

Urinalysis and Body Fluids CS

Unit 2; Session 9

Non-Routine Urinalysis

Session Outline

- Overflow versus Renal Disorders
- Newborn Screening for Inborn Errors of Metabolism
- Amino Acid Disorders (Aminoacidurias)
- Organic Acidemias
- Metabolic disorders of
 - Tryptophan
 - Cystine
 - Homocystine
 - Porphyrin
 - Mucopolysaccharide
 - Purine
 - Carbohydrate

Non - Routine Urinalysis

- **Overflow vs. Renal Disorders**
 - **Overflow** - over production of a normal or abnormal substance to the point that the tubules are not able to prevent it from escaping into the urine.
 - Increased levels in blood & urine
 - Inherited defect
 - Acquired defect
 - **Renal Disorders** - tubules fail to reabsorb substance
 - Increased levels seen in urine only.

Disorders Classified by Defect

Inherited Overflow	Acquired Metabolic Overflow	Renal
Phenylketonuria	Infantile Tyrosinemia	Hartnup disease
Tyrosinemia	Melanuria	Cystinuria
Maple syrup urine disease	5-Hydroxyindole-acetic acid	
Organic acidemias	Porphyria	
Cystinosis		
Porphyria		
Mucopolysaccharidoses		
Galactosemia		
Lesch-Nyhan disease		

Newborn Screening for Inborn Errors of Metabolism

- State public labs screen newborns for most inborn errors of metabolism.
- Performed on heelstick blood
- Screening includes amino acids, carbohydrates, and other metabolites.
 - Aminoacidurias are inborn errors of metabolism that result in excess amino acids in the blood and urine.

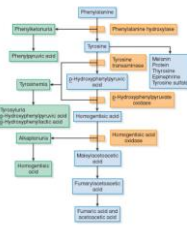


Phenylketonuria (PKU)

The normal metabolic pathway of phenylalanine

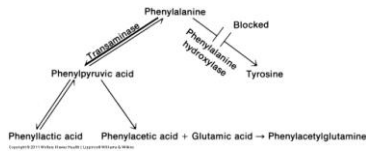
Notes:

- nearly every step listed requires an enzyme
- When enzymes are defective / missing abnormal products result
- Diagram from Susan Strassinger & Marjorie Di Lorenzo, Urinalysis and Body Fluids, 5th Ed.



Phenylketonuria (PKU)

- PKU - an Inborn Error of Metabolism disease
 - Absence or deficiency of *** *phenylalanine hydroxylase**.
 - Leading to increased formation of phenylalanine metabolites
 - PKU gets its name from presence of high levels of phenylketones
 - diagram from the reference author, Lillian Mundt & Kristy Shanahan, Graff's Textbook of Urinalysis and Body Fluids, 2nd Ed.



Phenylketonuria (PKU)

- Inherited autosomal recessive
 - 1 / ten thousand to 1/ twenty thousand live births
 - must inherit 2 defective genes
 - Early detection critical
 - Milk contains phenylalanine
 - If phenylalanine is not reduced in the diet early in life, severe brain damage and mental retardation can occur.
 - Blood level rises quickly and testing (state health dept as part of newborn screen) provides quicker results than urine.
 - The urine has a "Musty" or "Mousy" odor.



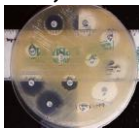
Phenylketonuria (PKU)

- PKU Management of disease
 - Diet to eliminate phenylalanine. Some foods & drinks carry warnings.
 - As individual develops, alternative pathways develop



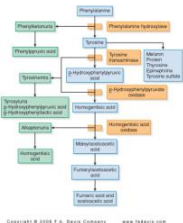
Tests for Phenylketonuria

- **Urine test (outdated)**
 - Urine and 5% ferric chloride produces a permanent green-blue color
- **Guthrie blood test (bacterial inhibition)**
 - Media containing beta-2-thienylalanine, an inhibitor of *Bacillus subtilis*, is streaked with the bacteria; blood-impregnated discs placed on the agar; phenylalanine counteracts the inhibitor, and bacteria grow around the disc
- Analysis by tandem mass spectroscopy (MS/MS)
- Genetic test



Tyrosyluria

- Inherited or transiently acquired.
- Newborns may acquire tyrosyluria as their livers may be underdeveloped
- Pathologic cases may show urinary crystals
 - leucine and tyrosine
- Urine Screening test
 - nitroso-naphthol test
 - Non-specific test capable of pick up other substances - pos is oran red color. Further testing is warranted.



Alcaptonuria

- Deficient enzyme
 - **homogentisic acid oxidase** - used in catabolism of phenylalanine and tyrosine
- Homogentisic acid (alkapton) excreted
 - **brown pigment** accumulates in blood, tissues, and urine.
 - May lead to arthritis, liver, cardiac disorders.
- No mental retardation
- Not usually diagnosed until adult
- Urine becomes dark brown / black upon standing. (as it becomes alkaline - it turns dark in color due to alcapton bodies)

Melanuria

- Another alternative pathway in the metabolism of tyrosine
 - Deficiency results in albinism
 - Increased levels strongly suggestive of malignant melanoma
 - Initially a colorless precursor produced which is oxidized to melanogen (also colorless) and further oxidized to melanin (brown-black)

Melanuria

- **Melanuria Testing**
 - Ferric chloride - gray or black precipitate
 - Sodium nitroprusside test (Acetest) - red color
 - be aware of interferences by acetone / creatinine)
 - Must differentiate from homogentisic acid (Alcapton bodies)
 - either substance will turn the urine dark.
 - Homogentisic acid urine will turn dark after becoming alkaline
 - Melanin urine becomes dark with exposure to oxygen

Branched - Chain Amino Acid Disorders

- **Amino acids with a methyl group**
 - Leucine
 - Isoleucine
 - valine
- **Two groups of disorders:**
 - Maple syrup urine disease (MSUD); early degradation products accumulate
 - Organic acidemias; accumulation of organic acids further down in pathway
- Patients have positive ketones

Branched - Chain Amino Acid Disorders

- **Maple - Syrup Disease**
 - Characteristic odor to urine
 - Elevated levels of valine, leucine, and isoleucine in blood and urine
 - Defective enzyme is branched chain keto acid decarboxylase
 - Rare disease (autosomal recessive)



Branched - Chain Amino Acid Disorders

- **Maple - Syrup Disease**
 - some cases have been controlled by early diagnosis, dialysis and treatment and near elimination of valine, leucine & isoleucine from diet
- Detection / diagnosis
ketonuria
- DNPH test - (2,4 dinitrophenylhydrazine) Add to urine, yellow precipitate forms.

Branched - Chain Amino Acid Disorders

- **Organic Acidemias**
- Other branched chain disorders include isovaleric, propionic, and methylmalonic aminoacidemias/acidurias
- Symptoms: vomiting, metabolic acidosis, hypoglycemia, ketonuria, increased blood ammonia levels.
- Three more common ones:
 - isovaleric acidemia - (isovaleryl co-enzyme A deficiency. Urine and sometimes patient smell like sweaty feet.)
 - propionic acidemia
 - methylmalonic acidemia
- Urine = emerald green with p-nitroalanine

Tryptophan Disorders-Indicanuria

- This disorder can accompany various intestinal disorders
- Most often associated with Hartnup disease
- Tryptophan is:
 - converted to indole in the gut
 - reabsorbed into the blood
 - excreted in the urine
 - causing a bluish urine, or "blue diaper syndrome."

Tryptophan Disorders- 5-HIAA

- 5-hydroxyindoleacetic acid-(5-HIAA)
 - derived from serotonin
 - made by the argentaffin cells from tryptophan
 - malignancy of the argentaffin cells cause excess serotonin and excess 5-HIAA in the urine.

Cystine Disorders

- Two distinct disorders
 - Both result in sulfur odor
 - Both produce positive cyanide-nitroprusside test
 - Quantitative test for presence of cystine: A stable red-purple color is positive for presence of cystine
- Cystinuria
 - Presence of cystine (and often other amino acids) in the urine due to inability of renal tubules to reabsorb them. Patient often has kidney stones. Urine and stones can be screened for cystine using cyanide-nitroprusside,
- Cystinosis
 - inborn error of metabolism, where cystine is incompletely metabolized resulting in cystine deposits in tissues. Isothenuria common.

Porphyrin Disorders

- Porphyrin Disorders
- Result of blockage of normal pathways in heme production. When blocked, a buildup of the previous product is seen.
- Disorders of porphyrin metabolism = porphyrias
 - Inherited
 - Acquired - lead, alcohol and other toxins, iron deficiency, renal or liver malfunctions.

Porphyrin Disorders

- Urinary indication of the possible presence of a porphyria (prophyrinuria) is the observation of red to port wine colored urine.
- Testing
 - Ehrlich Watson test - outdated test to differentiate between urobilinogen and porphobilinogen.
 - Urobilinogen is extractable into either chloroform or butanol.
 - Porphobilinogen is neither, and is left behind.
 - Hoesch rapid screening test for porphobilinogen
 - Fluorescent technique for other porphyrins.
 - Mauzerall-Granick - more reliable screening test
 - Quantitative testing - aminolevulinic acid and total porphyrins

Mucopolysaccharide Disorders

- Hunter's syndrome
 - Abnormal skeletal structure, severe mental retardation, X-linked recessive - rare in females
- Hurler's syndrome
 - Abnormal skeletal structure, severe mental retardation, corneal damage. Autosomal recessive
- Sanfilippo's syndrome
 - Mental retardation. Autosomal recessive
- Screen C.T.A.B. (cetyl trimethyl ammonium bromide)
- Positives must be referred to state health dept. for quantitative testing.

Purine Disorders

- Number of disorders of purine metabolism.
- Lesch-Nyhan disease
 - Inherited X-linked, recessive
 - Excess uric acid builds in the urine due to a lack of the gene for the enzyme hypoxanthine guanine phosphoribosyltransferase
 - Patients have mental retardation, motor defects, gout, renal stones, and a hallmark tendency towards self destruction.
 - High number of uric acid crystals are seen in the urine
 - appears as orange crystalline sand in infant's diaper.

Purine Disorders

- Gout
 - 1-2% Western population will have flare-up
 - Men over 30 and women over 50 yr.
 - Increase in life expectancy
 - Changes in diet
 - Increase in diseases associated
 - Patients with gout or gout symptoms very frequently have increased uric acid in their body fluids and often uric acid crystals.



"The Gout", James Gilray, 1799, from Philadelphia Museum of Art (in public domain - due to its age.)

Carbohydrate Disorders

(other than diabetes mellitus / glucose)

- Melituria - (presence of any sugar in the urine)
- Lactose (lactosuria)
 - Seen in urine late in pregnancy, during lactation
- Fructose (essential fructosuria)
 - Benign condition, patient unable to process fructose or sucrose
- Pentose (pentosuria)
 - Ingestion of large amounts of fruit
- *Galactose - sugar found in milk

Carbohydrate Disorders - Galactose

- A sugar derived from lactose (milk sugar).
- Normally metabolized into glucose.
- Galactosemia is the condition resulting from the inability to metabolize galactose.
 - Inherited autosomal recessive
 - Mutation of a gene on chromosome 9 results in deficiency of galactose-1-phosphate uridyl transferase (GALT) enzyme.
 - Molecular testing for defective gene.
 - Found @ 180 mutations, 7 of which account for 80-90 % galactosemia alleles.
- Clinitest positive



Reference Listing

- Please credit those whose work and pictures I have used throughout these presentations.
- Lillian Mundt & Kristy Shanahan, Graff's Textbook of Urinalysis and Body Fluids, 2nd Ed.
- Susan Strassinger & Marjorie Di Lorenzo, Urinalysis and Body Fluids, 5th Ed.
- Wikipedia, the free encyclopedia
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