STXBP1-Encephalopathy: a multifaceted cohort study into the clinical, electroencephalographical and cellular profile of STXBP1-E patients

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Primary Objective:To characterize a cohort of STXBP1-encephalopathy patients in a standardized, integrative manner, including in-depth clinical profile characterization and EEG recordings. Moreover, for a subgroup of patients, iPSC-derived induced...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neurological disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON48953

Source
ToetsingOnline

Brief title
STXBP1-E: A multilevel investigation

Condition

- Neurological disorders congenital

Synonym
Early infantile encephalopathy; intellectual disability and developmental delay

Research involving
Human

Sponsors and support

Primary sponsor: Functionele Genoomanalyse, Klinische Genetica

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Developmental delay, Early infantile encephalopathy, Intellectual disability, STXBP1-mutations

Outcome measures

Primary outcome

1. To generate and maintain a database containing clinical profiles of patients carrying an STXBP1 mutation, assessed in a standardized manner. The aim is to assess whether there is a correlation between genotype (specific mutation in STXBP1-gene) and phenotype (specific symptoms, progresion, success of particular treatment strategies).

2. Identify any EEG biomarkers that may in the future aid diagnosis and/or prognosis for specific patients or across the cohort of STXBP1 encephalopathy patients. This will be investigated in an explorative manner, as well as by quantifying the excitation/inhibition balance in order to test the hypothesis that there is an imbalance in the brain of STXBP1-E patients.

3. To generate an in vitro cell model of human neurons with the exact genetic make-up of STXBP1-E patients, to study the functional effects of disease-associated STXBP1 mutations in order to gain a deeper understanding of the pathophysiological mechanisms at the synaptic level. Cellular and molecular laboratory technieken will be employed to measure the excitation/inhibition balance at the cellular level as well.

Secondary outcome

Not applicable.

Study description

Background summary

STXBP1-encephalopathy is a relatively rare disorder. Patients have (usually severe-profound) developmental delay, intellectual disability, and in the majority of cases epileptic seizures or spasms starting at a very young age. The hypothesis is that STXBP1-E mutations cause haploinsufficiency of the protein STXBP1/MUNC18-1. MUNC18-1 is essential for neurotransmission between nerve cells in the brain. One hypothesis is that haploinsufficiency causes an imbalance between excitatory and inhibitory drive in the brain's circuitry. Previous studies in our lab have indicated that there may be a differential effect of lacking half of the usual MUNC18-1 protein levels between excitatory and inhibitory neurons, however, whether this is the case in human patients remains elusive.

Thus far, most scientific studies have reported on a single, or a few, patients. The aim of this study is to characterize a larger cohort of STXBP1-E patients in a standardized manner, characterizing a 'clinical profile', brain activity using EEG, and cellular phenotypes. Generating a cellular model of STXBP1-E including the genetic background of patients will allow investigations into the cellular and molecular consequences of STXBP1 mutations and may in the future also be used for screening of therapeutic strategies.

Study objective

Primary Objective:
To characterize a cohort of STXBP1-encephalopathy patients in a standardized, integrative manner, including in-depth clinical profile characterization and EEG recordings. Moreover, for a subgroup of patients, iPSC-derived induced neurons will be generated to create an in vitro model of STXBP1 encephalopathy in human neurons, which will be used to gain a deeper understanding of the cellular and molecular effects of STXBP1 mutations.

Study design

Observational study.

Study burden and risks

The risk associated with medical history, interview/physical examination and EEG recordings is negligible, since these are non-invasive techniques. It is possible that an 'accidental finding' will occur. In that case, the primary physician of the participating patient will be informed.
Skin biopsies are associated with some minimal risk of bleeding or irritation. This procedure will be carried out by a clinician and local anaesthetics will be used to minimize patient discomfort. It is possible to participate in the study without the skin biopsy procedure, since biopsies will only be taken from a subgroup of patients.

The total duration of the procedures will be one day, and one additional day during the 'follow-up'. During the 'Clinic' day, there will be opportunity to meet other patient (families) and researchers involved in STXBP1 research. If desired, the procedures can also be planned on a separate day (with shorter total duration).

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

Identified mutation in the STXBP1-gene

Exclusion criteria

Severe language barrier that is likely to hinder the procedure of informed consent.

Study design

Design

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

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-10-2018
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO

Date:	30-08-2018
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL66152.029.18