Outcome measures in children with Angelman syndrome

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

Summary

ID

NL-OMON49460

Source
ToetsingOnline

Brief title
Rotterdam Angelman Outcome Study

Condition

- Neurological disorders congenital

Synonym
Angelman syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Stichting Vrienden van het Sophia;en verdere financiering nog te verkrijgen

Intervention

Keyword: Angelman syndrome, feasibility, natural history, outcome measures

Outcome measures

Primary outcome

Feasibility of functional Near Infrared Spectroscopy (fNIRS), eye-tracking, the Zeno Walkway Gait Analysis System, Indirect Calorimetry (IC), the BOD POD, and Bio-Impedance Analysis (BIA) in children with Angelman syndrome.

Secondary outcome

The study*s secondary objective is to further unravel the phenotype of Angelman syndrome, i.e., deep phenotyping.

For the secondary objective, we will:

1. Collect additional measures to complement our existing natural history database.

2. Relate the variables of our primary objective to a) each other; b) the variables of our secondary objectives, and; c) the variables of our existing natural history study.

3. Relate the genotype to several of the primary and secondary outcome variables.

Study description

Background summary

Angelman syndrome (AS) is a rare genetic disorder resulting in severe intellectual disability/developmental delay, speech impairment, and problems

with movement or balance. Children with AS often have epilepsy, psychiatric symptoms (short attention span, anxiety, autistic features), sleeping, and feeding problems. Since 2010, 125 AS patients are seen for prospective, structural and multidisciplinary follow-up at our ENCORE Expertise Center for Genetic Neurodevelopmental Disorders, resulting in a large set of natural history data (non-WMO protocol VOLG ENCORE MEC-2015-203).

Knowledge on the feasibility of sensitive outcome measures for children with AS is lacking. Standard outcome measures are often less suitable for AS patients. Characteristics of AS such as speech impairment, inattention, behavioural problems (motivation and anxiety), tiredness due to sleep problems, and epilepsy can bias the outcome of such tests. This lowers the test's validity and reliability. It can also result in a floor effect, lack of variance between individuals, and therefore the inability to detect change in treatment studies. Current treatment studies often use outcome measures that are less suitable for children with AS, thus raising questions about the reliability and validity of such studies.

Current therapeutic strategies for AS are symptomatic. However, treatment studies for etiologic (targeted) therapy are anticipated. An antisense oligonucleotide treatment has been developed, and promising results in preclinical mice studies foresee treatment studies in patients in the near future. No one knows what such a treatment will mean for AS patients. It is unclear in which domains they may show improvement with treatment, what the size of the effect will be, what the lag time between administration of the treatment and clinical improvement will be, or what the influence of age of the patient will be on the potential effect. For the design of future treatment studies, it is of vital importance to identify feasible outcome measures that will likely be sensitive to relevant treatment effect. These measures are currently lacking.

Furthermore, new insights and hypotheses based on recent literature and clinical experience have led to new interests regarding natural history variables, for example concerning metabolic, endocrine, and autonomic (dis)function in AS. These variables cannot yet be included into our ENCORE clinical follow-up, but are of major importance to gain further insight into the AS phenotype.

Study objective

The primary objective of this study is to investigate the feasibility of several promising outcome measures in children with AS, which may later serve as potential outcome measures for treatment studies and other research.

The study*s secondary objective is to further unravel the phenotype of Angelman syndrome, i.e., deep phenotyping.

For the secondary objective, we will:
1. Collect additional measures to complement our existing natural history database.
2. Relate the variables of our primary objective to a) each other; b) the variables of our secondary objectives, and; c) the variables of our existing natural history study.
3. Relate the genotype to several of the primary and secondary outcome variables.

Study design

This is an observational cross-sectional study.

The study design is as follows:

1) Telephone call with the parent(s)/caregiver(s): explaining the study and answering questions, eligibility interview (20 min total).

2) 'Home assessments', to be carried out by the parent/caregiver (total duration 130 minutes). The home assessments do not have to be completed all at once, but completion can be spread over multiple moments of the parent/caregiver*s own choosing. The questionnaires are on the behaviour and medical history of the child. Additionally, there is a food diary for the child (3 days).

The assessments ential:
• Temperature measurements of the child (3x).
• Urine collection of the child (1x).
• Fluid balance for the child (1 day).
• Look up GGD growth data of the child.

3) Visit 1 will take place in our mobile research lab (the Sophia Research Bus) at a location of the participant*s choosing. This minimizes the burden of travelling for the study visit. The total task time during this visit is 80 minutes, we will have 1 or multiple breaks in consultation with the parent and child.

Tasks during this visit:
• While the child watches pictures and videos, we simultaneously conduct eye-tracking and fNIRS measurements.
• Short physical examination.
• Gait assessment (m-POMA-G). The child is asked to walk a few meters (with their own walking aid if needed).
• We cut a few hairs from the head in order to measure cortisol.
• Venipucture.
• If genotype is incomplete, we take an additional tube of blood for exact genotyping (only when the participant's legal representative has given consent

for this on the informed consent form).
• We conduct a short interview with the parent/caregiver (CGI-S-AS).

4) 'Home assessments', to be carried out by the parent/caregiver (total duration 120 minutes). The home assessments do not have to be completed all at once, but completion can be spread over multiple moments of the parent/caregiver*s own choosing. The questionnaires are about sleep of the child. Additionally, parents are asked to fill in a sleep diary for the child and for themselves (2 weeks).

The assessments entail:
• Collecting some saliva for melatonine measurements, which will be obtained using cotton wool dots (see C1. Protocol Appendix I for a comprehensive descriptiono this measurement). Children can chew on them for several seconds, or parents can swipe the cavity of the child*s mouth, or parents can collect the saliva that drips out of the child*s mouth. Since most children with Angelman syndrome have a tendency to drool, this will be not difficult to achieve. This will be done during one natural day, every hour from 17.00 (<12 years) or 18.00 (>12 years) to onset sleep, once during the night (only if the child and parent are already awake due to other factors), once in the morning after awakening, and once at noon on the next day.
• Actigraphy: a non-invasive measure of activity and heath beat. A small actimeter device can be worn as an ankle band or be attached to the clothing if that makes it more acceptable for the patient. The actigraph should be worn during 14 consecutive nights and days. As participants will likely get used to the actigraph while they wear it, we advise to not take the device off during these days. The only task for the parent is to put on the actimeter once.
• The researcher will install an infrared video camera in the bedroom of the child after the first study visit. The camera will automatically turn on and off, and film only during the participant's bed time. Using the videos, nightly physical activity can be registered and checked for the kind of movement or activity (e.g., turning in sleep, actual awakening, or epileptic seizures). The camera films during 4 nights, of which 3 will be used for analyses, and 1 serves as stand-by in case of technical difficulties with the camera - after quality control the unnecessary nights will be removed.

5) Visit 2 will be in the Erasmus MC - Sophia. The total task time during this visit is 80 minutes, we will have 1 or multiple breaks in consultation with the parent and child.

Tasks during this visit:
• Zeno Walkway Gait Analysis System: measuring spatiotemporal gait parameters.
• Indirect Calorimetry: measuring resting energy expenditure
• Measuring body composition in two ways, to compare which one is most feasible and accurate in children with AS.
- BOD POD: Body-composition assessment via air-discplacement plethysmography
- Bio-impedance analysis: through electrodes, a weak electric current flows

through the body and the voltage is measured in order to calculate impedance (resistance) of the body. The child does not feel the current.

Participation in all assessments and visits of this study is desirable, but not mandatory for study inclusion. Participants can choose if they want to participate in the full study, just one of the study visits and the home assessments, or even only the home assessments.

Study burden and risks

The risks and inconveniences of this study are negligible: there are no known risks or side effects to the measurements we use. It is possible that a participant may experience a particular measurement as unpleasant, scary, or stressful. If the participant shows signs of discomfort or objection (as described in the 'Code of conduct relating to the expression of objection by people with mental disabilities in the context of the WMO'), or if the parent/caregivers objects, we will at all times stop the measurement.

We have undertaken additional measures to reduce the chance of possible inconveniences for the participant. To reduce the possible inconvenience of the venipucture, we will apply EMLA cream as topical anesthetic and distract the participant during the venipuncture. During the BOD POD and IC measurements, the children can watch distracting movies. Concerning the fNIRS measurement, the tightness of the fNIRS cap (like a swimming cap) and may induce an uncomfortable sensation in those participants that are highly sensitive to touch. A practice fNIRS cap will be send home so that the child can practice and acclimate to the situation before the actual study visit. The fNIRS measurement is silent, and children can move freely because of the wireless cap (in contrast to a more invasive fMRI measurement). Eye-tracking is non-invasive.The parent(s)/caregiver(s) will receive individually tailored counselling how to best prepare the participant for the above measurements using pictures. Individually tailored behavioural support and distraction will be offered during the measurement by the executive researcher.

The total burden of participation will be two visits of 80 minutes for the child and the parent/caregiver. For the first study visit, we will visit participants at a location of their choosing with the Sophia Research Bus, minimizing the burden of travelling. The second study visit can be combined with a regular clinical visit, if desired by the parent/caregiver. One or more breaks can be taken during the study visits, in close consultation with the parent and child (time for breaks is not included in the 80 minutes yet). The additional burden of participation for the parent/caregiver will be two series of home assessments of 130 and 120 minutes. The home assessments do not have to be completed all at once, but completion can be spread over multiple moments of the parent/caregiver*s own choosing. Participation in all assessments and visits of this study is desirable, but not mandatory for study inclusion. Participants can choose if they want to participate in the full study, just one

of the study visits and the home assessments, or even only the home assessments. Furthermore, should a participant or parent/caregiver refuse to participate in a specific task or questionnaire, he/she can still continue with the rest of the study or visit.

Scientific benefit will be gained by pointing out feasible and suitable outcome measures in children with AS. These outcome measures can be used in future treatment studies, thereby facilitating improved assessment of treatment efficacy. These outcome measures can additionally be used in other scientific research, and maybe in clinical practice. Moreover, benefit will be gained by further elucidating the AS phenotype in great detail, thus aiding knowledge on the natural history of the syndrome, which can guide treatment studies and may contribute to a clearer prognosis for children with Angelman syndrome.

The current study can only be performed using the current population of children with Angelman syndrome, because the main goal is to find feasible outcome measures for this population and clarify the natural history of this syndrome. Feasibility of outcome measures for mentally competent individuals would not generalize to this unique population of children with Angelman syndrome.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Wytemaweg 8
Rotterdam 3015 CN
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Wytemaweg 8
Rotterdam 3015 CN
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Genetically confirmed diagnosis of Angelman syndrome;
• Age between 6 months and 18 years;
• Informed consent given by legal representative (parent or caregiver);
• Parent(s)/caregiver(s) should have an adequate command of the Dutch language.

Exclusion criteria

• Current non-convulsive status epilepticus or inter-current somatic illness influencing daily functioning;
• The presence of a mosaic form of Angelman syndrome;
• Severe visual problems that will interfere with the participant*s ability to perceive the stimuli on the screen during the fNIRS and eye-tracking tasks.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-04-2021
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	05-10-2020
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

ID: 23075
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL73550.078.20
Other	NL8550 (NTR)
OMON	NL-OMON23075