BRAINmodel: Clinical characterization and understanding of excitation/inhibition ratio homeostasis in children with genetic syndromes caused by chromatin- or synapse regulatory factors.

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In this study we aim to further characterize E/I balance (at different translational levels), and its relation to metabolic- and immune processes, clinical profiles, behavior and cognition

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

Summary

ID

NL-OMON53929

Source
ToetsingOnline

Brief title
BREIN

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Developmental disorders NEC

Synonym
autism spectrum disorder, monogenetic syndrome

Research involving

Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: autism, excitation, inhibition, neurodevelopment

Outcome measures

Primary outcome

Per participant:

1. Neurophysiological profile, including relative and absolute power spectra, mean frequencies, functional excitation/inhibition (fE/I) ratio, measured on different translational levels (clinical EEG measurement and patient-derived IPSC-based models)

2. Metabolic profile (based on medical history, physical examination, blood measures, urine sample, X-hand)

3. Immunlogical profile (based on medical history, physical examination, blood measures)

4. Outcomes of neurocognitive and behavioral measures: Vineland adaptive behavior scale (3rd edition), WISC-V or WPPSI-IV, and PAROM (or alternative tools, depending on the developmental age of the participant)

5. Knowledge on participant-specific medications which are in vitro effective to restore the neuronal E/I balance

Secondary outcome

not applicable

Study description

Background summary

Neurodevelopmental disorders (NDDs), including intellectual disability (ID), autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), are complex and the etiology of these disorders is barely understood. Monogenetic NDDs (mNDDs) are a subclass of the NDDs, caused by rare gene mutations in 1 out of the >1000 NDD genes known today. The with mNDD associated life-long medical, psychiatric, and developmental vulnerability results in tremendous suffering for patients and their relatives. Until now, no effective treatments are available for ID and ASD, and none of the NDDs can yet be cured. Pathophysiology of mNDDs is multifactorial and include the genetic defects, and dysregulation of molecular/synaptic, metabolic and immune processes. Genetic mutations and dysregulation of molecular/synaptic, metabolic and immune processes, disturb the E/I homeostasis. Moreover, E/I balance dysregulation in mNDDs is an underlying cause of disrupted brain functioning, altered social behavior, cognitive impairment, increased seizure susceptibility and information processing disorder. As E/I balance can be considered as translational framework in many forms of mNDDs, intervening in the E/I balance dysregulation might lead to the development of targeted treatments, to correct either the precipitating defect (metabolic and/or immune dysfunction) and/or the E/I balance regulation itself.

Study objective

In this study we aim to further characterize E/I balance (at different translational levels), and its relation to metabolic- and immune processes, clinical profiles, behavior and cognition

Study design

Multi-center Prospective Observational study with minimally invasive measurements.

Study burden and risks

Participants will receive characterization of clinical, laboratory and neurocognitive profiles and they receive their individual research results, which may be of help in more targeted medical guidance. Second, participants will contribute to syndrome-specific knowledge, and the results obtained through this study may guide in better counseling, screening and understanding of these disorders in the future. Ultimately, this knowledge results in the availability of evidence-based precision medicine for the participants, the included mNDDs, and mNDDs with comparable clinical profiles. Moreover,

participants in this study may be invited to take part in future follow-up studies, in which medication is tested in vitro and in n=1 (individualized) clinical trials, providing novel perspectives.

Minimal risks of the study for individual participants are:
- Blood drawing: hematoma and pain at the site of venapuncture
- Blood collection and EEG measurement might cause psychological stress and anxiety in patients which will be reduced by careful explanations of the procedure and the assistance of social childcare workers in calming procedures if needed. Because we only make an EEG in resting state and during auditive Evoked Related Potentials, there is no risk for provoking epilepsy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

- Written informed consent to participate in this study
- Molecularly confirmed pathogenic defect in one of the following genes: EHMT1, SETD1A, KMT2A, KMT2C, KMT2D, KDM3B, KDM6B, DNMT3A, (Chromatinopathies) or STXBP1, SYT1, SNAP25, RIMS1 (SNAREopathies)
- Age >=5 or <=17 years old

Exclusion criteria

- No molecular confirmed diagnosis of a defect in one of the following genes: EHMT1, SETD1A, KMT2A, KMT2C, KMT2D, KDM3B, KDM6B, DNMT3A (Chromatinopathies) or STXBP1, SYT1, SNAP25, RIMS1 (SNAREopathies).
- Additional or larger genetic defects that influence the gene of interest related phenotype
- Age <=4 or >=18 years old
- Extremely or very preterm birth (<32 weeks of pregnancy)
- Presence of serious, unstable illnesses (including gastro-intestinal, respiratory, cardiovascular, endocrinologic, metabolic)
- Presence of severe psychiatric disease (e.g., current major depression or psychosis)
- Inability to visit the outpatient clinic of Radboudumc or N=You Amsterdam UMC

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:	Recruiting
Start date (anticipated):	03-12-2022

Enrollment:	75
Type:	Actual

Ethics review

Approved WMO Date:	26-09-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-05-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-11-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL81570.091.22