What is the role of amplitude-integrated Electroencephalography (aEEG) in patients with metabolic disorders?

**Metabolic disorders with ENCEPHALOPATHY:**

- **diagnose/confirm** the encephalopathy through detection of its EEG correlate
- **assess severity** of the encephalopathy
- **evaluate changes in the severity and characteristics of the encephalopathy over time** (with or without treatment)
What is the role of amplitude-integrated Electroencephalography (aEEG) in patients with metabolic disorders?

For metabolic disorders with SEIZURES:
• detect seizure activity (with or without clinical correlates)
• assess seizure frequency
• assess response to treatment (or lack thereof...)

In addition aEEG may have a role in non-metabolic genetic disorders:

Patients with non-metabolic genetic conditions often experience seizures:
• Search of POSSUM (a computer based system that allows search for genetic syndromes by traits) reveals:
  o 588 syndromes with “seizures of any type”
  o including 376 syndromes with “abnormal nervous system structure”
What's known about aEEG in metabolic disorders:

Previous published reports of aEEG use in patients with metabolic disorders

Background of this presentation:

Request for collaboration made after a presentation at last year's 2nd Neonatal Brain Monitoring Conference in Florida (Glycine encephalopathy: Characteristics of amplitude-integrated EEG tracing in a patient with early symptoms of disease)

9 Contributors from six Countries!

23 aEEG tracings submitted

over 12 different diagnoses
Metabolic conditions with several patient tracings available:

**Glycine encephalopathy (GE/NKH)**  
(non-ketotic hyperglycinemia)  
\[ n=4 \]

Inborn error of glycine degradation leading to accumulation of large quantities of glycine in all body tissues

Glycine is a neurotransmitter with part inhibitory and part excitatory effects

Typical EEG changes are seen in this patient: burst suppression like pattern characterized by high voltage complexes separated by low amplitude sequences - short interburst intervals
This patient with a similar aEEG tracing - again short interburst interval. Note appearance of tracing at time of hiccups (which are typically seen in patients with GE/NKH).

This patient also with similar aEEG tracing but baseline not as suppressed: 32.5% of individual EEG segments analyzed do not show burst suppression (early tracing at 46 hours of age).
Some patients with NKH survive and stabilize - long term outcome extremely guarded though. Note: changed amplitude range later in course

Patient 2: aEEG DOL 2

This patient also shows burst suppression when monitoring started at day of life (DOL) 4: Note transient increases in baseline also. 
Later tracing shows slight improvement but still appears discontinuous...
Metabolic conditions with several patient tracings available:

**Peroxisomal disorders**

*n=4*

Group of genetic conditions with defects of peroxisome assembly and function; most disorders in this group with elevation of very long chain fatty acids.

3 patients with **Zellweger Syndrome**

**Zellweger Syndrome:**

Disorder of **Peroxisome biogenesis**.

Multiple biochemical markers abnormal. Can be clinically diagnosed at birth. Seizures due to neuronal migration defects.
Patient with Zellweger Syndrome (DOL5):
Normal voltage background pattern;
Multiple seizures are marked.

Patient with Zellweger Syndrome (DOL5):
Treatment with lidocaine and midazolam resulted in intubation for recurrent apneas;
aEEG background becomes more discontinuous.
Another patient with Zellweger Syndrome: intermittent seizure activity noted

Zellweger Syndrome (Patient 3):
First aEEG done early in course when seizures clinically suspected: continuous with sleep cycling.
Second aEEG at age three months: again continuous with sleep wake cycling. Two conventional EEGs on DOL 1 and a week later: no electrical seizures documented

Patient 4: Peroxisomal biogenesis disorder:
Clinical seizures with EEG correlate
Metabolic conditions with several patient tracings available:

**Disorders with Hyperammonemia**

n=4

Urea cycle converts ammonia to urea. An intact urea cycle is essential for the excretion of excess nitrogen produced during the metabolic breakdown of amino acids.

**Hyperammonemia** results in severe encephalopathy.

Patient with **Urea Cycle Defect**
aEEG tracings covering DOL3 to 13

DOL 3: Clinical seizures

DOL 7: Ammonium levels decreased after treatment with peritoneal dialysis and arginine but clinically not much improved

Hyperammonemia: Patient 1
Patient with **Urea Cycle Defect:**

- aEEG tracings covering DOL 3 to 13:
  - Seizures, encephalopathy, then inactive tracing

  - DOL 11: No clinical improvement.
  - DOL 13: Inactive tracing. Patient died later that day.

  Hyperammonemia: Patient 1

---

Patient with **Ornithine Transcarbamylase Deficiency:**

- Severe encephalopathy

  - Patient improved and hyperammonemia resolved after dialysis - but he died at a later time.

  - Hyperammonemia: Patient 2
**Patient with HMG-CoA Lyase Deficiency:**

Enzyme deficiency interferes with leucine degradation and fatty acid oxidation and results in accumulation of 3-OH-methyl-glutaryl-CoA - which inhibits gluconeogenesis (leads to hypoglycemia) and inhibits the urea cycle (thus resulting in hyperammonemia).

This patient presented DOL 3 with respiratory distress, hypotonia and convulsions - ammonia 359 mmol/l; also in renal failure - received peritoneal dialysis.

Treated with special diet and eventually discharged home.

Hyperammonemia: Patient 3

At the time the aEEG tracing below was obtained on DOL 3, the patient had received midazolam and chloralhydrate and was without clinical seizures.
Patient with N-Acetylglutamate synthase deficiency:

N-Acetylglutamate (NAG) **activates Carbamyl phosphate synthase I**, the enzyme that catalyzes the first committed step of the urea cycle (regulatory effect on the urea cycle).

**NAG is synthesized** from glutamate and acetyl-CoA **by NAG synthase**. Deficiency leads to hyperammonemia.

This patient **presented on DOL 1 with convulsions**.

Treatment included **peritoneal dialysis**.

Final discharge home in neonatal period on DOL 20.

Hyperammonemia Patient 4

---

N-Acetylglutamate synthase deficiency:

Patient at DOL 16:

**Readmission to hospital with seizures**

Hyperammonemia Patient 4
Metabolic conditions with several patient tracings available:

**Disorders affecting Energy Metabolism**  
\(n=6\)

Affected metabolic pathways include:
- Deficient mitochondrial fatty acid oxidation
- Deficient mitochondrial respiratory chain
- Deficiencies to transport substrate across the mitochondrial membrane
- Decreased conversion of substrate for entry into Krebs Cycle / Citric Acid Cycle

**Patient with long chain 3-ketothiolase deficiency:**
35 week infant; consanguineous parents. Did not feed well. Clinical picture complicated by bloody stool, presumed NEC, surgery for presumed bowel perforation. Acidotic with elevated lactate. Initial ECHO normal but after infant continued to be acidic, repeat ECHO revealed very poor contractility. Died despite full intensive-care support.

Monitoring initiated after surgery: discontinuous pattern
Patient with long chain 3-ketothiolase deficiency:

Deterioration from discontinuous to burst suppression pattern

Patient with fatty acid oxidation defect

Less impressive aEEG findings despite clinical manifestations:

Infant presented DOL 3 for jaundice but was severely hypoglycemic (5 mg/dl). Apneic spell leads to intubation. Clinical convulsions. Patient with fatty acid oxidation defect - no specific enzyme identified.

Conventional EEG done later during hospital stay showed epileptic activity and abnormal posterior baseline activity. Discharge on “special formula” and Carnitine.
Patient with respiratory chain defect:

Despite clinical seizures - no clear seizure correlate identified on aEEG.

Depression after midazolam. Later aEEG pattern suggestive of seizure activity.

No aEEG abnormalities may be found when patient asymptomatic:

Patient with Carnitine Palmitoyl Transferase Deficiency (a defect that results in an inability to transport certain fatty acids across the outer mitochondrial membrane).

Patient presented DOL 2 with hypotonia was found to be hypoglycemic. Treated with glucose infusion and diet. AEEG obtained 3 days later.
Disorders affecting energy metabolism: E3 pyruvate dehydrogenase deficiency

Two patients born to consanguineous parents with a previous child diagnosed with E3 pyruvate dehydrogenase deficiency.

E3 pyruvate dehydrogenase is part of an enzyme complex that converts pyruvate to acetyl-CoA - the “entry reaction” to the Krebs cycle / Citric Acid Cycle (a pathway with ATP production).

Older sibling: With acidosis, admitted to NICU, clinical convulsions were treated with Phenobarbital.

Younger sibling: With acidosis, admitted to NICU, no convulsions.
Other metabolic conditions:

Disorders of Amino Acid Metabolism

n=2

Patient 1:
Methylmalonic acidemia

Patient 2:
Maple syrup disease

aEEG tracings analyzed but not included in this presentation for the following conditions:
Sulfite oxidase deficiency (unremarkable)
Pyridoxine dependent seizures (cessation of seizures with pyridoxine treatment)

Patient with Methylmalonic Acidemia:
Typical presentation with increasing lethargy, acidosis, leukopenia, thrombocytopenia.
aEEG started after “staring episode” and apnea; Phenobarbital was given.
Patient with Methylmalonic Acidemia:
Multiple areas with ictal discharges

Patient with Maple Syrup Urine Disease:
Infant with hypotonia, failure to gain weight, hepatomegaly, compensated metabolic acidosis, urine ketones positive. No clinical seizures.

Patient's clinical status improved on diet.

aEEG obtained 10 days after presentation; conventional EEG obtained 6 days later with paroxysmal activities: mainly generalized sharp, slow waves.
SUMMARY AND CONCLUSIONS (1):

aEEG monitoring is abnormal in a number of metabolic disorders with discontinuous tracing, burst suppression patterns and/or seizures.

Disorders with most pronounced changes are often characterized by presence of toxic metabolites or severe energy failure.

SUMMARY AND CONCLUSIONS (2):

Seizures in certain metabolic disorders and other genetic conditions may alternatively be due to dysgenesis of the central nervous system, including neuronal migration defects.

To summarize and interpret the aEEG findings in metabolic disorders beyond “individual observations” is hindered by their low occurrence rate and the use of aEEG in a “non-standardized fashion”.
SUMMARY AND CONCLUSIONS (3):

Protocols should be developed that would encourage a more uniform approach to monitoring and collection of other data in the aEEG monitoring of patients with metabolic disorders and other genetic conditions.

SUMMARY AND CONCLUSIONS (4):

Establishment of an International Registry to collect data of patients with metabolic disorders and other genetic conditions seems desirable.

The authors e-mail address is: ctheda@jhmi.edu