Interindividual variability in brain vulnerability to elevated blood phenylalanine concentrations in PKU patients - pilot study on amino acid transport in fibroblasts as a representative of the blood-brain barrier

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To further characterize the transport of phenylalanine and other large neutral amino acids across the blood-brain barrier in PKU patients with high and low brain vulnerability to elevated blood phenylalanine concentrations, we will investigate...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Protein and amino acid metabolism disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON44921

Source
ToetsingOnline

Brief title
Variable brain vulnerability to high blood phenylalanine levels in PKU

Condition

- Protein and amino acid metabolism disorders NEC

Synonym
Phenylketonuria, PKU

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Amino acid transport, Blood-brain barrier, Fibroblasts, Phenylketonuria

Outcome measures

Primary outcome

The primary endpoints of this study will include:

-kinetic parameters (Km and Vmax values) for transport of phenylalanine across fibroblast membranes of subjects from the different study groups.

Secondary outcome

The secundary endpoints of this study will include:

-kinetic parameters (Km and Vmax values) for transport of tyrosine and tryptophan across fibroblast membranes of subjects from the different study groups.

-expression of amino acid transporters in fibroblasts of subjects from the different study groups.

-transport characteristics for phenylalanine and other large neutral amino acids will be determined in microvascular endothelial cells.

-variances in genes involved in amino acid transport between subjects from the different study groups.

Study description

Background summary

At this moment, each single child with a positive heelstick for phenylketonuria (PKU) and a confirmed diagnosis of PKU is put on the same strict dietary treatment. However, this diet for life is socially demanding and quite expensive, so treatment adherence usually declines with age. The question is whether target phenylalanine levels should be the same for each patient, and whether poor treatment adherence will have the same consequences for neuropsychological outcome in all PKU patients.
In PKU, differences in brain vulnerability to elevated blood phenylalanine concentrations are observed between patients. This can be best exemplified by the fact that some late diagnosed PKU patients seem to have escaped from mental retardation and have only been detected through affected siblings or children. MRS examination in some of these patients revealed less increased brain phenylalanine concentrations, despite markedly elevated blood phenylalanine concentrations, possibly indicating a difference in the transport characteristics of at least phenylalanine in these patients. However, in the one gene investigated thus far that encodes for the LAT1 transporter, no DNA polymorphisms have been identified that are associated with reduced brain vulnerability to elevated blood phenylalanine concentrations.

Study objective

To further characterize the transport of phenylalanine and other large neutral amino acids across the blood-brain barrier in PKU patients with high and low brain vulnerability to elevated blood phenylalanine concentrations, we will investigate transport characteristics for phenylalanine, tyrosine, and tryptophan as well as expression of different amino acid transporters in fibroblasts of these patients. Based on these transport characteristics, we aim to identify DNA polymorphisms in genes involved in amino acid transport, that are associated with reduced brain vulnerability to elevated blood phenylalanine concentrations in PKU patients.

Study design

Descriptive pilot study with an observational cross-sectional control group design

Study burden and risks

Of each subject, fibroblasts, a single blood sample and urine will be collected. Moreover, an IQ test will be performed in part of the subjects. Regarding the group relatedness, this study will investigate the underlying

physiological mechanisms as well as the genetic basis for the difference in brain vulnerability to elevated blood phenylalanine concentrations that can be observed between individual PKU patients. To this purpose, as a first step, the most extreme examples of patients with either a high or a low brain vulnerability to elevated blood phenylalanine concentrations will be investigated. The current neonatal screening programme and the direct institution of a phenylalanine-restricted diet result in a near optimal outcome for all PKU patients and thereby have made these differences in brain vulnerability largely disappear. The only PKU patients who have clearly shown to have either a high or low brain vulnerability to elevated blood Phe concentrations are those who have been late-diagnosed and have either developed severe mental retardation or have escaped from severe mental retardation. We hypothesize, however, that PKU patients with a low brain vulnerability to elevated blood Phe concentrations, who are early-diagnosed and have been treated with a phenylalanine restricted diet from birth, may manifest with behavioural problems due to brain deficiencies of essential amino acids other than phenylalanine. As behavioural problems such as ADHD or autism spectrum disorders are especially observed in some PKU children, this requires specific PKU children to be included as well.

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)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible for participation in one of the defined study groups, for each specific study group, subjects should meet the following inclusion criteria:;Group 1:
- Subjects meet NIH-diagnostic criteria for phenylketonuria
- PKU treatment has been initiated after 6 months of age
- Being able to perform daily living activities without the help of specialized caregivers and/or defined IQ score > 80
- Aged >= 18 years;Group 2:
- Subjects meet NIH-diagnostic criteria for phenylketonuria
- PKU treatment has been initiated after 6 months of age
- Living in an institute for mentally retarded persons and/or defined IQ score < 50
- Aged >= 18 years;Group 3:
- Subjects meet NIH-diagnostic criteria for phenylketonuria
- Early- (within 1 month after birth) and continuously-treated
- > 75% of historical data on plasma phenylalanine concentrations below target levels (< 12 years of age: < 360 µmol/L; <= 12 years of age: < 600 µmol/L)
- Diagnosed with ADHD or an autism spectrum disorder
- Aged >= 8 years and to whom the procedure can well be explained ;Group 4:
- Subjects meet NIH-diagnostic criteria for phenylketonuria
- Early- (within 1 month after birth) and continuously-treated
- >67% of historical data on plasma phenylalanine concentrations below target levels (<12 years of age: <360 µmol/L; >=12 years of age: <600 µmol/L)
- Aged >=18 years ;Group 5:
- Aged >= 18 years

Exclusion criteria

For each of the defined study groups, patients will be excluded in case of the following:;Group 1:
- IQ score < 80 after assessment;Group 2:
- IQ score > 40 after assessment;Group 4:
- Diagnosed with ADHD or an autism spectrum disorder;Group 5:
- Diagnosed with PKU

- ADHD or autism spectrum disorder
- Known disorder of amino acid transport

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	18
Type:	Anticipated

Ethics review

Approved WMO Date:	13-03-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-08-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL48594.042.14