

Newborn Screening for Disorders of Amino Acid Metabolism, Urea Cycle Metabolism, and Organic acid Metabolism

AMINO ACIDS

- Amino acids are the building blocks that proteins are made from.
- When we ingest protein, we first break it down into individual amino acids and then use these amino acids to make our own body's protein. This is particularly important in a growing infant.
- After those amino acids necessary for growth are used, the rest are either used to make other amino acids or are burned for energy. This is called amino acid metabolism.

AMINO ACIDS 2

- Because we normally ingest more protein (and thus amino acids) than we need, only a small % is used to make new protein. For example, less than 5% of the amino acid, phenylalanine is used even in a growing child and even less in a grown adult. All the rest is burned as energy or converted to another amino acid called tyrosine and other amino acids important to the way the brain functions.

AMINO ACIDS 3

- When an infant can not burn an amino acid normally, several things happen:
 - 1. Excess is converted in the body to other compounds, many of which are toxic
 - 2. There can be a deficiency of some compounds which are made from that amino acid—often things important for brain function.

AMINO ACIDS 4

- Therefore, the goal of therapy in these children is to give them just enough normal protein (amino acid) to grow on, but not enough to become injured by the excess.
- In most disorders of metabolism, this can only be done with a synthetic formula which does not contain the toxic amino acid. Treatment becomes a balancing act between giving enough to grow but no more. It must be monitored with frequent blood levels.

AMINO ACIDS 5

- Children and adults with these disorders are monitored in several ways:
- Blood levels are drawn **both** to look for excess of the toxic compound and to look for deficiency of this and other substances.
- Patients are examined looking for neurological changes.
- Patients are monitored for other signs of deficiency. We assume that these synthetic diets are not perfect.

Inheritance

- Almost all of the disorders which are mentioned in this talk are inherited.
- Most have to come from both the mother and the father who are carriers. Therefore, they are more common when relatives marry.
- A few come only from the maternal side and usually only males are affected
- Therefore, it is important to understand the list to subsequent children in the family.

Amino acid Metabolism

- The first step in amino acid metabolism involves either converting the amino acid to another amino acid ---for example, converting phenylalanine to tyrosine----or removing the ammonia group
- Defects in these early stages of metabolism lead to increased levels of amino acids and are classified as defects in amino acid metabolism.

Metabolism 2

- The subsequent steps in metabolism after the ammonium is removed are very much like fatty acid metabolism, but the compounds are called organic acids .
- If the defect in metabolism, is more than 1 or 2 steps after removing the ammonia group, then only the organic acid accumulates.
- Therefore, these diseases are considered organic acid diseases

Metabolism 3

- Because ammonia is toxic, the body must dispose of it. It uses a series of enzymes called the urea cycle.
- When one of these enzymes is defective, ammonia accumulates and the infant is said to have a urea cycle defect.
- Most of the parts of the urea cycle are amino acids, and the diseases are named either for the amino acid that accumulates or the specific enzyme that is missing.

Phenylketonuria (PKU)

- In this disorder phenylalanine can not be converted to tyrosine. The phenylalanine accumulates and interferes with brain development. There may also be a deficiency of tyrosine, further compromising brain and nerve function.
- Excess phenylalanine is also converted to phenylketones, bad smelling compounds for which the disease was named.

PKU 2

- PKU was the first disease to be screened for in infants and the first where a successful dietary treatment was developed.
- Management of the diet requires frequent blood levels because the amount of phenylalanine the child is allowed to consume depends on growth rate and must be adjusted regularly.

PKU 3

- The incidence of PKU is highest in people of northern European background and in people from Turkey. Therefore, as the percentage of Afro-American and Latino births has increased in Missouri, the incidence of the disease has decreased from 1 in 8000 births to about 1 in 10-12000 births. In Missouri, about 6 children with 'classical' PKU are born each year and about another 3 or 4 with milder disease.

PKU 4

- Some children with PKU, particularly those with milder variants of the disease, respond to a compound which functionally increases the enzyme activity.
- Some older individuals who have a hard time keeping to a diet, are helped by taking compounds which interfere with phenylalanine going into the brain.

Maple Syrup Urine Disease (MSUD)

- MSUD is the inability to metabolize the three branched chain amino acids, leucine, isoleucine, and valine.
- The breakdown products of these amino acids, alpha-keto acids, accumulate and have the odor of maple syrup or burned caramel.
- If this disease is not treated, the infants become severely acidotic and may die.

MSUD 2

- The disease has a low incidence in the general population, about 1 in 244,000 births but has a very high incidence in Old Order Mennonites, about 1 in 120 births.
- Because all of the Old Order Mennonites have the same mutation in their DNA, our laboratory tries to screen all married couples to see who is at risk to have an affected infant and then does DNA on all infants at birth of these couples.

MSUD 3

- Like PKU, the primary treatment of this disease is dietary restriction. However, the diet is much more restricted than in PKU infants. Essentially, these children live on a totally synthetic diet.
- Whereas the effects of going off the diet are only slowly evident in PKU patients, MSUD patients become rapidly very ill.
- Because the diet is so limited, problems with nutritional deficiencies are common and must be treated.

Defects in Tyrosine Metabolism

- There are three major defects in tyrosine metabolism, labeled type I , type II and type III.
- Type I leads to rapid liver failure and the need for a liver transplant.
- Type II and Type III are milder and more varied diseases, sometimes only transient.
- Unfortunately, newborn screening is much better at finding types II and III disease than type I disease. Only about 40% of type I disease are found on newborn screening.

Tyrosine 2

- Type I is fortunately quite rare in Missouri.
- The other types are also very uncommon but there are false positives seen in premature infants which can be confusing.
- Type II and III are usually treated with diet.
- Some of the infants, particularly the premies, respond to vitamin C.

Disorders of Sulfa-Amino Acid Metabolism

- The pathway leading from the amino-acid methionine through homo-cystine to cystine is screened for by looking at elevations in methionine
- This screening is not perfect because some defects in patients do not cause elevations in methionine in the newborn period giving false negatives and
- Some patients, particularly those with liver disease and small premature infants, can have elevated methionine without having one of these defects, false positives.

Sulfa-amino acids 2

- The most common disease in this pathway is homocystinuria.
- This disease leads to vascular problems like stroke, dislocated lenses, and often learning or psychiatric problems.
- In the past it often was not detected until the child had a stroke following minor surgery as a teenager.

Sulfa-amino acids 3

- Homocystinuria can be treated with diet, but large doses of vitamins, B6 and Folate, and other compounds with help to eliminate the homocystine are usually more effective
- Only one case of this problem has been confirmed in Missouri since screening began.
- The other diseases in this pathway cause a variety of learning disorders and are rarely described and are not well characterized.

Disorders of Urea Metabolism

- Amino acids are made up of a carbon backbone which forms an acid and an ammonia group or groups.
- The carbon backbone of amino acids are metabolized just like fatty acids.
- Before that can happen, the ammonia must be removed and converted to urea.
- The conversion of ammonia to urea is a complicated process which is called the urea cycle.

Urea 2

- Defects in urea metabolism led to high blood ammonia which can seriously damage the brain and cause death.
- Unfortunately, the most common of the defects in urea metabolism (OTC deficiency) can not be detected by newborn screening. It is usually evident, in any case, soon after birth and before the screening is done.

Urea 3

- The other defects in the urea cycle are named either for the compound that accumulates or the missing enzyme.
- These include citrullinemia, argininemia, and arginocuccinic acidemia.
- Citrullinemia can be a very serious disease. At least 3 cases are followed in Missouri.

Urea 4

- Newborn screening has discovered a very mild form of citrullinemia for which no treatment seems to be necessary. 2 cases of this mild form have been found in Missouri. These children are not sick as infants, but will still need to be followed to be sure there are no long term effects.

Urea 5

- Urea cycle defects can be very difficult to treat successfully.
- Protein intake has to be drastically restricted because all protein (amino acids) contain ammonia.
- Medicines which dispose of ammonia by means other than the urea cycle are used
- In some cases, the only treatment is liver transplant

Disorders of Organic Acid Metabolism

- Because the amino acids are metabolized in many different ways, there are many, many different enzymes involved, and many possible defects. Like the urea cycle defects, these are named either for the compound that accumulates or for the specific enzyme deficiency. Most of these diseases are pronounceable only by biochemists and geneticists.

Organic Acids 2

- The true wonder of the MS/MS machine is that it is able to diagnose most of these varied disorders all at the same time. It does this by counting the size of the compounds that accumulate.
- The way the machine works, it just tells how many carbon and hydrogen atoms the compound contains and whether or not they contain oxygen

Organic Acids 3

- Thus reports say things like C3 is elevated, meaning an organic acid with three carbons is elevated or that a compound has 3 carbons and one extra oxygen.
- Although there are only a limited number of things in the human that can be represented by these results, none-the-less, in many cases several different diseases can give the same result. **Therefore, screening is only screening and not a specific diagnosis.**

Organic Acids 4

- Most of these diseases are quite rare except in some population groups, but because so many of them can be detected by the same test the overall incidence in Missouri is not low.
- Nine cases were found in 2007 and 6 cases in 2008. Collectively, they have about the same incidence as PKU

Congenital Hypothyroidism

- This disease is the most common screened for in Missouri and is only very rarely inherited.
- The screening in Missouri is only designed to find primary thyroid failure and is not designed to find defects in the pituitary gland which can cause secondary hypothyroidism
- The incidence is about 1 in 3000 births, about 30 cases are found each year in Missouri.
- Most cases are relatively easy to treat with thyroid hormone replacement.

Congenital Adrenal Hyperplasia CAH

- CAH leads to adrenal failure in the newborn and to the masculinization of female infants
- Only the most common form of this disorder is screened for. About 90% are found.
- CAH is most common in people with southern German and Swiss heritage. Therefore, this disorder is relatively common in Missouri.
- The incidence found on newborn screening in Missouri is 1 in 13000 births.
- Because infants have hormones from their mothers, male children usually present at 8 to 10 days of age in adrenal failure. The females are usually found at birth because of changes in their genitalia.