Vitamin/Cofactor-responsive Metabolic Encephalopathies

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Disclosures

Canadian Institutes of Health Research

Canadian Foundation of Innovation

United Mitochondrial Diseases Foundation

Physicians' Services Incorporated Foundation

Heart and Stroke Foundation

Rare Diseases Foundation

Myositis Association

Vitamin/Cofactor Responsive Encephalopathies : Learning Objectives

- To recognize clinical phenotypes of treatable metabolic etiologies of early-onset encephalopathies with seizures
- To select appropriate diagnostic investigations
- To apply effective treatment trials

Vitamin/Cofactor Responsive Neurological Conditions

- Vitamin A - retinal disease
- Biotinidase deficiency
- Vitamin B12 responsive MMA
- Vitamin B12 deficiency
- Carnitine (OCTN2) transporter def.
- Creatine deficiency disorders: creatine transporter, AGAT, GAMT
- Vitamin D - role in MS
- Vitamin E deficiency - ataxia
- Folate responsive disorders
- Folinic acid responsive seizures
- Folic acid transporter defect
- GLUT1 transporter defect
- Niacin/nicotinamide deficiency and with Hartnup's disease
- Pyridoxine dependent seizures
- Pyridoxal phosphate responsive seizures
- Coenzyme Q10 deficiency
- Riboflavin responsive disorders
- Serine deficiency disorders
- Thiamine responsive PDH def.
- Thiamine transporter defect
- Thiamine deficiency states

Common Features: Key message

1. Early onset Seizures/Encephalopathy
2. Developmental/Cognitive Delays ± Regression
3. Speech Delay
4. ± Movement Disorder
5. + Additional Distinguishing Features
6. Do not respond well to standard AED's -> require specific vitamin/cofactor

* Early recognition and treatment is critical to outcome

Glucose transporter defect - GLUT 1

Clinical

- Infantile seizures - GTC, clonic, myoclonic, atypical absence, atonic
- Developmental delay and speech delay
- Acquired microcephaly
- Pyramidal, extrapyramidal, cerebellar signs
- Sleep disturbance, headaches
- 3 phenotypes
  - Type 1: classic - seizures, microcephaly, delay, spasticity, confusion, pyramidal, extrapyramidal, cerebellar
  - Type 2: delay, dysarthria, dystonia, ataxia
  - Type 3: choreoathetosis, dystonia, paroxysmal eye and head movements, delay, dysarthria, hypotonia

Biochemical

- CSF/blood glucose < 0.4 X 3 (absence of infection)
- Low CSF lactate
- Reduced RBC glucose transporter activities

Glucose Transporter Defect - GLUT 1

Pathology

- Impaired blood brain barrier glucose transport
- Glucose serves as fuel and signalling molecule

Treatment

- Ketogenic diet (6 -28 wks of age) (Klepper et al 2002)
- At glucose of $\leq$ 40 mg/dl, asymptomatic in presence of ketones
- MCT or LCT - renal stones in one
- Good control seizures & motor symptoms, less effect on cognition

Genetics

- Autosomal dominant transmission
- Hemizygous or heterozygous mutations resulting in truncation of GLUT1 protein
- Gene (SLC2A1)
- 1p35-p31.3

X-linked Creatine transporter defect

Clinical

- Boys most severely affected
- Seizures
- Severe developmental delay or regression (or learning disabilities in females) and severe speech delay
- Hypotonia
- Behaviour problems, autistic features
- Midfacial hypoplasia
- GI disturbances - constipation, megacolon, ulcers, perforations

Biochemical

- ^{1}H-MRS brain - absence of creatine signal
- Severe depletion creatine/phosphocreatine in brain
- Increased creatine in plasma & urine, ⇑ urine creatine/creatinine
- Some have low plasma creatine, GAA normal
- Decreased Cr uptake in fibroblasts
- X-linked

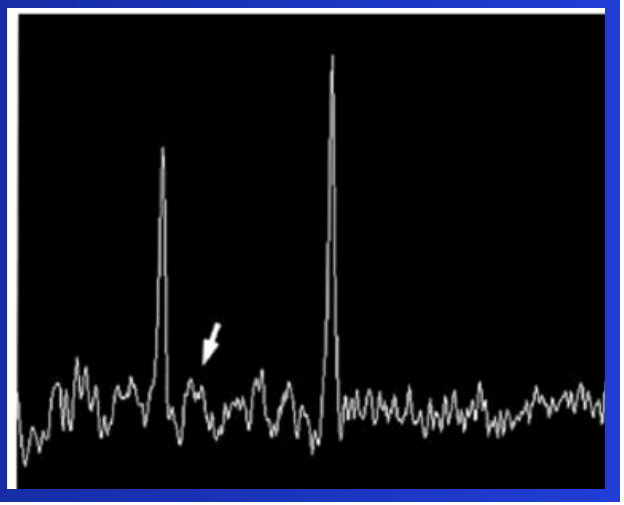
X-linked Creatine transporter defect

Treatment

- Creatine supplementation - does not correct cerebral creatine deficiency
- L-arginine (substrate for AGAT) X 9 mos - no improvement in speech, behaviour, motor skills or brain creatine (Fons et al 2008)
- in another study of 1 year therapy with L-arginine in 9 year old, found improvement in neurological, language and behavioural status and increased brain creatine (Chilosi et al 2008)

Genetics

- SLC6A8 gene maps to Xq28
- Hemizygous mutations



Arginine:glycine amidinotransferase deficiency (AGAT)

Clinical

- Severe developmental delay/regression
- Severe expressive speech delay, autistic features

Biochemical

- Severe depletion of creatine/phosphocreatine in brain
- AGAT catalyzes transfer of a guanido group from arginine to glycine, forming guanidinoacetic acid, precursor of creatine
- Blood & urine guanidinoacetate ⇓; Blood creatine low or normal

Treatment

Some improvement with oral creatine

Early treatment (e.g. 2 mos) prevents phenotypic expression

Genetics

- Autosomal recessive at 15q12

Guanidinoacetate methyltransferase deficiency (GAMT)

Clinical

- Severe developmental delay/regression
- Severe expressive speech delay, autistic features
- Severe seizure disorder - GTC, absence
- Hypotonia, pyramidal signs
- Movement disorder - extrapyramidal (ataxia, myoclonus, dystonia)

Biochemical

- Severe depletion of creatine/phosphocreatine in brain
- Converts guanidinoacetate to creatine with S-adenosylmethionine (SAM) as methyl donor
- Plasma creatinine low normal, 24 hr urine creatinine decreased
- Accumulation of guanidinoacetate in brain and body fluids which may be responsible for intractable seizures and movement disorder

Guanidinoacetate methyltransferase deficiency (GAMT)

Pathology

Marked myelination delay

Treatment

- Oral creatine partly successful
- Arginine restriction + ornithine substitution to decrease GAA improves clinical outcome

Genetics

- Autosomal recessive at 19p13.3

Serine Deficiency Disorders

Clinical

- Congenital microcephaly ± congenital cataracts
- Early onset seizures or juvenile onset absence seizures
- Moderate developmental delay
- Symmetric postnatal growth retardation and hypogonadism
- Chronic axonal sensorimotor polyneuropathy (Meneret et al 2012)

Biochemical - rare defects in biosynthesis of L-serine

- Low fasting plasma and CSF serine and glycine
- 3-phosphoglycerate dehydrogenase deficiency - locus 1p12 - AR
- 3-phosphoserine phosphatase deficiency - locus 7p11.2
- Serine deficiency etiology NYD

Pathology

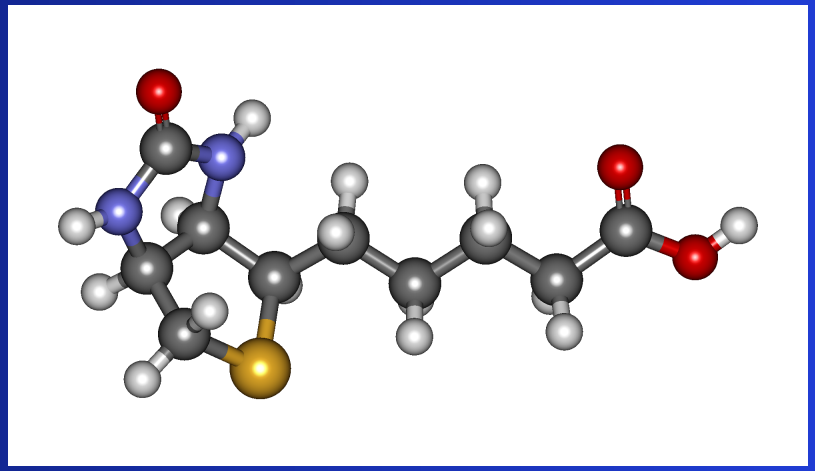
- L-Serine is precursor for nucleosides, phospholipids and neurotransmitters glycine and D-serine
- 3-PGDH - dysmyelination - needs antenatal treatment *

Treatment

- Respond well to serine therapy ± glycine (de Koning et al 2006) which may improve seizures and cerebral growth

Biotin

- Vitamin H or B7
- Cofactor in the metabolism of fatty acids and leucine and in gluconeogenesis
- Sources: royal jelly, brewer's yeast, swiss chard, tomatoes, romaine lettuce, carrots, almonds, eggs, onions
- Deficiency is rare



Biotin Deficiency

Relatively rare and mild

Causes

- Excessive consumption raw egg whites (avidin)
- Low levels of biotin have been reported in patients with gastrectomy, achlorhydria, burns, epilpetic patients, athletes
- Pregnancy and lactation may have increased demand for biotin

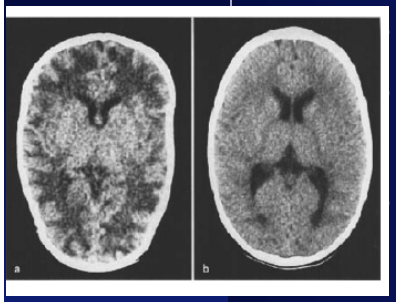
Clinical

- Signs: decreased appetite and growth, alopecia, perosis, fatty liver and kidney syndrome

Biotin Biochemistry

- Biotin is cofactor responsible for CO_2 transfer in several carboxylase enzymes
  - Acetyl - CoA carboxylase α
  - Acetyl - CoA carboxylase ß
  - Methylcrotonyl - CoA carboxylase
  - Propionyl - CoA carboxylase
  - Pyruvate carboxylase

Biotinidase Deficiency
(late onset multiple carboxylase deficiency)



Incidence Affects 1/60,000 newborns

Clinical variable phenotypes

Severe (< 10 %) and partial (10-30 % activity) and asymptomatic

Onset by ~ 3 mo with seizures as most frequent initial symptom (may have Otohara syndrome or infantile spasms)

Main features: hypotonia, cognitive delay, ataxia (may be intermittent), SN hearing loss, optic atrophy, skin rash, alopecia, recurrent infections

Biochemical profile

- ketoacidosis, lactic acidosis
- OA: 3-0H isovaleric acid, ß-methylcrotonylglycine, 3-0H-propionic acid

Pathology

- Diffuse atrophy, cerebellar atrophy, may have basal ganglia calcifications

Treatment

- Biotin - rapid clinical and biochemical improvement but some have residual CNS damage (MR, ataxia, SN hearing loss, visual defects)

Genetics Autosomal recessive, mutations in BTD gene 3p25.1

Folic Acid (Vitamin B9)

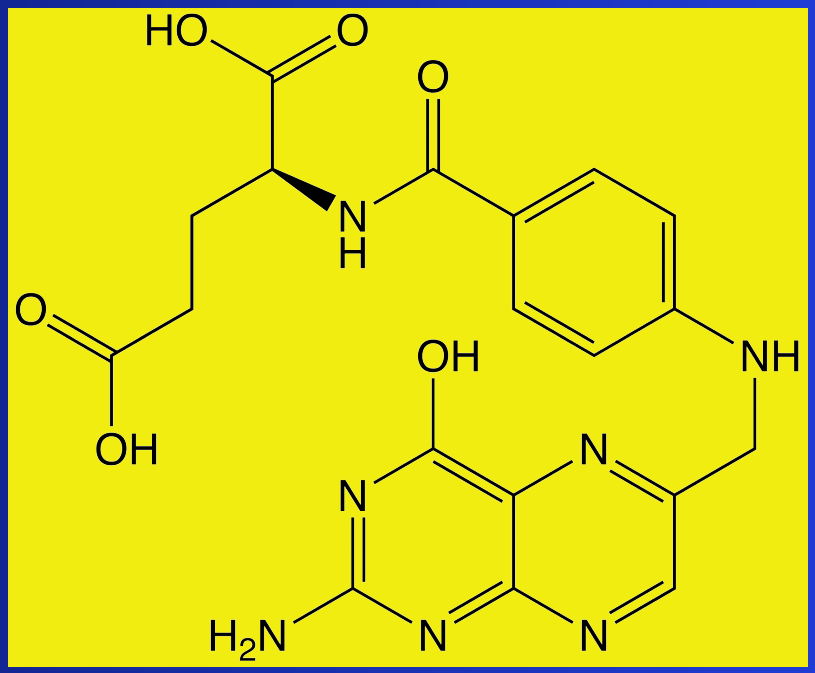
Sources - leafy vegetables
spinach, lettuce,
dried beans, peas,
fortified cereals,
sunflower seeds

Roles

- Synthesis of DNA (thymine + purine bases)
- Cell division

Drugs interfering with metabolism
methotrexate, trimethoprim,
sulfonamides, dilantin,
primidone, metformin

Deficiency
megaloblastic anemia
neural tube defects



Folic Acid Deficiency

- Clinical Manifestations
  - Diarrhea, anorexia, weight loss, palpitations
  - Weakness, headaches, irritability, behavioural disorders
  - Megaloblastic anemia
  - Folate deficient mothers - LBW and premature infants
    - Infants with neural tube defects
- Causes
  - Pregnancy and lactation (breast feeding)
  - Alcoholism
  - Tobacco smoking
  - Malabsorption, including celiac disease
  - Renal dialysis
  - Liver disease
  - Medications

Folic Acid Responsive Disorders

Disorder	Gene locus	Response
Folic acid transport defect in intestine and blood-brain barrier SLC46A1	17q11.2	+/-
Cerebral folate transport defect FOLR1	11q13.4	+
5,10- methylenetetrahydrofolate reductase (MTHFR) deficiency	1p36.3	+, betaine
Homocystinuria Cystathionine ß-synthase defect	21q22.3	+, B12, B6, low Met diet
Homocystinuria due to MTHFR deficiency	1p36.3	+, B6

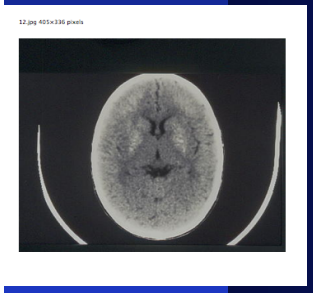
Hereditary folate malabsorption SLC46A1

Clinical

- Early infantile onset
- Megaloblastic anemia, pancytopenia, diarrhea, vomiting, infections
- Seizures, cognitive delay, drowsiness
- Movement disorder - ataxia, athetosis
- Peripheral neuropathy responsive to IM folinic acid (Steinschneider et al 1990)

Biochemistry

- Defect in intestinal and CNS blood-brain barrier folate transport
- Folate deficiency in RBC, serum, CSF



Neuroimaging - basal ganglia calcifications (Lanzkowsky 1970)

Genetics - autosomal recessive; SLC46A1 gene at 17q11.2

Treatment - parenteral folinic acid, methionine, B12 (Corbeel et al 1985)

- Normal growth and hematology, but continued low IQ and seizures

Cerebral folate transport defect- FOLR1

Clinical

- Late infantile onset
- Severe developmental regression
- Seizures, drowsiness
- Progressive movement disorder - ataxia, athetosis

Biochemistry

- Defect in cerebral folate transport due to mutations in folate receptor 1 gene coding for folate receptor alpha (FRα)
- Severe folate deficiency in CSF (Steinfeld et al 2009)

Neuroimaging - severe hypomyelination affecting periventricular and subcortical white matter; decreased choline and inositol peaks in parieto-occipital white matter on brain MRS (Steinfeld et al 2009)

Genetics - autosomal recessive; FOLR1 gene at 11q13.4

Treatment - oral folinic acid leads to clinical improvement in CNS function and in CSF MTHF and glial choline and inositol (Steinfeld et al 2009)

5,10-Methylenetetrahydrofolate Reductase Deficiency (MTHFR)

- Clinical - severe e.g. < 20 % residual activity to asymptomatic adults
  - Severe - Infancy onset with apnea, seizures, coma (Narisawa 1977)
  - Severe cognitive impairment, seizures, microcephaly
  - Weakness, gait abnormalities, thrombotic strokes (Visy et al 1991)
  - Psychiatric disorders e.g. schizophrenia, catatonia, psychosis
  - May have demyelination in brain & subacute combined degeneration of spinal cord (Hyland et al 1988)
- Biochemistry - ⇑ plasma homocysteine, ⇓ plasma methionine, ⇓ folate in serum and RBCs, homocystinuria
  decreased MTHFR in fibroblasts or leukocytes
- Genetics - consanguinity, AR, MTHFR gene at 1p36.22 (Goyette et al 1994)
- Treatment - folinic acid, methyltetrahydrofolate, betaine, methionine (Haworth et al 1993)

Pyridoxine - Vitamin B6

Chemistry - converted to biologically active form of pyridoxal 5-phosphate

Functions

- Assists in balancing sodium and potassium
- Promotes RBC production
- Decreases formation of homocysteine
- Prevents excema, psoriasis
- Required for production of monoamine neurotransmitters serotonin, dopamine, noradrenaline, adrenaline
- Precursor for pyridoxal phosphate: cofactor for aromatic amino acid decarboxylase which converts 5-HTP into serotonin and L-DOPA into dopamine, noradrenaline and adrenaline - implicated in treatment of depression and anxiety

- Sources - dragon fruit (South East Asia), grains, nuts

Pyridoxine

- Medicinal Roles
  - Given with isoniazid at 10-50 mg/day to prevent peripheral neuropathy and CNS toxicity
- Toxicity
  - If > 200 mg/day for long periods in adults
  - Sensory nerve toxicity - numbness in hands and feet, decreased light touch, temperature and vibration sense
  - ataxia

Pyridoxine Deficiency

- Clinical
  - Cheilitis and conjunctivitis
  - Sideroblastic anemia
  - CNS - neonatal onset seizures, irritability, confusion

Pathophysiology

impairment of decarboxylation of Glu to GABA

impairment of transamination of Glu to α-ketoGlu

Pyridoxine Dependent Epilepsy
AASA Dehydrogenase Deficiency

Prevalence - 1 in 20,000-400,000 (European, Turkish, Arabic, Asian)

Clinical

- May have intrauterine seizures
- Seizure onset usually day 1, but up to 3 wks possible
- Intractable Clonic, generalized tonic, myoclonic
- Resistant to AEDs - complete + immediate cessation with B6
- Other: respiratory distress, acidosis, abdominal distension/vomit
- Despite early tx and good Sz control, most have mild to severe developmental delay with speech delay

Biochemical Diagnosis

- Defect in α-aminoadipic semialdehyde DH in pipecolic acid pathway of lysine catabolism
- Increased plasma, urine, CSF pipecolic acid and AASA

Genetic - AR - mutations in antiquitin (ALDH7A1) gene, 5q31

Pathophysiology -P6C (piperideine-6-carboxylate) inactivates PLP

Pyridoxamine 5'-Phosphate Oxidase Deficiency
PNPO (rate-limiting enzyme for B6 synthesis)

Clinical

- Often premature birth - seizure onset day 1 or in utero
- Neonatal onset seizures (clonic), status epilepticus, myoclonus
- Rotatory eye movements, hyperexcitability, hypersalivation
- EEG - severe burst suppression pattern or myoclonic epilepsy
- One infant survived newborn period, but exhibited seizures, dystonia, microcephaly and severe delay at 2 years

Biochemical

- Hypoglycemia, early acidosis, pancytopenia, coagulopathy
- evidence in CSF and urine of biochemical profile consistent with reduction of PLP-dependent enzyme aromatic L-amino acid decarboxylase (⇑ in plasma, 0% liver)
- Raised glycine, threonine, taurine, histidine, and low arginine

Pyridoxamine 5’-Phosphate Oxidase Deficiency
PNPO (rate-limiting enzyme for B6 synthesis)

- Pathophysiology - disturbance of neurotransmitter metabolism
- Neuroimaging - progressive hypomyelination, global atrophy
- Genetics - AR, mutation in PNPO gene, 17q21.32
- Treatment - rapid response to pyridoxal 5’-phosphate (PLP)

Treatable Metabolic Causes of Early Onset Encephalopathy and Epilepsy

Disorder	Investigation	Treatment
Pyridoxine dependent epilepsy	α-AASA and pipecolic acid in blood, urine, CSF Sz and EEG response to 100 mg IV pyridoxine	15-30 mg/kg/d in 3 divided doses up to 200 mg/day in neonates and up to 400-500 mg/day in adults
PNPO	PLP 10 mg/kg	PLP 30-50 mg/kg/d in 3 divided doses
Folinic acid responsive	CSF marker with peak 'X'	3 - 5 mg/kg/day divided in 3 doses
Biotinidase deficiency	Trial biotin 5 mg bid, plasma biotinidase assay	Biotin 5-10 mg/day

Treatable Metabolic Causes of Early Onset Encephalopathy and Epilepsy

Disorder	Investigation	Treatment
GLUT 1 Deficiency	CSF glucose < 2.2 mM, CSF/ plasma glucose < 0.4 RBC glucose transport SLC2A1 mutation analysis	Ketogenic diet
Serine deficiences	⇓ fasting plasma serine & Gly ⇓ CSF serine & glycine Fibroblast enzyme assay PHGDH and PSAT1 genes	Serine 200-600 mg/kg/ day (glycine 200-300 mg/kg/ day)
Creatine deficiencies	Urine creatine/creatinine ratio Urine GAA/creatinine ratio ⇓ CSF creatine & MRS Cr peak Fibroblast GAMT assay, Cr uptake GAMT, AGAT, SLC6A8 genes	CrT: creatine + Arg + Gly AGAT: creatine 400 mkd GAMT tx: creatine 500-2000 mg/kg/day + Low Arg diet + Orn (100-400 mg/kg/d)
PKU	Plasma Phe, PAH gene	Phe restricted diet

Approach to Unexplained Frequent or Intractable Neonatal Seizures

1. Pyridoxine 100 mg bolus IV with EEG - be prepared to support apnea
   - Then 10 mg/kg q8h po X 24 hrs
   - If no definite response (EEG normalization or Sz control)

2. Folinic acid 5 mg/kg q 24 hrs po X 3 days
   if no definite response

3. PLP 10 mg/kg q 8h po X 3 days

OR ***preferable: PLP + folinic acid until biochemical/genetic results
for more rapid seizure control

Work-up

Serum glucose, lactate, NH3, quantitative amino acids (AA), acylcarnitines
biotinidase, α-amino adipic semialdehyde (αAASA), pipecolic acid

Urinary amino acids, organic acids, αAASA, sulfocysteine

CSF glucose, lactate, AA (glycine), neurotransmitters, αAASA, peak 'X'

Gene if indicated by screens -> sequencing of candidate gene ie antiquitin

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