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Biotinidase activity and deoxy-sphingolipids as biomarkers in glycogen storage disease type 1

Submission date
21/02/2017

Recruitment status
No longer recruiting

Registration date
28/02/2017

Overall study status
Completed

Last Edited
14/08/2018

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims:
Glycogen storage disease type 1 (GSD1) is an inherited disorder caused by a problem with an enzyme called glucose-6-phosphatase, which is responsible for the breakdown of stored sugar (glycogen) in the body's cells into sugar (glucose) that can be used for energy. This causes glycogen to build up in the body's tissues, stopping vital organs from functioning properly and lowering blood sugar levels (hypoglycaemia). In GSD1, increased activity of the enzyme biotinidase is often observed, and this enzyme may serve as a biomarker (natural chemical indicator) for GSD1. Biotinidase is an enzyme allows the body to use and to recycle the B vitamin biotin, which interacts with enzymes that digest carbohydrates, fats and amino acids (protein building blocks). It is possible that a higher demand of biotin in GSD1 may lead to increased biotinidase activity. One reason for this may be increased fat production. The primary aim of this study is to explore the metabolic (breakdown) factors determining biotinidase activity as a biomarker in GSD1. Secondly, early data show that GSD1 patients have increased concentrations of an abnormal type of lipid (fat) called deoxysphingolipids (deoxySL). In another inherited disease primarily affecting deoxysphingolipid production, high deoxysphingolipids levels cause an inherited axonal neuropathy (a disorder that affects the way nerves carry signals). This study will also explore the value of deoxysphingolipids as new biomarkers in GSD1, and examine patients for the presence of related nervous system problems (neuropathy). In addition, the role of biotinidase activity and deoxysphingolipids will also be studied in patients with other disorders of lipid (fat) and carbohydrate metabolism (breakdown).

Who can participate?
Patients aged 16 years and over who have GSD1 or other disorders of lipid and carbohydrate metabolism, and healthy volunteers of the same age.

What does the study involve?
For GSD1 patients, blood samples for scientific analyses are collected repeatedly as part of routine medical care (GSD1 patients) over the course of two years. One measurement of nerve conduction velocity by electroneurography is also performed. This involves stimulating specific nerves using electricity to find out how well the signal travels along them. For patients with

other disorders of lipid and carbohydrate metabolism, blood samples are collected at two regular outpatient appointments. For healthy participants, the study includes a single blood draw at the start of the study.

What are the possible benefits and risks of participating?
At this time, there is no direct benefit for study participants. However, this study will broaden our knowledge about metabolic disturbances in glycogen storage disease type 1, and the value and utility of novel biomarkers are explored. This may help to optimize monitoring and treatment of the disease in future. As there is no study specific intervention, there is no specific risk of participating in this study.

Where is the study run from?
University Hospital Zurich (Switzerland)

When is study starting and how long is it expected to run for?
April 2014 to October 2017

Who is funding the study?
University of Zurich, Clinical Research Priority Program (CRPP) radiz - Rare Disease Initiative Zurich (Switzerland)

Who is the main contact?
Dr Michel Hochuli
michel.hochuli@usz.ch

Contact information

Type(s)
Scientific

Contact name
Dr Michel Hochuli

Contact details
University Hospital Zurich
Department of Endocrinology, Diabetes and Clinical Nutrition
Raemistrasse 100
Zurich
Switzerland
CH-8091

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

KEK-ZH Nr. 2013-0632

Study information

Scientific Title
The role of biotinidase activity and deoxy-sphingolipids in glycogen storage disease type 1 and other disorders of carbohydrate and lipid metabolism

Study objectives
The aim of this study is to evaluate the pathophysiological background and clinical utility of two biomarkers (biotinidase activity and deoxy-Sphingolipids) in glycogen storage disease type 1.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee Zurich, 07/05/2014, ref: 2013-0632

Study design
Mono-centric epidemiological observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
No participant information sheet available

Health condition(s) or problem(s) studied
Glycogen storage disease type 1

Interventions
GSD1 patients: The total duration of observation after enrolment is two years. Usual medical and dietary treatment is continued during the study (no study specific treatment intervention). Blood samples for analysis of study specific laboratory tests (biotinidase activity, plasma fatty acid profiles, sphingolipid profiles, metabolite profiles) are collected at each regular consultation during the study period (usually every 4-6 months). A single measurement of nerve conduction (electroneurography) is performed any time during the observation period.

Patients with hypertriglyceridemia, Diabetes mellitus or NAFLD: Blood samples for the study specific laboratory tests are collected on the occasion of two regular outpatient consultations during 12 months.

Healthy controls: A single blood sample is collected at time of enrolment.

Intervention Type
Other

Primary outcome measure
1. Biotinidase activity in plasma is measured using a standardized colorimetric assay at the time of each regular consultation during the study period (usually every 4-6 months) for patients and at the time of enrollment for healthy controls
2. Concentration of deoxy-Sphingolipids in plasma is measured using GC-MS at the time of each regular consultation during the study period (usually every 4-6 months) for patients and at the time of enrollment for healthy controls

Secondary outcome measures
Motor and sensory nerve conduction velocity is measured using electroneurography (ENG), one single any time during the observation period (only GSD1 patients).

Overall study start date
01/04/2014

Completion date
31/10/2017

Eligibility

Key inclusion criteria
Patients:
1. Over 16 years of age)
2. Signed informed consent
3. Diagnosis of Glycogen storage disease type 1, hypertriglyceridemia, diabetes mellitus or non-alcoholic fatty liver disease (NAFLD)

Healthy controls:
1. Male or female aged 18 years and over
2. Healthy, no chronic disease, no intercurrent disease at time of examination/blood draw, normal weight (BMI 19-25 kg/m2), no excessive alcohol consumption
3. Signed informed consent

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
At least 10 GSD1 patients. 30 healthy controls

Key exclusion criteria
Patients:
1. Contraindications on ethical grounds
2. Hepatocellular carcinoma (GSD1)
3. Women who are pregnant or breast feeding

Health Controls:
Any relevant chronic or intercurrent disease at the time of examination.

Date of first enrolment
01/04/2014

Date of final enrolment
01/10/2017

Locations

Countries of recruitment
Switzerland

Study participating centre
University Hospital Zurich
Department of Endocrinology, Diabetes and Clinical Nutrition
Raemistrasse 100
Zurich
Switzerland
CH-8091

Sponsor information

Organisation
University Hospital Zurich

Sponsor details
Raemistrasse 100
Zurich
Switzerland
CH-8091

Sponsor type
University/education

ROR
https://ror.org/01462r250

Funder(s)

Funder type
University/education

Funder Name
University of Zurich, Clinical Research Priority Program (CRPP) radiz - Rare Disease Initiative Zurich

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal, with intent to publish around one year after your overall trial end date.

Intention to publish date
31/10/2017

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/09/2018		Yes	No