



Clinical Chemistry Trainee Council

Pearls of Laboratory Medicine

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TITLE: Porphyrrias

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Slide 1:

Hello, my name is Dr. Laura Parnas. I am the Associate Medical Director of Laboratory Services at the Palo Alto Medical Foundation. Welcome to this discussion on porphyrias. The porphyrias are a group of rare inborn errors of metabolism associated with defects in the heme biosynthetic pathway. Enzymatic deficiencies during heme biosynthesis result in accumulation and excretion of pathway precursors and intermediates, causing unique biochemical features and disease symptoms.

Slide 2: Heme

Heme is a crucial component of cellular hemoproteins that fulfill essential functions, including oxygen transport and storage, electron transport, and oxidation-reduction reactions.

Heme biosynthesis occurs in all nucleated cells in the human body, primarily in developing red blood cells of the bone marrow where hemoglobin is produced, and to a lesser extent in hepatocytes, where cytochromes and other heme-containing enzymes are generated.

Slide 3: Heme Biosynthesis

Heme is enzymatically produced in sequential steps that occur in two cellular compartments; the first and last three steps occur in the mitochondrion and the intermediate steps take place in the cytosol. Eight enzymes catalyze formation of protoporphyrin IX and iron chelation to form heme.

The initial and rate-limiting step is the condensation of glycine and succinyl-CoA to form δ -aminolevulinic acid (ALA). Then, condensation and polymerization reactions occur to form hydroxymethylbilane. Cyclization of hydroxymethylbilane can occur spontaneously to generate type I isomers, but the enzymatically-generated type III isomers are most abundant and physiological. The last steps include decarboxylation, oxidation, and insertion of iron to complete the cycle.

Under normal conditions, the pathway is extremely efficient and tightly regulated, and only minimal amounts of heme precursors and intermediates accumulate in body fluids.

Slide 4: Porphyrias

The porphyrias result from defects in the different enzymes involved in heme biosynthesis. Most of these enzymatic deficiencies are inherited as autosomal dominant traits, with one functional gene copy remaining that preserves sufficient activity to prevent anemia. However, pathway precursors and intermediates that precede the enzymatic blockage accumulate in body fluids causing signs and symptoms of the different porphyrias. The nine different types of porphyrias can be classified into acute and non-acute, according to their clinical manifestations. There are other extremely rare forms of porphyrias that are not covered in this Pearl.

Slide 5: Acute Porphyrias

The classic autosomal dominant acute porphyrias include acute intermittent porphyria (AIP), variegate porphyria (VP), and hereditary coproporphyria (HC). AIP is the second most common of all porphyrias. The autosomal recessive aminolevulinic acid dehydratase porphyria (ADP) is extremely rare. The main clinical phenotype of the acute porphyrias is acute neurovisceral attacks consisting of diffuse, severe abdominal pain, peripheral neuropathies, and mental disturbances. As autosomal dominant disorders, enzyme activity is present in reduced amounts that are sufficient to allow heme biosynthesis. Therefore, these diseases have low penetrance and, consequently, many individuals remain asymptomatic for life.

Slide 6: Acute Porphyrias – Biochemistry

About 20% of individuals affected with an acute porphyria display symptoms. Massive excretion of porphyrin precursors (δ -aminolevulinic acid and porphobilinogen) occurs during an acute attack, precipitated by triggering of hepatic heme biosynthesis upon exposure to endogenous and/or exogenous factors. These agents include stress, infection, hormones, and certain drugs. An increase of at least 5 times, frequently 20-50 times, in urinary excretion of porphobilinogen (PBG) and δ -aminolevulinic acid (ALA) is characteristic during an acute attack and at least one week thereafter.

Slide 7: Non-acute porphyrias

The classic autosomal dominant non-acute porphyrias are porphyria cutanea tarda (PCT) and erythropoietic protoporphyria (EPP). The autosomal recessive congenital erythropoietic porphyria (CEP) is extremely rare. PCT is the most common of all porphyrias, and can also occur sporadically with an acquired defect of urodecarboxylase.

The clinical phenotype is characterized by chronic dermatologic photosensitization. Two distinct groups of symptoms can be observed upon sun exposure of unprotected skin areas (back of the hands, forearms, neck, and face). Burning, itching, and erythema following sun exposure that present in early childhood are characteristic of EPP. Increased skin fragility with erosions and blistering that leaves hypo- or hyper-pigmented scars and present later in life are typical of PCT.

The acute porphyrias, variegate porphyria and hereditary coproporphyria, may present with skin symptoms only, which cannot be discriminated from PCT by clinical or histological examinations, but only by biochemical examination (e.g. fecal porphyrins).

Slide 8: Non-acute porphyrias – Biochemistry

Development of cutaneous symptoms results from the light-absorbing properties of the porphyrin ring. Excess circulating porphyrin intermediates (uroporphyrin, coproporphyrin and other intermediates, or protoporphyrin) are generated in the liver or the bone marrow and accumulate in the skin. These compounds absorb energy from sun exposure and transfer this energy to chemical reactions that disrupt intracellular processes, particularly at the vascular level. Downstream inflammatory processes are activated, which ultimately cause the characteristic skin erosions, blistering, and fragility symptoms.

Slide 9: Porphyria Testing

Porphyrias are characterized either by potentially repetitive attacks of severe abdominal pain with accompanying symptoms including vomiting, constipation, tachycardia, hypertension, and hyponatremia, or by skin symptoms limited to sunlight-exposed skin areas. The latter may either be very characteristic skin blisters of 1-2 cm diameter and skin fragility or acute phototoxic skin reactions occurring within minutes of sunlight exposure. Dependent on the clinical signs, the laboratory evaluations will be selected.

In the presence of an acute attack of abdominal pain and up to at least one week after beginning of symptoms, concentration of the urinary precursor PBG is at least 5 times elevated above the upper limit of normal in the acute porphyrias (AIP, VP, HC). Additional testing in other body fluids is used to differentiate among these disorders. Excretion of fecal porphyrins within the reference interval and decreased PBG-deaminase activity in the erythrocytes indicates AIP as the cause of the attack. Elevated fecal protoporphyrin and coproporphyrin are evidence of VP, together with a characteristic peak of porphyrin fluorescence in serum. Increased fecal coproporphyrin alone suggests HC. In both of these porphyrias, VP and HC, the ratio of coproporphyrin I to III isomer exceeds 2.

When cutaneous manifestations are suspicious of porphyria, quantification of fractionated urinary porphyrins is the test of choice. Increased excretion of urinary uroporphyrin and heptacarboxylate porphyrin is a diagnostic pattern of PCT. If acute phototoxic skin reactions are present with first manifestation in early childhood and the urinary porphyrin profile is normal or slightly increased, measurement of porphyrins in erythrocytes is recommended. Elevated concentrations of erythrocyte protoporphyrin exceeding 5 times the upper limit of normal substantiate the diagnosis of EPP.

Although assays for enzyme activity are available, they are rarely necessary to make a diagnosis. Genetic testing allows identification of the specific disease-causing mutation, and recent advances in the understanding of the molecular pathogenesis of porphyrias are paving the way for more accurate diagnosis and appropriate targeted treatment.

Slide 10: Other causes of increased porphyrins

A number of conditions other than the inherited porphyrias can impair the metabolism of heme precursors and intermediates, resulting in patterns of elevated porphyrins in body fluids. Porphyrinuria, more specifically coproporphyrinuria, can be caused by various disorders, especially those that affect liver or bone marrow, and by exogenous factors that affect heme biosynthesis or metabolism. Alcohol overconsumption and hepatobiliary disorders, including cholestasis and obstructive jaundice cause isolated increases in urinary coproporphyrins. Similar patterns are observed in the presence of inherited disorders of bilirubin metabolism, including Dubin-Johnson syndrome, Rotor syndrome, and Gilbert's disease.

Heavy-metal poisoning is another cause of increased urinary porphyrins. Lead, and to a lesser extent, mercury and arsenic toxicity mimic acute porphyria attacks and can trigger porphyria investigations. Lead exposure causes characteristic ALA and coproporphyrin III isomer excretion in urine, and accumulation of zinc-protoporphyrin (ZPP) in red blood cells. The elevation of urinary ALA is caused by ALA-dehydratase (ALAD) inhibition due to lead displacement of zinc at the enzyme's catalytic center, resembling ALAD deficiency. The increase in coproporphyrin III is caused by lead inhibition of coproporphyrin oxidase. The accumulation of ZPP results from lead causing an intracellular iron deficiency allowing zinc to become the substrate for ferrochelatase. Definitive diagnosis is achieved by demonstrating the presence of toxic concentrations of the suspected heavy metal in blood and/or urine.

Slide 11: Points to remember

1. The laboratory plays an essential role in the diagnosis of acute and non-acute porphyrias
2. Acute porphyrias are diagnosed by the presence of increased porphobilinogen in urine
3. Presence of characteristic patterns of urinary porphyrin excretion aids in the differentiation of cutaneous porphyrias
4. Other non-hereditary conditions affecting the liver can cause elevation of porphyrins in body fluids

Slide 12: References