THE NORTHERN HOSPITAL

PORPHYRIA (ACUTE)

"King George III in old age", mezzotint engraving, published 24 February 1820, Samuel William Reynolds, National Portrait Gallery London.

"The King shew'd his backside to his attendants saying that he had not the gout. He pull'd off Sir George Baker's wig and made him go upon his knees to look at the stars; he begins by beating the palms of his hands, then crying and then howling, he got naked out of bed but C(olonel) Digby threaten'd him back".

Georgiana Cavendish, Duchess of Devonshire, Dairies 1789

In the Autumn of 1788, alarming rumors began to circulate the Royal Court. Something was drastically wrong with the King! Nobody quite knew what to make of them and reports from the King's doctors were contradictory and confused which only added to the general alarm. Even The Times complained of the "truly ridiculous" contradictions of the official bulletins. In the face of unreliable information about that nature of the King's malady, bizarre reports began to be circulated by court gossips such as the Duchess of Devonshire. Some were reassuring but others positively startling; a characteristic one had it that the King had walked up to an oak tree in Windsor Great Park, took a branch in his hand, shook it, and entered into a conversation in the belief that he was talking to the King of Prussia! Once incident was recorded that the King flew into a seething rage at one of his doctors, Sir George Baker, for three long hours. Dr Baker reported, "the look of his eyes, the tone of his voice, every gesture of his whole deportment represented a person in a most furious passion of anger. One medicine had been too powerful, another had only teased him without effect the importation of senna ought to be prohibited, and he would give orders that in future it should never be given to the Royal Family…Having no opportunity of speaking to the Queen, I wrote a note to Mr. Pitt immediately on my return to town and informed him that I had just left the King in an agitation of spirits nearly bordering on delirium…"

As his illness progressed his speech became incomprehensible; constantly relentless without break, mostly gibberish and jumping from one topic to the next in an instant so that no one could keep up with his line of thought. He became paranoid, accusing people of stealing from him. He suffered the severest of abdominal pains, that he described as "a pretty smart bilious attack". He also developed mysterious rashes, which he showed to his daughter Princess Elizabeth. She was shocked at what she saw, exclaiming that the King had "great weals, as if scourged with cords". It was also noticed that his urine had turned quite brown. The Kings doctors were at a complete loss as to what was wrong with the him. Many medical experts were called in, but most were merely intimated by the King's rantings and none would dare commit to a definite prognosis, let alone a diagnosis. They tormented him with every archaic medical treatment of the Eighteen century including the administration of antimony and blistering of his shaven scalp to draw out poisonous humors from his brain, all of which had the least effect. He began to develop strange delusions - imagining that London was flooded and that he could see Hanover through Herschel's telescope. Eventually it fell to an obscure Lincolnshire "mad-doctor", Francis Willis, who was called in, in desperation despite his inferior social rank, to take charge of the King. It was Willis and his son who was finally able to at least take some semblance of control of the situation, largely by showing firmness and authority in their dealings with him, including the liberal use of, as well as the unqualified threat of, the straight jacket.

If it wasn't so deadly serious, the whole situation could have almost seemed amusing! But most serious it was. All official political opposition to the Government of William Pitt and the King had come to center on the Prince of Wales. Ever since the beginning of the Prince's close friendship with Pitt's arch political rival, Charles Fox, he had been increasingly identified with Foxite Whig politics and Whig society in general. It was no secret that the King did not get on with his son, and so all political opposition to the government gravitated to the Prince in the hope that one day he would succeed his father and a Whig government could then be formed. The King's illness did not show the Prince in a favorable light. It was clear that he could barely contain his excitement at the prospect of becoming Regent, and so de facto King of England, should George III be declared mad. Then to the immense disappointment of the Prince and his Foxite friends, the King, just as suddenly as he had appeared to go mad, recovered his senses in late 1789. The Prince feigned great relief and joy, but of course he was desperately frustrated. He gave up politicking and immediately returned to his dissolute womanizing, gluttony, gambling and drinking.

For ten years George III remained lucid. His mad episode of 1788-89 seemed to be a strange distant memory then in 1801 just as inexplicably as in 1788, his symptoms returned with a terrible vengeance. He began uttering embarrassing obscenities, and declared his love for Lady Pembroke in the most inappropriate of ways. But again the symptoms resolved just as quickly as they had appeared. For another three years things seemed to have settled once again, but then symptoms retuned for a third time in 1804. He was taken to Weymouth to effect a cure by the fresh seas air, but his incoherent outbursts merely became ever more violent. He again raved about Lady Pembroke and also Lady Yarmouth, and made a very obscene suggestion to a Mrs. Drax on board a yacht during one of his cruises, which "convulsed" the sailors so much that several had to retire below deck, "to have their laugh out". But it was not amusing for all. The King had brief lucid moments and by now he had insight that he was losing his mind. Poignant moments are recorded with both his wife and sons and daughters when he would break down and cry upon realizing how he hurt them and the embarrassment he had brought to them all. Even the Prince of Wales shed a genuine tear with his father. But the King recovered for a third time and remained relatively well for six final years before the symptoms returned again in 1810, but this time there would be no recovery. The Prince of Wales finally got his wish and became Regent for the rest of this father's life.

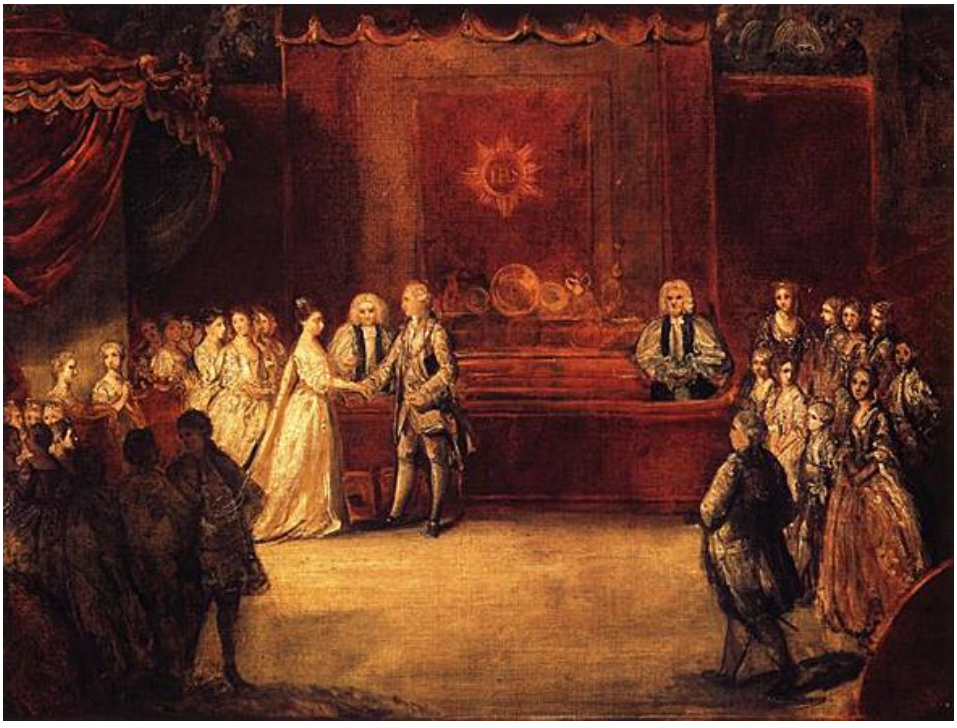
Very occasionally small lucid periods intervened, some showing the King to be intelligent, quick witted and with a good sense of humour. On one occasion when he discovered that his tormentor Dr Willis had once been in Holy Orders, he quipped to him, "I am sorry for it! You have quitted a profession I have always loved, and you have embraced one I most heartily detest". To which Willis replied, "Sir, our Saviour Himself went about healing the sick". "Yes, Yes", conceded the King crossly, "But He had not 700 pounds a year for it, hey!"

A poignant moment is also recorded that was spent with his old Prime Minister Lord North, who was also in poor health at the time. Lord North was allowed to visit the King during one of his lucid moments in the hope that it would cheer him up. The two of them quietly reflected on their past lives together and reminisced over a lost world of the past. Later George sadly commented, "North might have recollected me sooner. However he,

poor fellow, has lost his sight, and I my mind. He meant well to the Americans - just to punish them with a few bloody noses, and then make bows for the future happiness of both countries. But want of principle got into the Army, want of energy and skill in the First Lord of the Admiralty, (the Earl of Sandwich), and want of unanimity at home…We lost America…Tell him not to call again".

For ten long years during the regency George III, kept away from society, declined into complete madness. He went deaf and blind, trapped in a dark twilight world of his own terrifying imaginings. He died, forgotten by his subjects, in 1820. His son succeed him as King George IV.

Ever since the death of George III, historians and physicians have passionately agonized, pondered and argued over the exact nature of his illness. The doctors of his day were at a complete loss to explain it. In 1969, two psychiatrists and historians of Medicine Dr Ida Macalpine and Dr Richard Hunter proposed the fascinating theory that George III had suffered from acute intermittent porphyria. This diagnosis certainly fits many of his symptoms. Great controversy has raged over this theory ever since, but the argument is hauntingly compelling. In truth we can never be definite about the cause of illness of a person that died nearly two centuries ago. Perhaps the final say should be left to one of King George's more recent biographers, E.A Smith: "The fashionable claim that George III suffered from porphyria…is supposition, not proven fact. Historians must be cautious when leaving their area of professional competence, as must medical practitioners in venturing into territories where modern diagnostic techniques were unavailable. The present writer prefers to reserve judgment and believes that certainty on the point may never be achieved".



George III in happier times: "The Marriage of George III to Charlotte Sophia, Princess of Mecklenburg-Strelitz", oil on canvas, 1761, Sir Joshua Reynolds.

PORPHYRIA (ACUTE)

Introduction

The hereditary porphyrias are a group of **eight metabolic disorders** of the **haem biosynthesis** pathway.

Porphyrins are precursors of heme, a part of the hemoglobin molecule. Porphyrins are toxic when the build up in the body.

Defects of enzymes needed at various steps of heme synthesis result in distinct clinical syndromes known as porphyrias.

Acute porphyrias present clinically with acute attacks, that primarily consist of various combinations of:

- GIT upset
- Neurological symptoms:
- Skin reactions:
- Chronic haemolysis.

People with autosomal dominant acute porphyrias - acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria - can present with a sudden life threatening crisis.

Porphyrias are under diagnosed as diagnosis is difficult as attacks are infrequent and symptoms are non-specific.

Simple first-line tests can be used to establish the diagnosis in all symptomatic patients.

Diagnosis is essential to enable specific treatments to be started as soon as possible to prevent complications.

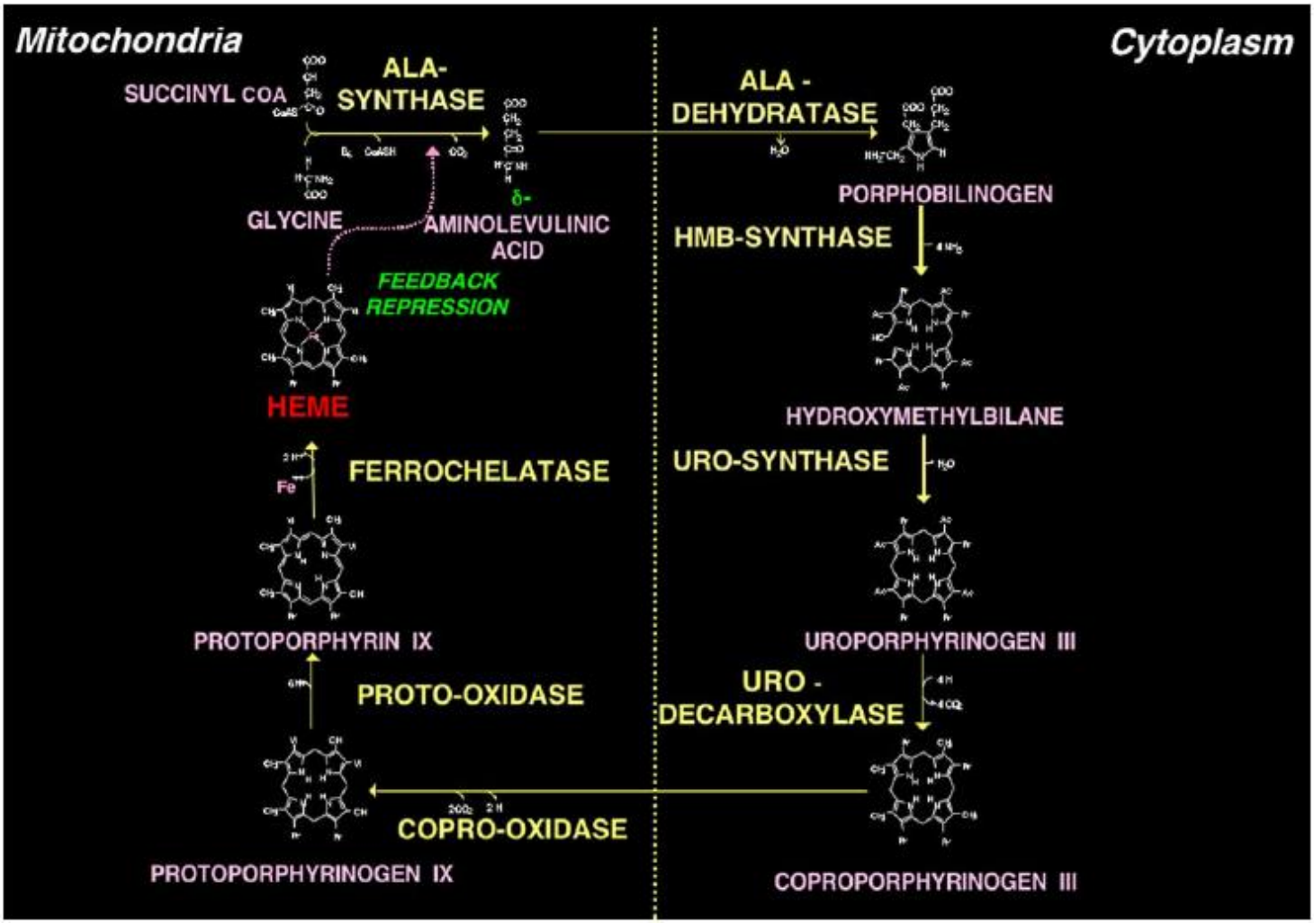
Screening of families to identify presymptomatic carriers is crucial to decrease risk of overt disease of acute porphyrias through counselling about avoidance of potential precipitants.

Biochemistry

Eight enzymes bring about haem synthesis from glycine and succinyl CoA.

The biosynthetic pathway begins in the mitochondria and, after three cytoplasmic stages, the final steps of haem formation take place back in the mitochondria (see below).

Although haem is synthesised in every human cell for respiratory and oxidation-reduction reactions, it is mostly produced in the erythropoietic cells for haemoglobin synthesis and the liver parenchymal cells for synthesis of cytochromes and haemoproteins.



The human heme biosynthetic pathway: *The pathway consists of 8 enzymatic steps: 4 localized in mitochondria and 4 in the cytosol. Only the type III isomers of uroporphyrinogen and coproporphyrinogen are metabolized to heme. Heme is exported from mitochondria for incorporation into cellular hemoproteins and, particularly in liver, exerts feedback regulation on 5-aminolevulinic acid synthase (ALAS1).*

Pathophysiology

Porphyrias are a group of eight panethnic **inherited metabolic disorders** of haem biosynthesis.

Rarely they can be acquired from environmental toxins. During the period 1955-1959, approximately 4000 people in southeast Anatolia (Turkey) developed porphyria due to the ingestion of hexachlorobenzene (HCB), a fungicide that was added to wheat seedlings.

Each results from a specific enzymatic alteration in the haem biosynthesis pathway.

Specific patterns of accumulation of the haem precursors 5-aminolaevulinic acid, porphobilinogen, and porphyrins are associated with characteristic clinical features.

Genetics:

With the exception of congenital erythropoietic porphyria (CEP), which is autosomal recessive, all other porphyrias are inherited as **autosomal dominant disorders.**

Classification:

Porphyrias are often pathologically classified as **hepatic** or **erythropoietic** depending on whether most of the heme biosynthetic intermediates arise from, and accumulate in, the liver or in developing erythrocytes.

The hepatic porphyrias are characterized by overproduction and initial accumulation of the porphyrin precursors, ALA and PBG, and/or porphyrins primarily in the liver. In the erythropoietic porphyrias, there is overproduction and initial accumulation of the pathway intermediates occur primarily in bone marrow erythroid cells.

Alternatively the 8 major porphyrias can be put into 3 clinical groups:

- The 4 acute hepatic porphyrias
- The single hepatic cutaneous porphyria, PCT
- The 3 erythropoietic cutaneous porphyrias

Of the 5 hepatic porphyrias, 4 characteristically present with acute attacks of neurologic manifestations - hence the designation *acute porphyrias*, a term that does not fully describe the clinical features, which can be prolonged and chronic. There can also be some overlap between the syndromes.

Clinical features

Acute attacks happen in all acute porphyrias.

People with autosomal dominant acute porphyrias - **acute intermittent porphyria, variegate porphyria,** and **hereditary coproporphyria** - can present with a sudden life threatening crisis.

Congenital and erythropoietic porphyrias have a chronic, relatively stable natural history, with more skin involvement.

No single sign or symptom is universal, and 5-10 % of patients may not have the most common features, such as abdominal pain and tachycardia.

Acute porphyrias present with acute attacks, that may consist of various combinations of:

- GIT upset:
  - ♥ Severe abdominal pain, nausea, vomiting, constipation.
  - ♥ Abdominal pain is the most common symptom.
  - ♥ Pain is characteristically appears out of proportion to the clinical examination findings.
- Neurological symptoms:
  - ♥ Prodromal symptoms of minor behavioural changes such as anxiety, restlessness, and insomnia.
  - ♥ In 20 - 30% of patients, signs of more severe mental disturbance are seen such as disorientation, hallucinations, paranoia, frank psychosis or confusional states.
  - ♥ The most severe manifestation is seizures which can be **life-threatening.**
  - ♥ Neuropathies:

    These are mostly motor - in the early stages, myalgias in the arms and legs is very common.

    Weakness generally begins in the proximal muscles, more frequently in the arms than in the legs.

    Limb paresis, when it occurs, can be very local. Muscle weakness can progress and lead to tetraplegia, with respiratory and bulbar paralysis and death.

    Pyramidal signs, cerebellar syndrome, transitory blindness, or consciousness abnormalities (from somnolence to coma) can arise.

    Recovery from paralysis is gradual and in some cases incomplete, with sequelae mostly in the arms and legs.
- Skin reactions:
  - ♥ Acute painful photosensitivity
  - ♥ Skin fragility with blistering.

- Chronic haemolysis.

Additional features can include:

- CVS:

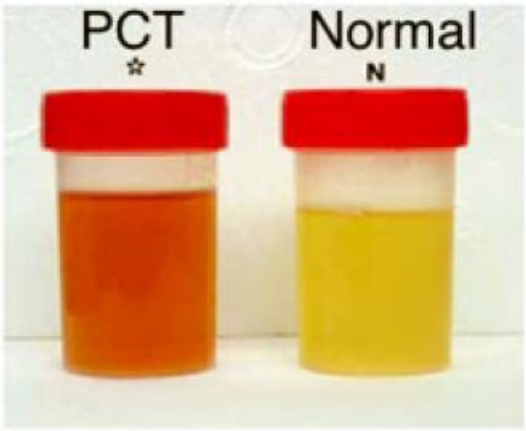
  Increased sympathetic activity is often present: sweating, hypertension, tachycardia.

- During acute attacks, patients frequently become dehydrated and electrolyte imbalanced.

- SIADH:

  - ♥ Hyponatraemia attributable to inappropriate anti diuretic hormone secretion syndrome develops in 40% of cases, and when severe can lead to convulsions.

- Occasionally, excretion of red or dark-coloured urine



Urine from a symptomatic porphyria cutanea tarda patient left, and right from a healthy control in daylight.

Most patients have one or a few attacks and then recover fully for the rest of their lives. Less than 10% develop recurrent acute attacks without clearly identified precipitating factors.

Most acute attacks last for up to **1-2 weeks.**

Precipitation of acute porphyrias

Acute attacks are precipitated by events that either directly induce ALAS1 or increase the demand for haem synthesis in the liver and subsequently deinhibit ALAS1.

Precipitants include:

- Hormonal fluctuations during the menstrual cycle
- Fasting
- Smoking
- Infections.
    - ♥ Inflammatory and infectious diseases induce hepatic expression of the acute-phase protein haem oxygenase 1, which catabolises haem.
- Exposure to porphyrinogenic drugs:
    - ♥ Most drugs that exacerbate porphyria are closely associated with induction of cytochrome P450 enzymes, which increase hepatic haem turnover.

Investigations

Biochemical analysis is necessary for diagnosis of an acute attack and to define the type of porphyria.

Bloods

1. FBE
2. U&Es/ glucose:
    - Hyponatremia.
3. Magnesium:
    - Hypomagnesaemia
4. LFTs

CSF

- Cerebrospinal fluid is normal in most cases.

Urine

Examination of urine for excess porphobilinogen is the essential first-line test for patients with a suspected attack of acute porphyria.

The urine should be protected from light and refrigerated.

Urinary **porphobilinogen** and **5-aminolaevulinic acid** are increased in all three acute hepatic porphyrias (**acute intermittent porphyria**, **hereditary coproporphyria**, and **variegate porphyria**) although the concentrations are higher and longer lasting in acute intermittent porphyria than in the other two types (hereditary coporphyria and variegate porphyria).

Note that measurement of urinary porphyrins is unhelpful and might be misleading because of frequent and nonspecific coproporphyrinuria in many common disorders.

With a recorded porphobilinogen over excretion(> 10 times the upper limit), treatment can be started immediately, with further laboratory investigations used to define the porphyria type in the proband (see appendix 1 below).

24 hour collections of urine are **not** necessary for the diagnosis of an acute attack.

Plasma fluorescence emission spectroscopy

Plasma fluorescence emission spectroscopy is a first-line test because a peak at 624 - 628 nm establishes the diagnosis of **variegate porphyria.**

However, it does not distinguish acute intermittent porphyria from hereditary coproporhyria, for which the emission peak at 620 nm is usually present for both types.

Faecal porphyrin

Total faecal porphyrin concentration is increased in variegate porphyria, with protoporphyrin concentrations (protoporphyrin IX) greater than those for coproporphyrin, whereas it is usually normal in acute intermittent porphyria.

Total faecal porphyrin concentration is raised in hereditary coproporphyria, with coproporphyrin as the main component and a ratio of isomer III to isomer I greater than 2·0.

When present, a 50% decrease of porphobilinogen-deaminase activity can positively identify acute intermittent porphyria patients.

Management

1. Correct any fluid and electrolyte disorders.

    - Carbohydrate loading, usually with intravenous glucose (at least 300 grams/day), may be effective in milder acute attacks (without paresis, hyponatremia, etc).

2. Avoid or treat and precipitating factors.

3. Symptomatic and supportive treatments:

- Titrated opioids for severe abdominal pain.
- Haemolytic anaemia may require blood transfusion.
- Photoprotection: sunlight avoidance, protective clothing, and opaque sunscreens.

4. Specific treatments: **Haemin:**

   - Intravenous haemin administration, inhibits ALA synthetase activity and curtails urinary excretion of 5-aminolaevulinic acid and porphobilinogen. It is the specific (or aetiopathogenic) treatment of choice.
   - The usual dosing rate is **4 mg/kg per day for 3 - 4 consecutive days**
   - Most patients with uncomplicated attacks improve within 5 days.
   - Human haemin will not reverse an established neuropathy, but might prevent neuropathy onset and halt further progression if given sufficiently early.
   - Measurement of urinary porphobilinogen excretion is useful to document the metabolic response to human haemin.

5. Liver transplant:

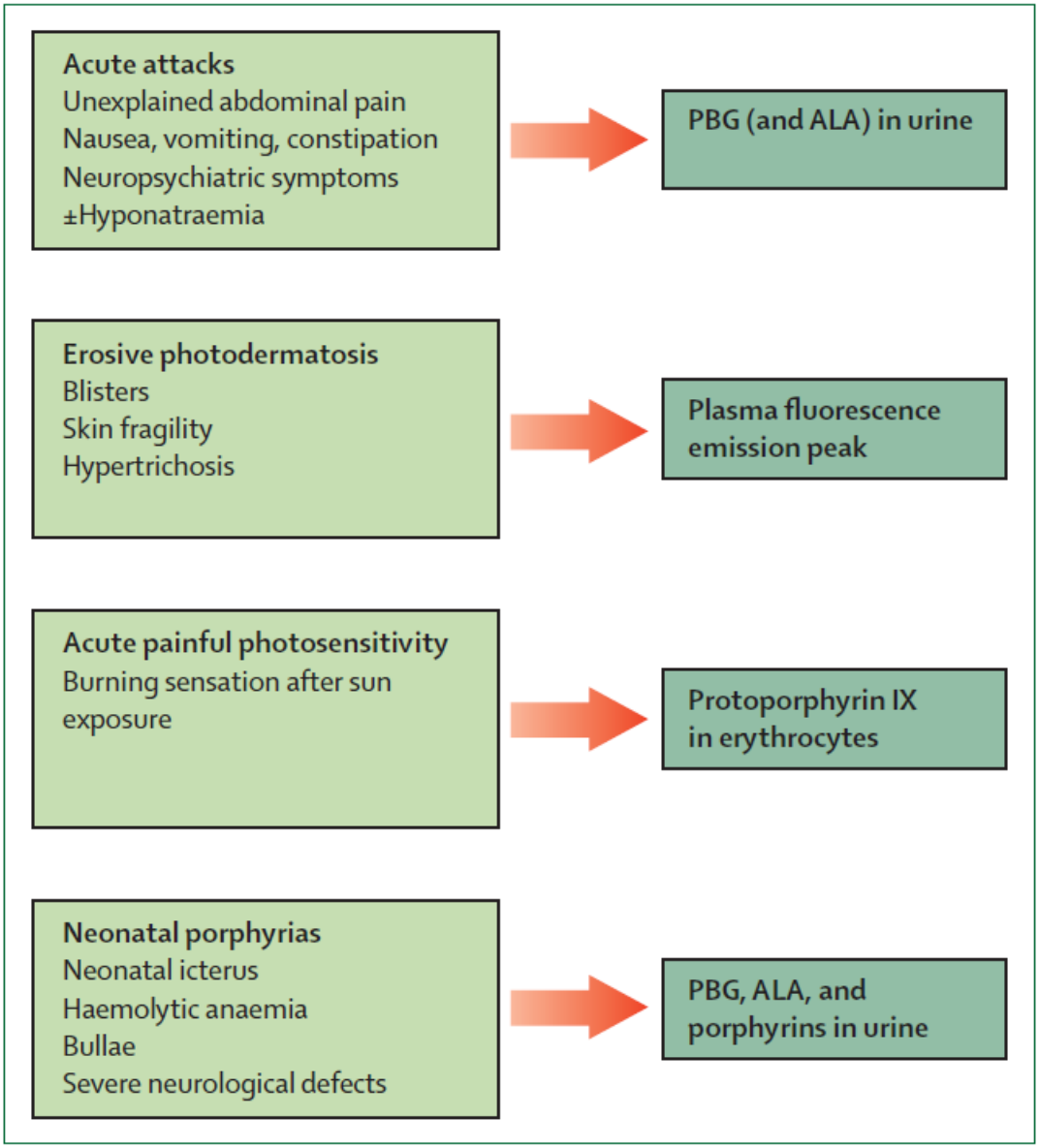
   - A few patients with severe acute intermittent porphyria have received liver transplants.
   - This intervention returns 5-aminolaevulinic acid and porphobilinogen excretion to normal, abolishes acute attacks, and improves quality of life.
   - Thus, liver transplantation should be considered for selected patients with the most severe form of acute intermittent porphyria.

Resources

- Porphyrias and Drugs:
  - ♥ www.drugs-porphyria.com
- Porphyria Australia:
  - ♥ www.porphyria-australia.org
- European Porphyria Initiative
  - ♥ www.porphyria-europe.org

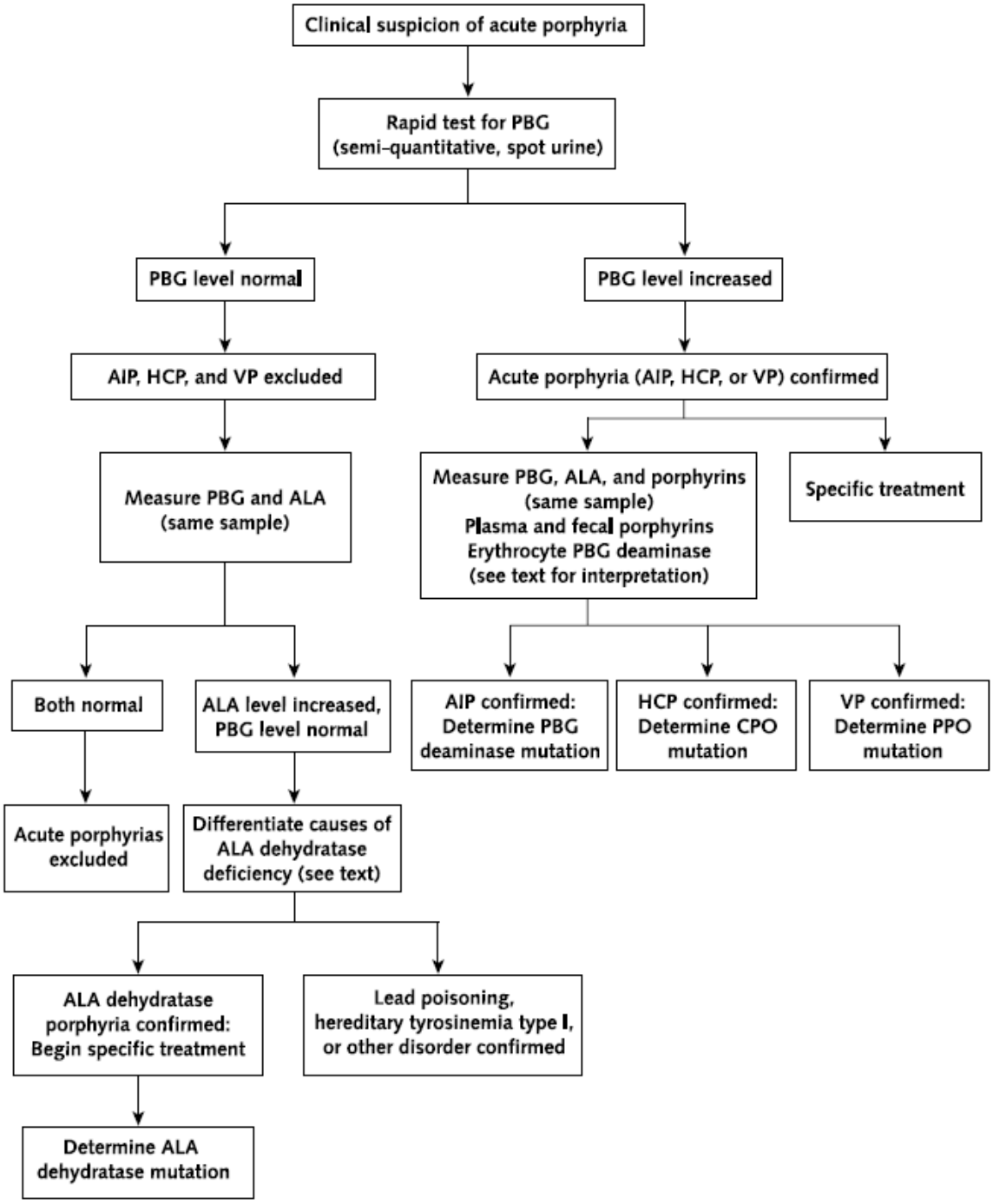
- American Porphyria Foundation
    - ♥ www.porphyriafoundation.com

Appendix 1



First-line tests for diagnosis of porphyrias PBG = porphobilinogen. ALA = 5-aminolaevulinic acid.

Porphyria Investigation:



References

1. Hervé Puy et al. Porphyrias. *Lancet* 2010; 375: 924 - 37.

2. Karl E. Anderson et al. Recommendations for the Diagnosis and Treatment of the Acute Porphyrias. Ann Intern Med. 2005;142: 439 - 450.

3. Manisha Balwani and Robert J. Desnick. The porphyrias: advances in diagnosis and treatment. Blood. 2012; 120 (23): 4496 - 4504.

   doi:10.1182/blood-2012-05-423186

Further Reading:

"George III and the Mad-Business"**,** Ida Macalpine and Richard Hunter, Allen Lane, 1969.

Dr J. Hayes.
April 2014.