Optimizing treatment and follow-up for acute porphyric patients.

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(also see: C1. Protocol, page 12, paragraph 2)Primary Objective:Improving risk assessment of acute porphyric attacks and complications in patients with acute porphyria.Secondary Objectives: 1. Obtain and describe basic demographics and statistics,...

Ethical review	Approved WMO
Status	Pending
Health condition type	Metabolic and nutritional disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON41815

Source
ToetsingOnline

Brief title
Acute Porphyria

Condition

- Metabolic and nutritional disorders congenital
- Hepatobiliary neoplasms malignant and unspecified
- Inborn errors of metabolism

Synonym
(layman's term not used by patient groups, not applicable), Porphyria

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Stichting Lever Onderzoek

Intervention

Keyword: Hepatocellular carcinoma, Hypertension, Porphyria, Renal failure

Outcome measures

Primary outcome

(also see: C1. Protocol, page 19, paragraph 8.1.1)

Retrospective family cohort study:

Complete family tree obtainment. Pedigree information including date of birth, date of death and cause of death of family members, will be collected through patient interview (either during clinic visits or by mail or phone). Patient information will be cross-referenced with Dutch genealogy databases to ensure accuracy. Data will be used for estimation of a standardized mortality ratio and other statistics of the Dutch porphyria cohort.

Prospective genotype-fenotype variation case-control study:

- Acute porphyric attacks (Definition of acute attack is : abdominal pain with a steep increase in delta-aminolevulinic acid levels (plasma or urine), with a pain duration of >= 1 day.)
- Renal function / incidence of renal insufficiency
- Blood pressure / incidence of hypertension
- Incidence and prevalence of hepatocellular carcinoma

Secondary outcome

(also see: Protocol C1, page 19/20, paragraph 8.1.2 - 8.1.3)

Secondary study parameters/endpoints

- Blood pressure

- Renal function (Creatinine and GFR)

- Plasma/urine porphyrin and precursor levels

- Pregnancy complications

- Previous attacks with pain measures based on VAS scales (0-10); past and present physical complaints: abdominal pain, paresis, psychosis, epilepsy

- DNA methylation PBGd gene in blood samples and hepatocytes

- Heart rate variability assessment, with EKG for 1 hour

- Enzyme activity in hepatocytes

- Hair cortisol

- Specific enzyme activity and specific mRNA levels in erythrocytes, fibroblasts and / or hepatocytes

- Liver function

- Liver fibrosis/ cirrhosis

- Incidence and prevalence of hepatocellular carcinoma

Other study parameters

- QOL questionnaire scores: SF36, DS14, HADS, Open qualitative questionnaire directed at burden by acute porphyria

- Perceived Stress Scale (PSS) (to correlate perceived stress with hair cortisol levels)

Study description

Background summary

Acute porphyrias are a group of metabolic disorders, characterized by attacks of abdominal pain and neuropathy. These attacks can be provoked by fasting, porphyrinogenic drugs, menstrual cycle, alcohol and smoking. Severe attacks can be accompanied by hypertension, tachycardia, hyponatremia, and neurologic symptoms, such as pareses, psychosis, epilepsy, coma and can lead to severe morbidity and even death.

Acute porphyric attacks are caused deminished activity of enzymes involved in haem-synthesis by steep increases in delta-aminolevulinic acid (ALA) and porphyrin levels. Attacks can occur in patients with a latent decreased activity of specific enzymes in the hepatic heme synthesis, namely porphobilinogen deaminase (acute intermittent porphyria), protoporphyrinogen oxidase (variegate porphyria), and coproporphyrinogen oxidase (hereditary coproporphyria).

The acute porphyria's are autosomal dominant disorders and screening/councilling for family members can be important. This way attacks may be recognised early and with lifestyle changes might be prevented. About 20% of patients with acute porphyria has at least one attack during his/her lifetime and about 5% has frequent recurrent attacks requiring constant therapy and painkillahs. In families with one type of porphyria there are usually a lot of different phenotypes, thus far it's unknown what causes this variation in phenotype.

Besides the chance to get an acute attack patients with porphyria also have a higher chance to develop long-term complications of the disease: hypertension, chronical kidney disease and hepatocellular carcinoma. The risk for hepatocellular carcinoma in this patient group without liver cirrhosis is comparable with patients suffering of hepatitis C induced liver cirrhosis.

Study objective

(also see: C1. Protocol, page 12, paragraph 2)
Primary Objective:
Improving risk assessment of acute porphyric attacks and complications in patients with acute porphyria.

Secondary Objectives:
1. Obtain and describe basic demographics and statistics, such as mortality and morbidity.
2. Determine disease modifiers for porphyric attacks and complications.
3. Evaluation of current follow-up (FU) for complications and prevention of

attacks.

Main question is: can improved genotyping and improved phenotyping provide a more accurate risk assessment to predict those at risk of a (life-threatening) porphyric attack, or at risk for hypertension, RF and HCC

Specific research questions:
1. Is there a historically increased mortality in the pedigrees of acute porphyria families compared to the Dutch population?
2. Can we predict those at risk for attacks and / or complications?
3. Can we continue with the current FU schedule (half yearly liver ultrasound in those over age 50 years and earlier with high levels of plasma PBG/ALA).
4. Is the prognosis of HCC found by screening better than diagnosed after occurrence of symptoms? Can HCC diagnosed by screening be treated curatively?
5. What is the burden of screening for patients / carriers? Based on quality of life (QOL) and qualitative assessments.
6. Can the difference in frequency of acute porphyric attacks be explained by differences in hepatic enzyme activity between patients?
7. Do patients with episodes of acute porphyric attacks have more stress, higher levels of hair cortisol, compared to asymptomatic cases and controls?

Study design

(also see: C1. Protocol, page 13, paragraph 3)
The study comprises two parts:
A retrospective family cohort study and a prospective genotype-phenotype variation case control study.

Study population for the retrospective part:
The genealogical data of all families with a DNA-confirmed diagnosis.

Study population for the prospective part:
Cases are all identified patients with acute porphyria in the Netherlands.
Controls are non-carrier, sibs and / or unrelated neighbours / friends / partners of the patients, preferably age matched on a group level.

Study burden and risks

(also see: C1. Protocol, page 27/28, paragraph 11.4

The burden of our study for porphyric patients will not deviate from standard care for these patients given inside our hospital, besides the extra time needed (about 1 hour) that will be spent filling in questionaires. Tests such as blood pressure measurements, blood/urine sampling and fine needle liver biopsies are all part of the standard care for porphyric patients and thus

indicate no extra burden. Patients will be included in the study during routine check-ups so no extra visits are required. The risks of venapuncture are haematoma and / or infection at the place where blood was drawn.

The controls will be asked to join patients during routine visits since the controls will be sibs, friends, partners of the patients. They will be informed about all the aspects of the study by one of the researchers and especially the risks associated with fine needle biopsy (20G-FNB).

Most studies on complications of biopsy are based on complications rates in patients with liver disease. Since the livers of our cases and controls are considered to be non-cirrhotic, we expect lower complication rates in our study. The risk of a liver biopsy in patients with cirrhosis are post-biopsy complications such as bleeding or pain. The risk for complications using 16G needles consists mostly of pain and minor haemorrhage and is 5,6%. There*s a 1.7% risk for severe complications (extended hospital stay, severe haemorrhage requiring intervention; the risk of death is 0,06%.

Only cases and controls, aged > 18 years and without risk factors for complications (paragraph 4.3), can choose to participate in the study with or without the liver 20G-FNB. It's possible for subjects to enter the study without giving consent to the liver biopsy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

(see Protocol C1. page 14, paragraph 4.2 Inclusion criteria)
Acute porphyria patients:
- Age 12 years and older
- Decreased enzyme activity of porphobilinogen deaminase (acute intermittent porphyria), protoporphyrinogen oxidase (variegate porphyria), and coproporphyrinogen oxidase (hereditary coproporphyria), or an inactivating mutation in the relevant gene or both.
- Symptomatic and asymptomatic patients with an identified acute porphyria mutation or biochemical proof of an acute porphyric attack/episode;Healthy controls are unaffected sibs, spouses or friends selected via the cases.;For both groups a signed informed consent form is required.

Exclusion criteria

(see Protocol C1. page 14)
Subjects with an increased risk of complication will be excluded from liver biopsy according to guidelines of the American Association for the Study of Liver Diseases, and other risk factors based on local experience.;Contraindications for fine needle biopsy with a 20G needle:;-Under 18 years of age
-Uncooperative patient
-Unable to give informed consent
-Severe coagulopathy
-Infection of the hepatic bed
-Extra hepatic biliary obstruction
-Ascites
-Morbid Obesity
-Possible vascular lesions
-Amyloidosis
-Hydatid disease
-Liver fibrosis/ cirrhosis

-Pre-existent malignancy in the liver
-Any bleeding disorder, including those on aspirin and NSAIDS or any other anticoagulant

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2015
Enrollment:	1326
Type:	Anticipated

Ethics review

Approved WMO

Date:	29-06-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL49954.078.14