HIE on therapeutic hypothermia
- monitor patients with repeated neonatal seizures (to look for subclinical seizures)
- look for burst suppression pattern in neonatal metabolic disorders

Box 5. Why a normal EEG does NOT rule out epilepsy?

- Minority of patients with epilepsy never show epileptiform discharges even on long records
- Epileptiform abnormalities are intermittent and could be occasional – can be missed during the short recording (sampling error)
- Epileptiform abnormalities may be so localized in certain electrode channels which may not be included in the montage (e.g., midline electrodes)
- Low amplitude epileptiform discharges may be buried in the background activity
- Deep seated seizure focus may not show abnormalities on the scalp surface
- Inappropriate EEG filter settings falsely filter out the epileptiform activity or make it appear like a background rhythm

Myths about EEG

Most common myth about EEG is that a normal EEG excludes epilepsy. It is crucial to understand that a normal EEG does not exclude epilepsy for the reasons listed in Box 5.

Another common myth is that an interictal EEG distinguishes between seizures and seizure mimics. But this is not true. Ictal video-EEG recording of the habitual episodes make this distinction possible but not the interictal EEG.

It is best to record an EEG as soon as possible after a seizure. This is because the yield of the EEG is maximal closer to the episode, in most cases. There is no need to wait for a few weeks before ordering EEG.

Technical factors in recording and reporting EEG in children

Recording EEGs in children with development delay, autism, hyperactivity and other behavior problems can be quite challenging. Both the EEG technician and the parents need patience and perseverance to be successful. Yield of the EEG could be increased by following the simple steps (Box 6). Pre-requisites for getting a good quality EEG recording are listed in Box 7.

Box 6. How to increase the yield of EEG?

- Include sleep recording routinely in all EEGs
- Activation procedures like hyperventilation and photic stimulation
- Sleeping 1 hour later the previous night and waking early on the day of EEG, in older children
- Record EEGs for 40-60 minutes if no abnormalities are found in first 30 minutes

Box 7. Pre requisites for a good quality EEG recording and reporting

- Good quality EEG machine with adequate sampling rate
- Qualified and well-trained EEG technician familiar with pediatric EEG recordings
- Child friendly staff and EEG lab ambience
- Clear instructions given to parents before EEG appointment (clean dry hair without oil, do not skip routine medications, sleep deprivation if needed, etc.)
- Good skin preparation before applying electrodes
- All 21 electrodes applied according to the standard International 10-20 system[4]
- Good electrode contacts with skin to achieve low impedance
- Appropriate EEG montages used for recording
- Appropriate filter settings used
- Preferably simultaneous video is recorded to aid interpretation
- Supervised EEG recording and appropriate annotations by the technician
- EEG traces are read and interpreted in the computer system (not on paper print outs)
- Periodic training of reporting personnel (pediatric neurologists)

Box 8. Common errors in interpreting pediatric EEG

- High amplitude physiological waves (sleep transients) are mistaken as abnormal
- Benign EEG variants are misclassified as abnormal
- Sharply contoured waves are misinterpreted as abnormal

It is not practical to record EEG in patients' home setting, though many parents request for the same. Home recorded EEG tracings are poor in quality, as there is no grounding of the electrical appliances. Sleep EEG (either spontaneous or induced with Triclofos[3] or melatonin) is good enough for the clinical diagnostic purposes, in young children. Oral sedatives and AEDs do not affect the diagnostic yield of the EEG adversely. Bedside, EEG is recorded in the ICU or in the wards when the patient is sick to be shifted to the EEG laboratory.

Many abnormal EEG patterns are peculiar to children and interpretation differs significantly compared to adults. Ideally pediatric EEGs should be reported by the neurologists who are familiar and conversant with the pediatric EEGs to avoid misinterpretation (Box 8). Periodic training and re-orientation in reporting of pediatric EEGs is the way forward. Single most important pitfall is that the EEG interpretation is arbitrary and operator dependent. The complexity of the EEG wave forms makes the standardization of EEG reporting and interpretation difficult, if not impossible.

Abnormal EEG patterns

Abnormal EEG patterns could be classified into abnormalities of the background rhythms or transient abnormalities that are epileptiform or non-epileptiform.

Box 9. Background abnormalities

- Diffuse or generalized slowing of the background rhythms (e.g., encephalopathy of any etiology, encephalitis, etc.)
- Hemispheric slowing (e.g.,stroke, Rasmussen encephalitis, etc.)
- Polymorphic focal slowing (indicative of underlying focal structural pathology) or
- Rhythmic focal slowing (could be benign variant as in occipital intermittent rhythmic delta activity)
- Attenuation of faster rhythms (indicative of lytic lesions such as gliosis or porencephalic cyst)

EEG background abnormalities are mostly non-specific and are not indicative of epilepsy by themselves (Box 9). In most cases, the background EEG abnormalities are not indicative of underlying etiology.

Though diffuse slowing is mostly nonspecific, certain genetic syndromes show rhythmic delta activity on EEG (e.g., long runs of frontal predominant rhythmic 2-3 Hz delta activity in Rett syndrome and Angelman syndrome, long runs of bilateral paroxysmal high voltage slow waves with occasional spikes over the fronto-polar regions in ring chromosome 20 and posterior predominant rhythmic 4-6 Hz theta activity in Angelman syndrome, etc.).

On the other hand, inter-ictal epileptiform abnormality has high specificity (78-98%) for associated epilepsy, but has low sensitivity. Epileptiform abnormality can be generalized or focal. Many clinicians interpret that the inter-ictal epileptiform discharges per se are seizures themselves. This is not true as these are only "inter-ictal" abnormalities which are more prevalent in patients with epilepsy than those without.

In children, certain epileptiform abnormalities have "low association with seizures". This means, many children showing these epileptiform patterns on EEG, would never have had seizures in the past or will have seizures only rarely, if at all, in future. That is, not all the children with these patterns will have epilepsy. These EEG patterns include centro-temporal spikes, central spikes in children with developmental delay or cerebral palsy[5], stereotyped focal occipital spikes, and bursts of irregular generalized spikes only on falling asleep. Up to 2-6 % of normal school going children can show one of these epileptiform abnormalities as incidental findings.[6] Thus, abnormal EEG showing epileptiform activity per se is not diagnostic of epilepsy.

Box 10. Indications for short-term video-EEG

- To record ictal events that occur in a predictable manner (absence seizures on hyperventilation, epileptic spasms on waking from sleep, sleep myoclonus on falling asleep, benign neonatal sleep myoclonus, etc.)
- To record and characterize habitual episodes (occurring multiple times per day)
- To induce episodes by suggestion in cases of psychogenic non-epileptic attacks

Short-term video-EEG

Though simultaneous video recording is preferred in all routine EEGs, this may not be feasible. Short term video-EEG recordings are preferred when habitual episodes occur multiple times daily and could be recorded in a predictable manner (Box 10). Electro-clinical diagnosis of specific epilepsy syndrome is possible with video-EEG recording of ictal events. Whenever feasible, it is prudent to record infantile spasms in short-term video-EEG to confirm the diagnosis of West syndrome and to avoid misclassification. This is essential because finding hypsarrhythmia in inter-ictal EEG is arbitrary and operator dependent. Video-EEG is the gold standard to confirm psychogenic non-epileptic attacks.[7] Families get convinced of psychogenic non-epileptic attacks when demonstrated on video-EEG.

Long-term video-EEG[1, 7]

Any video-EEG that is recorded overnight or for more than 12 hours can be considered as long-term. Long-term video-EEGs are usually recorded in the inpatient settings (Box 11). Overnight video-EEG is recorded whenever the classification of epilepsy is uncertain even after serial routine out-patient EEGs. Nocturnal seizures can be differentiated from other paroxysmal nocturnal episodes with certainty when recorded in video-EEG.

Precise localization of seizure focus for presurgical evaluation requires recording of at least few habitual seizures in video-EEG. Anti-epileptic medication doses may be gradually reduced to record habitual seizures if the usual seizure frequency is less than few per week.

Detailed review of nerve conduction study, electromyography, BERA and VEP is outside the scope of this article. Hence, some essential clinical points and indications are discussed.

Box 11. Indications for long-term video-EEG[1, 7]

- When epilepsy classification is unclear (generalized vs focal epilepsy)
- When nature of the episodes is unclear (nocturnal seizure vs parasomnia)
- When precise localization of epileptic focus is desired (pre-surgical work up)
- When seizure load needs assessment (epileptic spasms, electrographic seizures)
- When overnight sleep record is desired (to look for spike load in well controlled juvenile absence epilepsy or juvenile myoclonic epilepsy to decide on cessation of medications)

Box 12. Indications for nerve conduction study[8]

- Guillain-Barre syndrome
- Chronic inflammatory polyradiculo-neuropathy
- Polyneuropathy in hereditary or acquired systemic diseases
- Hereditary motor sensory neuropathy
- Mononeuritis multiplex
- Brachial or lumbar plexopathy
- Foot drop, carpal tunnel syndrome, traumatic neuropathy
- Chemotherapy and other drug related neuropathy (subclinical/clinical)

Nerve conduction study

Nerve conduction study (NCS) and EMG are essentially an extension of the clinical examination. Clinicians need to provide the detailed clinical data and differential diagnoses to the neurologist interpreting these investigations to get the maximum yield. Ideally, it is desirable that the reporting neurologist examine the patient clinically before proceeding with the nerve conduction study and needle EMG as these investigations cannot be interpreted and reported in isolation. Common indications for nerve conduction study in children are given in Box 12.

Motor and sensory nerve conduction velocity, latencies and amplitude of the responses are measured. These parameters are compared with the counterparts in opposite limb. Age-specific nomogram is utilized as the parameters of NCS differ significantly as a function of age.[9] NCS parameters could be within normal limits in cases of Guillain Barre syndrome (GBS) early in the course of the disease and should be repeated 4-7 days later if GBS is strongly suspected. Absent or prolonged F wave latencies are the earliest finding in GBS. One important caveat is that F waves could be physiologically absent during sleep.

Needle EMG

Special EMG needle is inserted in different muscles to record spontaneous activity, to demonstrate the maximal volitional capacity and muscle recruitment pattern. Spontaneous activity like fasciculations are noted in neuropathic conditions and are indicative of ongoing

Box 13. Indications for needle EMG[8]

- To differentiate between neuropathy and myopathy
- Inflammatory muscle disease - juvenile dermatomyositis
- To localize level of lesion in brachial[10] or lumbar plexopathy
- Juvenile motor neuron disease
- To demonstrate myotonia

denervation. Ideally, EMG is performed while the child is awake and co-operative, to assess the maximum volitional activity and recruitment pattern. But children get frightened by the needle and the painful procedure. Only spontaneous muscle activity can be assessed while the child is asleep and sleep EMG is enough to demonstrate myotonia.

In the era of genetic molecular diagnosis, the indications for NCS and EMG are shrinking (Box 12 & 13). Thus, nerve conduction study and needle EMG are no longer performed in cases of suspected spinal muscular atrophy (SMA), muscular dystrophy (including DMD) and most other congenital neuro-muscular diseases, as the genetic testing is the first line investigation of choice. As far as possible, invasive, frightening and painful tests such as needle EMG should be avoided in children. In the same way, muscle biopsies are performed now-a-days only rarely, when the genetic panel is inconclusive or negative.

Brainstem evoked response audiometry

BERA should be performed at the age 1-3 months in high risk newborns who are preterm < 34 weeks, very low birth weight, who had neonatal sepsis with or without meningitis and hyperbilirubinemia (Box 14). BERA is an objective test and the patient co-operation is not necessary. BERA can be recorded under sedation or during natural sleep in young children. Multiple sound clicks stimuli at 40, 50, 60, 70, 80 dB are presented through a headset to the right or left ear, one ear at a time. The response is recorded through the recording electrode placed just behind the recording ear. There are five standard wave forms (I-V) noted in BERA.

Box 14. Indications for BERA

- Those who fail hearing screen (OAE, audiometry, etc.)
- Preterm< 34 weeks/very low birth weight infants
- Hyperbilirubinemia, neonatal sepsis and meningitis
- TORCH infection sequelae, hydrocephalus
- Meningoencephalitis
- Traumatic brain injury
- Speech delay, suspected hearing loss
- External ear and other head and neck malformations
- Genetic syndromes with hearing loss
- Family history of sensory-neural hearing loss

Presence or the absence of wave forms, latencies of each waveform and inter-waveform latencies are noted. In profound sensory-neural hearing loss, all waveforms may be absent completely. Oto-acoustic emissions (OAE) should be used as a routine screening tool at around age 3 months in all infants.[11] Those who fail OAE in one or both ears should undergo BERA for confirmation.

Visual evoked potential

Visual evoked potential (VEP) tests the integrity of visual pathway from the retina to the occipital cortex. Stimuli are presented either in the form of pattern (on/off or pattern reversal) or flash light.[12] Pattern VEP is preferred whenever the patient can co-operate and can sustain visual fixation in the central red dot. Flash VEP is less reliable and is used in young and uncooperative children who cannot sustain fixation. Recording VEP is highly technical. If the patient is not fixing properly on the target or not looking at the flashes, the recorded data is unreliable. Two recording electrodes are placed on the scalp, one over the occipital and another over the frontal midline. Two wave forms (N75 and P100) are noted. The latencies of these two waveforms have nomogram. If the latencies are more than two standard deviations it means that nerve conduction in the optic pathway is slower. Common indications for VEP are given in Box 15.

Box 15. Indications for VEP

- Suspected poor vision or vision loss, amblyopia
- Cortical visual impairment (parieto-occipital gliosis)
- To assess visual function of infants
- Bilateral cataract before surgery - for prognostication
- Optic neuropathy of any etiology
- Acute demyelination - to detect subclinical involvement of optic nerves[13]
- Suspected cases of functional visual loss (conversion or malingering)[13]

Points to Remember

- ***Epilepsy is a clinical diagnosis and EEG is not a confirmatory test.***
- ***Inter ictal EEG does not distinguish between seizures and seizure mimics.***
- ***Some epileptiform patterns in EEG have low association with seizures in children.***
- ***Video-EEG is the gold standard to confirm psychogenic non-epileptic attacks.***
- ***Genetic testing is the investigation of choice in suspected cases of muscular dystrophy or spinal muscular atrophy; nerve conduction and EMG do not add value in these conditions.***

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CLIPPINGS

Neutrophil Volume, conductivity and scatter (VCS) as a screening tool in neonatal sepsis.

The objective of this study was to establish changes in Neutrophil volume conductivity scatter (VCS) in neonatal sepsis and to determine appropriate cut off levels using receiver operating characteristic (ROC) curves. 304 children were studied with 144 children in sepsis group and 166 in no sepsis group. mean neutrophil volume (MNV) and volume distribution width (VDW) MNV and VDW had good sensitivity (95%, 82%) and specificity (86%, 74%) for diagnosis of sepsis. The authors have concluded that Neutrophil VCS parameters, especially MNV, can be incorporated with other sepsis screen parameters in diagnosis of neonatal sepsis.

Nesargi P, Niranjan HS, Bandiya P, Benakappa N. Neutrophil Volume, conductivity and scatter (VCS) as a screening tool in neonatal sepsis. Sci Rep 10, 4457 (2020). https://doi.org/10.1038/s41598-020-61434-z.