Inborn Errors of Metabolism involving Proteins

Phenylketonuria

Phenylketonuria (**PKU**) is an autosomal recessive metabolic genetic disorder characterized by a deficiency in the hepatic enzymephenylalanine hydroxylase (PAH).[1]:541 This enzyme is necessary to metabolize the amino acid phenylalanine ('Phe') to the amino acidtyrosine. When PAH is deficient, phenylalanine accumulates and is converted into phenylpyruvate (also known as phenylketone), which is detected in the urine.[2]

Since its discovery, there have been many advances in its treatment. It can now be managed by the patient with little or no side-effects, just the inconvenience of managing the treatment. If, however, the condition is left untreated, it can cause problems with brain development, leading to progressive mental retardation, brain damage, and seizures. In the past, PKU was treated with a low-phenylalanine diet. Latter-day research now has shown that diet alone may not be enough to prevent the negative effects of phenylalanine levels. Optimal treatment involves lowering blood Phe levels to a safe range and monitoring diet and cognitive development. Lowering of phenylalanine levels to a safe range may be achieved by combining a low-phenylalanine diet with protein supplements. There is currently no cure for this disease; however, some treatments are available with varying success rates. In general, PKU is detected through newborn screening and diagnosed by a geneticist. PKU clinics around the world provide care for PKU patients to optimize phe levels, dietary intake, and cognitive outcomes.

History

Phenylketonuria was discovered by the Norwegian physician Ivar Asbjørn Følling in 1934[3] when he noticed that hyperphenylalaninemia (HPA) was associated with mental retardation. In Norway, this disorder is known as **Følling's disease**, named after its discoverer.[4] Dr. Følling was one of the first physicians to apply detailed chemical analysis to the study of disease. His careful analysis of the urine of two affected siblings led him to request many physicians near Oslo to test the urine of other affected patients. This led to the discovery of the same substance that he had found in eight other patients. The substance found was subjected to much more basic and rudimentary chemical analysis (taste). He conducted tests and found reactions that gave rise to benzaldehyde and benzoic acid, which led him to conclude the compound contained a benzene ring. Further testing showed the melting point to be the same as phenylpyruvic acid,

which indicated that the substance was in the urine. His careful science inspired many to pursue similar meticulous and painstaking research with other disorders.

Screening and presentation

PKU is normally detected using the HPLC test, but some clinics still use the Guthrie test, part of national biochemical screening programs. Most babies in developed countries are screened for PKU soon after birth.[5]

If a child is not screened during the routine newborn screening test (typically performed 6 -14 days after birth, using samples drawn byNeonatal heel prick), the disease may present clinically with seizures, albinism (excessively fair hair and skin), and a "musty odor" to the baby's sweat and urine (due to phenylacetate, one of the ketones produced). In most cases, a repeat test should be done at approximately 2 weeks of age to verify the initial test and uncover any phenylketonuria that was initially missed.

Untreated children are normal at birth, but fail to attain early developmental milestones, develop microcephaly, and demonstrate progressive impairment of cerebral function. Hyperactivity, EEG abnormalities and seizures, and severe learning disabilities are major clinical problems later in life. A "musty or mousy" odor of skin, hair, sweat and urine (due to phenylacetate accumulation); and a tendency to hypopigmentationand eczema are also observed.

In contrast, affected children who are detected and treated are less likely to develop neurological problems or have seizures and mental retardation, though such clinical disorders are still possible.

Pathophysiology

Classical PKU is caused by a mutated gene for the enzyme phenylalanine hydroxylase (PAH), which converts the amino acid phenylalanine to other essential compounds in the body. Other non-PAH mutations can also cause PKU. This is an example of genetic heterogeneity.

Classical PKU

The PAH gene is located on chromosome 12 in the bands 12q22-q24.1. More than four hundred disease-causing mutations have been found in the PAH gene. PAH deficiency causes a spectrum of disorders including classic phenylketonuria (PKU) and hyperphenylalaninemia (a less severe accumulation of phenylalanine).[6]

PKU is known to be an autosomal recessive genetic disorder. This means that both parents must have at least one mutated allele of the PAH gene. The child must inherit both mutated alleles, one from each parent. Therefore, it is not impossible for a parent with the disease to have a child without it if the other parent possesses one functional allele of the gene for PAH. Yet, a child from two parents with PKU will inherit two mutated alleles every time, and therefore the disease.

Phenylketonuria can exist in mice, which have been extensively used in experiments into an effective treatment for PKU.[7] The macaque monkey's genome was recently sequenced, and it was found that the gene encoding phenylalanine hydroxylase has the same sequence that, in humans, would be considered the PKU mutation.[8]

Tetrahydrobiopterin-deficient hyperphenylalaninemia

A rarer form of hyperphenilalaninemia occurs when PAH is normal but there is a defect in the biosynthesis or recycling of the cofactor tetrahydrobiopterin (BH_4) by the patient.[9] This cofactor is necessary for proper activity of the enzyme.

Levels of dopamine can be used to distinguish between these two types. Tetrahydrobiopterin is required to convert phenylalanine to tyrosine, but it is also required to convert tyrosine to DOPA (via the enzyme tyrosine hydroxylase), which in turn is converted to dopamine. Low levels of dopamine lead to high levels of prolactin. By contrast, in classical PKU, prolactin levels would be relatively normal. Tetrahydrobiopterin deficiency can be caused by defects in four different genes. These types are known as HPABH4A, HPABH4B, HPABH4C, and HPABH4D.

Metabolic pathways

The enzyme phenylalanine hydroxylase normally converts the amino acid phenylalanine into the amino acid tyrosine. If this reaction does not take place, phenylalanine accumulates and tyrosine is deficient. Excessive phenylalanine can be metabolized into phenylketones through the minor route, a transaminase pathway with glutamate. Metabolites includephenylacetate, phenylpyruvate and phenethylamine.[11] Elevated blood just because phenylalanine and detection of phenylketones in the urine is diagnostic.

Phenylalanine is a large, neutral amino acid (LNAA). LNAAs compete for transport across the blood-brain barrier (BBB) via the large neutral amino acid transporter (LNAAT). If phenylalanine is in excess in the blood, it will saturate the transporter. Excessive levels of phenylalanine tend to decrease the levels of other LNAAs in the brain. However, as these amino acids are necessary for

protein and neurotransmitter synthesis, phenylalanine buildup hinders the development of the brain, causing mental retardation.[12]

Treatment

If PKU is diagnosed early enough, an affected newborn can grow up with normal brain development, but only by managing and controlling phenylalanine (Phe) levels through diet, or a combination of diet and medication. When phenylalanine cannot be metabolized by the body, abnormally high levels accumulate in the blood and are toxic to the brain. When left untreated, complications of PKU include severe mental retardation, brain function abnormalities, microcephaly, mood disorders, irregular motor functioning, and behavioral problems such as ADHD.

All PKU patients must adhere to a special diet low in phenylalanine for at least the first 16 years of their lives. This requires severely restricting or eliminating foods high in phenylalanine, such as meat, chicken, fish, eggs, nuts, cheese, legumes, cow milk and other dairy products. Starchy foods such as potatoes, bread, pasta, and corn must be monitored. Infants may still be breastfed to provide all of the benefits of breastmilk, but the quantity must also be monitored and supplementation for missing nutrients will be required. Many diet foods and diet soft drinks that contain the sweetener aspartame must also be avoided, as aspartame consists of two amino acids: phenylalanine and aspartic acid.

Supplementary infant formulas are used in these patients to provide the amino acids and other necessary nutrients that would otherwise be lacking in a low-phenylalanine diet. As the child grows up, these can be replaced with pills, formulas, and specially formulated foods. (Since phenylalanine is necessary for the synthesis of many proteins, it is required for appropriate growth but levels must be strictly controlled in PKU patients). In addition, tyrosine, which is normally derived from phenylalanine, must be supplemented.)

The oral administration of tetrahydrobiopterin (or BH4) (a cofactor for the oxidation of phenylalanine) can reduce blood levels of this amino acid in certain patients.[13][14] The companyBioMarin Pharmaceutical has produced a tablet preparation of the compound sapropterin dihydrochloride (Kuvan),which is a form of tetrahydrobiopterin. Kuvan is the first drug that can help BH4-responsive PKU patients (defined among clinicians as about 1/2 of the PKU population) lower Phe levels to recommended ranges.[15] Working closely with a dietitian, some PKU patients who respond to Kuvan may also be able to increase the amount of natural protein they can eat.[16] After extensive clinical trials, Kuvan has been approved by the FDA for use in PKU therapy.

Researchers and clinicians working with PKU are finding Kuvan a safe and effective addition to dietary treatment and beneficial to patients with PKU.[17][18]

There are several other therapies currently under investigation, including gene therapy, large neutral amino acids, and enzyme substitution therapy with phenylalanine ammonia lyase (PAL). In the past, PKU-affected people were allowed to go off diet after approximately 8, then 18 years of age. Today most physicians recommend that PKU patients must manage their Phe levels throughout life.

Maternal Phenylketonuria
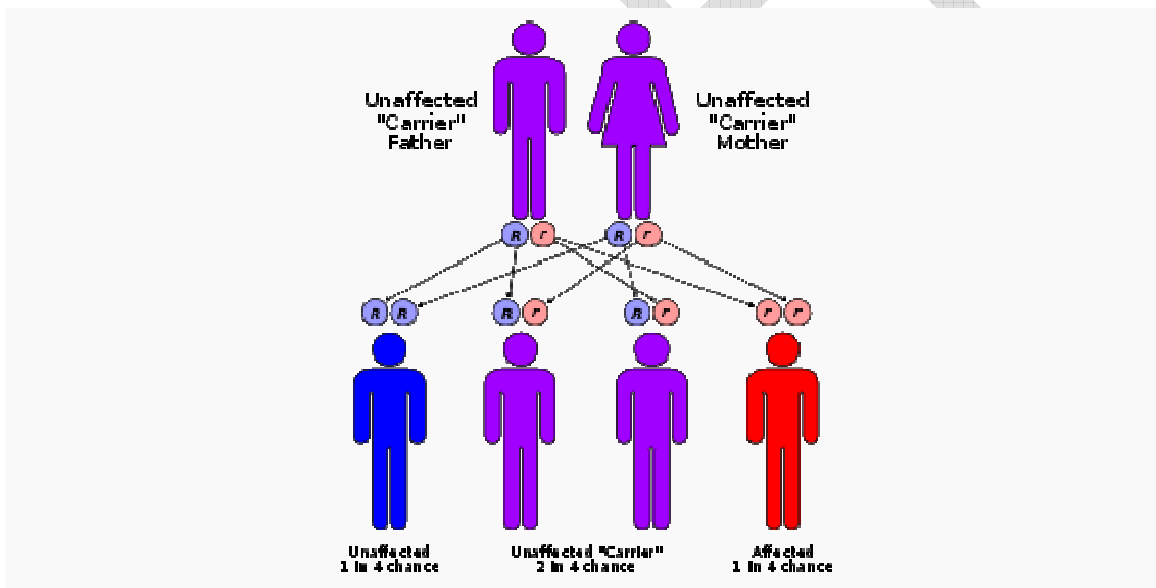
For women affected with PKU, it is essential for the health of their child to maintain low-phenylalanine levels before and during pregnancy.[19] Though the developing fetus may only be a carrier of the PKU gene, the intrauterine environment can have very high levels of phenylalanine, which can cross the placenta. The result is that the child may develop congenital heart disease, growth retardation, microcephaly and mental retardation.[20] PKU-affected women themselves are not at risk from additional complications during pregnancy.

In most countries, women with PKU that wish to have children are advised to lower their blood phenylalanine levels (typically to between 2 and 6 micromol/deciliter) before they become

pregnant, and carefully control their phenylalanine levels throughout the pregnancy. This is achieved by performing regular blood tests and adhering very strictly to a diet, in general monitored on a day-to-day basis by a specialist metabolic dietitian. In many cases, as the fetus' liver begins to develop and produce PAH normally, the mother's blood phenylalanine levels will drop, requiring an increased phenylalanine intake to remain within the safe range of 2-6 micromol/dL. The mother's daily phenylalanine intake may double or even triple by the end of the pregnancy, as a result. When maternal blood phenylalanine levels fall below 2 micromol/dL, anecdotal reports indicate that the mothers may suffer adverse effects including headaches, nausea, hair loss, and general malaise. When low phenylalanine levels are maintained for the duration of pregnancy, there are no elevated levels of risk of birth defects compared with a baby born to a non-PKU mother.[21] Babies with PKU may drink breast milk, while also taking their special metabolic formula. Some research has indicated that an exclusive diet of breast milk for PKU babies may alter the effects of the deficiency, though during breastfeeding the mother must maintain a strict diet to keep their phenylalanine levels low. More research is needed.

Incidence

The incidence of PKU is about 1 in 15,000 births, but the incidence varies widely in different human populations from 1 in 4,500 births among the population of Ireland[22] to 1 in 13,000 births in Norway[23] to fewer than one in 100,000 births among the population of Finland.[24] Turkey, at 1 in 2600, has the highest incidence rate in the world. The illness is also more common in Italy and China, as well as in Yemeni populations.[25]

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Maple syrup urine disease

Maple syrup urine disease (MSUD), also called **branched-chain ketoaciduria**, is an autosomal recessive[1] metabolic disorder affectingbranched-chain amino acids. It is one type of organic acidemia.[2] The condition gets its name from the distinctive sweet odor of affected infants' urine.[3]

Diagnosis and symptoms

MSUD is caused by a deficiency of the branched-chain alpha-keto acid dehydrogenase complex (BCKDH), leading to a buildup of thebranched-chain amino acids (leucine, isoleucine, and valine) and their toxic by-products in the blood and urine.

The disease is characterized in an infant by the presence of sweet-smelling urine, with an odor similar to that of maple syrup. Infants with this disease seem healthy at birth but if left untreated suffer severe brain damage, and eventually die.

From early infancy, symptoms of the condition include poor feeding, vomiting, dehydration, lethargy, hypotonia, seizures, ketoacidosis,opisthotonus, pancreatitis, coma and neurological decline.

Classification

Maple syrup urine disease can be classified by its pattern of signs and symptoms, or by its genetic cause. The most common and severe form of the disease is the classic type, which appears soon after birth. Variant forms of the disorder may appear later in infancy or childhood and are typically less severe, but still involve mental and physical problems if left untreated.

There are several variations of the disease:

- Classic Severe MSUD
- Intermediate MSUD
- Intermittent MSUD
- Thiamine-responsive MSUD
- E3-Deficient MSUD with Lactic Acidosis

Management

Keeping MSUD under control requires careful monitoring of blood chemistry and involves both a special diet and frequent testing.

A diet with minimal levels of the amino acids leucine, isoleucine, and valine must be maintained in order to prevent neurological damage. As these three amino acids are required for proper metabolic function in all people, specialized protein preparations containing substitutes and adjusted levels of the amino acids have been synthesized and tested, allowing MSUD patients to meet normal nutritional requirements without causing harm.[4]

Usually, patients are also monitored by a dietitian. Their diet must be adhered to strictly and permanently. However, with proper management those afflicted are able to live healthy, normal lives and not suffer the severe neurological damage associated with the disease.

Genetic prevalence
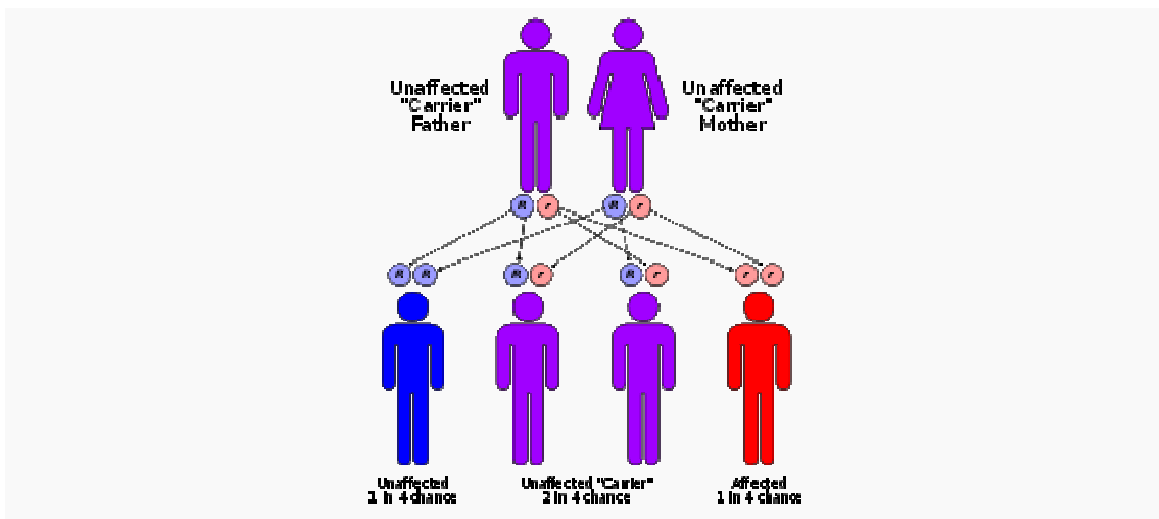
Maple syrup urine disease affects approximately 1 out of 180,000 infants.[5] Due in part to the founder effect,[6] however, MSUD has a much higher prevalence in children of Amish, Mennonite, and Jewish descent.[7][5][8]

Mutations in the following genes cause maple syrup urine disease:

- BCKDHA (Online 'Mendelian Inheritance in Man' (OMIM) 608348)
- BCKDHB (Online 'Mendelian Inheritance in Man' (OMIM) 248611)
- DBT (Online 'Mendelian Inheritance in Man' (OMIM) 248610)
- DLD (Online 'Mendelian Inheritance in Man' (OMIM) 238331)

These four genes produce proteins that work together as the branched-chain alpha-keto acid dehydrogenase complex. The complex is essential for breaking down the amino acids leucine, isoleucine, and valine, which are present in many kinds of food (particularly protein-rich foods such as milk, meat, and eggs). Mutations in any of these genes reduce or eliminate the function of the enzyme complex, preventing the normal breakdown of isoleucine, leucine, and valine. As a result, these amino acids and their by-products build up in the body. Because high levels of these substances are toxic to the brain and other organs, this accumulation leads to the serious medical problems associated with maple syrup urine disease.

This condition has an autosomal recessive inheritance pattern, which means the defective gene is located on an autosome, and two copies of the gene - one from each parent - must be inherited to be affected by the disorder. The parents of a child with an autosomal recessive disorder are carriers of one copy of the defective gene, but are usually not affected by the disorder.

Glutaric aciduria type 1

Glutaric acidemia type 1 (or "Glutaric Aciduria", "GA1", or "GAT1") 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) can accumulate and cause damage to the brain (and also other organs[1]), but particularly the basal ganglia, which are regions that help regulate movement. 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; some individuals are only mildly affected, while others have severe problems. 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 unusually large heads (macrocephaly). Macrocephaly is amongst the earliest signs of GA1. It is thus important to investigate all cases of macrocephaly of unknown origins for GCDH deficiency[2][3], given the importance of the early diagnosis of GA1[4]. Macrocephaly is a "pivotal clinical sign" of many neurological diseases. Physicians and parents should be aware of the benefits of investigating for an 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 (which 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 ir her own advantage (see picture; note the care with which minimal pressure is applied while ensuring safety).

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

Correction of secondary carnitine depletion

Like many other organic acidemias, GA1 causes carnitine depletion[5]. Whole-blood carnitine can be raised by oral supplementation. However, this does not significantly change blood concentrations of glutarylcarnitine or esterified carnitine,[4] suggesting that oral supplementation is suboptimal in raising tissue levels of carnitine. In the field of clinical nutrition, researchers come to the same conclusion, that oral carnitine raises plasma levels but doesn't affect muscle carnitine, where most of it is stored and used.[6]

- In contrast, 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."[5]
- Choline increases carnitine uptake and retention[7]. Choline supplements are inexpensive, safe (probably even in all children requiring anticholinergics) and can provide spectacular

evidence of the suboptimal efficiency of carnitine supplementation by increasing exercise tolerance, truncal tone and general well-being.

Precursor restriction

Dietary control may help limit progression of the neurological damage.

Selective precursor restriction

Tryptophan

Formulas such as *XLys, XTrp Analog*, *XLys, XTrp Maxamaid*, *XLys, XTrp Maxamum* or *Glutarex 1* are designed to provide amino acids other than lysine and tryptophan, in order to tentatively prevent protein malnutrition.

The entry of tryptophan to the brain is crucial in the proper synthesis of the neurotransmitter serotonin in the brain. One way to acutely cause depression or bulimia or anxiety in humans, in order to assess an individual's vulnerability to those disorders, is to supplement with a formula with all or most amino acids except tryptophan. The protein synthesis elicited by the amino acids leads circulating amino acids, including tryptophan, to be incorporated into proteins. Tryptophan thus lowers in the brain as a result of the protein synthesis enhancement (causing circulating tryptophan to lower more than other amino acids),[8] and perhaps also competition of large neutral amino acids for transport across the blood-brain barrier through the large neutral amino acid transporter 1 (LNAA1). The consequence is acute tryptophan depletion (ATD) in the brain and a consecutive lowering of serotonin synthesis. ATD, which is basically a diagnostic procedure, is not a treatment for GA1.

In the Amish community, where GA1 is overrepresented (Morton, 2003), patients with GA1 did not and still don't receive tryptophan-free formulas, neither as the sole source of amino acids, nor as a supplement to protein restriction. Doctor D. Holmes Morton, the 1993 Albert Schweitzer Prize for Humanitarianism laureate, is taking care of patients affected with GA1 and other metabolic diseases in this community in his Clinic for Special Children.

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, considering the risks associated with the procedure. However, the evidence in favour of selective tryptophan restriction remains insufficient and the consensus evolves towards the restriction of lysine only (Kolker & al. 2006).

Lysine

Lysine restriction, as well as carnitine supplementation, are considered the best predictors of a good prognosis for GA1 (Kolker & *al.*, 2006). This excludes, however, 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

Vegetarian diets and, for younger children, breastfeeding[9]are common ways to limit protein intake without endangering tryptophan transport to the brain.

Enhancement of precursor's anabolic pathway

Lysine and hydroxylysine anabolic pathway enhancement

A possible way to prevent the build-up of metabolites is to limit lysine and hydroxylysine degradation, as lysine is one of the most abundant amino acids and tryptophan is one the least abundant amino acids.

Interaction of GCDH deficiency with GLO deficiency

While GCDH deficiency is a rare disease, GLO deficiency is the most common of metabolic diseases affecting Humanity, limiting ascorbic acid biosynthesis to a minute fraction of what other non-primate species synthesize. It was thus called by OMIM (Online Mendeleian Inheritance in Man) a "public" error of metabolism. Ascorbic acid (Vitamin C) is a necessary cofactor for the utilization of lysine in collagen synthesis. Collagen, the most abundant protein in the human body, requires great amounts of lysine, the most abundant amino acids in proteins. Ascorbic acid, the main hydroxyl radical quencher, works as the cofactor providing the hydroxyl radical required to collagen cross-linking; lysine thus becomes hydroxylysine.

GA1 worsens during stresses and catabolic episodes, such as fasts and infections. Endogenous catabolism of proteins could be an important route for glutaric acid production. It thus follows that collagen breakdown (and protein breakdown in general) should be prevented by all possible means.

Ascorbic acid is used to prevent multiple organ failure and to lessen mortality and morbidity in intensive care units.[10] It thus appears reasonable to include sufficient doses of ascorbic acid to the

treatment protocol during stresses and other challenges to growth in order to stimulate collagen synthesis and thus prevent lysine breakdown.

Tryptophan anabolic pathway enhancement

The conversion of tryptophan to serotonin and other metabolites depends on vitamin B_6.[11] If tryptophan catabolism has any impact on brain glutaric acid and other catabolite levels, vitamin B_6 levels should be routinely assayed and normalized in the course of the treatment of GA1.

Management of intercurrent illnesses

Stress caused by infection, fever or other demands on the body may lead to worsening of the signs and symptoms, with only partial recovery.

Genetics

The condition is inherited in an autosomal recessive pattern: mutated copies of the gene *GCDH* must be provided by both parents to cause glutaric acidemia type 1. The *GCDH* gene encodes the enzyme glutaryl-CoA dehydrogenase. This enzyme is involved in degrading the amino acids lysine, hydroxylysine and tryptophan. Mutations in the *GCDH'* gene prevent production of the enzyme or result in the production of a defective enzyme with very low residual activity, or an enzyme with relatively high residual activity but still phenotypic consequences[12][13]. This enzyme deficiency allows glutaric acid, 3-hydroxyglutaric acid and (to a lesser extent) glutaconic acid to build up to abnormal levels, especially at times when the body is under stress. These intermediate breakdown products are particularly prone to affect the basal ganglia, causing many of the signs and symptoms of glutaric acidemia type 1.

Glutaric acidemia type 1 occurs in approximately 1 of every 30,000 to 40,000 births. It is much more common in the Amish community and in the Ojibway population of Canada, where up to 1 in 300 newborns may be affected.

Relatives of children with GA1 can have very low GCDH activity: in an early study of GA1, GCDH activity was found to be 38%, 42%, and 42% of controls in three of the four relatives tested[14]. Those levels are close to those found by Christensen & all[15] in some heavily symptomatic GA1-affected children.

Epistemology

GA1 can be described as a metabolic disease, a neurometabolic disease, a cerebral palsy or a basal ganglia disorder (it is also misdiagnosed as shaken baby syndrome). Depending on the paradigm adopted, GA1 will mostly be managed with precursor restriction or with neurorehabilitation (or with incarceration of the parents in the case of presumed shaken baby syndrome).

So-called "orphan diseases", such as GA1, can be *adopted* into wider groups of diseases (such as carnitine deficiency diseases, cerebral palsies of diverse origins, basal ganglia disorders, and others); Morton at al. (2003b) emphacize that acute striatal necrosis is a distinctive pathologic feature of at least 20 other disorders of very different etiologies (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")).

Amongst 279 patients who had been reported to have GA1, 185 were symptomatic (*two thirds*); being symptomatic was seen as an indication of "*low treatment efficacy*". High risk screening, neonatal screening and a diagnosis of macrocephaly were the ways to identify bearers of the *GCDH'* defective gene who weren't frankly symptomatic. Macrocephaly remains the main sign of GA1 for those who aren't related to GA1 in any way or benefit from no screening program. GA1 was considered as a "treatable disease"[16]. *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.

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Urea cycle disorder

An **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. Normally, the urea is transferred into the urine and removed from the body. In urea cycle disorders, the nitrogen accumulates in the form of ammonia, a highly toxic substance, and is not removed from the body.

Urea cycle disorders are included in the category of inborn errors of metabolism. There is no cure.

Incidence

Inborn errors of metabolism are generally considered to be rare but represent a substantial cause of brain damage and death among newborns and infants. Because many cases of urea cycle disorders remain undiagnosed and/or infants born with the disorders die without a definitive diagnosis, the exact incidence of these cases is unknown and underestimated. It is believed that up to 20% of Sudden Infant Death Syndrome cases may be attributed to an undiagnosed inborn error of metabolism such as urea cycle disorder. In April 2000, research experts at the Urea Cycle Consensus Conference estimated the incidence of the disorders at 1 in 10000 births. This represents a significant increase in case diagnosis in the last two years.

Symptoms

The neonatal period

Children with very severe urea cycle disorders typically show symptoms after the first 24 hours of life. The baby may be irritable at first, followed by vomiting and increasing lethargy. Soon after, seizures, hypotonia (poor muscle tone), respiratory distress, and coma may occur. If untreated, the child will die. These symptoms are caused by rising ammonia levels in the blood. Acute neonatal symptoms are most frequently seen in, but not limited to, boys with OTC Deficiency.

Childhood

Children with mild or moderate urea cycle enzyme deficiencies may not show symptoms until early childhood, or may be diagnosed subsequent to identification of the disorder in a more severely affected relative or through newborn screening. Early symptoms may include hyperactive behavior, sometimes accompanied by screaming and self-injurious behavior, and refusal to eat meat or other high-protein foods. Later symptoms may include frequent episodes of vomiting, especially following high-protein meals; lethargy and delirium; and finally, if the condition is undiagnosed and untreated, coma and death. Children with this disorder may be referred to child psychologists because of their behavior and eating problems. 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. Childhood onset can be seen in both boys and girls.

Adulthood

Recently, the number of adult individuals being diagnosed with urea cycle disorders has increased at an alarming rate. Recent evidence has indicated that these individuals have survived undiagnosed to adulthood, probably due to less severe enzyme deficiencies. 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. However, without proper diagnosis and treatment, these individuals are at risk for permanent brain damage, coma, and death. Adult-onset symptoms have been observed following viral illnesses, childbirth, and use of valproic acid (an anti-epileptic drug).

The six urea cycle disorders

There are six disorders of the urea cycle. Each is referred to by the initials of the missing enzyme.

Location	Abb.	Enzyme	Disorder	Measurements
Mitochondria	NAGS	N-Acetylglutamate synthetase	N-Acetylglutamate synthase deficiency	+Ammonia
Mitochondria	CPS1	Carbamoyl phosphate synthetase I	Carbamoyl phosphate synthetase I deficiency	+Ammonia
Mitochondria	OTC	Ornithine transcarbamylase	Ornithine transcarbamylase deficiency	+Ornithine, +Uracil, +Orotic acid
Cytosol	AS	Argininosuccinic acid synthetase	"AS deficiency" or citrullinemia	+Citrulline
Cytosol	AL	Argininosuccinase acid lyase	"AL deficiency" or argininosuccinic aciduria (ASA)	+Citrulline, +Argininosuccinic acid
Cytosol	AG	Arginase	"Arginase deficiency" or argininemia	+Arginine

Individuals with childhood or adult onset disease may have a partial enzyme deficiency. All of these disorders are transmitted genetically as autosomal recessive genes - each parent contributes a defective gene to the child, except for one of the defects, Ornithine Transcarbamylase Deficiency. This urea cycle disorder is acquired in one of three ways: as an X-linked trait from the mother, who may be an undiagnosed carrier; in some cases of female children, the disorder can also be inherited from the father's X-chromosome; and finally, OTC deficiency may be acquired as a

"new" mutation occurring in the fetus uniquely. Recent research has shown that some female carriers of the disease may become symptomatic with the disorder later in life, suffering high ammonia levels. Several undiagnosed women have died during childbirth as a result of high ammonia levels and on autopsy were determined to have been unknown carriers of the disorder.

Treatment

The treatment of urea cycle disorders consists of balancing dietary protein intake in order that the body receive the essential amino acids responsible for cell growth and development, but not so much protein that excessive ammonia is formed. 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. The treatment may also include supplementation with special amino acid formulas developed specifically for urea cycle disorders, multiple vitamins and calciumsupplements. Frequent blood tests are required to monitor the disorders and optimize treatment, and frequently hospitalizations are necessary to control the disorder.

At the most extreme end of the spectrum, a few liver transplants have been done successfully as a cure to the disorder. This treatment alternative must be carefully evaluated with medical professionals to determine if potential of success as compared to the potential for new medical concerns.

Inborn Errors of Metabolism Involving Carbohydrates

Galactosemia

Galactosemia (British **Galactosaemia**) is a rare genetic metabolic disorder that affects an individual's ability to metabolize the sugargalactose properly. Galactosemia is not related to and should not be confused with lactose intolerance. Galactosemia follows an autosomal recessive mode of inheritance that confers a deficiency in an enzyme responsible for adequate galactose degradation.

Goppert first described the disease in 1917,[1] with its cause as a defect in galactose metabolism being identified by a group led by Herman Kalckar in 1956.[2]

Its incidence is about 1 per 60,000 births. It is much rarer in Japan and much more common in Italy, specifically the traveler region. Galactosemia is also very common within the Irish Traveller population. This is attributed to inbreeding within a relatively small gene pool.[citation needed]

Cause

Lactose in food (such as dairy products) is broken down by the enzyme lactase into glucose and galactose. In individuals with galactosemia, the enzymes needed for further metabolism of galactose are severely diminished or missing entirely, leading to toxic levels of galactose in the blood, resulting in hepatomegaly (an enlarged liver), cirrhosis, renal failure, cataracts,brain damage, and ovarian failure. Without treatment, mortality in infants with galactosemia is about 75%.

Types

Galactose is converted into glucose by the action of three enzymes, known as the Leloir pathway. Accordingly, there are 3 known types of Galactosemia; type 1, 2 and 3:

Type	Diseases Database	OMIM	Gene	Locus	Enzyme	Name
Type 1	5056	230400	*GALT*	9p13	galactose-1-phosphate uridyl transferase	classic galactosemia
Type 2	29829	230200	*GALK1*	17q24	galactokinase	galactokinase deficiency
Type 3	29842	230350	*GALE*	1p36-p35	UDP galactose epimerase	galactose epimerase deficiency, UDP-Galactose-4-epimerase deficiency

The order of these three types is not the same as the order that the enzymes are encountered by galactose on its metabolic path (which is closer to GALK, GALT, and then GALE, though many variations can occur.)[citation needed]

Diagnosis

Infants are now routinely screened for galactosemia in the United States, and the diagnosis is made while the person is still an infant. Infants affected by galactosemia typically present with symptoms of lethargy, vomiting, diarrhea, failure to thrive, and jaundice. None of these symptoms are specific to galactosemia, often leading to diagnostic delays. Luckily, most infants are diagnosed on newborn screening. A galactosemia test is a blood test (from the heel of the infant) or urine test that checks for three enzymes that are needed to change galactose sugar that is found in milk and milk products-into glucose, a sugar that your body uses for energy. A person with galactosemia doesn't have one of these enzymes. This causes high levels of galactose in the blood or urine.

Galactosemia is normally first detected through newborn screening, or NBS. Affected children can have serious, irreversible effects or even die within days from birth. It is important that newborns be screened for metabolic disorders without delay. Galactosemia can even be detected through NBS before any ingestion of galactose-containing formula or breast milk.

Detection of the disorder through newborn screening (NBS) does not depend on protein or lactose ingestion, and, therefore, it should be identified on the first specimen unless the infant has been transfused. A specimen should be taken prior to transfusion. The enzyme is prone to damage if the sample is delayed in the mail or exposed to high temperatures. The routine NBS is accurate for detection of galactosemia. Two screening tests are used to screen infants affected with galactosemia - the Beutler's test and the Hill test. In fact a third test, called the "Florida test", is also normally performed on all galactosemia positives. The Beutler's test screens for galactosemia by detecting the level of enzyme of the infant. Therefore, the ingestion of formula or breast milk does not effect the outcome of this part of the NBS, and the NBS is accurate for detecting galactosemia prior to any ingestion of galactose.

Treatment

The only treatment for classic galactosemia is eliminating lactose and galactose from the diet. Even with an early diagnosis and a restricted diet, however, some individuals with galactosemia experience long-term complications such as speech difficulties, learning disabilities, neurological

impairment (e.g. tremors, etc), symptoms have not been associated with Duarte galactosemia, and many individuals with Duarte galactosemia do not need to restrict their diet at all. Infants with classic galactosemia cannot be breast-fed due to lactose in human breast milk and are usually fed a soy-based formula.[3]

Galactosemia is sometimes confused with lactose intolerance, but galactosemia is a more serious condition. Lactose intolerant individuals have an acquired or inherited shortage of the enzyme lactase, and experience abdominal pains after ingesting dairy products, but no long-term effects. In contrast, a galactosemic individual who consumes galactose can cause permanent damage to their bodies.

Long term complication of galactosemia includes:

- Speech deficits
- Ataxia
- Dysmetria
- Diminished bone density
- Premature ovarian failure
- Cataract

Glycogen storage disease

Glycogen storage disease (**GSD**, also **glycogenosis** and **dextrinosis**) is the result of defects in the processing of glycogen synthesis or breakdown within muscles, liver, and other cell types.[1] GSD has two classes of cause: genetic and acquired. Genetic GSD is caused by any inborn error of metabolism (genetically defective enzymes) involved in these processes. In livestock, acquired GSD is caused byintoxication with the alkaloid castanospermine.[2]

Overall, according to a study in British Columbia, approximately 2.3 children per 100 000 births (1 in 43,000) have some form of glycogen storage disease.[3] In the United States, they are estimated to occur in 1 per 20,000-25,000 births.[4] A Dutch study estimated it to be 1 in 40,000.[5]

Types

There are eleven distinct diseases that are commonly considered to be glycogen storage diseases (some previously thought to be distinct have been reclassified). (Although glycogen synthase deficiency does not result in storage of extra glycogen in the liver, it is often classified

with the GSDs as type 0 because it is another defect of glycogen storage and can cause similar problems.)

- GSD type VIII: In the past, considered a distinct condition.[6] Now classified with VI.[7] Has been described as X-linked recessive.[8]

- GSD type X: In the past, considered a distinct condition.[9][10] Now classified with VI.[7]

Number[M]	Enzyme deficiency[M]	Eponym[M]	Incidence[M]	Hypoglycemia?[M]	Hepatomegaly?[M]	Hyperlipidemia?[M]	Muscle symptoms[M]	Development/prognosis[M]	Other symptoms[M]
GSD type I	glucose-6-phosphatase	von Gierke's disease	1 in 50,000[4]-100,000[11]births	Yes	Yes	Yes	None	Growth failure	Lactic acidosis,hyperuricemia
GSD type II	acid maltase	Pompe's disease	1 in 60,000-140,000 births[5]	No	Yes	No	Muscle weakness	*Death by age ~2 years (infantile variant)	heart failure
GSD type III	glycogen debrancher	Cori's disease orForbes' disease	1 in 100,000 births	Yes	Yes	Yes	Myopathy		
GSD type IV	glycogen branching enzyme	Andersen disease		No	hepatosplenomegaly,cirrhosis	No	None	Failure to thrive, death at age ~5 years	
GSD type V	muscle glycogen phosphorylase	McArdle disease	1 in 100,000[12]	No	No	No	Exercise-induced cramps,Rhabdomyolysis		Renal failurebymyoglobinuria
GSD type	liver glycogen	Hers' disease	1 in 65,000-	Yes	Yes	No	None		

VI	phosphorylase		85,000 births[13]					
GSD type VII	muscle phosphofructokinase	Tarui's disease		No	No	No	Exercise-induced muscle cramps and weakness (sometimes rhabdomyolysis)	growth retardation	Haemolytic anaemia
GSD type IX	phosphorylase kinase, PHKA2	-		No	No	Yes	None	Delayed motor development, Growth retardation	
GSD type XI	glucose transporter,GLUT2	Fanconi-Bickel syndrome		Yes	Yes	No	None		
GSD type XII	Aldolase A	Red cell aldolase deficiency		?	?	?	Exercise intolerance, cramps		
GSD type XIII	β-enolase	-		?	?	?	Exercise intolerance, cramps		
GSD type 0	glycogen synthase	-		Yes	No	No	Occasional muscle cramping		