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Neonatal cerebral function monitoring – understanding the amplitude integrated EEG

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ABSTRACT

Amplitude integrated electroencephalography (aEEG) is produced by cerebral function monitors (CFM), and is increasingly used in neonates following research into hypothermia for hypoxic ischaemic encephalopathy in term infants. Formal training packages in aEEG in term infants are limited. aEEG is used less often in clinical practice in preterm infants, and requires an understanding of the normal changes seen with increasing gestational age. A number of classifications for aEEG interpretation exist; some purely for term neonates born, and others encompassing both preterm and term neonates. This article reviews the basics of aEEG, its indications and limitations. We also discuss its role in prognostication in term and preterm infants.

INTRODUCTION

Amplitude integrated EEG (aEEG) is becoming a standard of care in the UK for term neonates with hypoxic ischaemic encephalopathy (HIE). aEEG and the raw EEG, which the aEEG is derived from, can:

- determine the severity and prognosis of HIE
- assess improvement in encephalopathy with time
- detect some epileptic seizures.

In our experience, aEEG is also being used increasingly in term neonates without HIE, such as those with seizures from different aetiologies, and in late-preterm infants with HIE. However, interpretation can be difficult, especially in infants who are preterm. This article discusses:

- what aEEG is
- the indications for aEEG
- the advantages and disadvantages of aEEG
- the proposed classifications of preterm and term aEEG
- the prognostic abilities of aEEG.

For more details on neonatal electroencephalograpy (EEG), please refer to our companion article.

WHAT IS AMPLITUDE INTEGRATED EEG?

aEEG is a simplified, compressed trace derived from EEG. Electrical signals are recorded from scalp electrodes attached to the head using adhesive pads, silver cups glued to the scalp, or subcutaneous needles. Whilst standard EEG uses many different leads to record signals from a wide area, aEEG uses fewer leads: often only one pair of electrodes crossing the midline over either the parietal or central regions (figure 1). These positions were originally chosen because they covered the vascular watershed areas and avoided muscle artefact. Another electrode, called the ground, is also placed, usually about an inch anterior to the vertex. This aids suppression of any interfering

signals recorded. Increasingly, modern monitors may use additional leads and display aEEG from two regions of the brain: either anterior and posterior, or the left and right hemispheres (figure 1).

The EEG leads record the spontaneous extracellular electrical activity of the brain. The monitor rectifies the signal, meaning biphasic waveforms are converted to a monophasic waves, and filters it to remove activity <2Hz and >15Hz. This helps reduce the effect of artefacts from, for example, handling the baby or mains-powered electrical equipment. The signal is compressed in time. The amplitude of the recorded activity is displayed on a partly logarithmic y-axis: up to 10 µV amplitudes are plotted in linear fashion, 10 - 100 µV is shown logarithmically. The x-axis represents time, and is compressed to around 6cm/hour. The results are visualised as a thick band: the lower margin represents the minimum amplitudes recorded and the upper margin shows the maximum.

Electrode impedance is also displayed and reflects the opposition to flow of the electrical current. It is used as a measure of the quality of electrode contact with the skin.

The terminology is used interchangeably and incorrectly: aEEG is the trace itself and CFM is the monitor. Modern CFM also show raw, real time EEG and are digital, allowing for easy review of the aEEG over time, and correlation between abnormalities and the time-locked EEG trace. CFAM is the name of an earlier monitor that displayed the relative amounts of electrical activity in certain frequency bands (alpha, beta, delta, theta) in addition to aEEG. More modern machines do not display this extra information and are not CFAM.

INDICATIONS FOR aEEG

The main use of aEEG is to monitor trends in the electrical activity of the brain over time, and helps assess encephalopathy severity and recovery. aEEG can also provide useful prognostic information, and may help determine whether abnormal movements are seizures, or whether electrographic seizures without clinical features are occurring.

LIMITATIONS OF aEEG

- Standardised training in aEEG interpretation for nurses and trainees is limited
- Standard EEG is needed for more detailed evaluation of background activity
- Gestational age (GA) needs to be taken into account during interpretation of aEEG, so clinicians need an understanding of its normal maturation
- The raw EEG trace on some CFM monitors is difficult to interpret
- Artefacts can also be misdiagnosed as seizures
- Short lasting seizures (<30s), those with low amplitude or distant from the electrodes can be missed
- aEEG has a poor sensitivity for recognising seizures compared to standard EEG. Studies comparing the two demonstrate that aEEG identifies 1/3 of single seizures and 2/3 of repetitive seizures, although this is clearly superior to clinical observation. Attempts to improve seizure detection on aEEG include the use of two channels (4 electrodes) and automatic seizure detection algorithms, which are not used in routine clinical practice in all UK neonatal units.

THE EVOLUTION OF THE NORMAL aEEG FROM PRETERM TO TERM

The EEG and aEEG change from preterm towards term age. As discussed in our companion article, the normal preterm EEG is discontinuous, meaning that bursts of high voltage electrical activity are separated by periods of relative electrical inactivity. The bursts can be far apart at 24 weeks

gestational age, with the electrical inactivity lasting up to 60 seconds. As a neonate matures, the bursts last longer and the periods of inactivity shorten: the EEG becomes more continuous. This maturation in the EEG explains the changes seen in the aEEG.

Electrical inactivity on EEG is of low amplitude, so the bottom band of the aEEG will be low where this is frequent. The voltage of the upper aEEG band depends on the frequency and size of the bursts, and will increase where the bursts become frequent and higher voltage. Thus, as a preterm neonate matures, the lower and upper border increase, until the familiar aEEG trace of a term infants is seen (table one).

The EEG and aEEG are also affected by sleep states. The EEG in a term neonate, which is normally continuous in the awake state and during active sleep, can be discontinuous in quiet sleep. The period of discontinuity causes the aEEG band to broaden and the lower border to drop slightly (figure 1b). This is sleep wake cycling (SWC).

In the preterm infant, the earliest signs of immature SWC may be seen between 24-29 weeks, but its absence is not necessarily a worrying feature. More mature SWC should be seen from 30 weeks GA. Burdjalov et al studied patterns similar to sleep wake cycling in preterm infants and argued this was not correlated to sleep states. However, no data was provided to confirm this assertion. In this article we have retained the term SWC for all ages for ease of understanding, but acknowledge this issue is not fully understood in preterm infants.

FEATURES OF AN ABNORMAL aEEG

An abnormal background is one in which any of the following are observed:

- The upper and / or lower borders (i.e. background EEG) are not within the normal range (figure 2b-f),
- SWC is absent (figures 1c, and figure 2)
- Seizures are present (figure 3a-d).

During seizures, the usual background trace is lost and the minimum amplitude of the raw EEG tracing is increased, leading to the lower margin of the aEEG moving up (figure 3). The upper margin often increases slightly too because seizure discharges have higher amplitudes than standard cerebral activity. This increase may not be as great as for the lower margin, so the width of the band may narrow. During status epilepticus the trace takes on a saw-tooth appearance (figure 3d) or a constant narrow band with high amplitude. Care should be taken not to mistake artefacts for abnormalities (figure 4).

CLASSIFICATIONS OF aEEGs

A number of different classifications exist for abnormal aEEGs. The most frequently used in the UK is that of al Naqeeb et al (table two). This classification divides the trace into categories depending on the voltage seen, and comments on the presence or absence of seizures. However, it ignores SWC and also the maturation of the aEEG towards term, so it cannot be used in preterm infants.

Hellstrom-Westas et al have recently proposed a new classification (table two), utilising the same terminology used in EEG. This helps clinicians to understand how EEG and aEEG relate to each other. The classification involves assessing the following:

1. Background activity

This can be:

- Continuous: upper margin 10 – 25 µV (or higher in term infants), lower margin 4-10 µV (figure 1b and c).
- Discontinuous: lower margin <5 µV, upper margin >10 µV (figure 2b). This would be consistent with a “moderately abnormal” aEEG trace according to Al Naqeeb et al’s classification.
- Burst suppression: a discontinuous trace with the lower margin between 0 and 2 µV punctuated by bursts of activity with amplitudes >25 µV (figure 2c and d). Burst suppression ‘+’ refers to over 100 bursts per hour, whilst ‘-’ indicates less than 100 bursts per hour.
- Continuous low voltage: low amplitude traces with an upper margin of ≤5µV and bursts <25µV (figure 2e)
- Inactive / flat trace: flat (isoelectric) traces without bursts which have an amplitude <5 µV microvolts (figure 2f)

2. SWC

Comment should be made to:

- “no SWC”;
- “imminent / immature SWC” (where some is seen but not gestationally appropriate),
- “developed” (i.e. normal, with a cycle lasting at least 20 minutes).

3. Seizure activity

Divided into:

- no seizure
- single seizure

- repetitive seizure (single seizures occurring more than once in a 30 minute interval)
- status epilepticus - continuous seizures for >30 minutes (Figure 3d).

Thus, a normal aEEG in a term infant would be “continuous with developed SWC and no seizures.” Although this classification sounds more complex, it offers more information to the clinician, and can also be used in preterm infants, with a decision subsequently made as to whether this is normal for the gestational age.

A further classification and scoring system was proposed by Burdjalov et al, and is applicable to both term and preterm infants (table two). This classification scores the aEEG trace in four areas: 1) “continuity”; 2) cycling; 3) amplitude of the average of lower border of the aEEG, at its narrowest point if cycling was seen; 4) bandwith and amplitude of the lower border combined. The maximum score is 13, with the development of cycling felt to have the best correlation to gestational age. In our view, this scoring system is useful for long-term monitoring, such as following preterm birth, and in research studies where objective comparisons need to be made between groups. However, the classification doesn’t comment on the presence or absence of seizures, and little data is published on its ability to detect specific pathologies / brain injuries or provide prognosticate. We therefore recommend Hellstrom-Westas’ classification for clinical practice.

AMPLITUDE INTEGRATED EEG AND PROGNOSTICATION IN TERM NEONATES

Hypoxic ischaemic encephalopathy

An abnormal aEEG background pattern and seizures are known to be associated with increasingly severe abnormalities on MRI, but do they predict

outcome? Firstly, it should be noted that antiepileptic medications like midazolam, phenobarbital, and pyridoxine could alter the aEEG, so caution should be made in its interpretation when these medications have been given.

Classifying the aEEG using al Naqeeb's method within 6 hours of birth is modestly predictive of death or adverse outcome at 18 months, and this does not significantly change using the Hellstrom-Westas classification. Looking at the recovery of aEEG over a longer period of time has shown an abnormal background, even if inactive / flat or burst suppression, could be associated with good outcome if normalisation began by 12-24 hours in non-cooled neonates. The earlier the aEEG returns to normal, the better the outcome. However, a normal aEEG at 24-36 hours could still be associated with poor outcome if magnetic resonance imaging of the brain is abnormal. Persistent aEEG abnormalities, particularly an isoelectric / flat trace or burst suppression, at 24 – 36 hours are associated with death or severe disability.

In hypothermia trials, the positive predictive value of aEEG predicting neurodevelopmental difficulties was 0.5 at 6 hours, 0.65 at 24 hours, 0.82 at 48 hours and 0.92 at 60 hours. SWC also provided useful information, with the early return of SWC associated with better neuro-developmental outcome. The optimal time to interpret aEEG for prognostication is neonates receiving hypothermia is suggested to be 48 hours of age.

Other pathologies

Limited data exists on the association between aEEG and outcome in neonatal sepsis / meningitis, but a normal background and SWC by 24 hours is associated with good outcome.

AMPLITUDE INTEGRATED EEG AND PROGNOSTICATION IN PRETERM NEONATES

Many studies of prognostication in preterm infants focus on short-term outcomes / survival, or neuroimaging findings. Brain abnormalities, like intraventricular haemorrhage, post haemorrhage hydrocephalus, and periventricular leukomalacia are associated with increasing severity of abnormal aEEGs. Preterm neonates with grade III or IV intraventricular haemorrhage who died or developed poor neurodevelopmental outcome have:

- a lower voltage pattern
- reduced scores for continuity, cycling and amplitude of the lower border of the aEEG trace.
- more seizures.

Some studies have shown that markedly abnormal aEEG early in life is associated with poor outcome. Burst suppression within the first 72 hours of life is associated with death or neurodevelopmental impairment at two years with a positive predictive value (PPV) of 63% and negative predictive value (NPV) of 91%. The PPV and NPV for the absence of continuous activity was 54% and 89% respectively, and the absence of SWC was 61% and 74%.

More prolonged records show that the evolution into more continuous aEEG with SWC within the first week of life was associated with good outcome, with a positive predictive value similar to cranial ultrasound. Scoring the aEEG within the first two weeks of life as per the Hellstrom-Westas classification had a sensitivity of 61%, specificity of 98%, PPV 95% and NPV 79% for outcome, including death, at three years. The prognostic ability was greater for the most preterm infants.

Overall, the evidence on the prognostic ability of aEEG in preterm infants is limited and associated with only short-term outcome. Other factors, such as late onset sepsis, necrotising enterocolitis and the use of postnatal steroids

for chronic lung disease mean that it is unlikely that aEEG will be a perfect prognostic tool in this cohort.

CONCLUSION

Amplitude integrated EEG and raw EEG are useful the monitor changes in brain activity over time, and to detect some, but not all, seizures. EEG and aEEG answer different clinical questions, and should be seen as complimentary to each other. To interpret the aEEG, an understanding of its normal maturation with increasing gestational age is needed. The trace can then be classified according to Hellstrom-Westas, whatever the gestation of the infant, with a decision subsequently made about whether it is normal or not. Good evidence exists that aEEG can help with prognostication in term infants with HIE, although other data like clinical history, examination and MRI should not be ignored. The data on prognostication with aEEG in preterm neonates is limited, and aEEG should be used cautiously in this population unless clinicians have a good understanding of the normal maturation of aEEG.

FINANCIAL DISCLOSURE
None

CONFLICTS OF INTEREST
No conflicts of interest are known.

ACKNOWLEDGEMENTS
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FURTHER READING

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Table one: Normal values for the median, 25th and 75th centiles for the upper and lower margins of the aEEG band according to gestational age (adapted from Zhang et al)

Gestational age of child (weeks and days)	**Upper margin – median value (25th and 75th centile)**		**Lower margin – median value (25th and 75th centile)**	
	Active sleep and awake state	Quiet sleep	Active sleep and awake state	Quiet sleep
30.0 - 33.6 weeks	29.0 (25.0, 33.0)	28.0 (24.0, 35.0)	5.5 (4.4, 6.3)	2.3 (2.1, 2.8)
34.0 - 35.6 weeks	26.0 (22.0, 26.0)	24.0 (20.0, 30.0)	8.5 (5.8, 9.5)	3.6 (3.1, 4.5)
36.0 – 37.6 weeks	23.0 (20.0, 27.0)	33.0 (26.0, 39.0)	8.9 (5.6, 11.0)	5.5 (3.4, 8.0)
38.0 – 39.6 weeks	20.0 (18.0, 22.0)	29.0 (24.0, 34.0)	7.4 (5.7, 9.6)	9.3 (6.6, 10.0)
40.0 – 41.6 weeks	20.0 (18.0, 22.0)	32.0 (26.0, 36.0)	7.5 (6.3, 9.6)	10.0 (8.6, 12.0)
42.0 – 43.6 weeks	18.0 (16.0, 22.0)	29.0	7.3 (5.2, 9.4)	11.0

		(27.0, 36.0)		(9.5, 12.0)
44.0 – 45.6 weeks	20.0 (17.0, 21.0)	33.0 (29.0, 34.0)	8.7 (7.7, 9.7)	14.0 (12.0, 16.0)
46.0 – 47.6 weeks	21.0 (19.0, 24.0)	35.0 (32.0, 41.0)	10.0 (9.2, 12.0)	16.0 (14.0, 19.0)
48.0 – 51.6 weeks	27.0 (22.0, 34.0)	44.0 (38.0, 54.0)	14.0 (11, 15.0)	21.0 (19.0, 25.0)
52.0 – 55.6 weeks	33.0 (28.0, 38.0)	56.0 (45.0, 63.0)	17.0 (12.0, 17.0)	26.0 (22.0, 30.0)

Table 2: The different classifications for aEEG in term and preterm neonates

Classification	**Components of classification**
al Naqeeb et al For use with term neonates only.	**Background voltage pattern:** • Normal Lower margin >5µV Upper margin >10µV The activity is continuous • Moderately abnormal Lower margin <5µV Upper margin >10µV The activity is moderately discontinuous • Severely abnormal/suppressed Lower margin <5µV Upper margin <10µV **Seizures:** • Present Characterised by a sudden change in amplitude, and often thinning of aEEG bandwidth • Absent *No reference is made to sleep wake cycling
Hellstrom-*Westas et al's* Comment should be made to each of the three criteria.	**Background pattern:** • Continuous Upper margin 10+ µV Lower margin 4-10µV

Can be used for preterm and term neonates.	• Discontinuous Upper margin >10μV Lower margin <5μV • Burst suppression + Lower margin 0-2μV Bursts >25μV More than 100 bursts/h • Burst suppression – Lower margin 0-2μV Bursts >25μV Less than 100 bursts/h • Continuous low voltage Upper margin <5μV • Inactive / flat trace Isoelectric trace Bursts <5μV **Sleep wake cycling:** • No cycling • Imminent / immature cycling • Developed sleep wake cycling **Seizures:** • No seizure • Single seizure • Repetitive seizures Single seizures more than once in 30mins

	• Status epilepticus Continuous seizures for more than 30min
Burdjalov et al Can be used in term and preterm neonates. A score is given for each section, with a maximum score of 13	**Continuity:** • Discontinuity – score 0 • Somewhat continuous – score 1 • Continuous – score 2 **Cycling:** • None – score 0 • Waves first appear – score 1 • Not definite, somewhat cycling – score 2 • Definite cycling, but interrupted – score 3 • Definite cycling, noninterrupted – score 4 • Regular and mature cycling – score 5 **Amplitude of lower border:** • *Severely depressed (<3μV)* – score 0 • Somewhat depressed (3-*5μV)* – score 1 • *Elevated (>5μV)* – score 2 **Bandwith span and amplitude of lower border:** • *Very depressed: low span (<15μV) and low voltage (5μV)* – score 0 • *Very immature: high span (>20μV) or moderate span (15-20μV) and low voltage (5μV)* – score 1 • *Immature: high span (>20μV) and high voltage (>5μV)* – score 2 • Maturing: moderate span (15-*20μV) and high voltage (>5μV)* – score 3 • Mature: low *span (<15μV) and high voltage (>5μV)* – score 4

Figure 1: a i-iv), Schematics of possible aEEG electrode placement. The most common electrode configurations and shown in i and ii. Some new machines use four electrodes which could look across (iii) or along (iv) hemispheres.

b) upper panel - continuous normal voltage aEEG with evidence of SWC; lower panel – a few seconds of normal raw EEG at time point marked with the dotted line.

c) upper panel – continuous normal voltage aEEG but with no SWC and no seizures. The classification described by Al Naqeeb et al would describe this as normal, but the absence of sleep wake cycling means it is not; lower panel – a few seconds of normal raw EEG at time point marked with the dotted line.

Figure 2: **a)** Upper panel – aEEG background shows abnormal continuous activity, SWC is absent and there is no definite seizure activity. Clinicians may suspect status epilepticus or artefact because of the high amplitude narrow band; lower panel – a few seconds of single channel EEG at time point marked with the dotted line showing no evidence of epileptic activity and probable artefact.

Comment - the high voltage, compressed aEEG band is abnormal and lacks sleep wake cycling. The trace should be correlated to the clinical picture but the reader should be suspicious of artefact, drug effects and status epilepticus. Further evaluation with standard EEG may be advised.

b) Upper panel – aEEG background is discontinuous with absent SWC and no seizures; lower panel – a few seconds of raw EEG at time point marked with the dotted line showing no evidence of epileptic activity.

Comment - the trace is discontinuous and is abnormal for a term infant.

c) Upper panel – aEEG background shows burst suppression "-" (less than 100 bursts per hour), SWC is absent and no seizures are seen; lower panel – a few seconds of raw EEG at time point marked with the dotted line showing electrical inactivity

Comment - Note the lower margin around 1-2μV punctuated by regular, comb-like high amplitude surges. This pattern warrants immediate attention and consideration of severe encephalopathy (including neonatal epileptic encephalopathy), status epilepticus and drug effects.

d) Upper panel – aEEG background shows burst suppression "+" (>100 bursts/minute). Towards the right, the aEEG becomes discontinuous normal voltage; lower panel – a few seconds of single channel EEG at time point marked with the dotted line showing electrical inactivity with a single high amplitude burst of activity

e) Upper panel – aEEG background is low voltage with absent SWC and no seizures; lower panel – a few seconds of raw EEG at time point marked with the dotted line which, which shows no evidence of epileptic seizures.

Comment – This aEEG could be said to be low voltage, though there are some spikes over 5μV. The tracing was evolving quickly from flat / inactive through low voltage to discontinuous. In our experience prolonged low voltage traces are rare and flat traces can appear similar if the amplitude is affected by artefact, particularly the ECG. Therefore, check the raw EEG for artefact before deciding if the aEEG is truly low voltage.

f) Upper panel – aEEG background is flat / inactive, SWC is absent and there are no seizures; lower panel – a few seconds of single channel EEG at time point marked with the dotted line showing no epileptic activity

Comment - this pattern may, depending on its change over time, carry a poor prognosis.

Figure 3:
a) upper panel – aEEG background is continuous normal voltage aEEG with absent SWC and recurrent seizures; lower panel – a few seconds of single channel EEG at time point marked with the dotted line showing repetitive, rhythmical spike wave patterns indicative of epileptic seizures

Comment - the aEEG reveals a number of episodes of seizure activity where the amplitude increases and bandwidth narrows

b) upper panel – aEEG background shows continuous low voltage, no SWC and the aEEG looks like recurrent seizures; lower panel - a few seconds of raw EEG at the point marked with the dotted line showing slow wave activity.

Comment - The initial aEEG has a low voltage appearance that is then interrupted but surges in overall amplitude (but still with a narrow aEEG band) that look like seizures. The raw EEG does not show typical pattern, but slow activity that could be respiratory artefact. This is an example where standard EEG should be performed to confirm seizure activity.

c) upper panel – aEEG background is of low voltage but the surges in amplitude are so frequent this becomes difficult to appreciate. SWC is absent and status epilepticus is noted; lower panel - a few seconds of single channel EEG at time point marked with the dotted line showing rhythmical slow waves in the delta range.

Comment - the aEEG trace has the rhythmical, repetitive saw tooth appearance consistent with status epilepticus but again the raw EEG does not show typical features of seizures, highlighting that the raw EEG can be confusing at times. Where doubt exists, standard EEG should be organised.

Figure 4:

a) upper panel – aEEG background shows low voltage continuous trace with possible superimposed bursts. No SWC is seen. Towards the right of the trace, the band moves upwards. A clinician could assume this is seizure activity or artefact; lower panel – a few seconds of single channel EEG at time point marked with the dotted line. Regular discharges can be seen throughout the window without any change in frequency of size.

Comment - this recording is contaminated with artefact. Given the rhythmicity and frequency of the discharges on the raw EEG, this probably arising from the ECG / heart. The bursts of activity in the upper panel probably reflect this artefact, otherwise the aEEG is likely to be flat.

b) upper panel – aEEG background shows periods of continuous and discontinuous activity. SWC is present and no seizures are present; lower panel – a few seconds of single channel EEG at time point marked with the dotted line displaying rhythmical discharges which do not alter in any way.

Comment - Careful inspection of all the information on the monitor reveals that, at the point of potential concern, the electrode impedance dramatically changes, just after 11.00 hours. The trace then becomes affected by artefact. It would be possible for an inexperienced operator misdiagnose the raw EEG seizure activity, highlighting the need for adequate training.

KEYPOINTS

- The aEEG is useful for monitoring changes in the background over time and a proportion of seizures, but misses both the detailed background information given by EEG and some seizures. The two modalities to should seen as complimentary to each other
- The aEEG changes from a preterm to a term pattern, and clinicians should be careful using aEEG in a preterm infant or they may incorrectly assume the tracing is abnormal
- Interpretation of the aEEG should include: background, sleep wake cycling and seizures. This classification is better than the older one used in term HIE because it is applicable to preterm infants also.
- The aEEG can offer prognostic information in term infants with HIE, and is best assessed at 48 hours in babies receiving hypothermia treatment. However, it should be used in conjunction with other clinical assessments, like examination and neuroimaging
- Further work is needed to assess the prognostic value of preterm aEEG