Tackling defective epigenetic assembly in psychopathology: Towards personalized intervention in Kleefstra syndrome

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We aim to prevent or reverse developmental regression in patients with Kleefstra syndrome. We hypothesise that the regression we observed is the result of a psychotic disorder, which isnot properly recognised by clinicians and often not treated...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Schizophrenia and other psychotic disorders
Study type	Observational non invasive

Summary

ID

NL-OMON45876

Source
ToetsingOnline

Brief title
Tackling the disordered brain in Kleefstra syndrome

Condition

- Schizophrenia and other psychotic disorders

Synonym
psychoses; disorganised behavior

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: vidi

Intervention

Keyword: Kleefstra syndrome, neurodevelopment, olanzapine, psychoses

Outcome measures

Primary outcome

The primary outcome of the present study will be the differences between

treated and

non-treated groups in regression (individual % reduction in adaptive

functioning based

on raw VABS score), to study if there is any benefit from early detection and

subsequent

treatment of olanzapine.

All data will be collected in the GCP-certified data monitoring system Castor.

Castor facilitates multicentre, international studies and gives the opportunity

for data collection at each

site. As main researchers we will be able to see all data and perform the

analyses. To make sure

that all data are collected according to good clinical practice criteria, all

sites participating in this study

will be visited and monitored by a certified person of our team.

Secondary outcome

Secondary outcomes comprise detailed knowledge on the window of treatment

opportunity to influence regression and association of urinary markers with

symptom

severity. Furthuremore, I will use the mini PAS ADD and PANSS scores to obtain

knowledge of the course of PD, presence of comorbid psychopathology and evaluate

treatment response in terms of severity and duration of the PD.

Study description

Background summary

Next generation genetic studies in rare neurodevelopmental disorders (NDs) have spectacularly
increased diagnostic yield. The majority of Mendelian causes of intellectual disability (ID) and autism
spectrum disorders (ASD) can now be identified. For the first time, this opens doors to detailed
characterization and identification of syndromes based on their genetic etiology. The aim of our
research group is to design personalized care for genetic NDs.
One of the major issues we experience in dealing with patients affected by ND syndromes is related to
their psychopathology and behavioural problems, which have a great impact on quality of life of
patients and their families. A better understanding of the underlying neurocognitive and biological mechanisms will open doors to investigate new therapeutic intervention and subsequent improvement of care. To move this field forward, we have
founded a network of dedicated professionals in the multidisciplinary expert clinic on rare genetic NDs
(www.radboudumc.nl/ontwikkelingsstoornissen). Our main focus is on patients with Kleefstra syndrome
(KS). After discovering the genetic cause of KS 10 years ago, we have spent most of my time unravelling
the pathogenesis of this syndrome and finding ways to improve therapeutic interventions for those
patients

Based on our historical observations and correspondence from (international) colleagues and patient
representatives, KS is characterized by (post-)puberty behavioural regression. Amongst the symptoms
that we have observed in KS patients are extreme apathy (a decline in

motivational behaviours),
catatonia, lack of task focus, sleep disorders (frequent nocturnal awakenings and daytime sleepiness),
and abnormal posturing of arms and hands. Based on these findings, we systematically assessed
the psychopathological phenotype in the Dutch cohort (n=24) of KS patients. Analyses based on
clinical interviews, i.e. ADOS-2 and the mini-PAS-ADD, showed that ASD was present in all individuals
with KS. We also noted high prevalence of depressive and obsessive compulsive disorders. Most
importantly, psychotic disorders and severe regression occur in an exceptionally high
percentage of KS patients. All patients above the age of 18 years in our cohort study (n=8)
have (had) a psychotic disorder and a severe loss of functioning . The general population
incidence of psychotic disorders is only 0.8%.
We observed that treatment with relatively high dosages of antipsychotics contributed
significantly to improvement of daily life functioning. Our experience with this syndrome forms the basis
for the present project.

Study objective

We aim to prevent or reverse developmental regression in patients with Kleefstra syndrome. We hypothesise that the regression we observed is the result of a psychotic disorder, which is
not properly recognised by clinicians and often not treated according to the guidelines for psychotic
disorders. Investigating development and sources of the behavioural problems and regression
requires the development of a strategy to implement longitudinal follow-up of patients with KS;
this is one of my key-objectives. In our retrospective descriptive study, we found that KS patients
had better response and fewer side effects on olanzapine, an atypical antipsychotic acting on multiple
neurotransmitter systems compared to others with predominantly dopaminergic receptor affinity.

Objective 1: to develop a longitudinal follow-up study of KS patients with special attention to
behavioural developmental changes

Objective 2: To perform an international study to test the effect of olanzapine

treatment in patients with KS with general regression

Objective 3: to study the in vitro effects of effective drugs like olanzapine by measuring neural
network activity in patient-derived induced neurons.

Study design

We need to develop such robust metrics. However, for patients with severe intellectual disability (IQ<50), few suitable validated instruments are available for diagnosing
psychopathology in a detailed and structured manner. Therefore, I will tailor our test battery to the
needs of KS population based on the explorative findings from our historical cohort. In addition to a
general examination to assess the level of functioning, this battery will comprise tests and
questionnaires adapted to the individual capacities of KS patients (table 1, page 8 application)
Moreover, we will collect baseline measures at t0 to prepare for treatment, which include a screen for
CYP1A2 and CYP2D6 polymorphisms to determine an optimal drug dosage regime (Box 1, page 9 application). Signs
and symptoms of psychotic disorder - which according to the diagnostic manual of ID (DM-ID)
characteristically consist of a loss of cognitive functions and (sudden) significant behavioural changes
in addition to hallucinations and delusions - as well as developmental regression, will be a particular
focus of our battery, to be assessed by VABS, Mini-PAS-ADD, and PANSS.
We will see the patients annually according to this evaluation scheme to prospectively collect detailed
longitudinal data on development and behaviour. In total, I expect to evaluate 40 patients at 3 or more
time points. Based on the results from this evaluation, the test battery and strategy for examining
psychopathology will be further optimized for patients with KS, which will serve as a model for similar
syndromes with low IQ. Moreover, we will identify additional endpoints to be used as outcome measures
in future intervention programs. In addition to the annual evaluation, biobanking of blood, urine, and a
skin biopsy for hIPSC generation are part of the assessment for studying objective 3

In our open label intervention, our team or the international collaborator psychiatrist will prescribeantipsychotic treatment, when psychotic disorder is

suspected on the basis of the indicators and
findings by psychiatric examination and observation, as described above. Both groups will be treated,
when applicable. According to the international guidelines (NICE + Multidisciplinary Guideline
Schizophrenia from the Netherlands, kinderformularium), the antipsychotic drug of choice depends on individual factors.
In this study, the treatment of first choice is olanzapine, not only as based on scientific findings, but
we also found it strikingly more effective in our previously treated patients compared to other
antipsychotics. In case of contra-indications, prescription of alternative medication will be discussed for
the specific patient by the expert team. Because of the risk of side effects, somatic screening will
continue during treatment according to international guidelines.
Adverse drug events will be evaluated by a clinical pharmacologist. A safety data monitoring team will
evaluate all data once a year.

We will perform an international open label trial according to a wellestablished design for (ultra)rare diseases using Bayesian statistics and sequential analyses. The cohort numbers are calculated for a power of .95 (.05 significance) on
the assumption that at least 1/3 of EDC will have PD and treatment will at least 50% of regression. we will collect data on all KS patients age >=12 years at t0 and divide them into two groups based on VABS/PANSS/Mini-PAS-ADD assessments:
I. Late detection Cohort (LDC): KS patients, who score positively on the life-time
prevalence of psychotic disorder (PD; with or without current suspicion on PD), with onset of first symptoms >2 years before t0 (already n=8 collected).
II. Early detection Cohort (EDC): those who have been so far without any PD, or with
suspicion of PD with start of symptoms <=2 years before t0.

Human induced pluripotent stem cells (hIPSCs) and neurons re-programmed from those,
represent a novel exciting avenue to study the underlying mechanisms of brain diseases
and for the design and optimization of new therapies (personalized medicine).In the Stem Cell Facility at our department,
differentiation protocols have been optimized to produce bona fide cortical excitatory and
dopaminergic neurons from hIPSCs. iNeurons from KS patients
with regression show severe disorganisation of synchronised synaptic bursting activity.

Here, we will use iNeurons from KS patients to get insight in the mode of action of drugs
and to predict the efficacy of specific drug interventions.
3a: Mode of action of olanzapine in KS. I am to elucidate how the beneficial effect of
olanzapine is mediated. In contrast to less effective antipsychotic drugs (risperidone and
haloperidol), olanzapine affects multiple neurotransmitter systems. Besides dopaminergic
neurons, which are targeted by all these drugs, olanzapine also acts on serotonergic and
cholinergic neurons. In addition to the established protocols for differentiating cortical
excitatory neurons and dopaminergic neurons, we will thus also generate serotonergic
and cholinergic neurons, using established protocols. Functional analysis will involve
the use of micro-electrode-arrays (MEAs), which allow repeated (every 2 days), passive
recording of spontaneously generated action potentials from the same culture. Such
action potentials become coordinated in space and time during maturation of the
neurons, which we will monitor in 24-well MEAs. We will determine whether olanzapine
can restore abnormal network activity, and whether its effect is specific for a particular type of neuron. We speculate that such effect
on MEA cultures will be predictive for its capacity to prevent regression.
3b: Predicting drug efficacy in vitro. It is possible that olanzapine will proof to be
effective in most, but not in all the KS patients. We will use the conditions established in
Objective 3a to investigate whether we can predict drug (olanzapine)-efficacy by comparative analyses with iNeurons from responsive and non-responsive individuals
(retrospective study). Moreover, I will conduct a prospective study with iNeurons derived
from patients with a KS-like phenotype caused by other genes that are part of the *KS
epigenetic module*. Our MEA studies have already established that haploinsufficiency
of such genes gives rise to highly similar neuronal network defects

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Study burden and risks

The study comprises low burden and risks. The burden for all included patients is In addition to a general examination to assess the level of functioning, the assessmnet of a battery of tests and questionnaires adapted to the individual capacities of KS patients . Moreover, we will collect baseline measures at t0 to prepare for treatment, which include a screen for CYP1A2 and CYP2D6 polymorphisms to determine an optimal drug dose regime.
In those individulas where we observe signs of psychotic disorder - which according to the diagnostic manual of ID (DM-ID) characteristically consist of a loss of cognitive functions and (sudden) significant behavioral changes in addition to hallucinations and delusions - as well as developmental regression, we will implement treatment witth antipsychotics and olanzapine as drug of first choice, as this is according to current best practice based upon our historical observation, This will not add extra burden or risks compared to the already excisting current situation where we advice the same strategy in clinicla practice. This study aims to evaluate the clinical effect of treatment with olanzapine.

The particular focus of our battery to screen for psychotic symptoms,, will be assessed by VABS, Mini-PAS-ADD, and PANSS. We will see the patients annually according to the evaluation scheme to prospectively collect detailed longitudinal data. Based on the results from this evaluation, the test battery and strategy for examining psychopathology will be further optimised for patients with KS, which will serve as a model for similar ND syndromes. In addition to the annual evaluation, biobanking of blood (only first occasion) and urine (all occasions) are part of the assessment.
regarding the tests/questionnaires (listed below) : the majority will be provided by the caregivers (VABS, MINI-PASSAD, QBCL).
Besides the general examination, only ADOS-2 (wil take 1 hour) , VMI, LTT (both only take less then 30 min) , (IQ test and CANTAB; depending on their developmental age which tests), will be requested to be performed by the patients.

Total list of tests/questionnaires:
-General examination: Includes height, weight, blood pressure, heartbeat frequency, abdominal circumference, biobank sampling (t0) and video-monitoring
-VABS: The Vineland Adaptive Behavior Scale to assess developmental age and possible developmental regression
-PANSS: Positive And Negative Syndrome Scale to measure both positive and negative psychotic symptoms
-Mini PAS-ADDMini Psychiatric Assessment Schedules for Adults with Developmental Disabilities
to measure a broad range of psychopathology
-ADOS-2: Autism Diagnostic Observation Schedule Standardized psychiatric observation of Autismspectrum symptoms
-CBCL: Child behavior checklist to asses behavioural difficulties
-Beery-VMI: Test for Visual-Motor Integration
-LLT: Location Learning Test to asses spatial learning and memory

-(IQ test)* Wechsler scale (WAIS-IV/WISC-V)
-(CANTAB) CAmbridge Neuropsychological Test Automated Battery
Computer based assessment of attention, memory and reaction time

Patients with the Kleefstra syndrome have an intellectual disability, so there is group relatedness.

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)
Elderly (65 years and older)

Inclusion criteria

- Confirmed molecular diagnoses of Kleefstra syndrome (EHMT1 mutation of small 9q34 deletion, < 1 MB)

- Age 12 year and older
- Longitudinal follow up and when diagnosed,treatment of patients when psychotic symptoms; Indicators by history of caregivers and as displayed in scores above cut-off on assessment batteries tailored to the patient population: Mini-PAS-ADD, PANSS and CBCL or reduction in adaptive functioning (VABS).

Exclusion criteria

- age below 12 years
- no confirmed diagnoses of Kleefstra syndrome
- long QT syndrome

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-04-2019
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	olanzapine
Generic name:	Zyprexa
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-01-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-02-2020
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
EudraCT	EUCTR 2018-002555-1-NL
CCMO	NL65650.091.18