

The information in this leaflet is based on best available evidence and the consensus of the acute hepatic porphyria clinical working group of EPNET, <https://porphyria.eu>.

Acute porphyria

Information for people with acute intermittent porphyria, variegate porphyria or hereditary coproporphyria and their families.

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1. What is acute porphyria?

Acute porphyria is a term that includes three similar, rare inherited conditions: acute intermittent porphyria (AIP), variegate porphyria (VP) and hereditary coproporphyria (HCP), and a fourth extremely rare porphyria called ALA dehydratase deficiency porphyria. They are grouped together because acute attacks of porphyria may occur in each one. Acute intermittent porphyria is the most common type of acute porphyria. In this condition, acute attacks may occur, but the skin is not affected. People with variegate porphyria and hereditary coproporphyria may experience acute attacks and/or skin problems, but not necessarily at the same time. Attacks and skin problems only affect some people with acute porphyria and most never have any symptoms at all.

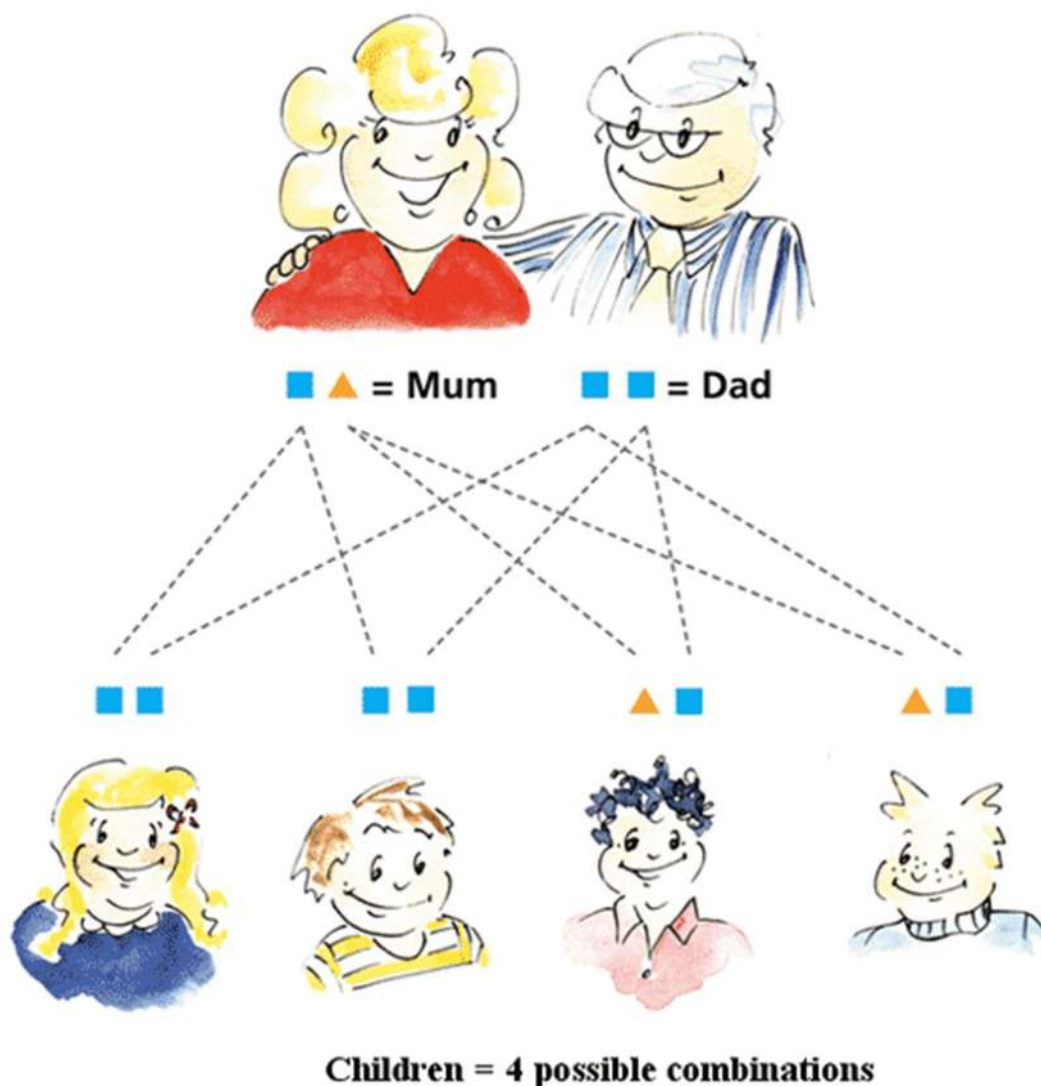
2. What is an acute attack of porphyria?

Acute attacks almost always start with severe pain, which is usually in the abdomen but may also be felt in the back or thighs. Nausea, vomiting and constipation are common. Some people have difficulty sleeping or become agitated or confused. Pulse rate and blood pressure are often increased. In severe attacks, there can be complications such as convulsions, or muscular weakness which may occasionally lead to paralysis. An acute attack usually lasts for no longer than one or two weeks. Severe attacks can occasionally be life threatening if there are serious complications like paralysis. However nowadays most patients recover from paralysis provided they receive appropriate treatment, although this takes many months.

Acute attacks are often provoked by drugs, alcohol, and hormonal changes, for example, those associated with the menstrual cycle. Infections and stressful situations (emotional or physical) may also precipitate an acute attack. The most common age for an acute attack is from the late teens to the forties. They are extremely rare in children before puberty. Women are about five times more likely to have an acute attack than men, mainly due to female hormones. Most people have only one or a few acute attacks in their whole life; only a minority suffer repeated – often called recurrent – attacks, sometimes over several years. Most people who have one or a few attacks of acute porphyria make a full recovery. They are then able to lead a normal life except they need to take a few simple precautions to reduce the risk of having another attack.

3. How is acute porphyria inherited?

Acute porphyria is caused by a change to a particle of DNA known as a gene; a different gene is affected in each of the different types of acute porphyria. Genes, which contain the blueprint for all the components required by the body, usually occur in pairs. One of each pair is inherited from each parent. Sometimes a small error can occur in the copying of one of these genes resulting in a permanent gene change (also called an alteration, mutation or variation). When a variant in only one of the pair of genes causes a disease, as is the case in the acute porphyrias (AIP, HCP, VP), this is called an autosomal dominant inheritance pattern.



Dad and 2 children have not got porphyria



Mum and 2 children have acute porphyria and are at risk of developing an acute attack

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This is an example of the inheritance of an acute porphyria. In this diagram mum is suffering from porphyria. She is carrying one normal gene ■ and one altered (mutated) gene ▲.

The risk of an affected person passing this variant gene on to any of his or her children is one chance in two (50%) (see diagram). This risk is the same even if the affected person has never had any symptoms of porphyria, so the disease often appears to have “skipped a generation”. Each person with porphyria may have a number of relatives who will also have inherited the altered gene. Some may not know that they have inherited an acute porphyria gene and are therefore at risk of developing porphyria symptoms. If you have not inherited the altered gene, you cannot pass it on to your children.

The extremely rare condition, ALA dehydratase deficiency porphyria, is inherited in a different way. The condition arises if someone has two copies of the gene variant, one inherited from each parent and is known as an autosomal recessive condition.

4. What is the risk of symptoms among those who have inherited an acute porphyria gene?

Most people who inherit acute porphyria will never experience an acute attack. In those who do become ill, additional factors are usually required for an attack to occur. Our knowledge of these factors/triggers is incomplete but among the most important are a number of medicines, alcohol, stress, fasting or restricting calorie intake, infections and smoking. Attacks are more common in women of child-bearing age due to normal hormonal changes of the menstrual cycle or associated with pregnancy. Sometimes acute attacks occur in the absence of any identifiable provoking factor. However, experience has shown that if people who have inherited one of the acute porphyrias are careful to avoid known triggers, their chance of becoming ill is much reduced.

5. How is an attack of acute porphyria diagnosed?

For diagnosis of an attack of acute porphyria and identification of the type of porphyria, samples of urine, blood and stool (faeces) need to be carefully tested in a laboratory that has expertise in porphyrias (usually porphyria specialist centres). The tests measure the concentration of porphyrins and their precursors ALA and PBG which will be very high in a patient with an attack of acute porphyria. It is important that these tests are carried out as soon as possible after the start of the illness as an accurate diagnosis may be difficult to establish after recovery from an acute attack, particularly after several months or years.

In a patient who is known to have inherited an acute porphyria, it may be difficult to decide whether symptoms are due to an attack of porphyria or an unrelated cause. In this situation, a urine test may help your doctor decide whether you are suffering from an acute attack or not. It is important that people with porphyria should not attribute all their illnesses to porphyria otherwise common but potentially serious conditions like appendicitis may be overlooked.

6. When is the best time to be tested for acute porphyria?

The best time to be tested for porphyria is at the earliest opportunity. In practice, this means that families should be offered screening for acute porphyria as soon as possible after a relative has been found to have the condition. When one or other parent is already known to have an acute porphyria, their children should be tested as soon as possible, and in some countries babies can be tested at or soon after birth. It may be necessary to wait until your child is older, but it is recommended that testing takes place before onset of puberty. It is

extremely rare for children to have a porphyria attack but there are two main advantages of early diagnosis. First, those who are found to have inherited one of the acute porphyrias can be advised about how to reduce their risk of an acute attack. Second, if an acute attack does develop, your doctor will be able to confirm the diagnosis and start treatment early.

7. How are relatives screened for acute porphyria?

For relatives who have not had an acute attack, and especially for children, urine testing for porphyria is usually unhelpful. For many families, it is now possible to use genetic tests to detect the gene variant that causes their porphyria. Genetic (DNA) tests are the most reliable way of testing for porphyria in relatives of an affected person. Your doctor will be able to help you arrange to be tested for porphyria and this may involve referring you to a porphyria specialist clinic.

8. What can I do to reduce my risk of having an acute attack?

Some acute attacks are precipitated by avoidable factors such as drugs, alcohol, fasting or dieting.

Drugs

People with acute intermittent porphyria must take great care with medication, as some medicines are capable of triggering an acute attack. **It is important ALWAYS to check the safety of any medicine or remedy with your doctor.** This includes prescription medicines as well as over-the-counter treatments, supplements purchased over the internet, tonics and herbal remedies, some of which have been known to cause attacks. Although many drugs are considered suspect, good alternatives can almost always be found. Even though acute attacks are very rare before puberty, it is safest for children if they also keep to drugs that are known to be safe in porphyria.

Sometimes people with porphyria need a drug, perhaps for a serious illness like cancer, that carries some risk of provoking an acute attack or which has been introduced so recently that there is little information about its safety in porphyria. In this situation, your doctor, after fully discussing and evaluating the risks in consultation with a porphyria specialist, may decide to prescribe the drug for you with special follow-up.

The response of people with porphyria to drugs that have been reported to cause acute attacks in others is unpredictable, and a reaction does not invariably follow in every case. When there is a reaction, it usually takes the form of an acute attack, which develops within days of taking the provoking drug. **Reactions such as dizziness, feeling faint, allergies or short-**

lived skin rashes, which may occur immediately or very soon after taking the drug are common and rarely have anything to do with porphyria.

Alcohol

There is evidence that alcohol can cause acute attacks, so you should not drink if you have any porphyria symptoms. Even if you have never had a porphyria attack, it is sensible to keep alcohol intake low.

Diet

Low calorie diets, such as those used to reduce weight, prolonged periods with little food, and weight reducing surgeries (such as gastric bypass) may sometimes provoke an acute attack. It is therefore important to keep to a normal diet with regular meals, eating enough to maintain a desirable body weight. For patients struggling with nausea or sickness, smaller meals or snacks eaten more regularly can be helpful.

Patients with severe porphyria, particularly those who have recurrent attacks, may need special dietary advice from their doctor and a dietician. If you are overweight and wish to lose weight, you should consult your doctor about the sort of diet that will allow you to lose weight gradually and safely.

Medical alert card / Warning jewellery



*The holder of this card has been diagnosed with a rare disorder called **acute hepatic porphyria**.*

Certain drugs are contra-indicated in patients presenting with this disorder.

You may want to wear a wrist bracelet, neck pendant and/or carry a card that warns that you have porphyria. Such warning is particularly helpful in a situation when you may not have an opportunity to explain that you have porphyria. Your porphyria specialist centre may be able to provide you with a porphyria warning card (more about porphyria specialist centres, <https://porphyria.eu/content/porphyria-centres>).

Details on warning jewellery can be obtained from the MedicAlert Foundation, www.medicalert.co.uk.

9. Surgery, dentist, vaccinations

Anaesthetics and surgical operations

You should tell your surgeon and anaesthetist in advance that you have porphyria. It is particularly important that they are aware of the drug restrictions in porphyria, and protective measures to avoid long fasting before surgery.

Dentist

You should tell your dentist that you have porphyria and make sure they are aware of the drug restrictions.

Vaccinations

There is no evidence that any vaccines cause particular problems for people with acute porphyria. It is therefore recommended that people with acute porphyria are vaccinated in accordance with national guidelines and practice.

10. Particular issues for women

Women are about five times more likely than men to experience an acute attack, due mostly to female hormones, particularly progesterone. This hormone is found in the combined oral contraceptive (the pill), as well as in hormone replacement therapy (HRT) which is frequently prescribed for post-menopausal women. Oral contraceptive and HRT preparations containing progesterone or related compounds (progestogens) should be avoided if at all possible by women with an acute porphyria. Injectable and implantable long-term hormone preparations are very dangerous and must always be avoided. Barrier contraceptives (condoms, caps, diaphragms, IUDs) are safe in porphyria. Hormonal IUDs which release small amounts of progesterone directly into the womb are usually well tolerated in patients with acute porphyria.

In special circumstances where the risk is low and the benefits high, your doctor may consider, after discussion with you and if possible with a porphyria specialist, that the use of progestogen-containing preparations is justified, particularly in replacement doses given through the skin from patches.

Pregnancy

Though nearly all pregnancies are uneventful, there is a small increased risk of having an acute attack during or after pregnancy. However, the chances and dangers of such an acute attack are much reduced if porphyria has been previously diagnosed. It is therefore very important for the doctors providing care during pregnancy to know that you have an acute porphyria.

11. Treatment of acute attacks

Importance of early recognition and accurate diagnosis:

Early recognition of an acute attack allows treatment to be started as soon as possible. The first symptoms are often easily recognised by those who have previously experienced an attack. If you think you have early symptoms of an attack, you should try to continue eating and drinking if you can, and it may be helpful to boost your intake of sugary and starchy foods. You should not drink any alcohol. If you have recently started taking new medication, you should check that it is on the porphyria safe drug list, and discuss with your doctor if an alternative treatment would be possible.

Recognising porphyria symptoms is more difficult for people who have inherited an acute porphyria but never experienced an acute attack. It is understandable that many people worry about aches and pains that usually turn out to be due to causes other than porphyria. People with porphyria commonly experience abdominal discomfort, just like those who do not have the condition, and a doctor will need to consider other medical conditions which may be causing your symptoms. These conditions include a range of bowel disturbances, urinary infection and sometimes other urgent medical problems such as appendicitis. In this situation, the diagnosis of acute porphyria can usually be confirmed or excluded by testing the urine for PBG.

Treatment of an acute attack:

If you think you may have early symptoms of an acute attack, you should contact your doctor to help you decide if you need to be admitted to hospital. If your symptoms are severe, you should attend hospital straightaway.

This will allow:

- Administration of medicines to treat the various symptoms accompanying the attack. These treatments are likely to include the use of drugs to relieve pain and sickness. It is also important to maintain an adequate intake of calories and fluids which may require an intravenous drip.
- Biochemical diagnosis of the acute attack by measuring PBG (and if possible ALA and porphyrins) in a light protected urine sample.
- Early start of specific treatment of the acute attack: for example, with intravenous human hemin.

Human hemin is the first choice treatment. If it cannot be obtained soon enough, large quantities of glucose, which can ameliorate a mild attack, may be administered in the meantime.

12. Recurrent attacks of porphyria

A few patients, mostly those with AIP, develop a pattern of recurrent attacks, usually defined as four or more attacks requiring admission to hospital for treatment in one or more years. In women these attacks may be related to the normal hormone changes of the menstrual cycle with symptoms typically starting in the week or so before menstruation, but in many patients, there is no clear trigger for their attacks. Patients with recurrent porphyria attacks should be referred to a specialist porphyria centre if possible so they can get the best possible care. The main treatment is to give regular infusions of hemin to try to prevent attacks. In very severe cases, liver transplantation may be considered. A new treatment for recurrent attacks of porphyria (RNA interference therapy) gave very promising results in clinical trials but is not yet available to patients in all countries.

13. Chronic pain

Some patients with porphyria, particularly those with recurrent acute attacks and those who have had severe porphyria in the past, experience almost continuous pain, which is believed to result from damage to nerves during past attacks. This chronic pain varies from day to day but may be severe, and flares of chronic pain may be difficult to distinguish from acute attacks. Chronic pain responds poorly to hemin and to opiates, but medication for nerve pain may be helpful, and some patients benefit from referral to a specialist pain management service.

14. Skin problems

The skin is not affected in acute intermittent porphyria. Skin problems occur in 10-20% of adults who have inherited the gene for variegate porphyria and are often their only porphyria symptom. Areas of skin exposed to sunlight, particularly the backs of the hands, face and legs, become fragile, break easily and form blisters. Identical skin problems may occur in hereditary coproporphyrinemia but these are usually only present during an acute attack of porphyria and are rarely persistent.

15. Long term follow up

People with acute porphyria, especially those who are most severely affected, are at risk of some long term complications including high blood pressure and reduced kidney function. There is also an increased risk of liver cancer mainly in older people. Porphyria specialists are in the process of agreeing recommendations for follow up care, and these will be published on this website when available. This is likely to include regular checks of blood pressure, blood tests to check kidney function and, in patients over the age of 50, liver imaging.

16. Conclusion

Most people who are found to have an acute porphyria are able to lead a normal healthy life provided they take the simple measures to reduce the risk of attacks that are described above. Even the few who do become ill usually make a complete recovery and have no more than one or two acute attacks in early adult life. As one grows older, the risk of an acute attack decreases, particularly after the age of forty, but it never completely disappears.

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