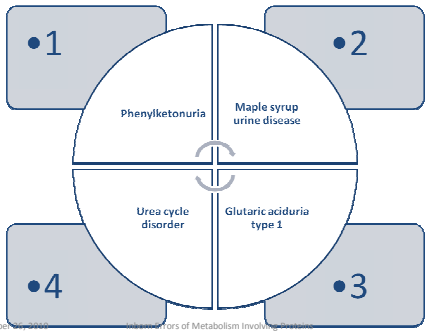
Inborn Errors of Metabolism Involving Proteins



1-Phenylketonuria (PKU)

- is an **autosomal recessive** metabolic **genetic disorder** characterized by a deficiency in the **hepatic enzyme phenylalanine hydroxylase** (PAH).
- This enzyme is necessary to metabolize the amino acid **phenylalanine** ('Phe') to the amino acid **tyrosine**.
- When PAH is deficient, phenylalanine accumulates and is converted into **phenylpyruvate** (**phenylketone)**.
- it can cause problems with brain development, leading to progressive mental retardation, brain damage, and seizures.
- It is treated with a **low-phenylalanine diet.**
- is detected through newborn screening and diagnosed by a geneticist.
- discovered by the **Norwegian** physician **Ivar Asbjørn Følling** in 1934

Screening

- detected using the **HPLC** test, and **Guthrie test**
- screening test (**Neonatal heel prick),** the disease may present clinically with **seizures, albinism** (due to **phenylacetate,** one of the ketones produced).
- Untreated children fail to attain early developmental milestones, develop **microcephaly**
- **Hyperactivity, EEG abnormalities** and **seizures,** and severe **learning disabilities** are major clinical problems later in life.
- **Hypopigmentation** and **eczema** are also observed.
- affected children who are detected and treated are less likely to develop neurological problems or have seizures and mental retardation.

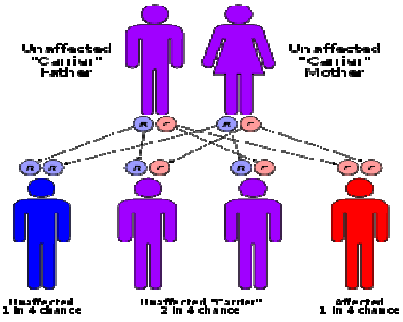
Pathophysiology

- **Classical PKU**
- **Tetrahydrobiopterin-deficient hyperphenylalaninemia**
  - defect in the biosynthesis or recycling of the **cofactor tetrahydrobiopterin** (BH_4)

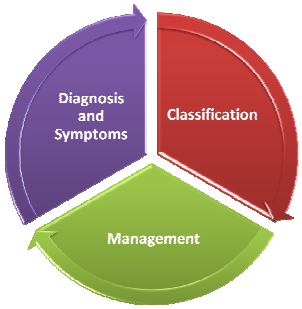
Metabolic Pathways

- **phenylalanine hydroxylase** normally converts the **amino acid phenylalanine** into the amino acid **tyrosine.**
- metabolized into phenylketones through the minor route, a **transaminase** pathway with **glutamate.**
- Metabolites include **phenylacetate**, **phenylpyruvate** and **phenethylamine.**
- Phenylalanine is a large, neutral amino acid
- LNAAs compete for transport across the **blood-brain barrier** via the **large neutral amino acid transporter**

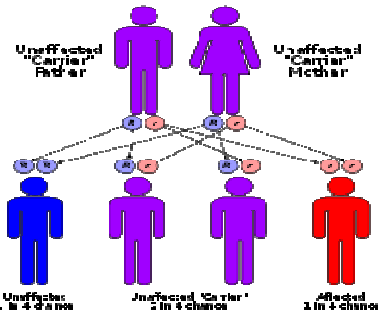
Maternal Phenylketonuria



2- Maple syrup urine disease
(branched-chain ketoaciduria,)



Genetic Prevalence



3- Glutaric Aciduria Type 1 (Glutaric Aciduria)

- is an inherited disorder in which the body is unable to break down completely the **amino acids lysine, hydroxylysine** and **tryptophan**.
- Excessive levels of their intermediate breakdown products (**glutaric acid, glutaryl-CoA, 3-hydroxyglutaric acid, glutaconic acid)**
- GA1 causes **secondary carnitine deficiency,** as **glutaric acid**, like other **organic acids**, is detoxified by **carnitine**.
- **Mental retardation** may also occur.

Signs and Symptoms

- The severity of **glutaric acidemia type 1** varies widely;
- GA1 can be defined as two clinical entities:
  - **GA1 before the encephalopathic crisis and**
  - **GA1 after the encephalopathic crisis.**

GA1 before the encephalopathic crisis
(Macrocephaly)

- Babies with glutaric acidemia type 1 often are born with large heads (**macrocephaly**).
- Macrocephaly is a **pivotal clinical sign** of many **neurological diseases**.
- underlying **neurological disorder**, particularly a **neurometabolic one**, in children with head circumferences in the highest percentiles.

GA1 after the encephalopathic crisis
Neuromotor aspects

- Affected individuals may have difficulty moving and may experience **spasms, jerking, rigidity** or **decreased muscle tone and muscle weakness**
- This symptomes may be the result of **secondary carnitine deficiency**.
- Glutaric aciduria type 1, in many cases, can be defined as a **cerebral palsy** of genetic origins.

Occupational Therapy

- A common way to manage **striatal necrosis** is to provide **special seating**.
- These special **wheelchairs** are designed to limit abnormal movements. However, spasticity can be worsened by constraint.
- Parents and caregivers can provide a more interactive occupational therapy by enabling the child to use his or her own excessive postural muscle tone to his or her own advantage
- The **excessive tone** can also be managed with **jolly jumpers** and other aids to the **upright stance** that do not constrain the child but help him or her gradually **tone down** the rigidity.

Bleeding Abnormalities

- Some individuals with **glutaric acidemia** have developed **bleeding in the brain or eyes** that could be mistaken for the **effects of child abuse.**

Treatment Methods

- **Correction of secondary carnitine depletion**
- **Precursor restriction**
  - Tryptophan
  - Lysine
- **Protein restriction**
  - Enhancement of precursor's anabolic pathway
  - *Tryptophan anabolic pathway enhancement*
- ***Management of intercurrent illnesses***

Correction of secondary carnitine depletion

- Like many other **organic acidemias, GA1** causes **carnitine depletion**.
- Whole-blood carnitine can be raised by **oral supplementation.**
- oral supplementation is **glutarylcarnitine** or **esterified carnitine**
- regular **intravenous infusions of carnitine** caused distinct clinical improvements :
  - decreased frequency of decompensations,
  - improved growth, improved muscle strength and
  - decreased reliance on medical foods with liberalization of protein intake.
- **Choline** increases **carnitine** uptake and retention.
- **Choline supplements** are inexpensive, safe (in all children requiring **anticholinergics**) and can suboptimal efficiency of carnitine **supplementation** by increasing **exercise tolerance, truncal tone** and **general well-being.**

Precursor Restriction

Selective precursor restriction

- **Tryptophan**
  - Formulas are designed to provide amino acids other than lysine and tryptophan
  - synthesis of the neurotransmitter **serotonin** in the brain.
  - is acute tryptophan depletion (ATD) in the brain and a consecutive lowering of **serotonin** synthesis.
  - **5-hydroxytryptophan,** the precursor of **serotonin** that is not metabolized to **glutaryl-CoA, glutaric acid** and **secondary metabolites**, could be used as an **adjunct** to selective **tryptophan restriction**.
- **Lysine**
  - **Lysine restriction**, as well as **carnitine supplementation**, are considered the best predictors of a **good prognosis for GA1.**
  - patients who already suffered an **encephalopathic crisis**, for whom the **prognosis** is more related to the treatment of their acquired disorder (**striatal necrosis, frontotemporal atrophy**).

Protein Restriction

- **Enhancement of precursor's anabolic pathway**
- ***Lysine and hydroxylysine anabolic pathway enhancement***
  - to limit **lysine** and **hydroxylysine** degradation
- **Interaction of GCDH deficiency with GLO deficiency**
  - **Ascorbic acid (Vitamin C)** is a necessary cofactor for the utilization of lysine in collagen synthesis.
  - Collagen requires great amounts of lysine.
  - **Ascorbic acid**,works as the cofactor providing the hydroxyl radical required to collagen cross-linking; lysine thus becomes **hydroxylysine.**
- ***Tryptophan anabolic pathway enhancement***
- ***Management of intercurrent illnesses***

Genetics

- is inherited in an **autosomal recessive** pattern:
- encodes the enzyme **glutaryl-CoA dehydrogenase**. enzyme is involved in degrading the amino acids **lysine, hydroxylysine** and **tryptophan.**
- This enzyme deficiency allows **glutaric acid, 3-hydroxyglutaric acid** and **glutaconic acid** to build up to abnormal levels,
- Glutaric acidemia type 1 occurs in approximately 1 of every 30,000 to 40,000 births.

Epistemology

- GA1 is a **metabolic disease**, a **neurometabolic disease**, a **cerebral palsy** or a **basal ganglia disorder.**
- e.g. **HIV encephalopathy-AIDS dementia complex, pneumococcal meningitis, hypoadrenal crisis, methylmalonic acidemia, propionic acidemia, middle cerebral artery occlusion, hypertensive vasculopathy, acute *mycoplasma pneumoniae* infection, 3-nitropropionic acid intoxication**, late onset **familial dystonia, cerebrovascular** abrupt and severe **neonatal asphyxia (selective neuronal necrosis).**
- **Macrocephaly** remains the main sign of GA1 for those who aren't related to GA1 in any way
- *Two thirds* of the patients who have GA1 will receive little benefit from the treatment for GA1 but can benefit from treatments given to victims of middle cerebral artery occlusion, AIDS dementia and other **basal ganglia disorders** : **brain implants, stem cell neurorestauration, growth factors, monoaminergic agents, and many other neurorehabilitation strategies.**

4-Urea Cycle Disorder

- **urea cycle disorder** or **urea cycle defect** is a **genetic disorder** caused by a deficiency of one of the **enzymes** in the **urea cycle** which is responsible for removing **ammonia** from the **blood** stream.
- The urea cycle involves a series of biochemical steps in which **nitrogen**, a waste product of **protein metabolism**, is removed from the blood and converted to urea.
- In urea cycle disorders, the nitrogen accumulates in the form of **ammonia**, a highly **toxic** substance, and is not removed from the body.

Incidence

- Are rare
- many cases remain undiagnosed.
- 20% of **Sudden Infant Death Syndrome** cases may be attributed to an undiagnosed inborn error of metabolism such as urea cycle disorder.
- incidence of the disorders at 1 in 10000 births.

Symptoms

- **The neonatal period**
  - increasing **lethargy. seizures, hypotonia (poor muscle tone), respiratory distress, and coma.**
  - **Acute neonatal symptoms** are in boys with **OTC Deficiency.**
- **Childhood**
  - Early symptoms are **hyperactive behavior,** sometimes accompanied by **screaming** and **self-injurious behavior,** and **refusal to eat meat** or **other high-protein foods**.
  - Later symptoms are **frequent episodes of vomiting**, especially following **high-protein meals**; **lethargy** and **delirium**; and finally, **coma** and **death**.
  - Childhood episodes of **hyperammonemia** (high ammonia levels in the blood) may be brought on by viral illnesses including **chicken pox,** high-protein meals, or even **exhaustion.**
  - The condition is sometimes misdiagnosed as **Reye's Syndrome.**
- **Adulthood**
  - These individuals exhibit **stroke-like symptoms**, **episodes of lethargy,** and **delirium**.
  - These adults are likely to be referred to **neurologists** or **psychiatrists** because of their **psychiatric symptoms.**
  - **Adult-onset symptoms** have been observed following **viral illnesses, childbirth**, and use of **valproic acid** (an anti-epileptic drug).

The Six Urea Cycle Disorders

Location	Enzyme	Disorder	Measurements
Mitochondria	N-Acetylglutamate synthetase	N-Acetylglutamate synthase deficiency	+Ammonia
Mitochondria	Carbamoyl phosphate synthetase I	Carbamoyl phosphate synthetase I deficiency	+Ammonia
Mitochondria	Ornithine transcarbamylase	Ornithine transcarbamylase deficiency	+Ornithine, +Uracil, +Orotic acid
Cytosol	Argininosuccinic acid synthetase	"AS deficiency" or citrullinemia	+Citrulline
Cytosol	Argininosuccinase acid lyase	"AL deficiency" or argininosuccinic aciduria (ASA)	+Citrulline, +Argininosuccinic acid
Cytosol	Arginase	"Arginase deficiency" or argininemia	+Arginine

Treatment

- This protein restriction is used in conjunction with **medications** which provide alternative pathways for the removal of ammonia from the blood.
- These medications are usually given by way of tube feedings, either via **gastrostomy tube** (a tube surgically implanted in the stomach) or **nasogastric tube** through the nose into the stomach.
- Treatment with multiple **vitamins** and **calcium supplements.**