Brain Lab Circuit for adults with rare intracellular calcium related synaptopathies. Identifying outcome measures for intervention trials.

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Primary1) Identify a selection of Child Brain Lab assessments that can serve as clinically relevant and feasible outcome measures for an anticipated gene therapy intervention trial in children & adults with calcium-related synaptopathies2)...

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

Summary

ID

NL-OMON57325

Source
ToetsingOnline

Brief title
Brain lab in adult synaptopathies.

Condition

- Neurological disorders congenital

Synonym
GRIA), GRIN, Intracellular calcium-related synaptopathy (CAMK2

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Dutch Brain Foundation;Dioraphte Foundation (Erasmus MC Foundation)

Intervention

Keyword: Calcium-related synaptopathies, Child Brain Lab assessments in adults with cognitive deficits, Outcome measures

Outcome measures

Primary outcome

Primary endpoint 1

Feasible outcome measures for follow-up & intervention trials

Identify a minimum of four CBL assessments that can capture patient*s main

clinical symptoms up into adulthood.

Our pilot data -using both caregivers and health care professionals as a

source- indicates that the following measurements hold promise:

o EEG background pattern (spectral analysis for the alpha, beta and theta bands

during resting and upon social and non-social videos. Spectral analysis is a

standard method for quantification of the EEG) and has been shown to be altered

in children with neurodevelopmental disorders [e.g. Hipp 2021, Frohlich 2019].

o Score on eye-tracking tasks (social paradigms) #

o ERP (auditive Event-Related Potential) #

o Communication skill measures

o OCT (retinal nerve layer thickness)

o Motor function (standing balance, gait deviation index)

o 24-hour movement behavior including sleep (activity tracker)

o Growth parameters (including head circumference), body composition and facial

shape (3D photography measures)

*For the proof-of-concept cohort, we expect adult patients to have a developmental age younger than 4 years. However, assessments can be adjusted to any developmental age using the standard CBL protocol.

Measurements performed in combination with EEG

Primary endpoint 2

Create detailed and standardized natural history data of adults with intracellular calcium-related synaptopathies to be used for primary aim 1 and secondary endpoint 2, in addition to provide better counseling of caregivers about prognosis and for the design of intervention studies. Once we have obtained a core set of assessments, we can expand this to other CAMK2 expertise centers around the world. Together with the parent organization, we are focusing on building a network of expertise centers, starting with North America.

Secondary outcome

Secondary endpoint 1

Create shared and disease-specific developmental curves with relevant and meaningful outcomes across four domains (cognition, behavior & language, neurophysiology, brain & craniofacial structure, and motor development) in children with intracellular calcium related synaptopathies, both from well-established and validated parameters in addition to newly developed parameters. This requires integration of parameters collected in time. We will start with outcomes in the domains cognition, behavior, language, and sleep.

Secondary endpoint 2

Develop biomarkers from neurophysiological, gait analyses, MRI metrics, 3D photogrammetry, and OCT data in collaboration with researchers from TU Delft that can be used to predict long term development. This will be part of the larger CBL initiative to use machine learning algorithms (both classic and more advanced neural network-based methods) to identify new biomarkers. The multi-domain nature of the data (OCT, EEG, patient reports, etc.) will allow to apply multi-modal types of AI algorithms, which will be trained on integrated information from different measurement modalities.

Study description

Background summary

The Pediatric Brain Center (PBC) is a collaboration of medical professionals and researchers in the Erasmus MC - Sophia Children*s Hospital who are involved in the clinical care for and research in children with conditions of the brain, nerves, senses and limbs. To improve family participation, quality of care and facilitate research and trials, the Child Brain Lab (CBL) has been established. The CBL is designed as a functional lab enabling standardized follow-up in relevant and meaningful domains for natural history building and for identification of biomarkers for prognosis and treatment evaluation. The CBL began actively recruiting patients in the summer of 2023 (MEC-2022-0606), including children with ultra-rare congenital brain conditions who are being treated by clinicians at the NFU-accredited ENCORE expertise center. In the current protocol, we seek approval to include (inter)national patients over the age of 18 years as this adult cohort offers crucial insights into the natural history of these (ultra) rare conditions and adult patients are eligible for gene-therapy approaches. The submitted protocol has only mild adaptations to the original protocol of the CBL (NL82466.078.22 / MEC-2022-0606).

One of the patient groups currently being recruited by ENCORE for CBL participation consists of children with a neurodevelopmental disorder caused by mutations in intracellular calcium-signaling genes. These disorders are collectively known as calcium-related synapthopathies, with CAMK2 syndrome being one example. ENCORE has extensive expertise in this specific synaptopathy

and established the world*s only center of expertise in 2019. Over the next five years, our neuroscientists aim to develop a personalized ASO gene therapy-based treatment, with a proof-of-principle focus on CAMK2 patients with gain-of-function (GOF) mutations, specifically targeting the Pro139Leu and Thr286X variants. This work is funded by the Dutch *Hersenstichting* (number grant application: DR-2023-00429) and *Dioraphte* (number grant application: 116320) foundations and is in close collaboration with the parent foundation: CAMK2 therapeutics network (https://www.camk2.org). In parallel, we as a clinical team are focused on identifying reliable and feasible clinical outcome measures to assess whether the ASOs can indeed significantly improve patients' quality of life. To accomplish this goal, we are utilizing the CBL facility.
Given that CAMK2 synaptopathy is an ultra-rare condition, with an even smaller subgroup of patients having these specific variants, international patients are also invited to visit the CBL at Erasmus MC. Under the Child Brain Lab protocol (NL82466.078.22), permission was obtained to allow children aged 0-18 years to participate in the study. In the current protocol, we seek approval to include (inter)national patients over the age of 18 years. As patients with CAMK2 GOF mutations are on the very severe end of the clinical spectrum with profound intellectual disability, wheel chair dependance and no speech, assessments in line with their developmental age are deemed appropriate. Moreover, our fundamental research team showed that adult restoration of CAMK2 in the brain, cures mice with CAMK2A-dependent NDD, hence an age-limited treatment window seems not applicable.

Study objective

Primary
1) Identify a selection of Child Brain Lab assessments that can serve as clinically relevant and feasible outcome measures for an anticipated gene therapy intervention trial in children & adults with calcium-related synaptopathies
2) Collect detailed and standardized natural history data of adult patients with calcium-related synaptopathies. We will start including CAMK2 patients on the severe end of the clinical spectrum as these will be the primary target for disease modifying (gene) therapies.

Secondary
1) Create shared AND disease-specific developmental curves in patients with intracellular calcium-related synaptopathies.
2) Use advanced data-analyses/statistical techniques and AI to identify early biomarkers that help predict long term development across intracellular calcium related-synaptopathies.

Study design

Observational cross-sectional study.

Study burden and risks

The burden of participating in the CBL test circuit is a time investment of 3 days in total extended by the time needed to travel to the Netherlands. Tests itself are non-invasive and not painful. However, due to their underlying genetic condition with intellectual disability, unique behavioral characteristics, and the absence of speech means that this patient group may respond differently to measurements than neurotypical individuals. Therefore, the travel and visit to the children's brain lab may be perceived as stressful or anxiety-inducing. To minimize negative experiences, caregivers can receive tailored counseling to prepare their child for the visits. Significant expertise has been gained within ENCORE (Angelman Syndrome) and through the pilot tests of the children's brain lab circuit. Moreover, we have had positive experiences with a similar NDD patient group (GRIN, n = 15) so far. During each measurement, the tester will evaluate whether the next measurement is feasible and acceptable, in close consultation with the family. We will terminate the measurement if the participant shows signs of anxiety, distress, or objection.

Patients carrying CAMK2B-p.(Pro139Leu) and CAMK2A-p.(Thr286X) variations will directly benefit from results. As this is a proof-of-concept study, we can and will extrapolate our results and methods to other CAMK2 mutations as well as other synaptopathies. Moreover, non-gene therapy interventional trials can benefit from study results also. F.e. tailoring alternative speech-language support, adaptation of drug treatment for symptom relief for common behavioral and sleep problems and/or epilepsy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Age >18 years old
- Genetic testing confirming a pathogenic variation (using international ACMG criteria) resulting in an intracellular calcium-related synaptopathy (CAMK2, GRIN, GRIA).
For the proof-of-concept study we start recruiting patients with a mutation in either the CAMK2B (Pro139Leu) or CAMK2A (Thr286Xvariants) gene.
- Able to provide written informed consent by a biological parent and/or legal representative.
- Caregivers are sufficiently proficient in either Dutch, English, French or Spanish in order to complete questionnaires.

Exclusion criteria

- Unable to understand or comply with the test circuit at the discretion of the treating physician (this concerns the parents of the patients as all are incapacitated).
- Patients with more than 1 genetic diagnosis.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2025
Enrollment:	25
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	03-03-2025
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	NL88035.078.24