Fact Sheets

Information for **DOCTORS** about the disorders included in the Expanded Newborn Screening Panel

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AMINO ACID DISORDERS

HOMOCYSTINURIA (HCY)

What is HCY?

Homocystinuria (Hcy), caused by cystathionine β-synthase deficiency, is an inborn error of the transsulfation pathway which causes an increase in levels of homocysteine and methinonine in blood.[1]

Clinical Manifestation

Patients affected with homocystinuria may present with (1) ectopia lentis, which is found in 85% of patients[2]; (2) skeletal abnormalities are prominent especially genu valgus, and patients are often described to have a "marfanoid habitus"; (3) mental retardation is common but not invariable and; (4) thromboembolism.[2,3]

Pathophysiology

Increased homocysteine levels is found to inhibit linking of collagen and elastic tissue, which predisposes zonule generation of the eye predisposing patients to myopia and lens dislocation.[4] Skeletal abnormalities are thought to result from damage to fibrillin in patients with cytathionine β-synthase and due to a reduction in collagen crosslinking[5] while the mechanism that contributes to the atherogenic propensity of hyperhomocystinemia are related to endothelial dysfunction and injury, which leads to platelet aggregation and thrombus formation.[6] Finally, chemical abnormalities and the repeated thromboemolic strokes may contribute to the mental retardation.[4,6]

Inheritance: autosomal recessive[7]

Confirmatory Testing

Total homocysteine in plasma. Amino acids in plasma, methylmalonic acid in urine, and enzyme study in fibroblasts may be used to confirm the diagnosis.[7]

Overview of Disease Management

The aim of treatment is to reduce the plasma total homocysteine through the following approaches: (1) large doses of pyridoxine (50-100mg/day) have been effective in reducing biochemical abnormalities in patients with cystathionine- β-synthase deficiency where about half respond partially (2) folic acid (10mg/day) may be given along with betaine (100mg/kg/day) that lowers homocysteine levels by remethylation dietary modification by giving a low-methionine/high-cystine diet. [2] Additional treatment may include Vitamin C (100mg/day) and hydroxocobalamin (1mg/day) starting at 5 yrs of age.

Prognosis

Early diagnosis and treatment can prevent thromboembolic events and reduce the complications brought about by increased levels of homocysteine.[2]

Preliminary / Initial Management During Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What To Do

If unwell and cannot tolerate oral intake:

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- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Collect samples for plasma amino acids. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D12.5% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Start betaine, folic acid and vitamin B6.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with HCY formula or protein free formula at maintenance rate
- Insert IV access. Collect samples for plasma amino acids. May request for investigations (i.e. CBC, etc.) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Start betaine, folic acid and vitamin B6.
- Monitor input and output strictly (q6 hours)

**Children should not be protein restricted for longer than necessary (24-28 hours)*

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Schulze A, Matern D, Hoffmann GF. Chapter 2: Newborn screening in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism.* New York:McGraw Hill, 2009 pp 17-32.

[2] Chapter 22 Homocystinuria. Nyhan WL, Barshop BA and Ozand P. *Atlas of Metabolic Diseases* 2nd ed. Great Britain:Oxford University Press, 2005 pp146-151.

[3] Cruysburg JR, Boers GHJ, Trijbels FMJ et al. *Delay in diagnosis of homocystinuria: retrospective study of consecutive patients.* BMJ 1996;313:1037-1040.

[4] Burke JP, O'Keefe M, Bowell R and Naughten ER. *Ocular Complications in Homocystinuria – Early and Late Treated.* Br J Ophthalmol. 1989 June;73(6):427-431.

[5] Mudd SH, Levy HL, Skovby F. *Disorders of transsulfuration.* In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. Vol 2. New York: McGraw-Hill, 2001:2007-2056.

[6] Boushey Cj, Beresford SA, Omenn GS, Motulsky AG. *A Quantitative Assessment of Plasma Homocysteine as a Risk Factor for Vascular Disease: Probable Benefits of Increasing Folic Acid Intakes*. JAMA 1995;274:1049-1057.

[7] Yap S. *Homocystinuria due to cystathionine β-synthase deficiency.* Orphanet 2005. http://www.orpha.net/data/photo/GBuk-CbS.pdf. Accessed 16 Feb 2012

[8] Ueland PM. *Homosysteine Species as Components of Plasma Redox Thiol Status*. Clin Chem 1995;41:340-342.

AMINO ACID DISORDERS

METHIONINE ADENOSINE TRANSFERASE (MAT) DEFICIENCY

What is Methionine Adenosine Transferase (MAT) Deficiency?

Isolated persistent hypermethioninamia has been defined as abnormal elevation of plasma methionine that persists beyond infancy and is not caused by homocystinuria due to cystathionine β-synthase deficiency, tyrosinemia type I or severe liver disease. [1] With rare exceptions, this abnormality has been found to be due to inactivating mutations in *MAT1A*, the gene that encodes the catalytically active subunit of the two isozyme forms of methinonine adenosyltransferase.[2]

Clinical Manifestation

The great majority of patients have no clinical abnormalities except for unpleasant, sulfurous breath odor but a few patients have shown neurologic abnormalities such as nystagmus, dysdiadochokinesis, increased tendon reflexes, mental retardation, dystonia and dysmetria associated with demyelination on MRI.[3] The complete lack of MAT I/III activity can represent a risk for development of brain demyelination, but some residual activity seems to be sufficient to maintain clinical well-being.[4]

Pathophysiology

The pathogenesis of this disease is not clearly elucidated and it might result from different factors: extraordinarily high plasma methionine levels can directly contribute to nuerological abnormalities, the lack of synthesis of S-adenosylmethionone (AdoMet)-dependent methylated products can cause demyelination and hyperhomocysteinemia might bring about an elevated risk of vascular and thrombotic dieases.[4]

Inheritance: autosomal recessive[4, 5]

Confirmatory Testing

High methinonine in plasma and urine without increased homocysteine.[5] Confirmation of the diagnosis by enzyme assay requires liver tissue and therefore is not routinely performed.[3]

Overview of Disease Management

Treatment is generally not indicated but in patients with evidence of demyelination, administration of S-adenosylmethinonine corrects deficiency of this compound.[3,5]

Prognosis

Abnormal elevations of plasma homocysteine have been reported among more severely affected MAT I/III deficient patients and might possibly increase the long-term risk for strokes.[4]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure

- Insert IV access. Collect plasma amino acid sample. May request for investigations (i.e. CBC, liver transaminases, blood gas, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D12.5% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with protein free formula at maintenance rate
- Insert IV access. Collect plasma amino acid sample. May request for investigations (i.e. CBC, liver transaminases, blood gas, etc.) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours).

**Children should not be protein restricted for longer than necessary (24-48 hours)*

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Mudd SH, Chamberlin ME, Chou JY. *Isolated persistent hypermethioninemia: genetic, metabolic and clinical aspects.* As cited in Kim SZ, Santamaria E, Jeong TE et al. Methionine adenosyltransferase I/III deficiency: two Korean compound heterozygous siblings with a novel mutation. J Inherit Metab Dis 2002;25:661-671.

[2] Kim SZ, Santamaria E, Jeong TE et al. *Methionine adenosyltransferase I/III deficiency: two Korean compound heterozygous siblings with a novel mutation.* J Inherit Metab Dis 2002;25:661-671.

[3] Fowler B. Chapter 16: Disorders of Transsulfuration in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism.* New York:McGraw Hill, 2009 pp 185-194.

[4] Martins E, Marcao A, Bandeira A et al. *Methionine Adenosyltransferase I/III Deficiency in Portugal: High Frequency of a Dominantly Inherited Form in a Small Area of Douro High Lands.* JIMD Reports 2011.

[5] Adria G, Fowler B, Sebastio G. Chapter 21: Disorders of Sulfur Amino Acid Metabolism in Fernandes J, Saudubray JM, van den Berghe G, Walter JH (eds). *Inborn Metbaolic Disease Diagnosis and Treatment* 4th ed. Germany:Springer Medizin Verlag, 2006 pp 278-279

AMINO ACID DISORDERS

MAPLE SYRUP URINE DISEASE [MSUD]

What is MSUD?

Maple syrup urine disease (MSUD) is due to a defect or deficiency of the branched chain ketoacid dehydrogenase complex in which elevated quantities of leucine, isoleucine, valine, and their corresponding oxoacids accumulate in body fluids.[1]

Clinical Manifestation

Infants with MSUD appear normal at birth.[2] There are different classifications of MSUD based on the enzyme activity and these include: classical, intermediate, intermittent, thiamine response, and E-3 deficient MSUD. Classical MSUD (residual enzyme ≤2%) is the most severe and common form with symptoms of poor suck, lethargy, hypo and hypertonia, opisthotonic posturing, seizures, and coma developing 4-7 days after birth.[3] The characteristic odor of maple syrup may be detected as soon as neurological symptoms develop.[2] Intermediate MSUD (residual enzyme 3-30%) have gradual neurologic problems resulting in mental retardation.[3] Intermittent form of MSUD go into metabolic crisis when there is a stressful situation such as an infection or after surgery.[2,3] Thiamine-responsive MSUD's clinical symptomatology and metabolic disturbance is ameliorated once pharmacologic dose of thiamine has been given.[3] E-3 deficient MSUD present with symptoms similar to those with intermediate MSUD but also have lactic acidosis.[2,3]

Pathophysiology

Due to a mutation of the branched chain keto-acid dehydrogenase enzyme, the levels of leucine, valine, and isoleucine increase in blood. The increase in leucine may cause competitive inhibition with other precursors of neurotransmitters causing the neurologic manifestations.[2]

Inheritance: autosomal recessive[2,3]

Confirmatory Testing

Diagnosis is confirmed by detection of the highly increased branched-chain amino acids levels via quantitative amino acid analysis and/or by increased urinary excretion of α-keto and hydroxyl acids and branched chain amino acids using GC-MS and quantitative amino acid analysis.[3]

Overview of Disease Management

Long term treatment of MSUD is based on dietary restriction of branched-chain amino acids and supplementation of thiamine if proven beneficial; valine and isoleucine supplementation is also recommended. [1,2,3] Frequent determination of leucine levels are likewise encouraged so that proper dietary adjustments be done for effective management of the condition.

Prognosis

Children with the classical form of MSUD have only a satisfactory prognosis if they are diagnosed and treated early.[3]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis, and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem except medications

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MAPLE SYRUP URINE DISEASE [MSUD]

- Ensure patient's airway is secure
- Insert IV access. Collect samples for plasma amino acids, dried blood spot (for leucine levels), blood glucose and urine ketones. May request for investigations (i.e. CBC, blood gas, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D12.5% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Start intralipid at 1g/kg/24 hours.
- Give valine (30-50mg/kg/day) in 6 divided doses
- Give isoleucine (20mg/kg/day) in 6 divided doses
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with BCAD milk formula or protein free formula at maintenance rate
- Give valine (30-50mg/kg/day) in 6 divided doses
- Give isoleucine (20mg/kg/day) in 6 divided doses
- Insert IV access. Collect samples for plasma amino acids, dried blood spot (for leucine levels), blood glucose and urine ketones. May request for investigations (i.e. CBC, blood gas, etc.) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours)

** Children should not be protein restricted for longer than necessary (24-48 hours)*

** If patient does not improve with the initial management (within 12 hours), hemodialysis may be indicated. Monitor patient clinically, the necessity of hemodialysis will depend on patient's clinical status.*

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Nyhan WL, Barshop BA and Ozand P. Chapter 24 Maple syrup urine disease. *Atlas of Metabolic Diseases* 2nd ed. Great Britain:Oxford University Press, 2005 pp 159-164.

[2] Schulze A, Matern D, Hoffmann GF. Chapter 2: Newborn screening in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism.* New York:McGraw Hill, 2009 pp 17-32.

[3] Hoffman GF and Schulze A. Chapter 7: Organic Acidurias in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism.* New York:McGraw Hill, 2009 pp 93-94.

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PHENYLKETONURIA

What is PKU?

Phenylketonuria (PKU) is a disorder of aromatic amino acid metabolism in which phenylalanine cannot be converted to tyrosine due to a deficiency or absence of the enzyme phenylalanine hydroxylase.[1] Phenylalanine hydroxylase requires the co-factor 6-pyruvoyltetrahydropterin or BH4 for activity in the hydroxylation to tyrosine, absence of this co-factor may present with an increase in plasma phenylalanine similar to phenylketonuria but is considered a separate disorder.[2]

Clinical Manifestation

Patients affected with PKU appear normal at birth.[2, 3] The most important and sometimes the only manifestation of PKU is mental retardation.[2] Patients may present with constitutional, intellectual, and neurologic abnormalities and signs as well as hypopigmentation of the skin and hair and iris rapidly develop due to impaired metabolism of melanin.[3] Seizures occur in a fourth of patients.[2]

The odor of the phenylketonuric patient is that of phenylacetic acid described as mousy, barny, or musty.[2]

Pathophysiology

PKU results from a deficiency of activity of a liver enzyme, phenylalanine hydroxylase leading to increased concentrations of phenylalanine in the blood and other tissues. Elevated phenylalanine interfere with myelination, synaptic sprouting, and dendritic pruning; and in addition, it competitively inhibits the uptake of neutral amino acids in the blood-brain barrier causing reduced tyrosine and tryptophan concentrations thereby limiting the production of neurotransmitters.[3]

Inheritance: autosomal recessive[2,3]

Confirmatory Testing

The demonstration of decreased enzyme activity is confirmatory.[3] However, in the presence of increased phenylalanine levels, it is important to differentiate phenylketonuria from a BH4 deficiency. This is accomplished through administration of tetrahydrobiopterin (doses of 2mg/kg intravenously and 7.5-20mg/kd orally), which leads to a prompt decrease to normal in the concentration of phenylalanine. Pterin metabolites in urine are likewise useful, demonstrating a very low biopterin and high neopterin levels.

Overview of Disease Management

Dietary management is key to treatment. The diet of patients has four components: (1) complete avoidance of food containing high amounts of phenylalanine; (2) calculated intake of low protein/phenylalanine natural food; (3) sufficient intake of fat and carbohydrates to fulfill the energy requirements of the patient and; (4) calculated intake of phenylalanine free amino acid mixture supplemented with vitamins, minerals and trace elements as the main source of protein.[3]

Prognosis

When treatment is started early and performed strictly, motor and intellectual development can be expected to be near normal.[3,4]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Collect dried blood spot for phenylalanine levels. May request for investigations (i.e. CBC, blood gas, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D12.5% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with PKU milk formula or protein free formula at maintenance rate
- Insert IV access. Collect dried blood spot for phenylalanine levels. May request for investigations (i.e. CBC, blood gas, etc.) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours)

** Children should not be protein restricted for longer than necessary (24-48 hours)*

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Nyhan WL, Barshop BA and Ozand P. Chapter 20: Phenylketonuria. *Atlas of Metabolic Diseases* 2nd ed. Great Britain: Oxford University Press, 2005 pp 127-133.

[2] Nyhan WL, Barshop BA and Ozand P. Chapter 21 Hyperphenylalaninemia and defective metabolism of tetrahydrobiopterin. Atlas of Metabolic Diseases 2nd ed. Great Britain:Oxford University Press, 2005 pp 136-145.

[3] Kaye CI and the Committee on Genetics. *Newborn screening fact sheets.* Pediatrics 2006;118:934-963.

[4] Schulze A, Matern D, Hoffmann GF. Chapter 2: Newborn screening in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism.* New York:McGraw Hill, 2009 pp 17-32.

[5] Burgard P, Lui X, Hoffmann GF. Chapter 13: Phenylketonuria in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism.* New York:McGraw Hill, 2009 pp 163-168.

AMINO ACID DISORDERS

HYPERPHENYLALANINEMIA

Hyperphenylalaninemia is a term that encompasses several disorders that result to increased phenylalanine in the body. In majority of cases, the cause is due to a deficiency of the enzyme phenylalanine hydroxylase. Other cases can be due to defects in the metabolism of the cofactor tetrahydrobiopterin.[1] In the Philippines, all cases of defects in tetrahydrobiopterin have been determined to be due to 6-pyruvoyl tetrahydropterin synthase {6-PTPS) deficiency.

What is mild hyperphenylalaninemia?

Mild hyperphenylalaninemia is a mild form of phenylketonuria. It is a condition often diagnosed only incidentally during screening for classic phenylketonuria and the increases in phenylalanine levels are insufficiently elevated to cause neurological damage.[2]

Clinical manifestation

Children are normal at birth and are often asymptomatic. Regular monitoring of phenylalanine levels should be done.

Pathophysiology

When the conversion of phenylalanine to tyrosine is blocked, phenylalanine that is not used for protein synthesis accumulates in body fluids or is converted to other metabolites.[1]

Inheritance: autosomal recessive [1•5]

Confirmatory Testing

Regular monitoring of phenylalanine levels is recommended monthly for the first year of life then every 3 months until 5 years of age.

Overview of Disease Management

Mild hyperphenylalaninemia does not require treatment. 5 But regular monitoring of levels until 5 years of age is needed. Should levels exceed 350, consult with a medical specialist is suggested.

Prognosis

Patients affected with mild permanent phenylalaninemia will develop normally without treatment .[1]

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HYPERPHENYLALANINEMIA

What is Hyperphenylalaninemia?

Hyperphenylalaninemia is a general term that means that phenylalanine, an amino acid, accumulates in the blood and tissue of the body. This can be detected through newborn screening. The cause of increase of phenylalanine may be due to either a lack of enzyme (chemical scissors) or a lack of the co-factor (a substance needed by the body to allow the enzyme to function properly).

What causes mild hyperphenylalaninemia?

Mild hyperphenylalaninemia is a mild form of phenylketonuria, a condition which causes accumulation of the amino acid phenylalanine in the body due to a slight decrease of the enzyme or chemical scissor known as phenylalanine hydroxylase.

This condition is inherited. The gene is contained in the genetic material that we inherited from our parents. Because one part of the genetic material comes from the father and the other from the mother, the gene comes in pairs. In order to work correctly, at least one of the pairs should be working.

Parents of children with mild hyperphenylalaninemia have one working and one non-working gene coding for mild hyperphenylalaninemia. They do not manifest the disease but can pass them on to their children. They are known as carriers.

If the child inherits the non-working gene from both parents, he or she will have the condition. Thus, in each pregnancy, there is a 25% chance that the child will have the disorder, 50% chance of beinga carrier and 25% chance of having two working genes.

What are the symptoms of untreated hyperphenylalaninemia?

Children with mild hyperphenylalaninemia do not have any symptoms. While the amino acid

-phenylalanine is increased in their body, it has been determined that these increases are not harmful to the child. However, monitoring of their blood phenylalanine levels are required.

What is the treatment of mild hyperphenylalaninemia?

There is no need to treat mild hyperphenylalaninemia and your child can have a regular diet. However, it is recommended that periodic monitoring of blood phenylalanine levels should be done.

What should I do if my baby is sick?

Since there is no treatment needed for this condition, there are no special recommendations to be done when your child is

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6-PTPS DEFICIENCY

What is 6-PTPS Deficiency?

Phenylalanine hydroxylase requires BH4 for activity in the hydroxylation to tyrosine.3 A deficiency of BH4 can result in increased phenylalnine levels in the blood. It is important to note that BH4 is also a co-factor of the enzymes tyrosine and tryptophan hydroxylase.[1]

Clinical Manifestation

Patients are normal at birth but some may present with early hyptonia; developmental delay may be apparent by the 2nd to 3rd month presenting with seizures and leading to a progressive neurological degenerative disease.3

Pathophysiology

The lack of the cofactor causes increases of phenylalanine in the blood and other tissues. Similar to phenylketonuria, elevated phenylalanine interfere with myelination, synaptic sprouting and dendritic pruning.4

Inheritance: autosomal recessive [1•3]

Confirmatory Testing

The administration oftetrahydrobiopterin (doses of 2mg/kg intravenously or7.5-20 mg/kg orally) leads to a prompt decrease to normal in the concentration of phenylalanine.[1•3] Pterin metabolites in urine are likewise useful, demonstrating a very low biopterin and high levels.

Overview of Disease Management

Patients with defects in pterin metabolism, especially with abnormalities of BH4 synthesis should be treated with BH4 with a daily dose of 2-Smg/kg.[3] Patients are also supplemented with levodopa {8-12 mg/kg/day) and 5-OH Tryptophan (6-9mg/kg/day)[5]

Prognosis

When treatment is started early, motor and intellectual development can be normal.[3]

*Patients with 6-PTPS Deficiencies are not prone to metabolic crisis. Medications are to be maintained when they are sick.

*If there are queries about the management, contact the metaboJic doctor on call.

However, for the enzyme to function properly, it needs the support of a co-factor. In this case, the co-factor is known as tetrahydrobiopterin or BH4. BH4 in turn is produced by our body through a series of metabolic processes which also makes

use of enzymes. A lack of the 6-PTPS enzyme causes a decrease in the production of BH4 which in turn affects the breakdown of phenylalanine.

This condition is inherited. The gene is contained in the genetic material that we inherited from our parents. Because one part of the genetic material comes from the father and the other from the mother, the gene comes in pairs. In order to work correctly, at least one of the pairs should be working.

Parents of children with 6-PTPS deficiency have one working and one non-working gene coding for 6-PTPS. They do not manifest the disease but can pass them on to their children. They are known as carriers.

If the child inherits the non-working gene from both parents, he or she will have the condition. Thus, in each pregnancy, there is a 25% chance that the child will have the disorder, 50% chance of being a carrier and 25% chance of having two working genes.

What are the signs and symptoms of untreated 6-PTPS deficiency?

Children are normal at birth although some may present with decreased muscle tone. At about 2-3 months of age, they may present with seizures and developmental delay which can progress.

What is the treatment of 6-PTPS deficiency?

Dietary control is not needed. Supplementation with BH4, levodopa and 5-0H tryptophan should be given daily in divided doses.

What should I do when my baby is sick?

The medications should be continued and consult with a doctor as needed should be done.

3 Nyhan WI., Barshop BA and AI-Aqeel A. Chapter 16: Hyperphenylalaninemia and defective metabolism of tetrahydrobiopterin. *Atlas of inherited Metabolic Diseases* 3rd ed. Great Britain:Oxford University Press, 2012 pp123-135

4 Kaye Cl and the Committee on Genetics. *Newborn screening fact sheets*. Pediatrics 2006;118:934-963

5 Zchocke J and Hoffmann GF, Vademecum Metabolicu, 3rd ed., Germany:Milupa Metabolics, 2011

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TYROSINEMIA TYPE I

What is Tyrosinemia Type I (Hepatorenal tyrosinemia)?

Tyrosinemia is also known as hepatorenal tyrosinemia, tyrosinemia type 1, tyrosinosis or hereditary tyrosinemia.[1] The deficient enzyme is fumarylacetoacetase.[2]

Clinical Manifestation

Tyrosine-I is usually asymptomatic in newborns, but if left untreated it affects liver, kidney, bone, and peripheral nerves.[3] Two patterns are reported: an acute or chronic form. The acute form presents with acute hepatic decompensation where infants are noted to have jaundice, abdominal distention, failure to thrive, ascites and hepatomegaly, renal disease is also prominent and a "boiled cabbage" odor in urine is observed; the chronic liver disease feature is that of hepatic cirrhosis.[4]

Pathophysiology

The deficient enzyme, fumarylacetoacetase catalyzes the last step in tyrosine degradation.[2] The increased concentrations of tyrosine and its metabolites is postulated to inhibit many transport functions and enzymatic activities.[3]

Inheritance: autosomal recessive[2]

Confirmatory Testing

Confirmation can be done through plasma amino acid levels (increased tyrosine) and urine metabolic screening (increased succinylacetone).[2]

Overview of Disease Management

Treatment options for tyrosinemia include dietary therapy (restriction of phenylalanine and tyrosine), liver transplantation and use of the pharmacologic agent 2(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione or NTBC (1mg/kg).[3]

Prognosis
If untreated, death from liver failure may occur in the first year of life.[4]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem except medications
- Ensure patient's airway is secure
- Insert IV access. Collect samples for blood glucose, plasma amino acids, liver function tests, coagulation studies and urine succinylacetone. May request for investigations (i.e. CBC, blood gas, etc.) as needed.
- May give fluid boluses if patient requires.

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TYROSINEMIA TYPE I

- Start D12.5% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Start nitisinone (2mg/kg) per orem
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with TYR milk formula or protein free formula at maintenance rate
- Insert IV access. Collect samples for blood glucose, plasma amino acids, liver function tests, coagulation studies and urine succinylacetone. May request for investigations (i.e. CBC, blood gas, etc.) as needed
- Start D12.5% 0.3NaCl at 5-10 cc/hr.
- Start nitisinone (2mg/kg) per orem
- Monitor input and output strictly (q6 hours)

** Children should not be protein restricted for longer than necessary (24-48 hours)*

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Nyhan WL, Barshop BA and Ozand P. Chapter 26: Hepatorenal tyrosinemia. *Atlas of Metabolic Diseases* 2nd ed. Great Britain:Oxford University Press, 2005 pp 175-179.

[2] Schulze A, Matern D, Hoffmann GF. Chapter 2: Newborn screening in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism*. New York:McGraw Hill, 2009 pp 17-32.

[3] Nyhan WL, Barshop BA and Ozand P. Chapter 26: Hepatorenal tyrosinemia. *Atlas of Metabolic Diseases* 2nd ed. Great Britain:Oxford University Press, 2005 pp 175-179.

[4] Pass Ka and Morrissey M. *Enhancing newborn screening for tyrosinemia type I.* Clin Chem 2008;54(4):627-629.

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TYROSINEMIA TYPE II

What is Tyrosinemia Type II?

Tyrosinemia Type II is also known as oculocutaneous tyrosinemia or Richner-Hanhart syndrome. The deficient enzyme is tyrosine aminotransferase.[1]

Clinical Manifestation

The most important manifestation are those involving the eye. which can lead to corneal scarring and permanent visual impairment .[1] Patients report lacrimation, photophobia and eye pain.[2] Cutaneous lesions are painful keratoses which occur particularly on peripheral pressure- bearing areas of the palms and soles.[1•2•3]

Pathophysiology

Tyrosine aminotransferase normally converts tyrosine to p-hydroxyophenylpyruvic acid which is the rate-limiting step in the metabolism of tyrosine. The increased concentration of tyrosine and its metabolites is postulated to inhibit many transport function and enzymatic activities.[2]

Inheritance: autosomal recessive [1.2.3]

Confirmatory Testing

Confirmation can be done through plasma amino acid analysis and enzyme testing [1•3]

Overview of Disease Management

The treatment consists of the institution of a diet low in tyrosine and phenylalanine through protein restriction and supplementation of a special milk formula.[1•2•3]

Prognosis

If left untreated, visual impairment and mental retardation may occur [1•3]

What to Do

If unwell and cannot tolerate oral intake

Nothing per orem

Ensure patient's airway is secure

Insert IV access. Collect samples for blood glucose, plasma amino acids, liver function tests and coagulation studies. May request for investigations (i.e., CBC, blood gas, etc) as needed

May give fluid boluses if patient requires

Start D12.55 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 to 1.Sxthe maintenance

Monitor input and output strictly (q6 hours)

If unwell and can take oral intake:

Insert oro- or asogastric tube and start continuous feeding with TYR milk formula or protein free formula at maintenance rate

Insert IV access. Collect samples for blood glucose, plasma amino acids, liver function tests and coagulation studies. May request for investigations (i.e., CBC, blood gas, etc) as needed

Start D12.5% 0.3 NaCl at 5-10 cc/hr Monitor input and output strictly (q6hours)

*Children should not be protein restricted for longer than necessary (24-48 hours)

*Inform metabolic doctor on call for further guidance regarding on-going management

1 Nyhan WL, Barshop BA and Al-Aqeel A. Chapter 20: Oculocutaneous tyrosinemia/tyrosine aminotransferase deficiency. *Atlas of inherited Metabolic Diseases* 3rd ed. Great Britain: Oxford University Press, 2012 pp164-170

2 Javadi MA, Mirdehghan SA, Bagheri A, Einollahi B and Dowlati Y. Two Cases of Tyrosinemia Type II, and its Rare Occurrence in Two Brothers. *Medical Journal of the Islamic Republic of Iran* 1996;10(2):169-173

3 Janakiraman I., Sathiyasekaran M, Deenadayalan M, Ganesh R and Mehesh U. Richner-Hanhart Syndrome. Indian J Pediatr 2006; 73 (2): 161-162

ENDOCRINE DISORDERS

CONGENITAL ADRENAL HYPERPLASIA (CAH)

What is Congenital Adrenal Hyperplasia (CAH)?

Congenital Adrenal Hyperplasia (CAH) is a group of disorders resulting from enzymatic defects in the biosynthesis of steroids. There are many enzymes involved in the synthesis of adrenal hormones but in about 90% of CAH, it is due to 21-dydroxylase deficiency. Others are due to cholesterol desmolase 11β-hydroxylase deficiency, 17β-hydroxylase deficiency and 3β-hydroxysteroid dehydrogenase. All forms of CAH are inherited in an autosomal recessive pattern. The Philippine NBS data as of December 2018 reports that 1 out of 19,668 screened newborns have CAH.

Pathophysiology

21-Hydroxylase deficiency results in decreased cortisol and aldosterone production which in turn causes increased adrenocorticotropic hormone (ACTH) secretion. High ACTH levels result in hyperplasia of the adrenal cortex. The precursor steroids behind the block are diverted to the androgen biosynthetic pathway, resulting in excess production of androgens that cause virilization in females and precocious puberty in males. The decrease in the production of aldosterone in CAH results in salt and water imbalance.

Clinical Features

- Salt-wasting
- Simple virilizing
- Late onset

Neonates with the salt-wasting (SW) form manifest adrenal crisis in the first 2-4 weeks of life characterized as poor feeding, vomiting, loose stools or diarrhea, weak cry, failure to thrive, dehydration and lethargy. If untreated, the affected newborn will die in a severe salt-losing crisis with hypoglycemia and hypotension. The baby who survives may have brain damage. Affected females usually present with ambiguous genitalia.

Diagnosis

Newborn Screening for 21-hydroxylase deficiency is done by measuring the 17-OHP level on dried blood spot. Infants with normal birth weight and a mild elevation of 17-OHP undergo repeat dried blood spot collection. Infants with moderate to severe elevation of 17-OHP and those who are low birth weight with mild elevation are referred to a pediatric endocrinologist for evaluation. Plasma 17-OHP, Na, K, cortisol and RBS are requested to confirm the condition. In cases of discrepancies between the plasma 17-OHP and clinical parameters, more extensive diagnostic evaluation is recommended: ACTH stimulation test and/or DNA mutation studies.

Treatment and Monitoring

The mainstay of treatment in CAH is glucocorticoid and mineralocorticoid replacement therapy which corrects the cortisol deficiency and reverses the abnormal hormonal patterns. Patients with deficiencies of mineralocorticoids require the appropriate replacement hormones. Glucocorticoid replacement must be increased during periods of stress. The majority of female patients with prenatal virilization require surgical repair. Heterozygous carrier detection, prenatal diagnosis, and prenatal therapy are available for families with 21-hydroxylase deficiency and are often used in 11β-hydroxylase deficiency. Regular endocrine clinic visits for monitoring of physical growth and development as well as biochemical 17-OHP and/or cortisol measurements are recommended for optimal management. Genetic counseling is recommended.

PROGNOSIS

Newborn screening makes early diagnosis and early treatment possible. Early treatment to prevent adrenal crisis is lifesaving in cases of salt-wasting CAH. Early diagnosis prevents inappropriate sex assignment for affected females of the simple virilizing (SV) form. This is very important due to the psychological and legal implications of wrong gender assignment. Progressive effects of excess androgens such as short stature and psychosexual disturbance in male and female patients are also prevented if appropriate treatment is given and monitored closely.

ENDOCRINE DISORDERS

CONGENITAL HYPOTHYROIDISM (CH)

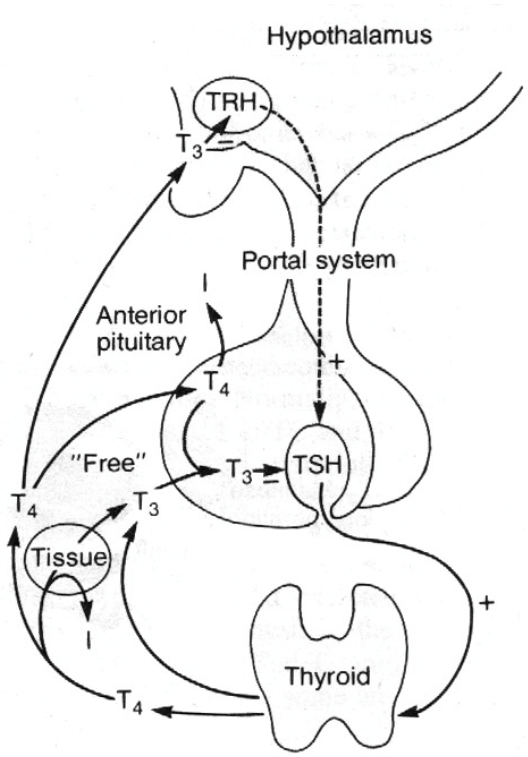
What is Congenital Hypothyroidism (CH) ?

Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation in children. According to the Philippine NBS data, (December 2018) 1 out of 2,805 screened newborns has CH. The most common etiology of CH is thyroid dysgenesis (TD): absent thyroid, ectopic or hypoplastic thyroid. In rare cases, CH results from mutations in the genes that control thyroid gland development including thyroid transcription factor (TTF-2) and paired box-8 protein (PAX-8). Rapid detection by newborn screening, prompt confirmatory testing and Levothyroxine administration can prevent severe mental retardation and impaired growth due to CH.

Pathophysiology

Normal thyroid hormone levels in the body are maintained by a feedback mechanism involving the hypothalmus, pituitary and thyroid gland. The hypothalamus senses low circulating levels of thyroid hormone (T3 and T4) and responds by releasing thyrotropin releasing hormone (TRH). TRH stimulates the anterior pituitary to produce thyroid stimulating hormone (TSH). TSH, in turn, stimulates the thyroid gland to produce thyroid hormone until levels in the blood return to normal. Normal thyroid hormone levels exert a negative feedback to the hypothalamus and the anterior pituitary, thus controlling the release of both TRH from hypothalamus and TSH from anterior pituitary gland. When the thyroid gland does not produce enough T4 and T3, the pituitary gland compensates by producing high levels of TSH. This biochemical profile of low T4 level and high TSH is a pattern consistent with Primary CH. Having the correct level of thyroid hormone in the body is important, especially in the first two years of life, because it ensures normal growth and normal development of the brain, bones and nervous system.

The hypothalamic-pituitary-thyroid axis (HPT axis)



ENDOCRINE DISORDERS

CONGENITAL HYPOTHYROIDISM (CH)

Clinical Features

Signs and symptoms of hypothyroidism:
- Decreased activity
- Large anterior fontanelle
- Poor feeding
- poor weight gain
- Small stature or poor growth
- Prolonged Jaundice
- Decreased stooling or constipation
- Hypotonia
- Hoarse cry or weak cry
- Developmental delay

Some physical signs of hypothyroidism that may or may not be present at birth:
- Coarse facial features
- Macroglossia
- Large fontanelles
- Umbilical hernia
- Mottled, cool, and dry skin
- Pallor
- Myxedema
- Goiter

Diagnosis

Newborn screening for primary CH is done by determining the thyroid stimulating hormone (TSH) level on a dried blood spot. If the TSH is significantly elevated, this signifies that the baby is at risk for CH and therefore needs confirmatory thyroid tests. An elevated serum TSH and a low serum FT4 confirms hypothyroidism. Thyroid imaging (thyroid scan or ultrasound) is recommended to document etiology of CH.

Treatment and Monitoring

Immediate diagnosis and treatment of congenital hypothyroidism in the neonatal period is critical to normal brain development and physical growth. Treatment started within the first two weeks of life usually prevents neurodevelopmental delays. Recommended treatment is the lifetime daily administration of Levothyroxine. Only the tablet form of Levothyroxine is currently approved for therapeutic use. The tablets should be crushed, mixed with a few milliliters of water, and fed to the infant directly into the mouth. It is not recommended that Levothyroxine be mixed with soy formula or with formula containing iron, as these interfere with absorption of the medication**.** Thyroid hormone replacement and medical monitoring are required for life.

Children with congenital hypothyroidism should be monitored clinically and biochemically. Clinical parameters should include linear growth, weight gain, head circumference, developmental progression, and overall well-being. Serum T4 or FT4 and TSH should be monitored at regular intervals. The following is the recommendation of the American Academy of Pediatrics

- at 2 and 4 weeks after initiation of T4 treatment
- every 1 to 2 months during the first 6 months of life
- every 3 to 4 months between 6 months and 3 years of age
- every 6 to 12 months thereafter until growth is completed
- after 4 weeks if medication is adjusted
- at more frequent intervals when compliance is in question or abnormal values are obtained.

However, these guidelines on biochemical parameters may be modified by the specialist depending on the clinical status of the patient.

Such evaluations are especially important in children whose treatment was delayed beyond 1 month of life, or in patients whose treatment is inconsistent (non-compliance).

Prognosis

Early diagnosis and optimal treatment of congenital hypothyroidism prevents severe mental retardation, neurologic complications and physical delays. Even with early treatment, some children may demonstrate mild delays in areas such as reading comprehension and arithmetic. Although continued improvement in IQ has been documented in treated patients through adolescence, some cognitive problems may persist. These may include problems in visuospatial, language, and fine motor function. Defects in memory and attention have been reported .

FATTY ACID OXIDATION DISORDERS [FAOD]

FAOD includes:

Medium chain acyl co-A dehydrogenase deficiency (MCAD)
Very long chain acyl Co- A dehydrogenase deficiency (VLCAD)
Long chain hydroxyacyl co-A dehydrogenase deficiency (LCHAD)
Trifunctional protein deficiency (TFI)
Carnitine Palmitoyl Transferase Deficiency Type 1
Carnitine Palmitoyl Transferase Deficiency Type 2
Carnitine Uptake Defect
Glutaric Aciduria Type 2

What are FAOD?

FAOD are a group of autosomal recessive disorders caused by the deficiency or absence of any of the enzymes needed for beta-oxidation. Children born with this condition appear normal at birth but untreated patients may present with low blood sugar which can lead to seizures, coma and death. One type of FAOD, VLCAD (or very long chain acyl-CoA dehydrogenase deficiency) may present with cardiomyopathy and increased creatine kinase (CK) levels.

Treatment of FAOD

Treatment is through the dietary restriction of fat. VLCAD patients are treated with a special milk formula containing medium chain triglycerides.

Preliminary / Initial Management During Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state and prevent hypoglycemia.

What to Do:

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. For patients with VLCAD, collect samples for serum CK. May request for other investigations (i.e. CBC, Blood gas) as needed. May give fluid boluses if patient requires.
- Start D10% 0.3 NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5X the maintenance.
- Monitor input and output strictly (q6 hours). Check for the color of urine.

If unwell and is able to tolerate oral intake:

- Insert oro- or nasogastric tube and start continuous feeding with a high glucose formula
- Insert IV access. Monitor glucose levels. For patients with VLCAD, collect samples for serum CK. May request for other investigations (i.e. CBC, Blood gas) as needed. May give fluid boluses if patient requires.
- Start D10% 0.3 NaCl at 5-10 cc/hr.
- Monitor input and output strictly (q6 hours). Check for the color of urine.

**Patients with VLCAD may have rhabdomyolysis. Monitor CK levels and hydrate adequately. If CK levels continually rise, hemodialysis may be indicated.*

** Inform metabolic doctor on call for further guidance regarding on-going management.*

FATTY ACID DISORDERS

MEDIUM-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY (MCADD)

What is MCADD?

Medium chain acyl-CoA dehydrogenase (MCAD) deficiency is the most common defect of fatty acid oxidation.[1]

Clinical Manifestation

MCAD deficiency has a very wide spectrum of clinical presentations ranging from benign hypoglycemia to coma and death.[2] Two presentations have been noted: (1) hypoketotic hypoglycemia or Reye syndrome which occurs within the first two years of life and (2) the chronic disruption of muscle function which include cardiomyopathy, weakness, hypotonia and arrhythmia.[2,3] In addition, MCAD deficiency has been shown to be associated with sudden infant death syndrome (SIDS).[4] A "metabolic stress" such as prolonged fasting often in connection with viral infections is usually required to precipitate disease manifestations but patients are completely asymptomatic between episodes.[2]

Pathophysiology

MCAD catalyzes the initial step in the β-oxidation of C12-C6 straight chain acyl-CoAs and MCAD deficiency results in a lack of production of energy from β-oxidation of medium chain fatty acids and hepatic ketogenesis and gluconeogenesis.[4]

Inheritance: autosomal recessive[4]

Confirmatory Testing

Urine organic acid profile will show medium chain dicarboxylic aciduria.[4] Measurement of the specific MCAD enzyme activity in disrupted cultures skin fibroblasts, lymphocytes, or tissue biopsies from muscle can confirm the diagnosis.[2] Rapid screening is available for two of the most common mutations which account for over 93% of all MCAD mutations (A985G and 4 bp deletion).[4]

Overview of Disease Management

Treatment consists of avoidance of prolonged fasting by instituting frequent feedings with a carbohydrate rich diet and provision of supplementary nocturnal uncooked cornstarch.[2] The use of carnitine is still under debate.[2,4]

Prognosis

Most authors report a mortality rate of 20-25% during the initial decompensation. Although the majority of children survive their initial episode, a significant amount of children who survived and perhaps children who have experienced clinically unrecognized episodes, suffer from long term sequelae and about 40% are judged to have developmental delay.[2] Long term outcome remains dependent on constant monitoring for early signs of illness and rapid medical intervention to prevent complications.[3]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if patient requires.

- Start D10% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Encourage regular feeding
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, etc.) as needed.
- Start D10% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours).

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Strauss AW, Andersen BS and Bennett MJ. Chapter 5: Mitochondrial Fatty Acid Oxidation Defects in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism.* New York:McGraw Hill, 2009 pp 60-62.

[2] Hsu HW, Zytkovicz TH, Comeau AM et al. *Spectrum of Medium chain acyl-coA dehydrogenase deficiency detected by newborn screening.* Pediatrics 2008;121:e1108-e1114.

[3] Nyhan WL, Barshop BA and Ozand P. Chapter 40: Medium chain acyl-CoA dehydrogenase deficiency. *Atlas of Metabolic Diseases* 2nd ed. Great Britain:Oxford University Press, 2005 pp 260-265.

[4] Wilson CJ, Champion MP, Collins JE et al. *Outcome of medium chain acyl-CoA dehydrogenase deficiency after diagnosis.* Arch Dis Child 1999;80:459-462.

[5] Liebig M, Schymik I, Mueller M et al. *Neonatal screening for very long chain acyl-CoA dehydrogenase deficiency: enzymatic and molecular evaluation of neonates with elevated C14:1-carnitine levels.* Pediatrics 2006;118(3):1064-1069.

FATTY ACID OXIDATION DISORDERS [FAOD]

VERY LONG-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY (VLCADD)

What is VLCADD?

Very long-chain acyl-CoA dehydrogenase catalyzes the dehydrogenation of C22-C12 straight chain fatty acids, and because the long chain fatty acids constitute a major proportion of the fatty acids, VLCAD deficiency is generally a more severe condition than MCAD or SCAD deficiency and multiple tissues are affected.

Clinical Manifestation

The clinical presentation of symptomatic VLCAD deficiency is heterogenous with phenotypes of different severities.' There are three forms described: (1) severe childhood form with neonatal onset and cardiomyopathy; (2) milder childhood form with delayed onset of symptoms often triggered by metabolic stress and presents as hypoketotic hypoglycemia and; (3) adult form which presents with isolated skeletal muscle involvement with recurrent episode of muscle pain, rhabdomyolysis and myoglobinuria.[1,2]

Pathophysiology

VLCAD catalyzes the dehydrogenation of acyl CoA esters of 14-20 carbon length in the first step of mitochondrial fatty acid oxidation.[2,3] VLCAD deficiency results in lack of production of energy from β-oxidation of long-chain fatty acids, because heart and muscle tissue depend heavily on energy from long chain fatty acid oxidation, a VLCAD deficiency severely affect these tissues.[1]

Inheritance: autosomal recessive[1]

Confirmatory Testing

The enzyme defect can be detected through culture skin fibroblasts.[1] The gene for VLCAD has been cloned and sequenced successfully and play a role in diagnosis of this disorder.[3]

Overview of Disease Management

Treatment of this disorder include avoidance of fasting by frequent feeding, overnight continuous feeding, reduction of amount of long chain fat in diet while supplying essential fatty acids in the form of canola, walnut oil or safflower oil and supplementation with medium chain triglycerides.[1,3]

For the adult muscular form, it is advised to have a high carbohydrate intake prior to exercise to prevent lipolysis and to restrict physical activity to levels that are not likely to precipitate an attack of rhabdomyolysis.[1]

Prognosis

Fifty percent of patients die within 2 months of initial symptomatology.[3] However, timely and correct diagnosis leads to dramatic recovery so that early detection could prevent the onset of arrhythmias, heart failure, metabolic insufficiency and death.

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

FATTY ACID OXIDATION DISORDERS [FAOD]

VERY LONG-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY (VLCADD)

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. Collect samples for urine ketones and serum creatine kinase (CK). May request for investigations (i.e. CBC, liver transaminases, blood gas, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D10% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours). Check color of urine and may request for urinalysis to check for urine myoglobin.

If unwell and can tolerate oral intake:

- Encourage regular feeding
- Insert IV access. Monitor glucose levels. Collect samples for urine ketones and serum creatine kinase (CK). May request for investigations (i.e. CBC, liver transaminases, blood gas, etc.) as needed.
- Start D10% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours). Check color of urine and may request for urinalysis to check for urine myoglobin.

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Hsu HW, Zytkovicz TH, Comeau AM et al. *Spectrum of Medium chain acyl-coA dehydrogenase deficiency detected by newborn screening.* Pediatrics 2008;121:e1108-e1114.

[2] Nyhan WL, Barshop BA and Ozand P. Chapter 41: Very long chain acyl-CoA dehydrogenase deficiency. *Atlas of Metabolic Diseases* 2nd ed. Great Britain:Oxford University Press, 2005 pp 267-270.

[3] Wood JC, Mager MJ, Rinaldo P et al. *Diagnosis of very long chain acyl-dehydrogenase deficiency from an infant's newborn screening card.* Pediatrics 2001l108:e19-e21.

[4] Moczulski D, Majak I, Mamczur D. *An overview of β-oxidation disorders.* Postepy Hig Med Dosw 2009;63:266-277.

FATTY ACID OXIDATION DISORDERS [FAOD]

LONG-CHAIN L-3-HYDROXY ACYL-COA DEHYDROGENASE [LCHAD] DEFICIENCY

What is LCHAD Deficiency?

Long chain L-3 hydroxyacyl-CoA dehydrogenase (LCHAD) is a component of trifunctional protein.[1] Isolated LCHAD deficiency catalyzes the third step in the fatty acid oxidation spiral, converting long chain 3-hydroxyacyl-CoA esters into long chain 3-keto-CoA species by using NAD as a cofactor.[2]

Clinical Manifestation

Patients exhibit moderate or severe multiorgan involvement either neonatally or during the first two years of life.[3] They may present in the first year of life with hypoketotic hypoglycemia and liver dysfunction, Reye syndrome-like symptoms, seizures, coma and death.[2] By adolescence, ophthalmologic abnormalities including loss of visual acuity, chorioretinal atrophy, progressive retinitis pigmentosa and peripheral sensorimotor polyneuropathy may be observed.[2,3,4] Up to 40% of symptomatic patients may have tachycardic arrhythmias, apneic episodes, cardiopulmonary arrest and unexplained death.[2]

Pathophysiology

Since the enzyme LCHAD is part of the fatty acid oxidation, a deficiency causes a problem in the energy utilization of the body which causes the presentation of signs and symptoms as listed above.[1]

Inheritance: autosomal recessive[2]

Confirmatory Testing

Confirmatory testing is done through enzyme assays performed in cultured cells such as skin fibroblasts.[2] The common mutation G1528C has been identified in affected individuals and may be used for confirmation.[3]

Overview of Disease Management

Primary goal of treatment is to avoid metabolic stress brought about by infection and long periods of fasting. Patients should be given frequent feedings, supplementation with medium chain triglycerides, an overnight infusion of cornstarch.[2,5] Treatment with L-carnitine remains controversial.[6]

Prognosis

Patients with LCHAD deficiency who present symptomatically often die during the acute episode or suffer from sudden, unexplained death and mortality occurs in approximately 38%.[2]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. Collect samples for urine ketones and serum creatine kinase (CK). May request for investigations (i.e. CBC, liver transaminases, blood gas, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D10% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours). Check color of urine and may request for urinalysis to check for urine myoglobin.

If unwell and can tolerate oral intake:

- Encourage regular feeding
- Insert IV access. Monitor glucose levels. Collect samples for urine ketones and serum creatine kinase (CK). May request for investigations (i.e. CBC, liver transaminases, blood gas, etc.) as needed.
- Start D10% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours). Check color of urine and may request for urinalysis to check for urine myoglobin.

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Nyhan WL, Barshop BA and Ozand P. Chapter 42: Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency. *Atlas of Metabolic Diseases* 2nd ed. Great Britain: Oxford University Press, 2005 pp 272-275.

[2] Hsu HW, Zytkovicz TH, Comeau AM et al. *Spectrum of Medium chain acyl-coA dehydrogenase deficiency detected by newborn screening.* Pediatrics 2008;121:e1108-e1114

[3] Eskelin P and Tyne T. LCHAD and MTP Deficiencies – *Two Disorders of Mitochondrial Fatty Acid Beta-Oxidation with Unusual Features.* Cur Ped Rev 2007;3:53-59.

[4] Moczulski D, Majak I, Mamczur D. *An overview of β-oxidation disorders.* Postepy Hig Med Dosw 2009;63:266-277.

[5] Gillingham M, Van Calcar S, Ney D et al. *Dietary management of long chain 3-hydroxyacyl-CoA dehydrogenase deficiency.* A Case report and survey. J Inherit Metab Dis 1999;22(2):123-131.

[6] Bilic E, Deliu M, Brinar V et al. *Carnitine palmitoyltransferase type 2 deficiency – case report and review of the literature.* Nurol Croat 2013;62:57-62.

FATTY ACID OXIDATION DISORDERS [FAOD]

TRIFUNCTIONAL PROTEIN (TFP) DEFICIENCY

What is TFP Deficiency?

The mitochondrial trifunctional protein (TFP) is a multienzyme complex of the β-oxidation cycle composed of four α-subunits harbouring long-chain enoyl-CoA hydratase and long chain L-3-hydroxyacyl-CoA dehydrogenase and four β-subunits encoding long chain 3-ketoacyl-CoA thoilase.[1] General or complete TFP deficiency is defined and occurs when markedly decreased activity of all three enzymatic components, LCHAD, long chain 2,3 enoyl CoA drasate and LKAT exist.[2]

Clinical Manifestation

General TFP deficiency has three phenotypes: the lethal phenotype presenting with lethal cardiac failure or sudden death due to arrhythmias, the hepatic phenotype and the neuromyopathic phenotype that has later-onset, episodic, recurrent skeletal myopathy with muscular pain and weakness often induced by exercise or exposure to cold and peripheral neuropathy.[2, 3]

It is important to note that fetuses with complete TFP deficiency can cause maternal liver diseases of pregnancy.[2]

Pathophysiology

Mitochondrial fatty acid β-oxidation is a major energy-producing pathway.[4] Any defect in any enzyme may cause the characteristic signs and symptoms which include hypoketotic hypoglycemia.[2]

Inheritance: autosomal recessive[2]

Confirmatory Testing

Confirmatory testing is through the demonstration of decreased enzyme activity on cultured fibroblast.[2] Mutations in the HADHA and HADHB genes may result in mitochondrial trifunctional protein deficiency[5] and may play a role in confirmation.

Overview of Disease Management

Treatment includes avoidance of fasting, reduced long-chain fat intake, supplementation with medium chain triglycerides, supplementation with fat-soluble vitamins, and avoidance of other potential stressors such as prolonged exercise.[2]

Prognosis

Patients with metabolic crises do well unless the hypoglycemia and seizures are prolonged and cause developmental delay, older onset patients with rhabdomyolysis can reduce episodes significantly with dietary management and do well.[2]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. Collect samples for urine ketones and serum creatine kinase (CK). May request for investigations (i.e. CBC, liver transaminases, blood gas, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D10% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours). Check color of urine and may request for urinalysis to check for urine myoglobin.

If unwell and can tolerate oral intake:

- Encourage regular feeding
- Insert IV access. Monitor glucose levels. Collect samples for urine ketones and serum creatine kinase (CK). May request for investigations (i.e. CBC, liver transaminases, blood gas, etc.) as needed.
- Start D10% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours). Check color of urine and may request for urinalysis to check for urine myoglobin.

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Speikerkoetter U, Khuchua Z, Yue Z et al. *General Mitochondrial Trifunctional Protein (TFP) Deficiency as a results of either α or ß-subunit mutations exhibits imilar phenotypes because mutation in either subunit alter TFP complex expression and subunit turnover.* Ped Res 2003l55(2):1-7.

[2] Hsu HW, Zytkovicz TH, Comeau AM et al. *Spectrum of Medium chain acyl-coA dehydrogenase deficiency detected by newborn screening.* Pediatrics 2008;121:e1108-e1114.

[3] Kamijo T, Wanders RJA, Saudubray JM et al. *Mitochondrial Trifunctional Protein Deficiency.* J Clin Invest 1994;93:1740-1747.

[4] Nyhan WL, Barshop BA and Ozand P. Chapter 37: Carnitine transporter deficiency. *Atlas of Metabolic Diseases* 2nd ed. Great Britain:Oxford University Press, 2005 pp 246-250.

[5] http://ghr.nlm.nih.gov/condition/mitonchondrial-functional-protein-deficiency Accessed 30 April 2012

FATTY ACID DISORDERS

CARNITINE PALMITOYLTRANSFERASE TYPE 1 DEFICIENCY [CPT1]

What is CPTI Deficiency?

CPT1 is an ezyme of the outer mitochondrial membrane that converts long chain fatty acyl molecules to their corresponding acylcarnitines which are then transported across the inner mitochondrial membrane for β-oxidation in the mitochondrial matrix. [1] CPT1 catalyzes the rate limiting step of long chain fatty acid import into the mitochondria and is the main regulatory enzyme of the system.[2]

Clinical Manifestation

This disorder presents usually in infancy, often in the second six months, with acute hypoketotic hypoglycemia, metabolic acidosis with raised transaminases, hepatomegaly, hepatosteatosis and mild to moderate hyperammonemia during an episode of fasting brought in by an intercurrent, usually viral illness, or gastroenteritis.[1,3] Patients may present with a range of cardiac arrhythmias including sudden cardiac arrest and death may occur during an acute presentation but surviving infants may suffer with severe developmental delay and intellectual impairment as a result of cerebral bioenergetic failure.[1] Cardiac or skeletal muscle involvement is not common.[4]

Pathophysiology

Three different isoforms exist including the liver, muscle and brain, with only the liver-type showing deficiency in humans.[3] Deficiency of CPT1 in the liver results in a failure of acylcarnitine formation and hence little or no entry of LCFA into mitochondria for oxidative metabolism.[1,3]

Inheritance: autosomal recessive[3]

Confirmatory Testing

There is note of high plasma carnitine concentrations with more than 90% in the free form.[1] Organic acid analysis of the urine is notable for the absence of dicarboxylic aciduria, hydroxycarboxylic aciduria and absence of ketones.[3] The condition is confirmed by the assay of CPT1 in fibroblasts whose activity is reduced to 5-20%.

Overview of Disease Management

The major element in management is the avoidance of fasting and in the presence of intercurrent infection or other cause of vomiting or anorexia in which the oral route is excluded, the provision of intravenous glucose is essential.[3] Reduction of intake of long chain fats appears prudent and medium chain triglycerides may be substituted.[1,3]

Prognosis

Survival through infancy without symptoms has been reported and between episodes of metabolic decompensation individuals appear developmentally and cognitively normal unless there has been previous neurologic damage secondary to a metabolic decompensation.[4]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

Nothing per orem

- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, CK, liver transaminases, blood gas, etc.) as needed.

- May give fluid boluses if patient requires.
- Start D10% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Encourage regular feeding
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, CK, liver transaminases, blood gas, etc.) as needed.
- Start D10% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours).

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Olpin SE. *Pathophysiology of fatty acid oxidation disorders and resultant phenotypic variability*. J Inherit Metab Dis 2013;36:645-658.

[2] Orgel A. *Carnitine Palmitoyl transferase II: Enzyme Deficiency*. http://www.userwebs.pomona.edu/~ejc14747/180/student%20presentations/Orgel%20carnitine%20paper.pdf Accessed 1 August 2014

[3] Chapter 39. *Carnitine palmitoyl transferase I deficiency.* Nyhan WL, Barshop BA and Ozand P. Atlas of Metabolic Diseases 2nd ed. Great Britain:Oxford University Press, 2005 pp 256-259.

[4] Bonnefont JP, Djouadi F, Prip-Buus C et al. *Carnitine palmitoyltransferases 1 and 2: biochemical, molecular and medical aspects.* Mol Asp Med 2004;25:495-520.

[5] Bilic E, Deliu M, Brinar V et al. *Carnitine palmitoyltransferase type 2 deficiency – case report and review of the literature*. Nurol Croat 2013;62:57-62.

FATTY ACID DISORDERS

CARNITINE PALMITOYLTRANSFERASE TYPE 2 DEFICIENCY [CPT2]

What is CPT2 Deficiency?

Carnitine Palmitoyltransferase Type II (CPT2) is responsible for the last step of the carnitine dependent transport system.[1] In these disorders, long-chain acylcarnitines are translocated across the inner mitochondrial membrane but are not efficiently converted to acyl-CoAs.[2]

Clinical Manifestation

CPT2 has three phenotypes: (1) a fatal neonatal-onset form with non-ketotic hypoglycemia, liver disease, hypotonia, cardiomyopathy and congenital abnormalities; (2) infantile form with or without cardiac disease presents with liver and skeletal muscle involvement with episodes of decompensation and; (3) adult form presenting with muscle pain, stiffness and myoglobinuria.[1, 3] The episodes are triggered by exertional exercise, cold, fever, infection or prolonged fasting.[3,4] CPT2 presents frequently in adults with rhabdomyolysis and myoglobinuria triggered most often by prolonged exercise.[4]

Pathophysiology

In the adult form of CPT2 deficiency, the triggering circumstances of myolysis attacks are consistent with the fact that long chain fatty acids are the main energy source for skeletal muscle during fasting or prolonged exercise.[1,3,4] It has been speculated that increased concentration of long-chain acylcarnitines in patient with the severe form of CPT2 deficiency may promote cardiac arrhythmia.[2] Why the two clinical presentations of CPT2 deficiency differ both in age of onset and tissue expression pattern remains unresolved.[2,3]

Inheritance: autosomal recessive[1]

Confirmatory Testing

The CPT2 activity measured in fibroblasts or lymphocytes from CPT2-deficient patients ranges from 5-25% of control values.[2]

Overview of Disease Management

Similar to all fatty acid oxidation defects, long term dietary therapy is aimed at preventing any period of fasting; restriction of long chain fat intake along with medium chain triglyceride supplementation is recommended and in the muscular form, preventive rhabdomyolysis attacks is based on frequent meals with carbohydrate extra-intake before and during prolonged exercise.[2]

Prognosis

The clinical condition of patients is normal between recurrent attacks and the frequency of attacks are variable ranging from asymptomatic to lethal but in all cases the symptomatology is restricted to the skeletal muscles without liver or heart involvement.[2]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure

- Insert IV access. Monitor glucose levels. Collect samples for urine ketones and serum creatine kinase (CK). May request for investigations (i.e. CBC, liver transaminases, blood gas, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D10% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours). Check color of urine and may request for urinalysis to check for urine myoglobin.

If unwell and can tolerate oral intake:

- Encourage regular feeding
- Insert IV access. Monitor glucose levels. Collect samples for urine ketones and serum creatine kinase (CK). May request for investigations (i.e. CBC, liver transaminases, blood gas, etc.) as needed.
- Start D10% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours). Check color of urine and may request for urinalysis to check for urine myoglobin.

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Orgel A. *Carnitine Palmitoyltransferase II: Enzyme Deficiency.* http://www.userwebs.pomona.edu/~ejc14747/180/student%20presentations/Orgel%20carnitine%20paper.pdf Accessed 1 August 2014

[2] Bonnefont JP, Djouadi F, Prip-Buus C et al. *Carnitine palmitoyltransferases 1 and 2: biochemical, molecular and medical aspects.* Mol Asp Med 2004;25:495-520.

[3] Olpin SE. *Pathophysiology of fatty acid oxidation disorders and resultant phenotypic variability*. J Inherit Metab Dis 2013;36:645-658.

[4] Bilic E, Deliu M, Brinar V et al. *Carnitine palmitoyltransferase type 2 deficiency – case report and review of the literature. Nurol Croat* 2013;62:57-62.

FATTY ACID DISORDERS

CARNITINE UPTAKE DEFECT (CUD)

What is CUD?

Carnitine uptake defect is also known as carnitine transporter deficiency. It is due to an abnormality in the transportthat facilitates carnitine's entry into certain cells. In some instances, it is has been found that neonates who test positive for this condition do not actually have the condition but instead reflect the decreased levels of their mothers.

Clinical Manifestation

Patients may present with hypoketotic hypoglycemia, modest hepatomegaly and Reye-like syndrome, progressive heart failure and muscle weakness. Most patients present with a progressive cardiomyopathy associated with skeletal myopathy.

Pathophysiology

Carnitine is necessary for transport of long-chain fatty acids into mitochondria to enter the β-oxidation cycle.[2] Genetic defects of the carnitine trasporter results in failure of tissues of the cardiac and skeletal muscle and in the renal tubules to concentrate intracellular levels of carnitine, thus reducing available cofactor for the carnitine cycle.[3]

Inheritance: autosomal recessive[2]

Confirmatory Testing*

Confirmation of the diagnosis can be made biochemically by monitoring the uptake of carnitine by skin fibroblasts in culture.[3]

Overview of Disease Management

Oral carnitine therapy at 100mg/kg/day into four divided doses is recommended.[2,3]

Prognosis

Patients on long term therapy report normal skeletal muscles tone, no episodes of metabolic decompensation, and essentially normal intellect.[3]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What To Do

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D10% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Encourage regular feeding
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, etc.) as needed.
- Start D10% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours)

Inform metabolic doctor on call for further guidance regarding on-going management

** If the baby's confirmatory test is negative, consider doing plasma acylcarnitine analysis of the patient's mother to rule out maternal CUD.*

[1] Chapter 37: Carnitine transporter deficiency. Nyhan WL, Barshop BA and Ozand P. *Atlas of Metabolic Diseases* 2nd ed. Great Britain:Oxford University Press, 2005 pp 246-250.

[2] Wilcken B. *Disorders of Carnitine Cycle and Detection by Newborn Screening*. Ann Acad *Med* 2008;37 (12):71-73.

[3] Hsu HW, Zytkovicz TH, Comeau AM et al. *Spectrum of Medium chain acyl-coA dehydrogenase deficiency detected by newborn screening.* Pediatrics 2008;121:e1108-e1114.

FATTY ACID DISORDERS

GLUTARIC ACIDURIA TYPE 2 [GA2]

What is GA2?

Multiple acyl-CoA dehydrogenation deficiency (MADD) ia disorder of fatty acid, amino acid and choline oxidation caused by defects in any one of two flavoproteins, electron transport flavoprotein (ETF) or ETF:ubiquinone oxidoreducatase (ETF-QO) which affect some 14 dehydrogenases.[1,2]

Clinical Manifestation

Patients may present with cyclical vomiting, loss of appetite, progressive proximal muscle weakness particularly affecting neck, shoulder, hip and/or respiratory muscles but also chronic leg weakness and exercise intolerance with occasional rhabdomyolysis.[1] The clinical phenotype is heterogenous and has been classified into three groups: neonatal onset with congenital anomalies (type 1), neonatal onset without anomalies (type 2) and mild and/or later onset (type 3).[3]

The infant affected with this disorder presents with life-threatening illness in the first day of life presenting with tachypnea or dyspnea, profound metabolic acidosis and impressive hypoglycemia within a few hours of birth.[2] The later on-set of this disorder has presented with considerable variety. In adolescents and adults, muscular or cardiac symptoms or episodic vomiting are usually first features suggestive for MADD.[3]

Pathophysiology

The metabolic defects result in impaired adenosine triphosphate (ATP) biosynthesis, excessive lipid accumulation in different organs and insufficient gluconeogenesis.[3] The most characteristic pathological feature of MADD is increased intracellular neutral lipid storage, especially in skeletal muscle and liver which is observed as increased intracellular lipid droplets in both size and number.[4]

Inheritance: autosomal recessive[2,3]

Confirmatory Testing

Diagnosis is based on both the urinary organic acid profile and the acylcarnitine pattern in dried blood/plasma. Acylcarnitine analysis usually revelas increased concentrations of several short-, medium- and long-chain acylcarnitines. The characteristic urinary organic acid pattern comprises elevated levels of glutaric, ethylmalonic, 3-hydroxyisovaleric, 2-hydroxyglutaric, 5-hydroxyhexanoic, adipic, suberic, sebacic and dodecanedioic acid without relevant ketonuria especially if combined with glycine conjugates of C4 and C5 acids.[3]

Overview of Disease Management

Therapeutic management mostly comprises a diet restricted in fat and protein and the avoidance of fasting.[1] Among the consequences of this disorder is a depletion of body stores of carnitine, thus, patients may benefit from carnitine supplementation.[2] Some forms of this disorder are responsive to riboflavin (100 to 300 mg/day)[2] and the clinical response to pharmacological doses of riboflavin is usually rapid and striking.[1]

Prognosis

Early onset MADD is a disease with high mortality, the prognosis of late-onset MADD seems to be good; nevertheless, 5% of patient reported in literature had died mainly during metabolic decompensations and in some patients, death could not be prevented despite the known diagnosis of MADD.[3]

Preliminary / Initial Management during Metabolic Crisis

FATTY ACID DISORDERS

GLUTARIC ACIDURIA TYPE 2 [GA2]

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, blood gas, kidney function etc.) as needed.
- May give fluid boluses if patient requires.
- Start D10% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with oresol at maintenance rate
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, blood gas, kidney function etc.) as needed.
- Start D10% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours)

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Olpin SE. *Pathophysiology of fatty acid oxidation disorders and resultant phenotypic variability.* J Inherit Metab Dis 2013;36:645-658

[2] Chapter 45. *Mutiply acyl Coa dehydrogenase deficiency (MASS)/Glutaric aciduria type II/Ethylmalonic-adipic aciduria.* Nyhan WL, Barshop BA and Ozand P. Atlas of Metabolic Diseases 2nd ed. Great Britain:Oxford University Press, 2005 pp 284-291

[3] Grunert S. *Clinical and fenetical heterogeneity of late-onset multiple acyl-coenzyme A dehydrogenase deficiency.* Orphanet J Rare Dis 2014;9(14):1-8.

[4] Liang WC and Nishino I. *Riboflavin-responsive multiple acyl-CoA dehydrogenase deficiency: a frequent condition in the southern Chinese population.* Neurol Clin Neurosci 2013;1:163-167.

ORGANIC ACIDURIAS

What are Organic Acidurias?

Organic acidurias are a group of autosomal recessive disorder caused by the deficiency or absence of any of the enzymes needed for the breakdown of some proteins. They derive their names from the substance that accumulates proximal to the block in the pathway. They are the following:

Propionic aciduria (PA) – due to a deficiency of propionyl-CoA carboxylase
Methylmalonic aciduria (MMA) – due to a deficiency of methymalonyl-CoA mutase
Isovaleric aciduria (IVA) – due to a deficiency of isovaleryl-CoA dehydrogenase
3– Methylcrotnyl CoA Carboxylase Deficiency [3-MCC]
Beta Ketothiolase Deficiency
Glutaric Aciduria Type 1
Multiple Carboxylase Deficiency

Untreated children with this condition may present with vomiting, irritability, drowsiness, rapid breathing and coma. Patients with propionic aciduria and isovaleric aciduria may also have hyperammonemia. As a result, untreated children may have encephalopathy, mental retardation or death.

Treatment of Organic Acidurias

Treatment is through the dietary restriction of protein. Children may be given a special milk formula that is protein free. Carnitine and/or glycine are also prescribed.

Preliminary / Initial Management During Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state and prevent essential amino acid deficiency.

ORGANIC ACIDURIAS

PROPIONIC ACIDEMIA

What is Propionic Acidemia (PA) ?

Propionic Acidemia (PA) is an organic acidopathy also known was propionic aciduria and ketotic hyperglycinemia.[1] It is due to the defective activity of propionyl CoA which is the first step in the pathway of propionate metabolism in which propionyl CoA, the product of the metabolism of isoleucine, valine, theronine and methionine is converted to methylmalonyl CoA acid then to succinyl CoA and oxidation in the citric acid cycle.[2]

Clinical Manifestation

Patients usually are healthy at birth but quickly develop overwhelming disease, which may be misinterpreted as sepsis or ventricular hemorrhage.[3] Additional symptoms include vomiting, acidosis, dehydration, lethargy to coma, recurrent ketotic episodes, hypotonia, seizures and hyperammonemia.[4] Some patients may have acute-onset neurological symptoms described as metabolic strokes, arrhythmias, cardiomyopathy and an exfoliative rash.[5]

Patients may also present with similar dysmorphic characteristics such as frontal bossing, widened nasal bridge, wide set eyes, epicanthal folds, long philtrum and upward curvature of the lips.[4]

Pathophysiology

Due to an increase in propionic acid, abnormal ketogenesis occurs because propionic acid is an inhibitor of mitochondrial oxidation and succinic and alpha-ketoglutaric acid.[4] Inhibition of glycine cleavage enzyme leads to hyperglycinemia adn the inhibition of N-acetylglutamate synthase, an enzyme of the urea cycle, causes hyperammonemia.[3]

Inheritance: autosomal recessive[5]

Confirmatory Testing

The predominant compound found in blood and urine is 3-hydroxypropionic acid; others may include tiglic acid, tiglyglycine, butanone and propionylglycine.[5] Highly elevated levels of glycine in plasma and urine can be observed but confirmatory testing is through the demonstration of low levels of enzyme on cultured fibroblasts.[3,5]

Overview of Disease Management

Long-term treatment is the lifelong dietary restriction of isoleucine, valine, threonine and methionine.5

Carnitine supplementation is also given as well as metronidazole (10 days per month at 10-20mg/kg/day) to reduce the significant propionate production of the bacterial intestinal flora.3

Prognosis

Despite early diagnosis and treatment, the neonatal onset form of PA is still complicated by early death in infancy or childhood while late onset forms reach adulthood but often are handicapped by severe extrapyramidal movement disorders and mental retardation; however, progress has been achieved in survival and prevention of neurologic sequelae in affected children with early diagnosis and treatment.[3]

ORGANIC ACIDURIAS

PROPIONIC ACIDEMIA

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem except medications
- Ensure patient's airway is secure
- Insert IV access. Collect samples for ammonia, blood gas, electrolytes and urine ketones. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D12.5% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Give carnitine (100mg/kg/day) q6 hours.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with protein free formula at maintenance rate
- Insert IV access. Collect samples for ammonia, blood gas, electrolytes and urine ketones. May request for investigations (i.e. CBC, etc.) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Give carnitine (100mg/kg/day) q6 hours.
- Monitor input and output strictly (q6 hours)

** Monitor serum ammonia every 4 hours, if ammonia remain above 200mmol/L for three consecutive collections, medical treatment or hemodialysis may be indicated*

** Children should not be protein restricted for longer than necessary (24-48 hours)*

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Chapman KA and Summar ML. *Propionic academia consensus conference summary.* Mol Gen Metab 2011 article in press.

[2] Nyhan WL, Barshop BA and Ozand P. Chapter 2: Propionic academia. *Atlas of Metabolic Diseases* 2nd ed. Great Britain:Oxford University Press, 2005 pp 8-15.

[3] Hoffman GF and Schulze A. Chapter 7: Organic Acidurias in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism.* New York:McGraw Hill, 2009 pp 93-94.

[4] Hoffman GF and Schulze A. Chapter 7: Organic Acidurias in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism.* New York:McGraw Hill, 2009 pp 93-94.

[5] Pena L, Franks J, Chapman KA et al. *Natural history of propionic academia.* Mol Gen Metab 2011: article under press

ORGANIC ACIDURIAS

METHYLMALONIC ACIDEMIA

What is Methylmalonic Academia (MMA)?

Methylmalonic academia (MMA) is due to a defect in metholmalonyl CoA mutase or a defect in the enzyme's vitamin B12 derived co-factor 5'-deoxyadenosylcobalamin.[1] Among patients with a defect of methylmalonyl CoA mutase, two subgroups exist: Mut^0 patients have no enzyme activity while Mut^- patients have a spectrum of residual activity.[2]

Clinical Manifestation:

Patients present with severe metabolic crisis in the first months of life, progressive failure to thrive, feeding problems, recurrent vomiting, dehydration, hepatomegaly, lethargy, seizures and developmental delay.[2] Some affected children may also have failure of linear growth, anorexia and developmental failure.[3] Patients may have metabolic decompensations following bouts of acute illness or minor infections.[2,3] They are prone to episodes of metabolic strokes that primarily affect the basal ganglia.[3]

Neonates affected with MMA share similar physical characteristics such as high forehead, broad nasal bridge, epicanthal folds, long smooth philtrum and triangular mouth.[3] Unique to this disorder is the development of chronic renal failure in the second decade in 20-60% of patients.[2]

Pathophysiology

Methylmalonyl CoA-mutase catalyzes the conversion of methylmalonyl CoA to succinyl CoA which can enter the tricarboxylic acid cycle. This causes the accumulation of methylmalonate in the body which may be toxic to the brain and the kidneys.

Inheritance: autosomal recessive[2]

Screening: increase in propionylcarnitine on MSMS[2,3]

Confirmatory Testing

Urine metabolic screening reveal elevated methylmalonic acid, propionylglycine, 3-hydroxypropionic acid and methylcitrate; plasma amino acids show elevated glycine, alanine and methionine.[2] Definitive testing is the demonstration of decreased enzyme activity through cultured fibroblasts.[3]

Overview of Disease Management

Vitamin B12 responsive MMA will benefit from the supplementation of the cofactor.[3] For patients with the absence or decreased activity of methylmalonyl CoA mutase are advised to limit natural protein intake and supplementation with an Amino Acid Mixture that is free of isoleucine, valine, methionine and threonine.[2] Carnitine supplementation is considered an adjunct to therapy.[3]

Intestinal bacteria can be a source of propionate and methylmalonate that is naturally produced in the gut, this can be reduced by giving metronidazole 10 days per month at 10-20mg/kg/day, colistin or neomycin.[2,3]

Prognosis

The long-term outcome of in MMA is influenced by the underlying defect.[4] Mut^0 patients have the worst prognosis, most of the patients may have very early onset signs and symptoms that occur even before the results of NBS are available, and die immediately or survive with significant neurodevelopmental disability.[3] Vitamin B12 responsive methylmalonic acidurias have a reasonable outcome.[2]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem except medications
- Ensure patient's airway is secure
- Insert IV access. Collect samples for ammonia, blood gas, electrolytes and urine ketones. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D12.5% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Give carnitine (100mg/kg/day) q6 hours.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with protein free formula at maintenance rate
- Insert IV access. Collect samples for ammonia, blood gas, electrolytes and urine ketones. May request for investigations (i.e. CBC, etc.) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Give carnitine (100mg/kg/day) q6 hours.
- Monitor input and output strictly (q6 hours)

** Children should not be protein restricted for longer than necessary (24-48 hours)*

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Nyhan WL, Barshop BA and Ozand P. Chapter 3: Methylmalonic Acidemia. *Atlas of Metabolic Diseases* 2nd ed. Great Britain:Oxford University Press, 2005 pp 18-26.

[2] Hoffman GF and Schulze A. Chapter 7: Organic Acidurias in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism.* New York:McGraw Hill, 2009 pp 93-94.

[3] http://www.e-imd.org/rc/e-imd/htm/Article/2011/e-imd-20110728-195831-072/src/htm_fullText/fr/MethylmalonicAciduria.pdf Accessed Feb 25, 2012.

[4] Cheng KH, Lie MY, Kao CH et al. *Newborn screening for methylmalonic aciduria by tandem mass spectrometry: 7 years' experience from two centers in Taiwan.* J Chin Med Assoc 2010;73(6)314-319.

ORGANIC ACIDURIAS

ISOVALERIC ACIDEMIA

What are Isovaleric Acidemia (IVA)?

Isovaleric acidemia (IVA) was the first organic acidemia to be described. It is caused by a deficiency of isovaleryl-CoA dehydrogenase, an enzyme located proximally in the catabolic pathway of the essential branched-chain amino acid leucine.[1]

Clinical Manifestation

The clinical manifestation of IVA may be acute or chronic. An acute or neonatal presentation is characterized by non-specific findings of vomiting, lethargy, poor feeding, seizures that may progress to a comatose state.[2] A characteristic odor in the urine described as "sweaty feet" or "dirty socks" has been reported among patients with IVA.[1,3] It has also been found that in bone marrow cultures, isovaleric acid is an inhibitor of granulopoietic progenitor cell proliferation which accounts for the pancytopenia or thrombocytopenia found in patients.[1] A chronic form may present with developmental delay or mental retardation.[1,3] Both acute or chronic patients may suffer from metabolic crisis and are sometimes misdiagnosed as suffering from diabetic ketoacidosis because of the similarity in presentation: acidosis, hyperglycemia and ketosis.[1]

Pathophysiology

At present, the specific pathophysiology of IVA is unclear. It is surmised that accumulating CoA derivative sequesters CoA, thereby disturbing the mitochondrial energy metabolism.[1]

Inheritance: autosomal recessive[1,3]

Confirmatory Test

There is note of increased isovalerylcarnitine and isovalerylglycine in plasma or urine. Enzymatic assay on cultured fibroblasts or mutation analysis may also be done.[1,3]

Overview of Disease Management

Dietary management involves limiting leucine intake. Detoxification of toxic metabolites by conjugation with glycine given at 150-600mg/kg/day and carnitine at 50-100 mg/kg/day should also be instituted.[1,3]

Prognosis

In a study by Grunert et al. (2012), among patients with IVA, the mortality rate is high in association with early neonatal presentation, neurocognitive outcome is better with early diagnosis and management and age of diagnosis but not the number of catabolic episodes contribute to the neurocognitive outcome.

Preliminary / Initial Management During Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

ORGANIC ACIDURIAS

ISOVALERIC ACIDEMIA

What To Do

If unwell and cannot tolerate oral intake:

- Nothing per orem except medications
- Ensure patient's airway is secure
- Insert IV access. Collect samples for ammonia, blood gas, electrolytes and urine ketones. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D12.5% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Give glycine (150mg/kg/day) q8 hours.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with protein free formula at maintenance rate
- Insert IV access. Collect samples for ammonia, blood gas, electrolytes and urine ketones. May request for investigations (i.e. CBC, etc.) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Give glycine (150mg/kg/day) q8 hours.
- Monitor input and output strictly (q6 hours)

** Monitor serum ammonia every 4 hours, if ammonia remain above 200mmol/L for three consecutive collections, medical treatment or hemodialysis may be indicated*

** Children should not be protein restricted for longer than necessary (24-48 hours)*

**Inform metabolic doctor on call for further guidance regarding on-going management*

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ORGANIC ACID DISORDERS

3– METHYLCROTNYL CoA CARBOXYLASE DEFICIENCY [3-MCC]

What is 3-MCC?

The deficiency of 3-methylcrotonyl CoA carboxylase (3MCC) is a disorder of leucine metabolism that was first described by Eldjarn et al. in 1970. In most instances, it has been found that neonates who test positive for this condition in expanded newborn screening do not actually have the condition but instead reflect the increased levels of the metabolites of their mothers.

Clinical Manifestation

There is a broad spectrum of clinical presentation ranging from no symptoms to failure to thrive, hypotonia, and cardiomyopathy to severe metabolic decompensation with metabolic acidosis and hypoglycemia. Some patients may have a late presentation (1-3 years old) with an acute episode of Reye syndrome, massive ketosis, acidosis, lethary, coma leading to a fatal outcome.[3,4]

Pathophysiology

3-methycrotonyl CoA carboxylase is responsible for the carboxylation of 3-methylcrotonyl-CoA, the fourth step in leucine catabolism; a deficiency of which causes a disturbance in leucine catabolism.

Inheritance: autosomal recessive[3]

Confirmatory Testing*

An increase in 3-hydroxyisovaleric and 3-methylcrotonyl glycine are found in urine, confirmatory testing is done through the demonstration of decreased enzyme activity in cultured fibroblasts.[3]

Overview of Disease Management

Treatment strategies include the restriction of natural protein intake and giving of carnitine supplementation (100mg/kg).[3]

Prognosis

3-MCC is a common, mostly benign condition; whether treatment with a low-protein diet, carnitine and glycine supplementation has the potential to change the clinical course in several affected patients remains to be elucidated.[5]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, blood gas, urine ketones) as needed.
- May give fluid boluses if patient requires.
- Start D12.5% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.

- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with protein free formula at maintenance rate
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, blood gas, urine ketones) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours)

Children should not be protein restricted for longer than necessary (24-48 hours)

Inform metabolic doctor on call for further guidance regarding on-going management

** If the baby's confirmatory test is negative, consider doing urine organic acid analysis of the patient's mother to rule out maternal 3-MCC deficiency.*

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ORGANIC ACID DISORDERS

BETA-KETOTHIOLASE DEFICIENCY

What is Beta-Ketothiolase Deficiency?

Beta ketothiolase deficiency is a defect of mitochondrial acetoacetyl-CoA thiolase involving ketone body metabolism and isoleucine catabolism.[1]

Clinical Manifestation

This rare disorder is characterized by normal early development followed by progressive loss of mental and motor skills, it is clinically characterized by intermittent ketoacidotic episodes with no clinical symptoms in between. Some patients may present with vomiting, hypotonia, lethargy, coma, hyperventilation and dehydration. Ketoacidotic crises may occur following a bout of infection or mild illness.[2]

Pathophysiology

Mitochondrial acetoacetyl CoA thiolase is responsible for the cleavage of 2-methylacetoacetyl CoA in isoleucine metabolism, acetoacetyl CoA formation in ketogenesis and acetoacetyl CoA cleavage in ketolysis.[2]

Inheritance: autosomal recessive[2,3]

Confirmatory Testing

An increased excretion of 2-methyl 3-hydroxybutyric and 2-methylacetoacetic acid in urine is observed but definitive diagnosis is established by demonstrating decreased enzyme activity in cultured fibroblasts.[3]

Overview of Disease Management

Due to the heterogeneity in the severity of clinical presentation, there should be individual treatment programs; general guidelines for treatment include dietary isoleucine restriction and to avoid fasting.[3]

Prognosis

The frequency of ketoacidotic attacks decreases with age.[3] Clinical consequences can be avoided by early diagnosis and appropriate management of ketoacidosis.[2]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, blood gas, urine ketones) as needed.
- May give fluid boluses if patient requires.

- Start D10% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with protein free formula at maintenance rate
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, blood gas, urine ketones) as needed.
- Start D10% 0.3NaCl at 5-10 cc/hr
- Monitor input and output strictly (q6 hours)

** Children should not be protein restricted for longer than necessary (24-48 hours)*

**Inform metabolic doctor on call for further guidance regarding on-going management*

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ORGANIC ACID DISORDERS

GLUTARIC ACIDURIA TYPE 1 [GA1]

What is GA1?

Glutaric Acidemia 1 (GA1) was first described by Goodman and colleagues in 1975. [1] It is caused by a deficiency of glutaryl-CoA dehydrogenase which catalyzes the oxidative decarboxylation of glutaryl-CoA, an intermediate in the degradation of the amino acids lysine and tryptophan. [2] This causes an increase in glutaric, 3-hydroxyglutaric, glutaconic and glutarylcarnitine.[1]

Clinical Manifestation

Two subsets of patients are characterized based on the levels of glutaric acid excreted in the urine: the low (<100 mmol/ mmol creatinine) and high excretors (>100 mmol/mmol creatinine). However, the risk of developing striatal injury resulting in neurologic dysfunction is the same regardless of excretion status.[3]

Patients with GA1 may present with hypotonia with head lag, feeding difficulties, irritability.[1] Macrocephaly is seen in about 75% of infants, but this is non-specific.[3] If left untreated, 90% of patients develop neurologic disease presenting as dystonic-dyskinetic posturing, athetoid movements, opisthotonus, spastic, rigidity, clenched fists, tongue thrust and profuse sweating.[1,3] The encephalopathic crises precipitated by immunization, infection, surgery and fasting results in the affectation of the basal ganglia and exaggerates the neurologic manifestations occur frequently until the 4th year of life.[1]

Pathophysiology

It was found that 3-hydroxglutaric and glutaric acid share structural similarities with glutamate which causes excitatory cell damage; further, the accumulation of these metabolites modulate glutamatergic and GABAergic neurotransmission resulting in an imbalance of excitatory and inhibitory neurotransmitters.[1]

Inheritance: autosomal recessive[1,3]

Confirmatory Test

Glutaric acid and 3-hydroxyglutaric acid is increased in urine.[1] Confirmatory testing is achieved through the demonstration of a decrease in enzyme activity in skin fibroblasts.[1,3]

Overview of Disease Management

The main goal of treatment is to prevent encephalopathic crises and neurological deterioration and this can be achieved through dietary management.[1,2] This includes lysine intake restriction, giving carnitine 50-100mg/kg/day, riboflavin 100mg/day and the use of neuropharmacologic drugs to control neurologic symptoms.[1,3]

Prognosis

The early diagnosis and treatment intervention in patients with GA1 prevents striatal degeneration in 80-90% of infants.[1] However, study by Beauchamp et al. (2009) showed that despite early treatment, patients with GA1 may have mild fine motor and articulation problems and raise the question of prenatal damage or subtle post-natal ongoing neurotoxic effects of glutaric and hydroxyglutaric acids or both.

Preliminary / Initial Management during Metabolic Crisis

ORGANIC ACID DISORDERS

GLUTARIC ACIDURIA TYPE 1 [GA1]

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, blood gas, urine ketones) as needed.
- May give fluid boluses if patient requires.
- Start D12.5% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Start IV carnitine (100mg/kg/day) q6 hours.
- Monitor input and output strictly (q6 hours).

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with GA1 milk formula or protein free formula at maintenance rate
- Insert IV access. Monitor glucose levels. May request for investigations (i.e. CBC, blood gas, urine ketones) as needed.
- Start D12.5% 0.3NaCl at 5-10 cc/hr
- Start IV carnitine (100mg/kg/day) q6 hours.
- Monitor input and output strictly (q6 hours)

** Children should not be protein restricted for longer than necessary (24-48 hours)*

** Co-management with a neurologist is indicated to control the dystonia*

**Inform metabolic doctor on call for further guidance regarding on-going management*

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ORGANIC ACID DISORDERS

MULTIPLE CARBOXYLASE DEFICIENCY [MCD]

What is Multiple Carboxylase Deficiency (MCD)?

Multiple carboxylase deficiency, also known as holocarboxylase synthase leads to a failure of synthesis of all carboxylases.

Clinical Manifestation

Most patients present acutely in the first few hours of life.[1] Patients may have dehydration, go into deep coma leading to death, ketosis, high anion gap metabolic acidosis, failure to thrive, alopecia and a characteristic erythematous eruption on the skin that can be bright, red, scaly or desquamative.

Pathophysiology

Holocarboxylase synthase binds biotin, an essential cofactor in gluconeogenesis, fatty acid synthesis and the catabolism of several amino acids.[1,] This in turn, leads to a failure of the synthesis of the active holocarboxylases which is the body's main source of biotin.[1]

Inheritance: autosomal recessive[3]

Confirmatory Testing

An increased methylcrotanylglycine and 3-hydroxyisovaleric acid in blood and urine with lactic acidosis can be observed but definitive testing is done through measurement of enzyme activity in fibroblasts.[3]

Overview of Disease Management

Treatment is through giving biotin 10-20mg/day.[1,3] The clinical response to treatment is dramatic, ketosis and acidosis disappear along with hyperammonemia; lethargy, hypotonia and ataxia disappear and dermatological effects of the disorder are reversed.[3]

Prognosis

Prognosis is good if treatment is initiated immediately and the clinical course is followed carefully by close monitoring of biochemical abnormalities.[1]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do If Unwell

Nothing per orem

- Ensure patient's airway is secure
- Insert IV access. Collect samples for serum ammonia and blood gas. May request for investigations (i.e. CBC, etc.) as needed.

- May give fluid boluses if patient requires.
- Start D10% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours).

[1] Hoffman GF and Schulze A. Chapter 7: Organic Acidurias in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism.* New York:McGraw Hill, 2009 pp 93-94.

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THALASSEMIAS AND HEMOGLOBINOPATHIES

What are Thalassemias and Hemoglobinopathies?

Thalassemias are characterized by a decreased production in either theα or β globin chains. They are grouped into αand β thalassemias.

Hemoglobinopathies, on the other hand, are structural abnormalities and are usually due to a single amino acid substitution.

ALPHA THALASSEMIAS

Alpha thalassemia may result from a defect in the alpha globin genes. There are 4 alpha globin genes so the defect or loss may be from one to four of the genes. The clinical symptomatology will depend on the number of gene deletions/ mutations. The loss of 4 genes results in **hydropsfetalis** which is fatal in utero. Loss of 3 genes indicates HbH disease which may manifest later in childhood as moderately severe anemia. Iron overload, secondary to either ineffective erythropoiesis or transfusion therapy, becomes a majorproblem when these patients reach puberty and adulthood. Loss of 2 genes (trait) or 1 (silent carrier) may result in mild anemia and these two are clinically insignificant.

The percentage of haemoglobin Bart's at birth may indicate the number of alpha gene loss. If the percentage is < 10% then the infant may have 1 or 2 gene loss. If the amount of Bart's is >20-25% then it may indicate a more severe form of alpha thalassemia such as HbH disease. Non-deletionalform of HbH disease such as HbH Constant Spring are clinically more severe.

Clinical Signs of Alpha Thalassemia

Loss of 1 or 2 α genes often asymptomatic with mild anemia at most. The smear will show microcytosis which is often mistaken for iron deficiency anemia. A child who does not respond to iron therapy for his/heranemia should be worked up for possible thalassemia. Iron supplements should be avoided thereafter. Parents of this childshould be assured that he or she will be symptom-free but they should also be made aware that the trait may run in their family. Folic acid is recommended for patients with alpha thalassemia with anemia.

If the Bart's is 20-25% and the infant is either South East Asian or from the Mediterranean region then HbH should strongly be considered and the family referred to a hematologist.

HbH disease is due to deletion of 3-alpha genes resulting in the formation of beta tetramers (β4). Clinically this isclassified as a form of **thalassemia intermedia**. A non-deletional form of HbH disease such as **HbH Constant Spring** is seen when 2 alpha gene deletion such as the --SEA deletion is seen in conjunction with anα gene mutation such as the Constant Spring mutation. Patients may have a variable clinical course with some pallor and jaundice after febrile episodes which may require transfusions or severe anemia requiring regular transfusions early in childhood resulting in iron overload later on in life. This may result in growth stunting, delayed sexual maturity, and heart failure if uncorrected. These patients will require special care.

THALASSEMIAS AND HEMOGLOBINOPATHIES

BETA THALASSEMIAS

Beta Thalassemia mutations may result in total absence of beta chain production (β°) or partial reduction of the chain (β+). A presumptive diagnosis of β thalassemia in the newborn is made if the HbF is the sole hemoglobin with absent or markedly decreased HbA. Decreased hemoglobin production leads to microcytosis, ineffective erythropoiesis and skeletal changes. A carrier state of beta thalassemia may be missed at birth because of the absence of Hgb A2 early in the neonatal period.

Clinical features may vary depending on the complete or partial absence of the beta chain. Beta thalassemia major patients (β°β°) seem healthy after birth but develop symptoms within the first year of life. They are transfusion dependent as early as the late infancy period while thalassemia intermedia (β°β+) or (β+β+) has less severe anemia and require infrequent transfusions. Children heterozygous for a normal and a beta thalassemia gene will have very mild anemia, microcytosis, and slight splenomegaly. Transfusion is usually not required.

There are individuals who are compound heterozygote for Hb E and β° thalassemia. HbE/β^{o} thalassemia presents in infancy as variably severe anemia with clinical phenotype ranging from complete lack of symptoms to transfusion dependence. Osteoporosis, iron overload, growth failure, pulmonary hypertension are commonly reported in both transfused and non-transfused parents. Patients presenting with thalassemia intermedia phenotype during childhood often become transfusion dependent as adults due to worsening anemia and fatigue. They may eventually develop iron overload andmay succumb to cardiac failure later in life.

Patients with beta thalassemia major are best managed in a specialized hospital as they will need regular transfusions and iron chelation. Those with the minor form of the disease will not need special care. However, it is important to have their future partner screened for the trait as their union may result in a baby with a severe case of thalassemia. Intermedia parents may need specialized care later in childhood as iron overload may present later in life so inadvertent and prolonged use of iron are discouraged in these patients.

HEMOGLOBIN E

Hemoglobin E (Hb E) is a variant hemoglobin with a mutation in the β-globin gene causing substitution of glutamic acid for lysine at position 26 of the β globin chain. **Hb E** is the most common hemoglobinopathy variant in South East Asia. The βE chain is synthesized at a reduced rateleading to an imbalance in the globin chains. **Hb E disease** is defined by the co-existence of two βE alleles, resulting into homozygous state EE.

Individuals with the genotype EE are usually completely asymptomatic. Hemoglobin level may be low and red cell indices are likewise low with significant morphological abnormalities including increased numbers of target cells. Homozygous Hb E individuals do not warrant special care.

HbE trait is defined by the heterozygous condition associating with one normal adult hemoglobin (HbA) β gene and one variant hemoglobin E β gene. **HbE trait** do not exhibit clinical disease. There may be slight anemia with microcytosis. Target cells are also seen in the smears. In most cases, children are symptom-free and will have normal growth and development.

In regions where there is a high incidence of α and β thalassemias such as the Philippines, HbE may be co-inherited with these disorders. Interactions with various forms of α and β thalassemia produce a very wide range of clinical syndromes of varying severity.HbE with HbH may result in moderately severe thalassemic findings similar to thalassemia intermedia.

HbE/β° on the other hand, may behave as thalassemia major and will need to be managed in a specialty center.

THALASSEMIAS AND HEMOGLOBINOPATHIES

OTHER HEMOGLOBINOPATHIES

HEMOGLOBIN C

Hemoglobin C (Hb C) is a variant hemoglobin with a mutation in the β globin gene causing substitution of glutamic acid for lysine at position 6 of the globin chain. **Hb C disease** is defined by the co-existence of 2 βC alleles (homozygous state CC).

Individuals with Hb C disease may have compensated hemolysis or mild to moderate anemia. They may also have splenomegaly and increased risk of cholelithiasis due to chronic hemolysis. This disorder is most common in individuals of African descent.

Hb C trait on the other hand is defined by the heterozygous condition associated with one normal adult hemoglobin (HbA) gene and one variant HbC β gene. Individuals with Hb C trait are clinically asymptomatic. Hemoglobin level is usually normal but mild microcytosis is common. This hemoglobin variant may be co-inherited with alpha thalassemia and beta thalassemia which may result in more serious clinical manifestations.

HEMOGLOBIN D

Hemoglobin D (Hb D) is a variant hemoglobin with a mutation in the β globin gene causing substitution of glutamine for glutamic acid in the β globin chain. **Hb D disease** is defined by homozygous state DD.

Individuals with Hb D disease are usually clinically asymptomatic. However, mild haemolytic anemia may develop in the first few months of life.

Hb D trait is defined by the heterozygous condition associated with one normal adult hemoglobin and one variant HbD β gene. Individuals with Hb D trait are clinically asymptomatic. This hemoglobin variant may also be co-inherited with alpha thalassemia and beta thalassemia which may result in more serious clinical manifestations.

SICKLE CELL

Sickle cell disease patients have predominant HbS. This condition is most common in Africa, Middle East and the United States. Affected infants are usually normal at birth but develop anemia later when the HbS concentration increases and the HbFdecreases. These patients are particularly susceptible to encapsulated bacterial infections such as Streptococcus pneumonia, Hemophilus influenzae, Staphylococcus aureus, and Salmonella. Prophylactic penicillin should be started early in infancy once diagnosis is made.

Heterozygotes (Hb AS) are usually asymptomatic and are referred to as trait. In most cases of sickle cell trait, children are symptom free and will have normal growth and development.

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THALASSEMIAS AND HEMOGLOBINOPATHIES

HEMOGLOBIN H DISEASE / ALPHA THALASSEMIA

The newborn screening result may be Hb FA Barts ≥ 25 %. Other diagnostic possibilities for this newborn screening result include Hb H Constant Spring disease and Alpha Thalassemia Trait.

What is Hemoglobin H Disease /Alpha Thalassemia?

Hemoglobin H Disease is a red blood disorder characterized by presence of fetal hemoglobin (F) and hemoglobin A, as well as hemoglobin Barts.

Confirmatory testing

DNA testing is used to confirm the diagnosis.

What should you do?

- Contact the family to inform them of the screening result. Recommend confirmatory testing if not yet done.
- Refer patient to a Pediatric hematologist.

Clinical Considerations

Hemoglobin Barts above 25% in the newborn indicates a possible hemoglobin H disease, a clinically significant form of alpha thalassemia. Deletion or dysfunction of 3 of the 4 alpha globin genes manifests as Hb H disease. This is characterized by variable clinical course with some exhibiting splenomegaly and pallor especially after febrile episodes and that may require intermittent transfusions. Absence of all four alpha globin genes results in hydropsfetalis and is usually fatal, in utero or shortly after birth.

Note: For hemoglobin Bart's <25%, parents or hematologists may opt for genotyping but this will not be covered by the program and is at the own expense of the patients. This may be taken into account when counselling is done by the pediatrician/hematologist.

THALASSEMIAS AND HEMOGLOBINOPATHIES

BETA THALASSEMIA MAJOR

The newborn screening result may be Hb F only. Other diagnostic possibility for this newborn screening result include premature infant.

What is Beta Thalassemia Major?

Beta Thalassemia Major is a red blood disorder characterized by a reduction in or lack of normal beta globin production and absence of Hb A (F [fetalHb] only).

Confirmatory testing

Capillary Electrophoresis (CE), CBC and red blood cell indices (MCH, MCV) testing for both child and parents, and DNA testing are used to confirm the diagnosis.

What should you do?

- Contact the family to inform them of the screening result. Recommend confirmatory testing if not yet done.
- Evaluate infant, assess for splenomegaly
- Refer patient to a Pediatric hematologist.

Clinical Considerations

Infants with this disorder may be normal until the 4-6 months of life. With beta-thalassemia, severe anemia may develop in the first few months of life. Moderate pallor may appear at this age often requiring regular blood transfusions. Complications later in childhood may include growth retardation, sexual immaturity, intercurrent infections, progressive hepatosplenomegaly, skeletal abnormalities, and severe iron overload. Comprehensive care including family education, immunizations, regular transfusions partnered with compliance to iron chelation therapy reduces morbidity and mortality.

THALASSEMIAS AND HEMOGLOBINOPATHIES

HEMOGLOBIN E DISEASE

The newborn screening result may be Hb FE. Other diagnostic possibility for this newborn screening result include Hemoglobin E thalassemia.

What is Hemoglobin E disease?

Hemoglobin E (Hb E) is a variant hemoglobin with a mutation in the β-globin gene causing substitution of glutamic acid for lysine at position 26 of the β globin chain. **Hb E disease** is defined by the co-existence of two βE alleles, resulting into homozygous state EE.

Confirmatory testing:

Capillary Electrophoresis (CE), CBC and red blood cell indices (MCH, MCV) testing for both child and parents, and DNA testing are used to confirm the diagnosis.

What should you do?

- Contact the family to inform them of the screening result. Recommend confirmatory testing if not yet done.
- Recommend CBC at 4-6 months. If with anemia, refer to a Pediatric hematologist.

Clinical Considerations

The disorder is basically benign and do not require specialized treatment.

THALASSEMIAS AND HEMOGLOBINOPATHIES

HEMOGLOBIN C DISEASE

The newborn screening result may be Hb FC. Other diagnostic possibility for this newborn screening result include Hemoglobin C thalassemia.

What is Hemoglobin C disease?

Hemoglobin C(Hb C) is a variant hemoglobin with a mutation in the β globin gene causing substitution of glutamic acid for lysine at position 6 of the globin chain. Hb C disease is defined by the co-existence of 2 βC alleles (homozygous state CC). The heterozygous form is benign.

Confirmatory testing

Capillary Electrophoresis (CE), CBC and red blood indices (MCH, MCV) testing for both child and parents, and DNA testingare used to confirm the diagnosis.

What should you do?

- Contact the family to inform them of the screening result. Recommend confirmatory testing if not yet done.
- Refer patient to a Pediatric hematologist.

Clinical Considerations

An affected neonate is likely to appear healthy, but has a risk for mild anemia and minor complications. Complications may include splenomegaly, jaundice and increased risk for gallstones.

THALASSEMIAS AND HEMOGLOBINOPATHIES

HEMOGLOBIN D DISEASE

The newborn screening result may be Hb FD. Other diagnostic possibility for this newborn screening result include Hemoglobin D thalassemia.

What is Hemoglobin D disease?

Hemoglobin D (Hb D) is a variant hemoglobin with a mutation in the β globin gene causing substitution of glutamine for glutamic acid in the β globin chain. **Hb D** disease is defined by homozygous state DD.

Confirmatory testing

Capillary Electrophoresis (CE), CBC and red blood indices (MCH, MCV) testing for both child and parents, and DNA testing

What should you do?

- Contact the family to inform them of the screening result. Recommend confirmatory testing if not yet done.
- Refer patient to a pediatric hematologist.

Clinical Considerations

Most individuals with Hb D disease do not have symptoms. However, some may have mild haemolytic anemia which may be associated with a slightly enlarged spleen. Treatment is usually not necessary. Individuals with Hb D are expected to live a normal life.

THALASSEMIAS AND HEMOGLOBINOPATHIES

SICKLE CELL DISEASE

The newborn screening result may be Hb FS. Other diagnostic possibilities for this newborn screening result include Sickle cell-β thalassemia and sickle cell-hereditary persistence of fetal hemoglobin.

What is Sickle Cell Disease?

Sickle cell disease patients have predominant HbS. This condition is most common in Africa, Middle East and the United States.Affected infants are usually normal at birth but develop anemia later when the HbS concentration increases and the HbFdecreases. These patients are particularly susceptible to encapsulated bacterial infections such as *Streptococcus pneumonia, Hemophilus influenzae, Staphylococcus aureus, and Salmonella.*

Confirmatory testing

Capillary Electrophoresis (CE), CBC and red blood cell indices (MCH, MCV) testing for both child and parents, and DNA testing are used to confirm the diagnosis.

What should you do?

- Contact the family to inform them of the screening result. Recommend confirmatory testing if not yet done.
- Immediately refer patient to a pediatric hematologist.
- If there are no pediatric hematologists, then start oral penicillin if below 6 months.

Clinical Considerations

Infants with this finding are usually normal at birth. However, severe anemia may develop in the first few months of life. Complications include growth retardation, intercurrent infections, progressive hepatosplenomegaly, skeletal abnormalities, and periodic episodes of pain. These episodes can occur when sickled red blood cells, which are stiff and inflexible, get stuck in small blood vessels. These episodes deprive tissues and organs of oxygen-rich blood and can lead to organ damage, especially in the lungs, kidneys, spleen, and brain. Comprehensive care including family education, immunizations, regular blood transfusions, pain control and prompt treatment of acute illness reduces morbidity and mortality.

THALASSEMIAS AND HEMOGLOBINOPATHIES

ALPHA THALASSEMIA TRAIT /ALPHA THALASSEMIA MINOR

The child's newborn screening test identified him/her as a possible carrier of Alpha Thalassemia, also referred to as **Alpha Thalassemia Trait/Minor**.

Clinical Expectations for Carriers of Alpha Thalassemia

Being a carrier of Alpha Thalassemia will not have an adverse influence on this child's life expectancy. The trait is basically silent and carriers are **not** more likely to get sick than any other child. In most cases, children are symptom-free and will have normal growth and development, hence do **not** need special medical care. Rarely, carriers can manifest with mild anemia.

Reproductive Risks

The results indicate that the child is a carrier of Alpha Thalassemia. It is important to remember that the trait may be transmitted by the child to his/her would-be children. Thus, it is extremely important to have his/her future partner screened for the hemoglobin disorders as their union may result in a baby with more severe form of alpha thalassemia. Also, in a population with high incidence of Hemoglobin E disease and beta thalassemia, co- inheritance with these conditions may present with more severe anemia. Family members of this child may also be at-risk for alpha thalassemia.

Important Considerations

- Coordination with a pediatric hematologist is advised to evaluate iron status of the patient before giving empiric iron supplements.
- Immunizations are not contraindicated for this condition and may be given as recommended by the Philippine Pediatric Society.

Note: Parents or hematologists may opt for genotyping but this will not be covered by the program and is at the own expense of the patients. This may be taken into account when counseling is done by the pediatrician/hematologist.

THALASSEMIAS AND HEMOGLOBINOPATHIES

BETA THALASSEMIA TRAIT /BETA THALASSEMIA MINOR

The child's newborn screening test identified him/her as a possible carrier of Beta Thalassemia, also referred to as **Beta Thalassemia Trait/Minor.**

Clinical Expectations for Carriers of Beta Thalassemia

Being a carrier of Beta Thalassemia will not have an adverse influence on this child's life expectancy. The trait is basically silent and carriers are **not** more likely to get sick than any other child. In most cases, children are symptom-free and will have normal growth and development, hence do **not** need special medical care. Rarely, carriers can manifest with mild anemia.

Reproductive Risks

The results indicate that the child is a carrier of Beta Thalassemia. It is important to remember that the trait may be transmitted by the child to his/her would-be children. Thus, it is extremely important to have his/her future partner screened for the hemoglobin disorders as their union may result in a baby with severe form of beta thalassemia. Also, in a population with high incidence of Hemoglobin E disease and alpha thalassemia, co- inheritance with these conditions may present with more severe anemia. Family members of this child may also be at-risk for beta thalassemia.

Important Considerations

- Coordination with a pediatric hematologist is advised to evaluate iron status of the patient before giving empiric iron supplements.
- Immunizations are not contraindicated for this condition and may be given as recommended by the Philippine Pediatric Society.

THALASSEMIAS AND HEMOGLOBINOPATHIES

HEMOGLOBIN E TRAIT OR HBFAE

The baby's newborn screening test identified him/her as a possible carrier of Hemoglobin E, also referred to as **Hemoglobin E Trait** or **HbFAE**.

Clinical Expectations for Carriers of Hemoglobin E

Being a carrier of Hemoglobin E will not have an adverse influence on this child's life expectancy. The trait is basically silent and carriers are not more likely to get sick than any other child. In most cases, children are symptom-free and will have normal growth and development, hence do not need special medical care. Rarely, carriers can manifest with mild anemia.

Reproductive Risks

The results indicate that the child is a carrier of the Hemoglobin E. It is important to remember that the trait may be transmitted by the child to his/her would-be children. Thus, it is extremely important to have his/her future partner screened for the hemoglobin disorders as their union may result in a baby with a hemoglobin E disease which, at most, may present with mild anemia. More importantly, in a population with high incidence of alpha or beta thalassemia, co- inheritance with these conditions may present with moderate to severe anemia. Family members of this child may also be at-risk for hemoglobin E disease.

Important Considerations

- Treatment is typically not needed.
- Immunizations are not contraindicated for this condition, and may be given as recommended by the Philippine Pediatric Society.

Note: Parents or hematologists may opt for genotyping but this will not be covered by the program and is at the own expense of the family. This may be taken into account when counseling is done by the pediatrician/hematologist.

THALASSEMIAS AND HEMOGLOBINOPATHIES

HEMOGLOBIN C TRAIT OR HBFAC

The child's newborn screening test identified him/her as a possible carrier of Hemoglobin C, also referred to as **Hemoglobin C Trait or HbFAC.**

Clinical Expectations for Carriers of Hemoglobin C

Being a carrier of Hemoglobin C will not have an adverse influence on this child's life expectancy. The trait is basically silent and carriers are **not** more likely to get sick than any other child. In most cases, children are symptom-free and will have normal growth and development, hence do **not** need special medical care. Rarely, carriers can manifest with mild anemia.

Reproductive Risks

The results indicate that the child is a carrier of the Hemoglobin C. It is important to remember that the trait may be transmitted by the child to his/her would-be children. Thus, it is extremely important to have his/her future partner screened for the hemoglobin disorders as their union may result in a baby with a hemoglobin C disease which, at most, may present with mild anemia. More importantly, in a population with high incidence of alpha or beta thalassemia, co- inheritance with these conditions may present with moderate to severe anemia Family members of this child may also be at-risk for hemoglobin C disease.

Important Considerations

- Treatment is typically not needed.
- Immunizations are not contraindicated for this condition, and may be given as recommended by the Philippine Pediatric Society.

Note: Parents or hematologists may opt for genotyping but this will not be covered by the program and is at the own expense of the family. This may be taken into account when counseling is done by the pediatrician/hematologist.

THALASSEMIAS AND HEMOGLOBINOPATHIES

HEMOGLOBIN D TRAIT OR HBFAD

The child's newborn screening test identified him/her as a possible carrier of Hemoglobin D, also referred to as **Hemoglobin D Trait or HbFAD.**

Clinical Expectations for Carriers of Hemoglobin D

Being a carrier of Hemoglobin D will not have an adverse influence on this child's life expectancy. The trait is basically silent and carriers are **not** more likely to get sick than any other child. In most cases, children are symptom-free and will have normal growth and development, hence do **not** need special medical care. Rarely, carriers can manifest with mild anemia.

Reproductive Risks

The results indicate that the child is a carrier of the Hemoglobin D. It is important to remember that the trait may be transmitted by the child to his/her would-be children. Thus, it is extremely important to have his/her future partner screened for the hemoglobin disorders as their union may result in a baby with a hemoglobin D disease which, at most, may present with mild anemia. More importantly, in a population with high incidence of alpha or beta thalassemia, co- inheritance with these conditions may present with moderate to severe anemia. Family members of this child may also be at-risk for hemoglobin D disease.

Important Considerations

- Treatment is typically not needed.
- Immunizations are not contraindicated for this condition, and may be given as recommended by the Philippine Pediatric Society.

Note: Parents or hematologists may opt for genotyping but this will not be covered by the program and is at the own expense of the family. This may be taken into account when counseling is done by the pediatrician/hematologist.

child's newborn screening test identified him/her as a possible carrier of Sickle Cell Disease (SCD), also referred to as **Sickle Cell Trait or HbFAS.**

Clinical Expectations for Carriers of Sickle Cell Disease

Being a carrier of Hemoglobin S will not have an adverse influence on this child's life expectancy. The trait is basically silent and carriers are **not** more likely to get sick than any other child. In most cases, children are symptom-free and will have normal growth and development, hence do **not** need special medical care. Rarely, carriers can manifest with mild anemia.

Reproductive Risks

The results indicate that the child is a carrier of the Hemoglobin S (Sickle cell Hemoglobin). It is important to remember that the trait may be transmitted by the child to his/her would-be children. Thus, it is extremely important to have his/her future partner screened for carrier state as their union may result in a baby with Sickle cell disease which will present with severe clinical manifestations. Also, in a population with high incidence of alpha or beta thalassemia, co- inheritance with these conditions may present with moderate to severe anemia. Family members of this child may also be carriers for sickle cell disease.

Important Considerations

- Treatment is typically not needed.
- Immunizations are not contraindicated for this condition and may be given as recommended by the Philippine Pediatric Society. It is particularly recommended that they be given Pneumococcal, Influenza and Haemophilusinfluenzae Type B (HiB) vaccines.

Note: Parents or hematologists may opt for genotyping but this will not be covered by the program and is at the own expense of the family. This may be taken into account when counseling is done by the pediatrician/hematologist.

The newborn screening result may be Hb FEA or Hb FE. HbE/β-thalassemia results from co-inheritance of a β-thalassemia allele from one parent and the structural variant Hemoglobin E from the other.

Confirmatory testing

Capillary Electrophoresis (CE), CBC and red blood cell indices (MCH, MCV) testing for both child and parents, and DNA testing are used to confirm the diagnosis.

What should you do?

- Evaluate infant and assess for splenomegaly
- Refer patient to a pediatric hematologist.

Clinical Considerations

Infants with this result are usually normal at birth. Clinical severity is influenced by the instability of the HbE and the degree and severity of the β thalassemia mutation. Hence,HbE/β^{o} will correspond to the clinical picture of thalassemia majorand will require life-long transfusion.While HbE/β+ will be similar to the presentation of thalassemia intermedia.

References:

American College of Medical Genetics. Newborn Screening ACT Sheet. Retrieved from: https://www.acmg.net/PDFLibrary/Hemoglobin-E-ACT-Sheet.pdf. Accessed 8 April 2020.

Fucharoen S and DJ Weatherall. The Hemoglobin E Thalassemias. *Cold Spring HarbPerspect Med.* 2012; 2:a011734.

Kohne, E., Compendium of Hemoglobinopathies, pp 49-53

The newborn screening result may be Hb FDA or Hb FD.HbD/β-thalassemia results from co-inheritance of a β-thalassemia allele from one parent and the structural variant Hemoglobin D from the other.

Confirmatory testing

Capillary Electrophoresis (CE), CBC and red blood cell indices (MCH, MCV) testing for both child and parents, and DNA testing.

What should you do?

- Evaluate infant and assess for splenomegaly
- Refer patient to a pediatric hematologist.

Clinical Considerations

Infants with this result are usually normal at birth. Clinical severity is variable and depends on the specific β-thalassemia mutation. The factor reliably responsible for the phenotype is the imbalance in the globin chain synthesis.If HbD/β+, a clinical presentation of thalassemia intermedia is observed. Clinical manifestations may range from microcytic, hypochromic anemia to hemolytic anemia and splenomegaly.

References

de Souza Torres L, Okumura JV, da Silva DGH and CR Bonini-Domingos. Hemoglobin D-Punjab: origin, distribution and laboratory diagnosis. *Brazilian Journal of Hematology and Hemotherapy*. 2015; 37(2): 120-126.

Kohne, E., Compendium of Hemoglobinopathies, pp 49-53

Shekhda KM, Leuva AC, Mannari JG *et al.* Co-Inheritance of Hemoglobin D Punjab and Beta Thalassemia – A Rare Variant. *Journal of Clinical and Diagnostic Research.*2017; 11(6): OD21-OD22.

The newborn screening result may be Hb FCA or Hb FC. Hb C/β-thalassemia results from co-inheritance of a β-thalassemia allele from one parent and the structural variant Hemoglobin C from the other.

Confirmatory testing

Capillary Electrophoresis (CE), CBC and red blood cell indices (MCH, MCV) testing for both child and parents, and DNA testing are used to confirm the diagnosis.

What should you do?

- Evaluate infant and assess for splenomegaly
- Refer patient to a pediatric hematologist.

Clinical Considerations

Infants are usually normal at birth.The combination of HbC/β-thalassemia on whether there is complete or partial production of Beta chain.If HbC/β+, the clinical presentation will correspond to thalassemia intermedia.The clinical manifestations may range from mild to moderate hemolytic anemia, splenomegaly and bone changes. Serious hemolytic anemia may be observed in the complete absence of Beta chain (β^0).

References:

American College of Medical Genetics. Newborn Screening ACT Sheet. Retrieved from: https://www.acmg.net/PDFLibrary/Hemoglobin-C-ACT-Sheet.pdf . Accessed 8 April 2020.

Fucharoen S and DJ Weatherall. The Hemoglobin E Thalassemias. *Cold Spring HarbPerspect Med.* 2012; 2:a011734.

Kohne, E., Compendium of Hemoglobinopathies, pp 49-53

INTERACTING A-THALASSEMIA WITH HEMOGLOBIN E

Hemoglobin (Hb)E is the most common abnormal hemoglobin in Southeast Asia countries. Alpha thalassemia is also prevalent in the region. Thus, the coinheritance of Hb E with α-thalassemia is frequently observed.

Confirmatory testing

Capillary Electrophoresis (CE), CBC and red blood cell indices (MCH, MCV) testing for both child and parents, and DNA testing are used to confirm the diagnosis.

What should you do?

- Evaluate infant and assess for splenomegaly
- Refer patient to a pediatric hematologist.

Clinical Considerations

The clinical manifestation ofHb E/α-thalassemia will depend on the number of deletions in the α gene. Hb E/ -α/αα (1 deletion), Hb E/ -α/-α (2 deletions) or Hb E/ --/αα(2 deletions) will give rise to a mild type of hypochromic anemia with mild splenomegaly. Hb E/ --/-α (3 deletions) may give to severe form of HbH disease requiring blood transfusions.

References:

Fucharoen S and DJ Weatherall. The Hemoglobin E Thalassemias. *Cold Spring HarbPerspect Med.* 2012; 2:a011734.

Fucharoen S and P Winichagoon. Hemoglobinopathies in Southeast Asia. *Indian J Med Res.* 2011; 134(4): 498 – 506.

Kohne, E., Compendium of Hemoglobinopathies, pp 49-53

Co-inheritance the two types of thalassemiasis relatively common in Southeast Asia. In a study on a Chinese population, one in every six β-thalassemia carriers co-inherits α-thalassemia.

Confirmatory testing

Capillary Electrophoresis (CE), CBC and red blood cell indices (MCH, MCV) testing for both child and parents, and DNA testing are used to confirm the diagnosis.

What should you do?

- Evaluate infant and assess for splenomegaly
- Refer patient to a pediatric hematologist.

Clinical Considerations

The clinical manifestation ofα-/β-thalassemia interaction shows considerable clinical heterogeneity. The clinical improvement depends on the severity of the β-thalassemia alleles and the number of functional α-globin genes. Co-inheritance of two α-globin gene deletions or a non-deletional α2-globin gene mutation in β0-thalassemia homozygotes is more likelyto produce a thalassemia intermedia phenotype. On the other hand, co-inheritance of a single α-globin gene deletion in the same group of patients is usually associated with athalassemia major phenotype. The SEA deletion (--/αα) improves the clinical presentation of β0/β+ but not necessarily of β0/β0-thalassemia. Co-inheritance of a single α-globin gene deletion in homozygous or compound heterozygous β+-thalassemia produces an improved phenotype. On the other hand, co-inheritance of Hb H disease with β0/β+-thalassemia present as β thalassemia minor.

Just as presence of α-thalassemia can improve the clinical severity of βthalassemia major, the co-inheritance of β thalassemia can improve presentation of non-deletional Hb H disease.

References:

Li J, Xie XM, Liao C, Li DZ. Co-inheritance of α-thlassaemia and β-thlassaemia in a prenatal screening population in mainland China. J Med Screen 2014. Vol 21(4)167-171

Kohne, E. Compendium of Hemoglobinopathies 2014. SEBIA Educational Library

THALASSEMIAS AND HEMOGLOBINOPATHIES

OTHER RARE INTERACTING THALASSEMIAS AND HEMOGLOBINOPATHIES

Other rare interacting thalassemias and hemoglobinopathies may be detected via the newborn screening. This will warrant confirmatory testing

Confirmatory testing

Capillary Electrophoresis (CE), CBC and red blood cell indices (MCH, MCV) testing for both child and parents, and DNA testing are used to confirm the diagnosis.

What should you do?

- Evaluate infant and assess for splenomegaly
- Refer patient to a pediatric hematologist.

Clinical Considerations

The clinical manifestations of the interacting thalassemias and hemoglobinopathies may vary depending on the combination. This may vary from mild to severe presentation.

UREA CYCLE DEFECTS

UREA CYCLE DEFECTS: Citrullinemia AND Argininosuccinic Aciduria

What are UCDs?

The urea cycle is the main pathway of the body to dispose of excess nitrogen. It allows for the conversion of ammonia into urea that can be excreted into the urine. Citrullinemia and Argininosuccinic Aciduria are inherited in an autosomal recessive manner. Citrullinemia occurs as a result of argininosuccinic synthase deficiency while argininosuccinic aciduria is due to a deficiency of argininosuccinic lyase. Both conditions may manifest with tachypnea, lethargy, vomiting, irritability, seizures, coma and ultimately death if left untreated. The increased levels of ammonia may cause brain damage.

Due to blocks in the urea cycle owing to the enzyme deficiency, patients with UCD have low levels of arginine. This makes arginine an essential amino acid among patients with UCD.

Treatment of UCDs

Treatment is through the dietary restriction of protein and the supplementation of a protein free formula. Sodium benzoate, an ammonia scavenger, is given as well as arginine supplementation.

Preliminary / Initial Management During Metabolic Crises

Metabolic crises may be caused by an excess intake of protein, illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state and prevent essential amino acid deficiency.

UREA CYCLE DEFECT

ARGININOSUCCINIC ACIDURIA (ASA)

What is ASA?

Arigininosuccinic aciduria is an inborn error of metabolism resulting from the deficiency of the enzyme argininosuccinic lyase.[1]

Clinical Manifestation

The classic presentation of argininosuccinic aciduria is an overwhelming illness in the newborn period presenting with vomiting, lethargy progressing rapidly to deep coma, apnea, seizures and death. 2 Patients may also have hair abnormalities (trichorrhexis nodosa).[1,2]

Pathophysiology

Argininosuccinate lyase is an enzyme that converts argininosuccinic acid to arginine, the absence of which causes an increase in argininosuccinic acid, citrulline and ammonia.[2]

Inheritance: autosomal recessive.[1,2]

Confirmatory Testing

Confirmatory testing may be done through plasma amino acid analysis (increased argininosuccinic acid, increased citrulline and decreased arginine), increased orotic acid and presence of argininosuccinic *acid* in the urine.[1,2] Enzyme analysis may also be done on fibroblasts.[1]

Overview of Disease Management

Long-term management, as with other urea cycle disorders, consists of a low protein diet supplemented with special milk formula, provision of arginine and sodium benzoate or phenylbutyrate.[1,2]

Prognosis

Prognosis for intellectual development probably depends on the nature of the initial hyperammoniemia, especially in duration or the nature of recurrent episodes.[2]

Preliminary/ Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

[1]Zchocke J and Hoffmann GF, *Vademecum Metabolicu*, 3rd ed., Germany:Milupa Metabolics, 2011

[2]Nyhan WL, Barshop BA and Al-Aqeel A. Chapter 27: Argininosuccinic aciduria. *Atlas of Inherited Metabolic Diseases* 3rd ed. Great Britain:Oxford University Press, 2012 pp216-222

UREA CYCLE DEFECT

ARGININOSUCCINIC ACIDURIA (ASA)

What to do

If Unwell and cannot tolerate oral intake

Nothing perorem

Ensure patient's airway is secure

Insert IV access. Collect sample for serum ammonia. May request for investigations (i.e.

CBC, etc.) as needed

May give fluid boluses if patient requires

Start 012.5% 0.3NaCI at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 to 1.5x of maintenance

Start IV sodium benzoate loading doe {250mg/kg) to run for 1-2 hours

Start IV arginine loading dose (250mg/kg} to run for 1-2 hours

Monitor input and output strictly (q6horus)

If Unwell and can tolerate oral intake

Insert oro- or nasogastric tube and start continuous feeding with protein free formula at maintenance rate

Insert IV access. Collect sample for serum ammonia. May request for investigations (i.e. CBC, etc.} as needed

May give fluid boluses if patient requires

Start 012.5% 0.3NaCI at 5-10 cc/hr.

Start IV sodium benzoate loading doe (250mg/kg) to run for 1-2 hours

Start IV arginine loading dose (250mg/kg) to run for 1-2 hours

Monitor input and output strictly (q6horus)

*Children should not be protein restricted for longer than necessary (24-48 hours)

If patient does not improve with the initial management (within 12 hours), hemodialysis may be indicated. Monitor patient clinically, the necessity of hemodialysis will depend on patient's clinical status.

*Inform metabolic doctor on call for further guidance regarding on-going management

UREA CYCLE DEFECT

CITRULLINEMIA

What is Citrullinemia?

Citrullinemia is an inborn error of metabolism resulting from the deficiency of arginosuccinate synthetase, an enzyme present in all tissues but the level of which is highest in the liver where it functions in the urea cycle.

Clinical Manifestation

Following a brief hiatus in which the newborn appears normal, anorexia, vomiting and therapy develop followed rapidly by progression to deep coma. The symptoms mimic that of sepsis and affected newborns present with severe lethargy, poor feeding to respiratory distress, jitteriness and seizures.

A late onset form may occur as late as 20 years old and present as symptoms such as slurred speech, irritability, insomnia or delirium.[3]

Pathophysiology

Argininosuccinate synthase is an enzyme that converts citrulline to arginosuccinate, the absence of which causes an increase in plasma citrulline and ammonia levels.

Inheritance: autosomal recessive

Confirmatory Testing

Confirmatory testing may be done through the demonstration of amino acids in plasma (decreased arginine and high citrulline), presence of orotic acid in urine and increased levels of ammonia in blood.[2,5]

Overview of Disease Management

Long-term steady state management can usually be provided with arginine (0.25-0.8g/kg/day), sodium benzoate, sodium phenylbutyrate and a diet modestly restricted in protein.[3]

Prognosis

Prognosis for intellectual development depends on the nature of the inital hyperammonemia especially its duration or those of recurrent episodes.[3]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do

If unwell and cannot tolerate oral intake:

- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Collect sample for serum ammonia. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if patient requires.

UREA CYCLE DEFECT

CITRULLINEMIA

- Start D12.5% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Start IV sodium benzoate loading dose (250mg/kg) to run for 1-2 hours.
- Start IV arginine loading dose (250mg/kg) to run for 1-2 hours.
- Monitor input and output strictly (q6 hours)

If unwell and can tolerate oral intake:

- Insert oro- or nasogatric tube and start continuous feeding with protein free formula at maintenance rate
- Insert IV access. Collect sample for serum ammonia. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D12.5% 0.3NaCl at 5-10 cc/hr.
- Start IV sodium benzoate loading dose (250mg/kg) to run for 1-2 hours.
- Start IV arginine loading dose (250mg/kg) to run for 1-2 hours.
- Monitor input and output strictly (q6 hours)

** Children should not be protein restricted for longer than necessary (24-48 hours)*

** If patient does not improve with the initial management (within 12 hours), hemodialysis may be indicated. Monitor patient clinically, the necessity of hemodialysis will depend on patient's clinical status.*

** Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Su TS, Bock HGO, Beaudet AL et al. *Molecular analysis of argininosuccinate syntehtase deficiency in human fibroblasts.* J Clin Invest 1982:70:1334-1339.

[2] Nyhan WL, Barshop BA and Ozand P. Chapter 31: Citrullinemia. *Atlas of Metabolic Diseases* 2nd ed. Great Britain:Oxford University Press, 2005 pp 210-213.

[3] Wasant P, Viprakasit V, Srisomsap C et al. *Argininosuccinate synthetase deficiency: mutation analysis in 3 Thai patients*. Southeast Asian J Trop Med Pub Health 2005;36(3):757-761.

[4] Nyhan WL, Barshop BA and Ozand P. Chapter 32: Arginosuccinic aciduria. *Atlas of Metabolic Diseases* 2nd ed. Great Britain:Oxford University Press, 2005 pp 216-219.

[5] Schulze A, Matern D, Hoffmann GF. Chapter 2: Newborn screening in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism.* New York: McGraw Hill, 2009 pp 17-32.

BIOTINIDASE DEFICIENCY

What is Biotinidase Deficiency?

Biotinidase deficiency is a form of multiple carboxylase deficiency in which the fundamental defect is an inability to cleave biocytin for biotin recycling. Biotin is a water-soluble vitamin of the B complex that acts as a coenzyme in each of 4 carboxylases in humans (pyruvate carboxylase, propionyl-coenzyme A carboxylase, β-methylcrotonyl CoA caorboxylase and acetyl-CoA carboxylase).[2]

Clinical Manifestation

Biotinidase deficiency presents with a median age of 3 months or as late as 10 years of age, symptoms include dermatologic affectation appearing as patchy desquamation and neurological manifestations such as seizures in 70% of patients and ataxia that can interfere with walking. Some patients may also have optic atrophy and hearing loss.[2] Individuals with partial biotinidase deficiency can present with skin manifestations and no neurologic symptoms.[2,3]

Pathophysiology

Biotinidase deficiency results in an inability to recycle endogenous biotin which means the brain is unable to recycle biotin adequately leading to decreased pyruvate carboxylase activity in the brain and accumulation of lactate which in turn causes the neurologic symptoms.[2]

Inheritance: autosomal recessive[3]

Confirmatory Testing

Confirmatory studies are performed by determining biotinidase activity in serum.[2]

Overview of Disease Management

Patients are treated with biotin (5-10mg/day).[2,3]

Prognosis

Once therapy is instituted, cutaneous symptoms resolve quickly as do seizures and ataxia, however other symptoms such as hearing loss and optic atrophy are less reversible.[2]

Preliminary / Initial Management during Metabolic Crisis

Metabolic crises may be caused by illness, prolonged fasting or stressful situations such as surgery and severe infection. The goal of treatment is to reverse the catabolic state, correct the acidosis and prevent essential amino acid deficiency.

What to Do If Unwell

- Nothing per orem
- Ensure patient's airway is secure
- Insert IV access. Collect samples for serum ammonia and blood gas. May request for investigations (i.e. CBC, etc.) as needed.
- May give fluid boluses if patient requires.
- Start D10% 0.3NaCl at full maintenance. Assess patient clinically, if there is need to increase fluid, may do so up to 1.2 or 1.5x the maintenance.
- Monitor input and output strictly (q6 hours).

BIOTINIDASE DEFICIENCY

**Inform metabolic doctor on call for further guidance regarding on-going management*

[1] Nyhan WL, Barshop BA and Ozand P. Chapter 6: Multiple carboxylase deficiency/biotinidase deficiency. *Atlas of Metabolic Diseases* 2nd ed. Great Britain: Oxford University Press, 2005 pp 42-48.

[2] Schulze A, Matern D, Hoffmann GF. Chapter 2: Newborn screening in Sarafoglou K, Hoffman GF and Roth KS (eds). *Pediatric Endocrinology and Inborn Errors of Metabolism.* New York:McGraw Hill, 2009 pp 17-32.

[3] Nyhan WL, Barshop BA and Ozand P. Chapter 6: Multiple carboxylase deficiency/biotinidase deficiency. *Atlas of Metabolic Diseases* 2nd ed. Great Britain:Oxford University Press, 2005 pp 42-48.

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GALACTOSEMIA (GAL)

What are Galactosemia?

Galactosemia is a rare genetic metabolic disorder that is inherited in an autosomal recessive manner. It is an inborn error of carbohydrate metabolism characterized by elevated levels of galactose and its metabolites due to enzyme deficiencies involved in its metabolism. Galactose is the sugar found mainly in milk and dairy products. It is also produced by the body. Milk contains a sugar called lactose, and during digestion, lactose is broken down into the sugars glucose and galactose. Glucose can immediately be used as a source of energy by the body, but galactose needs to be further broken down before it can be utilized. The birth incidence of classic galactosemia is about 1 per 47,000 in the Caucasian population. The Philippine NBS data as of December 2018 gives a prevalence of 1 : 134,439.

Pathophysiology

The galactose metabolic pathway with multiple enzymatic steps is shown. The enzymes allow the subsequent conversion of galactose to galactose-1-phosphate by GALK (1); galactose-1-phosphate and uridine diphosphate glucose (UDP glucose) to glucose-1-phosphate and UDP-galactose by GALT (2) and the interconversion of UDP-glucose and UDP-galactose by GALE (3). Children with galactosemia have very little or entirely lack an enzyme that helps the body break down galactose. There are three different enzyme problems that can lead to galactosemia. In the first type or classic galactosemia, the enzyme that is reduced or missing is called galactose-1-phosphate uridyl transferase (GALT). The GALT enzyme enables the body to break down galactose into glucose. The second type of galactosemia is due to a deficiency in uridine diphosphate galactose 4-epimerase (GALE). Its severe type clinically resembles classic galactosemia. The third type, is due to a deficiency in galactokinase (GALK), and presents primarily as cataracts in untreated patients.

Clinical Features

Patients can present with feeding problems, failure to thrive, hepatocellular damage, bleeding, and sepsis in untreated infants. In approximately 10% of individuals, cataracts are present. Failure to thrive is the most common initial clinical symptom of classic galactosemia. Vomiting or diarrhea usually begins within a few days of milk ingestion. Jaundice of intrinsic liver disease may be accentuated by the severe hemolysis occurring in some patients. Cataracts have been observed within a few days of birth. There appears to be a high frequency of neonatal death due to E. coli sepsis in patients with classic galactosemia.

The association of jaundice and hemorrhagic diathesis in the first 2 weeks of life is a clinical presentation in which galactosemia must be considered. Coagulopathy may also be present in galactosemia with little evidence of liver disease. Galactosemia also causes learning and language problems in children, bone mineral density problems and ovarian failure in girls.

Treatment and Monitoring

Dietary elimination of milk and milk products containing lactose is the treatment for all types of galactosemia. There is no chemical or drug substitute for the missing enzyme at this time. An infant diagnosed with galactosemia will have to be on a soy-based formula. Dietary management under the close supervision of a metabolic dietician and a metabolic doctor is a must. Regular monitoring of blood galactose levels and regular evaluation by the genetic metabolic team is important for optimal treatment.

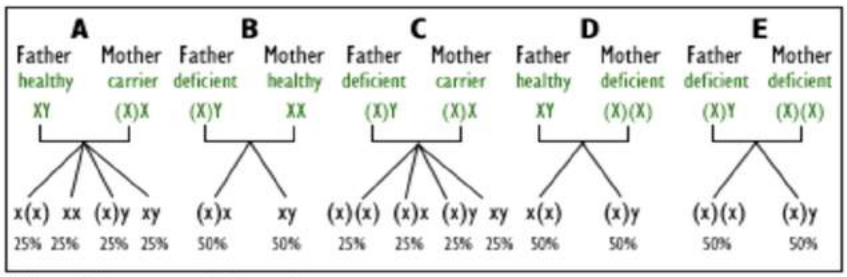
Prognosis

Despite an early galactose-free diet, long-term complications have been noted in older children and adults with classic galactosemia because of endogenous galactose production. These include speech problems, poor intellectual function, neurologic deficits (predominantly extrapyramidal findings with ataxia), and ovarian failure in females. Thus, the need for regular monitoring and evaluation is important.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

What is G6PD?

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an enzyme defect affecting around 400 million people worldwide.[5] According to the Philippine NBS data as of December 2018, 1 out of 61 screened newborns have G6PD deficiency.[4] G6PD-deficiency is an X-linked disorder found in both sexes but more males are affected. Female carriers are asymptomatic.

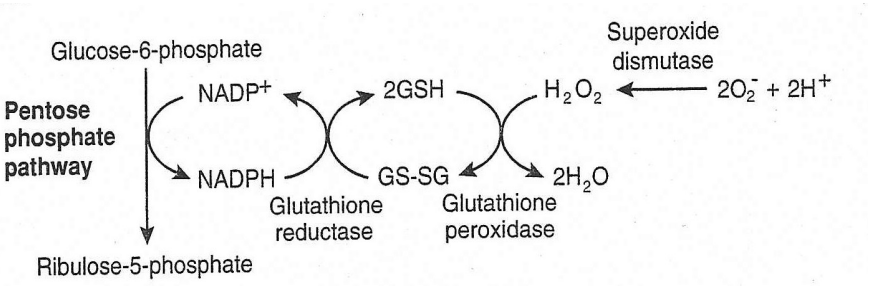


Inheritance of G-6-PD Deficiency

(X)Y – Deficient, Symptomatic
(X)(X) – Deficient, Symptomatic
(X)X – Carrier

Pathophysiology

G6PD is an enzyme that is present in all cells, but is much valued in red blood cells (RBCs). G6PD is needed for the first step in the Hexose Monophosphate Pathway (HMP). The pathway produces the reduced nicotinamide adenine dinucleotide phosphate (NADPH) that functions as an electron donor in maintaining glutathione in its reduced form (GSH). GSH serves as an antioxidant that protects the cells against oxidative damage. The HMP is the only source of NADPH in RBCs, thus the deleterious effect of G6PD deficiency in RBCs exposed to oxidative stress. Such oxidative stress is brought about by food products, drugs, chemical compounds, and infection. A short list of these agents is available on the succeeding pages.



Clinical Features

The most common clinical manifestation of G6PD deficiency is hemolytic anemia induced by various oxidative stresses as mentioned above. The patient presents sudden onset of tea-colored urine, jaundice and pallor. Hereditary nonspherocytic hemolytic anemia may also occur in patients with severe G6PD deficiency. In neonates, G6PD deficiency may present with prolonged jaundice which is attributed to impaired liver function as supposed to hemolysis. The dreaded effect of neonatal jaundice is kernicterus or the deposition of bilirubin (product of hemoglobin catabolism) which causes permanent damage to the brain or death. Other associated disorders to G6PD deficiency are decreased RBC lifespan and cataract formation. Although there is a high prevalence of G6PD deficiency, there are only few severe cases of hemolysis that has been documented and most of them are foreign reports.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

Diagnosis

The currently used method in the diagnosis of G6PD deficiency is the spot fluorescence test as part of the newborn screening panel. Screening-positive patients should immediately undergo confirmatory testing based on estimation of enzyme activity by quantitative analysis of the rate of NADPH production from NADP. DNA analysis is already available but is not used as a diagnostic method.

Management

There is no cure for G6PD deficiency, but the main goal in the management is avoidance of oxidative insults and blood transfusions for acute hemolytic crisis. Confirmed cases may also be referred to a specialist in Pediatric Hematology for assessment and advice.

Prognosis

Most G6PD-deficient patients live a normal life without the clinical features as indicated above. Since there is no way of telling who will develop hemolytic crisis, avoidance of oxidative stress and physician consult are advised if with febrile illness.

Patient Education

Parents should be educated regarding their child's disorder, specifically the drugs and food that cause oxidative stress, and thus should be avoided. It is also important to emphasize that infection is a common cause of hemolytic crisis in G6PD-deficient patients, hence all affected patients should see their doctor during febrile illness for management. Parents are also advised to mention to their physicians that the patient have G6PD deficiency during consults. As this is an inheritable disease, X-linked, genetic counseling should be done.

References and further reading materials:

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GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

FOODS, DRINKS AND CHEMICALS TO BE AVOIDED IN G6PD DEFICIENCY

I. DRUGS TO BE AVOIDED	
Generic Name	**Common Brand Names**
A. . Antibacterial	
**Nalidixic acid*	
Nitrofuran 1. nitrofurantoin 2. furazolidone 3. nitrofurazone / nitrofural	Macrodantin Diafuran, Diapectolin, Furoxone Furacin
**P- aminosalicylic acid*	
B. Analgesic/ Antipyretic	
**Acetanilid*	
C. Antihelmentic	
**B-naphthol*	
**Niridazole*	
**Stibophan*	
D. Sulfonamides and Sulphones	
Dapsone	Lepravir
**Glucosulphone sodium*	
Glyburide/ Glibenclamide	Euglucon Gluban Lodulce Orabetic
**Mafenide acetate*	
**Salicylazosulphapyridine/ Sulfasalazine*	
Stibophen	(2-(2-Oxido-3,5-Disulphonatophenoxy)-1,3,2,Benzodioxastibole-4-6-Disulphonate)
Sulphacetamide/ Sulfacetamide	Cetapred Sensocet
**Sulphadimidine*	
**Sulphafurazone*	
Sulphamethazole/ Sulfamethazole	Bacidal Bactille Forte Bactrim Bacxal DLI Cotrimoxazole Forteprim Globaxol Pharex Cotrimoxazole Ritemed Cotrimoxazole Septrin Trim S
Sulphanilamide/ Sulfanilamide	
Sulphapyridine	
**Sulphoxone/ Sulfoxone*	
Sulfasalazine, Salazosulfapyridine	Salazopyrin
E. Antimalarials	
Chloroquine	Aralen Chlorofoz
**Pamaquine*	
Primaquine	
Pentaquine	
F. Miscellaneous	
Acetylphenylhydrazine	
Dimercaprol	
Futamide	
Isobutyl nitrate	
Mepacrine	
Phenazopyridine	Azomir
Probenecid	
Thiazolesulfone	
Urate oxidase/ Rasburicase	
II. CHEMICALS TO BE AVOIDED	
Methylene Blue	
Arsine	
Phenylhydrazine	
Toluidine blue	
Trinitrotoluene	
Aniline dyes	
III. FOOD AND DRINKS TO BE AVOIDED	
Fava beans	Dingdong nuts, Mr. Bean
Red wine	
Legumes	Abitsuelas, Garbanzos, Kadyos, Munggo
Blueberry	
Soya food	Taho, Tokwa, Soy Sauce
Tonic water	
Bitter melon / ampalaya	
IV. AT IBA PA	
Menthol	Alaxan Gel Ben-gay Efficascent Oil
	Listerine mouthwash Listerine Pocketpacks Megascent Oil Mentopas Medicated Plaster Omega Pain Killer
Camphor	
Naphthalene	Moth balls
Henna	
Herbs	Cattle gallstone bezoar Honeysuckle flower Chimonanathus flower 100% pearl powder Figwortflower Acalypha indica
V. DRUGS SAFE TO TAKE IN THERAPEUTIC DOSES	
Acetaminophen	Paracetamol, tylenol
Acetophenetidin/ phenacin	
Aspirin/ Acetylsalicylic acid	Alka-seltzer Aspilets Cor-80 Cortal
Ascorbic acid	
Chloramphenicol	Chlormycetin Chloro-S Chlorsig Klorfen Oliphenicol Optomycin Pediachlor Penachlor Speradex
Ciprofloxacin	Ciprobay CIpromax Cipromet Qinosyn-500 Quilox Xipro
Diphenhydramine	
Isoniazid	
Phenytoin	
Quinidine	
**Vitamin K analogues/ Phytomenadione	Hema-K Konakion MM Phil Pharmawealth/ Atlantic Phytomenadione

**Not Available in the Philippines*
***Should be water soluble*