Porphyria / Questions and case studies

Questions

1. **Emergence of clinical symptoms (abdominal pain, neuropsychiatric symptoms) after administration of some drugs (barbiturates, anesthetics) is caused by**:
   - A - Inhibition of ferrochelatase and thus chelation of protoporphyrin IX with Zn.
   - B - Induction of increased delta-aminolevulinate synthase production in the liver.
   - C - Succinyl-CoA deficiency, which is necessary for the formation of the initial metabolite, i.e., delta-aminolevulinate.
   - D - Accumulation of delta-aminolevulinate and porphobilinogen, which inhibit ATPase in nervous tissue.
2. **Photosensitivity in some forms of porphyria is caused by**:
   - A - Accumulation of porphyrins whose conjugated double bonds of the porphyrin core absorb light at a wavelength of 400 nm, leading to the accumulation of free radicals.
   - B - Accumulated porphyrins inhibit the enzymes needed to form skin pigments - melanin.
   - C - Inhibition of glutathione reductase, which is needed to remove hydrogen peroxide.
   - D - Accumulation of porphobilinogen and delta-aminolevulinic acid, which cause the skin to be more sensitive to UV radiation.
3. **What is the pathobiochemical basis of exacerbation of porphyria variegata by ingestion of phenobarbital?**
4. **What are the consequences of Fe deficiency on the blood count?**
5. **Why is pyridoxine (vitamin B6) deficiency often associated with microcytic hypochromic anemia?**
6. **What is the effect of lead poisoning on porphyrin metabolism?**

Answers

Question 1.

- A - wrong- ferrochelatase defect makes it impossible to incorporate Fe^{2+} into the porphyrin ring: this disorder can be caused by lead poisoning.
- **B - correct- some drugs as well as alcohol increase the synthesis of delta-aminolevulinate in the liver by up to 50 times and thus significantly increase the intermediate products of porphyrin biosynthesis, which leads to exacerbation of clinical symptoms.**
- C - wrong- succinyl-CoA deficiency is not the cause of exacerbation of clinical symptoms of porphyria.
- **D - correct- excessive amounts of delta-aminolevulinate and porphobilinogen caused by the induction of delta-aminolevulinate synthase lead to inhibition of ATPase in nervous tissue, leading to impaired conduction of nerve action potential, which can lead to respiratory muscle paralysis and death.**

Question 2.

- **A - correct - conjugated double bonds of the porphyrin ring lead to increased absorption of light energy at a wavelength of about 400 nm; this releases free radicals that damage the surrounding tissue; the presence of Fe^{2+} in the hemoglobin molecule prevents this effect**
- B - wrong - increased amount of porphyrins does not affect the formation of melanins in melanocytes in the skin
- C - wrong - porphyrins do not affect glutathione reductase activity
- D - wrong - porphobilinogen and delta-aminolevulinic acid do not know the have conjugated double bonds, as is the case with porphyrins

Question 3.

- **In biotransformation in the liver, phenobarbital induces the synthesis of a system containing cytochrome P450, generating a greater need for heme for the synthesis of cytochrome P450. This will reduce the concentration of available heme in the hepatocyte, which will increase the production of δ-aminolevulinate and thus increase the production of the δ-aminolevulinate porphyrin precursor with additional toxic effects on the nervous system.**

Question 4.

- **Microcytic hypochromic anemia develops. It is manifested by low hemoglobin, low plasma Fe concentration, increased transferrin with low Fe saturation, low ferritin, and increased plasma transferrin receptor concentration.**

Question 5.

- **Heme synthesis requires the presence of pyridoxal phosphate (a pyridoxine derivative). Pyridoxal phosphate is a cofactor of δ-aminolevulinate synthase, which catalyzes the synthesis of δ-**

aminolevulinate (a precursor of porphyrins and thus heme) from succinyl-CoA and glycine.

Question 6.

- **Zn-containing ALA dehydratase and ferrochelatase are inhibited by Pb. This means δ-aminolevulinate and protoporphyrin IX are not metabolized, accumulating and leading to reduced heme production. The result is a reduction in hemoglobin production (→ anemia) and a lack of cytochromes (→ impaired electron transport in mitochondria → lack of ATP).**
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Case reports

A patient with abdominal pain

A young nurse from South Africa is emotionally upset with hysteria, a few days after a laparotomy for "intestinal problems". A week before the operation, she was taking barbiturates to sleep. Then she had severe abdominal and muscle pain, general weakness, tendon reflexes were not present, and she vomited. Urine was dark, giving a brilliant pink fluorescence in UV light. Paralysis occurred within 24 hours and death within 2 days.

Questions:

1. **What was the diagnosis?**
2. **Can her relatives have a similar illness?**
3. **What is the enzymatic defect?**
4. **What confirmatory tests to do?**

Answers

1. Porphyria variegata (acute attack after barbiturates a week before surgery). Barbiturates induce the synthesis of porphyrin precursors, which have a toxic effect on nervous tissue.
2. Yes, the disorder is inherited in an autosomal dominant manner
3. Protoporphyrinogen oxidase is missing
4. In stool, coproporphyrins and protoporphyrins should be present and when collecting history, ask about a previous experience with skin photosensitivity

A patient with anemia and diarrhea

A patient, 72 years old, suffered from intermittent diarrhea, weight loss, and loss of appetite and was pale. Liver is enlarged 9 cm below the costal arch.

Laboratory results

hemoglobin	66 g/l
S-Fe	4,5 µmol/l
Total iron binding capacity	88 µmol/l (physiological range: 45–72)
ferritin	6 µg/l (physiological range: 10–200 µg/l)
bilirubin	22 µmol/l
ALP	19,5 µkat/l
ALT	17,9 µkat/l
proteinemia	66 g/l

Blood Count

This is indicative of microcytic hypochromic anemia.

Questions:

1. **What are the causes of Fe deficiency anemia?**
2. **What is the best laboratory test to distinguish Fe deficiency anemia from anemia in chronic diseases?**

Answers

1. The deficiency in the diet, increased requirements (growth, convalescence, pregnancy, lactation); chronic serious diseases: malignancies, severe infections, collagenoses, renal failure; blood loss (digestive tract, bleeding after trauma, metrorrhagia)
2. Determination of soluble transferrin receptor in plasma. In Fe deficiency anemia, the values are increased. The ferritin/transferrin receptor index has an even better predictive value

Further course of the patient's disease: occult bleeding in the stool repeatedly positive. An X-ray found a growing tumor in the sigmoid colon.

Diagnosis: colon cancer (malignancy anemia), elevated ALP and ALT without a corresponding increase in bilirubin rose suspicion of liver metastases.

An alcoholic patient with a rash on the hands and face

A 48-year-old man who liked to drink heavily came to the clinic with a rash on his hands and face.

Laboratory results

bilirubin	16 µmol/l
ALT	3,8 µkat/l
GMT	5,0 µkat/l
ALP	2,1 µkat/l
U-porphobilinogen	11 µmol/l
U-uroporphyrin	2650 µmol/l
U-koproporphyrin	545 µmol/l

Questions:

1. **What diagnosis is most likely and why?**
2. **What is the probable enzyme defect?**

Answers

1. High levels of porphyrins in the urine indicate some form of porphyria. Positive "liver tests" indicate hepatopathy and are consistent with chronic alcohol abuse (especially increased GMT without a corresponding increase in ALP). Skin manifestations on the skin exposed to sunlight and their occurrence after a higher dose of alcohol (induction of porphyrin precursor synthesis) are compatible with the cutaneous form of porphyria (porphyria cutanea tarda). The significant increase in uroporphyrin and coproporphyrin in the urine and not porphobilinogen (an initial precursor that does not yet have a porphin cycle and therefore does not have conjugated double bonds that lead to photosensitivity of the skin) further supports this diagnosis.
2. Uroporphyrinogen decarboxylase is deficient in porphyria cutanea tarda

References

Related articles

- Anemia
- Iron
- Porphyria

Other chapters from the book MASOPUST, J., PRŮŠA, R .: Pathobiochemistry of metabolic pathways:

- Nutrition: Energy metabolism and its disorders • Nutritional disorders • Examination of nutritional status
- Carbohydrates: Glucose metabolism disorders • Glycogenosis
- Lipids: Disorders of lipid metabolism
- Other: Disorders of ureagenesis • Porphyria • Disorders of uric acid metabolism
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Source

- MASOPUST, Jaroslav and Richard PRŮŠA. *Pathobiochemistry of metabolic pathways.* 1st edition. Prague: Charles University, 1999. 182 pp. 120-122. ISBN 80-238-4589-6.