Transporter defects; a study of novel mechanisms of thyroid hormone resistance with dramatic consequences.

Published: 29-08-2006
Last updated: 14-05-2024

Our project focuses on the function of transporters and deiodinases in the (dys)regulation of intracellular T3 levels in patients with psychomotor retardation and abnormal serum thyroid hormone levels. The main objectives of our study are:1. To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON30085

Source
ToetsingOnline

Brief title
TOP-R Study (Thyroid hormone Origin of Pyschomotor Retardation Study)

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Mental impairment disorders

Synonym
Psychomotor retardation; physical and mental impairment

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: NWO: ZonMW

Intervention

Keyword: Deiodinase, Psychomotor retardation, Thyroid hormone resistance, Thyroid hormone transporter

Outcome measures

Primary outcome

1. Levels of serum thyroid hormone; if abnormal:

2. Possible mutations in thyroid hormone related candidate genes

3. Functional consequences of these mutations.

Secondary outcome

Linkage analysis to identify mutated gene.

Study description

Background summary

Recently, a novel syndrome combining severe psychomotor retardation and elevated levels of the bioactive hormone T3, caused by mutations in the MCT8 thyroid hormone transporter has been discovered by our laboratory. MCT8 is important for T3 entry in different tissues, in particular in central neurons which are the primary target for thyroid hormone*s crucial action during brain development. This T3 is provided by outer ring deiodination of the prohormone T4 by the type 2 deiodinase (D2) expressed in neighbouring astrocytes. T3 acts on nuclear receptors in neurons, and this action is terminated by the inner ring deiodinaton of T3 by the type 3 deiodinase (D3) also expressed in these cells. A defect in MCT8 results in a lack of T3 supply to neurons and, thus, in impaired neurological development and reduced T3 clearance. This syndrome represents a novel mechanism of thyroid hormone resistance. Until now, thyroid hormone resistance has been associated only with mutations in the beta type T3 receptor.
Two other thyroid hormone-specific transporters have recently been identified in brain, of which OATP1C1 is located in capillaries and astrocytes, and MCT10 has an unknown distribution. We hypothesize that also mutations in these transporters or in D2 or D3 result in abnormal brain and serum thyroid hormone levels as well as impaired neurological development.

Study objective

Our project focuses on the function of transporters and deiodinases in the (dys)regulation of intracellular T3 levels in patients with psychomotor retardation and abnormal serum thyroid hormone levels. The main objectives of our study are:
1. To determine the role of thyroid hormone related candidate genes in the development of psychomotor retardation.
2. To determine the functional consequences of the mutations found in the patients on transporter and deiodinase activities.

Study design

This observational study will be done by screening of affected patients for abnormal serum thyroid hormone levels and subsequently for mutations in the transporters and deiodinases.

Study burden and risks

Two blood samples will be taken during the annual venapuncture, which is usually performed in these patients. A potential, but minor risk of venapuncture may be a bruise or (small) hematoma.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Postbus 2040
3000 CA Rotterdam
Nederland
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Postbus 2040
3000 CA Rotterdam
Nederland

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

Unexplained psychomotor retardation.

Exclusion criteria

Overt thyroid disease.
Interference with thyroid metabolism.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2006
Enrollment:	1000
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	29-08-2006
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	NL12111.078.06