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Phelan-McDermid syndrome

Phenylketonuria and other hyperphenylalaninemias

orphanaesthesia

a project of the German Society
of Anaesthesiology and Intensive Care Medicine

SUPPLEMENT NR. 10 | 2023

OrphanAnesthesia –
ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patientinnen und Patienten mit seltenen Erkrankungen. Damit will OrphanAnesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patientinnen und Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesistinnen und Anästhesisten damit keine Erfahrungen gesammelt haben, sodass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem eine Anästhesistin bzw. ein Anästhesist sowie eine weitere Krankheitsexpertin bzw. ein weiterer Krankheitsexperte (z. B. Pädiaterin bzw. Pädiater oder Neurologin bzw. Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, sodass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

Ab Heft 5/2014 werden im monatlichen Rhythmus je zwei Handlungsempfehlungen als Supplement der A&I unter www.ai-online.info veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

Bisher in A&I publizierte Handlungsempfehlungen finden Sie unter:

www.ai-online.info/Orphsuppl
www.orphananesthesia.eu

OrphanAnesthesia –
a project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommenations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via www.ai-online.info. As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

Find a survey of the recommendations published until now on:

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a project of the German Society of Anaesthesiology and Intensive Care Medicine

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Anaesthesia recommendations for

Phenylketonuria and other hyperphenylalaninemias

Disease name: Phenylketonuria

ICD 10: E70.0, E70.1

OMI: 260600, 260630

GARD 7383

Synonyms: Phenylalanine hydroxylase deficiency, BH4 deficiency (dihydropterin reductase deficiency), PKU, Følling disease, Phenylpyruvic oligophrenia

Disease summary: Phenylketonuria (PKU) is an inherited error of metabolism. Its prevalence is estimated at 1/50.000 but ranges from 1/2600 in Turkey, 1/50.000 in the UK and 1/100.000 in Japan. In 98% of the cases, it is caused by the autosomal recessive transmission of a mutation of the PAH gene (12q23.2) which codes for phenylalanine hydroxylase (PAH), the enzyme that converts phenylalanine to tyrosine. In all other cases, it is caused by the autosomal recessive transmission of a mutation of one of the genes responsible for the synthesis or regeneration of tetrahydrobiopterin (BH4).These are: the GCH1 gene coding for GTP cyclohydroxylase1 (14q22.2), the PTS gene coding for 6-pyruvoyl-tetrahydropterine synthase (11q23.1), the PCBD gene coding for pterin-4α-carbinolamine dehydratase (10q22.2) or the QDPR gene coding for dihydropterin reductase (4p15.32). Most of these cases are caused by a dihydropterin reductase deficiency. They are called BH4 deficiency or defects in pterin metabolism. BH4 is a cosubstrate of phenylalanine hydroxylase (see figure at the end of the text) but it is also involved in the synthesis of the amino acids tyrosine, tryptophan and arginine. A deficiency in the production of these amino acids results in a deficiency of the neurotransmitters dopamine, serotonin and nitric oxide. In addition, in rare cases, hyperphenylalaninaemia may be caused by a mutation in DNAJC12, a protein responsible for the proper folding of PHA (4).

In developed countries, PKU is currently detected by a systematic screening (bloodspots 24–72 h after birth, “Guthrie’s test”). If the test is positive, the PAH deficiency is confirmed by other tests (including genetic testing). More than 950 different pathogenic variants have been described in PKU patients and they result in a reduced enzymatic activity of PAH. Depending on this residual enzymatic activity, the phenotype of PKU is highly variable. According to plasma Phe levels at diagnosis and tolerance, defined as the highest dietary Phe intake able to keep blood Phe levels within the safe range (120–360 µmol/l), PKU is classified into

- classic PKU, if the patient tolerates less than 250–350 mg dietary Phe per day,

- moderate PKU, if the patient tolerates 350–400 mg dietary Phe per day,

- mild PKU, if the patient tolerates 400–600 mg dietary Phe per day.

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- mild or non-phenylketonuric hyperphenylalaninaemia: the Phe levels are persistently below 600 µmol/l on a normal diet. These patients have a normal intellectual and behavioural development without treatment: whether this is a benign anomaly that requires no treatment is a matter of controversy.

According to the first European PKU guidelines, PAH deficiency is now classified into mild PAH deficiency (not needing treatment), BH4 responsive and BH4 unresponsive PKU.

If PKU is left untreated, the accumulation of Phe in the brain will lead to severe global developmental delay, intellectual disability, behavioural problems, epilepsy, movement disorders, and hypomelanosis with light skin, blond hair, blue eyes, an eczematous rash. In untreated BH4 deficiency, the patients present with microcephaly, developmental delay, intellectual disability, tremor, dystonia, uncoordinated movements, hyperthermia and epilepsy. In case of untreated DNAJC12 deficiency, the patient's phenotype varies from autistic features or hyperactivity to severe intellectual disability with dystonia and parkinsonism.

PKU is treated by initiating a lifelong diet that restricts the intake of high-protein food. The aim of the classical diet is to keep Phe blood levels between 120–360 µmol/l for the first 12 years of life and in case of wish to become pregnant and during pregnancy. In other age periods the target range is 120–600 µmol/l. The classical diet is very restrictive and time-consuming. Therefore many children, adolescence and adults struggle to adhere to the diet resulting in neuropsychological symptoms such as executive dysfunction, mood disorders, anxiety, reduced vigilance and attention deficit hyperactivity disorder. Some patients (often those with mild PKU) respond to a 48 h test with 20 mg/kg/d oral BH4 with a reduction of at least 30 % of the plasma Phe levels. In these cases, called BH4-responsive PKU, a daily intake of oral BH4 can be associated with a less restrictive diet. In case of hyper-phenylalaninemia with no in PAH nor pterin metabolism abnormalities, a mutation in DNAJC12 should be looked for using molecular biology.

A more "normal" and less protein restricted diet supplemented with large neutral amino acids (LNAA) is available [5]. Adherence to LNAA is typically better than to the classical diet making LNAA an excellent alternative in the treatment of PKU. The aim of this less-restricted diet is to keep Phe blood levels between 900–1500 µmol/l.

A new diet-free treatment modality has been recently approved by the FDA and EMA to maintain blood PHE close to normal in patients older than 16 years. It consists in the weekly subcutaneous injection of pegvaliase (2.5 to 40 mg/dose). It is the injectable form of phenylalanine ammonia lyase, an enzyme that metabolizes blood phenylalanine. This treatment allows a diet unrestricted in dietary proteins. The anaesthetic implications, if any, of this treatment is unknown.

The medical treatment of BH4 deficiency is more complex. In addition to the restrictive Phe-free diet, it involves: sapropterin dihydrochloride (BH4) 2-20 mg/kg/d in 2–3 doses; folic acid 15 mg/d; L-dopa 1–2 mg/d in 4 doses; 5-hydroxytryptophan 1–10 mg/kg/d in 4 doses; entacapone (a COMT inhibitor) 15 µg/kg/d in 2–3 doses; selegilin (a MAO-B inhibitor) 0.1–0.25 mg/kg/d in 3–4 doses and pramipexole (a dopa receptors agonist) 6–35 µg/kg/d in 2 doses. However, some like dihydropterin reductase deficiency are a contraindication to BH4 supplementation due to the risk of conversion into BH2.

Concerning anaesthesia, there are only a few concerns in patients with PKU who are under medical treatment since infancy. Patients should avoid protein catabolism (a short preanaesthetic fasting time and administration of glucose-containing IV electrolytic solutions), avoiding gelatin and aspartame-containing drugs as well as exposure to N_2O because there is a risk of dietary vitamin B12 deficiency. In case of parenteral nutrition, a solution without

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Phe should be used. The same concerns should be kept for patients with defects of pterin metabolism and BH4 responsive PKU, but their medical treatment should be continued up to the morning of anaesthesia.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

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Typical surgery

There is no surgery or procedure typical for this disease. These patients can undergo the same surgical procedures as patients not presenting this disease.

Type of anaesthesia [6,7]

Only a few cases of general anaesthesia have been reported so far.

Necessary additional preoperative testing (beside standard care) [3,8,9]

In addition to the usual preoperative examination, it is useful to contact the patient's paediatrician, physician or neurologist to find out whether this patient is usually stable, and if a control of their Phe blood level has recently been checked. It should ideally range between 120 and 360 µmol/l. In case of emergency or of fever, one should keep in mind that protein catabolism increases Phe blood levels. Although it is still unclear whether the incidence is higher than in the non-PKU population, adults with PKU may present with cardiovascular risk factors (see below): their cardiovascular status (ECG, echocardiography if needed) should therefore be evaluated before anaesthesia. As patients with classic PKU with long-term supplementation with Phe-free L-amino acids present frequently with proteinuria and a decreased glomerular filtration rate, their renal function should be checked, too.

Particular preparation for airway management

These patients are not at a higher risk of a difficult airway than the normal population.

Particular preparation for transfusion or administration of blood products

It should be kept in mind that blood and plasma contain proteins and could be a source of increased protein catabolism. Although gelatin-based colloids are eliminated unmetabolised in the urine, they are a potential source of Phe and should be used with care.

Particular preparation for anticoagulation

A high prevalence of cardiovascular risk factors is observed in adults with PKU following a Phe restricted diet since birth. They are: dyslipidemia with an atherogenic lipoprotein profile, overweight or obesity, systemic hypertension and some cases of hyperhomocysteinaemia. Moreover, endothelial dysfunction (correlated with increasing BMI) producing a decrease in post-ischaemic blood flow, and increased arterial stiffness are also observed. The same rules of thromboprophylaxis should be applied as in non-PKU patients.

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Particular precautions for positioning, transportation and mobilisation

No special precautions are necessary.

Interactions of chronic disease and anaesthesia medications

The main issues concern BH4 deficient patients including those with DNAJ12 deficiency because of their chronic medical treatment. This treatment should be continued up to the morning of anaesthesia and resumed as soon as possible. There are also some possible interactions with anaesthetic drugs. They are:

- sapropterin dihydrochloride (BH4) in 2–3 doses: no known interaction
- folic acid: no interaction.
- L-dopa in 4 doses; chronic use of L-dopa could favour orthostatic hypotension and decrease the pressor response to indirect **vasopressors** such as ephedrine; direct vasopressors could be a better option in case of hypotension. Moreover antagonists of dopamine such as metoclopramide and butyrophenones should be avoided.
- pramipexole (a dopa receptors agonist) in 2 doses: no known interaction.
- 5-hydroxytryptophan in 4 doses; no known interaction.
- entacapone (a COMT inhibitor) in 2–3 doses; it increases the sensitivity to direct vasopressors: their dose should be carefully titrated to effect.
- selegilin (a MAO-B inhibitor) in 3–4 doses: MAOB inhibitors have no interactions with anaesthesia at low dose but they behave as MAO inhibitors type A at doses over 10 mg/d.

Whether it is safe to use **setrons** (5HT3 inhibitors) as antiemetics in this context is currently unknown. However, because of its monoaminergic mechanism of action, **tramadol** should not be used in PKU type-2 patients.

Anaesthetic procedure [6,7]

Preanaesthetic fasting time should be kept as short as possible and the 6-4-1 or 6-4-0 rule can be safely applied. Once hyperphenylalaninemia is detected, infants are often not allowed to breastfeed and have to be fed with a special milk formula that is Phe-free because breast milk contains Phe. No special anaesthetic technique can be recommended. As vitamin B12 deficiency is possible in the patient with classic PKU whose daily intake of Phe-free supplementation is suboptimal, N_2O should be used with care and only for a short period of time (e.g., induction of anaesthesia or light sedation).

Particular or additional monitoring

As a glucose-containing IV electrolytic solution will be used to cover maintenance metabolic needs during anaesthesia, blood glucose and Na levels should be monitored.

Possible complications

As swallowed blood is a hidden source of proteins and thus of Phe, care should be taken to avoid any ingestion of blood during procedures involving the oropharyngeal cavity: dental care, tonsillectomy, adenoidectomy, cleft palate repair, or traumatic nasal intubation.

Pharyngeal packing and/or suction of the gastric content at the end of the procedure should be performed in these cases.

In case of fever, one should keep in mind that this increases protein catabolism and thus Phe blood levels.

Postoperative care

In case of fever, one should keep in mind that protein catabolism increases Phe blood levels. A glucose-containing IV electrolytic solution should be administered as long as the patients are not back to their usual diet. In case of parenteral nutrition, a Phe-poor IV solution should be used. Oral drugs containing gelatin or aspartame (which contains 50 % Phe) should be avoided because these substances are rich in Phe. If the patient's usual diet cannot be reintroduced early, blood Phe levels should be checked regularly according the patient's doctor advice.

Disease-related acute problems and effect on anaesthesia and recovery

The risk of acute complications related to the disease is minimal in stable PKU patients on Phe-restricted diet. In untreated patients, and patients who follow their treatment poorly there is the risk of vitamin B12 deficiency and thus of acute neurological complications if N_2O has been used as an anaesthetic or sedative agent. For patients with defects in BH4 metabolism (and also those with DNAJC12 deficiency), there is a risk of seizures and behavioural problems. Moreover, these patients are at risk of movement disorders and hyperthermia without infection.

Ambulatory anaesthesia

Ambulatory procedures under anaesthesia can safely be undertaken in PKU patients if the fasting time is short and the risk of postoperative protein catabolism is minimal.

Obstetrical anaesthesia [3,9]

In order to avoid that the new-born presents with maternal PKU syndrome (see Appendix), the Phe blood levels should be carefully maintained between 120 and 360 µmol/l both before and during pregnancy. A pregnancy in a PKU patient is therefore considered as a high-risk pregnancy that should be carefully planned. This implies weekly controls of the blood Phe levels and adapting her diet and its Phe content to compensate for the increased metabolic needs during pregnancy. In case of unplanned pregnancy, both quick dietary control of Phe blood levels and regular ultrasound evaluation of the foetus are necessary.

Childbirth and delivery are not different from non-PKU parturients. Phe-blood levels should be regularly checked after delivery in order to adapt the mother's diet to her blood Phe levels (increased metabolic needs vs uterine involution). Breastfeeding is allowed.

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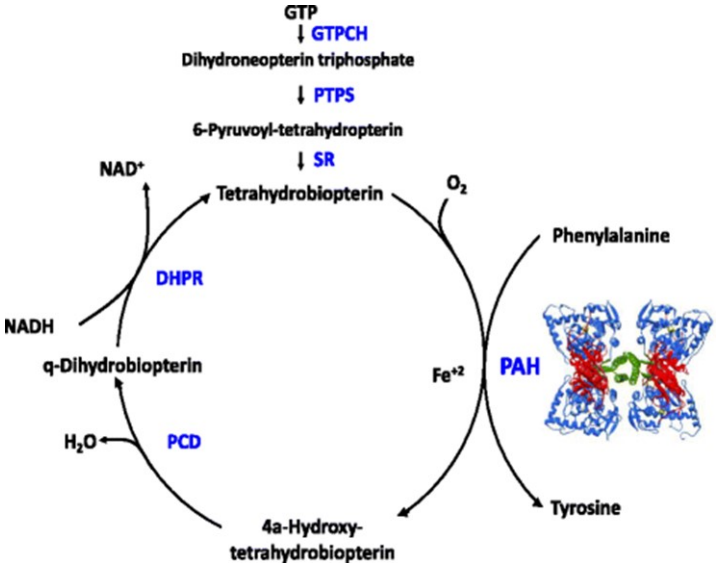
Appendix:



Maternal PKU syndrome

This is the syndromic association of malformations presented by non-PKU neonates born from a PKU mother whose Phe levels were not controlled and above 360 µmol/l during pregnancy.

They are:

- microcephaly,
- intrauterine growth retardation,
- a congenital heart disease: tetralogy of Fallot, ventricular septal defect, patent ductus arteriosus, aortic or mitral valve stenosis,
- mild facial dysmorphism: coloboma, malformed ears, cleft palate,
- others: oesophageal atresia, syndactyly, anal atresia, renal agenesis.

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Please note that this recommendation has not been reviewed by an anaesthesiologist and a disease expert but by two disease experts instead.

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