

Dental Treatment of the Patient with Porphyria

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Summary

Porphyria is a group of inherited diseases caused by defective enzymes on the biosynthetic pathway of heme. Depending on the specific enzyme defect different forms of porphyria can be differentiated. The consequence of the enzyme defect is the formation of abnormal amounts of porphyrins or precursors which accumulate in the tissues and are excreted in the urine and faeces. Almost all the clinical signs occur because of the effect of these compounds/products on the nervous system and skin. Numerous drugs, such as local anaesthetics (lidocaine), antibiotics (clindamycin, erythromycin, metronidazole) and others, can be precipitating factors and cause acute attacks. Patients with porphyria can safely be given bupivacaine, amoxicillin, clavulanic acid, acetylsalicylic acid and paracetamol (1, 2).

Thus it is important for the dentist to have certain guidelines with regard to the treatment of patients with acute form of porphyria.

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Introduction

The term porphyria encompasses a group of diseases of uncharacteristic symptomatology which all exhibit excessive excretion of one or more porphyrins, porphyrinogens and/or porphyrin precursors in the urine and faeces (1).

The incidence of porphyria ranges between 1:10 000 and 1:50 000 (1). Four exogenous factors - drugs, steroids, hunger and infection - can induce transition from the latent form of the disease into the acute form (3). Thus it is important for the dentist to know which drugs can cause an attack of porphyria, and those which can be applied safely.

Pathophysiology

Porphyrias are a group of diseases caused by defective enzymes on the biosynthetic pathway of heme (4).

Heme, a pigment which contains iron, is a non-protein active ingredient of haemoproteins which are present in all tissues. Heme is mainly formed in bone marrow, where it synthesises in haemoglobin and in the liver, where it synthesises in cytochromes, of which the most important is cytochrome P-450 which most frequently participates in drug metabolism (5).

Heme biosynthesis occurs with the assistance of eight different enzymes which catalyse individual

steps. Depending on the specific enzyme defect different types of porphyria can be differentiated. In all porphyrias there is a raised level of synthetase delta-aminolevulinic acid (ALA-synthetase), of the first enzyme on the biosynthetic pathway of heme (4). Heme inhibits further formation of ALA-synthetase (1). Certain drugs and hormones stimulate hepatocytes to increase the formation of ALA synthetase, heme and cytochromes (P-450) (3).

The consequence of the enzyme defect is the formation of abnormal amounts of precursor hemes (porphyrins) which accumulate in the tissues and are excreted in the urine and faeces (4). Clinical signs nearly always occur from the effect of these compounds on the nervous system and skin.

Classification of porphyria

According to the tissue in which porphyrins accumulate, porphyrias can be classified as *erythropoietic*, in which porphyrins accumulate in bone marrow, and *hepatic*, in which porphyrins accumulate in the liver. The erythropoietic group includes: *congenital erythropoietic porphyria*, *erythropoietic protoporphyria* and *X-linked siderblastic anaemia*. The hepatic group includes: *acute intermittent porphyria*, *cutanea tarda porphyria*, *hereditary coproporphyria*, *variegate porphyria* and *porphyria defect ALA dehydratase*.

A third group represents hepatoerythropoietic porphyrias which combine erythropoietic and hepatic porphyria (1, 6).

The most frequent forms of porphyria are:

- Acute intermittent porphyria (AIP).
- Late skin porphyria.
- Hereditary coproporphyria
- Variegate porphyria (South African genetic porphyria) (1, 4, 6).

Acute intermittent porphyria

For the dentist the most important, and at the same time the most frequent acute porphyria, is acute intermittent porphyria (AIP).

AIP is a hepatic porphyria. The prevalence of AIP in the world ranges from around 1:1000-10 000, with greater frequency in Scandinavian countries and Great Britain (3, 6). It manifests after puberty and is most frequent in women. Drugs are usually the precipitating factor. The majority of harmful drugs in acute porphyria induce hepatic ALA synthetase and enzyme cytochrome P-450. Other diseases, surgical operations, stress, menstrual cycle (second half) pregnancy, psychological problems, alcohol have also been reported to be precipitating factors.

Attacks develop over several hours or days and last from several days to several weeks. Symptoms arise as a result of damage to visceral nerves. Most frequently they include abdominal pain, nausea, vomiting, diarrhea and opstipation. The urinary bladder may be involved with urine retention, incontinence, dysurea and polakysurea. Tachycardia is usual with hypertension, perspiration and restlessness, caused by damage to the autonomic nervous system or high level of catecholamines in the blood. Motor neuropathy often occurs. Muscular weakness usually starts in the shoulders and arms, although it can involve any neurone, including the cerebral nerves. Severe paralysis and respiratory insufficiency may develop. Acute attacks carry a significant risk of death due to respiratory paralysis in 10-25% of patients (7).

Acute attacks require hospitalisation and infusions of glucose and i.v. administration of heme, which suppresses synthesis of the enzyme ALA synthetase by a feedback mechanism (3-5, 8, 9).

Late skin porphyria (Porphyria cutanea tarda) is the most frequent of all porphyrias. However, it is characterised only by skin symptoms, photosensitivity and the occurrence of bullae. Alcohol, iron and estrogens are reported to be precipitating factors (6).

Hereditary coproporphyria is a hepatic porphyria. Acute attacks cannot be differentiated from those of AIP, and the same therapy is carried out.

Variegate porphyria is characterised by acute episodes of neurological and psychic disorders, with sensitivity of the skin to sun and also to mechanical stimulation. It is treated as for AIP.

Drugs and porphyrias

When confronted with a patient suffering from an acute form of porphyria it is extremely important for the dentist to be aware of the drugs which are known to be precipitating factors. Many lists have been published on drugs which are classified as harmful or safe for application in those suffering from AIP (7, 10-12). Such lists are similar in many ways, due to the fact that they are compiled on the basis of *in vitro* study, experimental animal studies, case presentations and structural similarities with drugs that are known to be harmful to those suffering from AIP (e.g. new barbiturates or sulphonamides are considered harmful) (3,10). In the first case a false-positive result is often possible. The drawback of the second is the difference in physiological processes of the human and animal organism, and the third case is founded on anecdotal evidence (3). Thus, according to Moore, it is likely that all drugs which are marked as "safe" for application in porphyria are safe, while those which are marked "unsafe" are not necessarily so, but should be used with caution (10).

The harmlessness of *local anaesthetics* remains a controversial subject because of experimental evidence of the porphyriopathy of local anaesthetics tested on animals (lidocaine) and cell cultures (lidocaine, mepivacaine, bupivacaine) (10-12). For example, Nordman et al reports that prilocaine, lidocaine, bupivacaine and mepivacaine are "dangerous", and procaine "safe" (11). Moore reports that lidocaine is unsafe, and bupivacaine, procaine and prilocaine are safe (10). Moore and McColl report that mepivacaine is unsafe, prilocaine questionable, and bupivacaine and procaine safe (7). Nevertheless, clinical experience has shown that these medications can be applied to patients with acute porphyrias with no noticeable side-effects.

It is recommended that bupivacaine is used for infiltrational and conductive anaesthesia (0.25-0.5%) with adrenaline (1:200 000), and for topical lidocaine (gel 2%, spray 4-10%) (13).

Penicillin *antibiotics* can be used (penicillin G, penicillin V, amoxycillin, clavulanic acid), as opposed to clindamycin, erythromycin, metronidazole (2). However, situations have been described in which clindamycin was applied as a "safe drug"

because it had previously been used in the patient with no negative consequence with regard to induction of AIP (5).

Of the *analgesics* AS acid, paracetamol and ibuprofen can safely be applied.

Corticosteroids, which are used in the treatment of certain oral conditions such as lichen, recurrent aphthous stomatitis and pemphigus, can induce AIP (14).

Of other therapeutic factors the following should be mentioned: *ethanol* which is used as a vehiculum in solutions for mouth rinsing, *carbamazepine* which is used in the therapy of neuralgia n. trigeminus, and *chlorzoxazone*, a muscle relaxant of central effect, which can also induce AIP (2, 3).

Table 1 gives a comprehensive list of drugs which are of practical importance for the dentist, ensuring safe use in patients with acute forms of porphyria (2).

Conclusion

Treatment of patients with acute forms of porphyria represents a challenge for the dentist. With this in mind we give below general guidelines for carrying out safe and successful therapy in such patients.

1. While talking to the patient the dentist should ask about the frequency of acute episodes and when the last attack occurred. What factors induced it and whether there are prodromal symptoms which precede acute episodes. In what way were such attacks treated and was hospitalisation necessary?
2. The dentist should determine the name of the physician treating the disease and briefly discuss with him/her the plan for dental therapy. It is necessary to decide which anaesthetic, analgesic, antibiotic and sedative can be included in the therapy and to discuss emergency therapy protocol in the case of an acute attack.
3. The dentist should inform the patient about the harmfulness of strong carbohydrate diets, which are prescribed for such patients, oral health and taking relevant contra-measures with regard to increased hygiene, mouth rins-

ing with chlorzoxazone solution (which does not contain ethanol) and frequent check-ups (every 3-6 months).

4. In view of the history data the dentist should decide whether to refer the patient for treatment in an appropriate specialist institution (5).