SCN1A-related seizure disorders: prediction of clinical course based on advanced genotyping

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

Summary

ID

NL-OMON42281

Source
ToetsingOnline

Brief title
Prediction of clinical course in SCN1A related seizure disorders

Condition

- Neurological disorders congenital
- Seizures (incl subtypes)

Synonym
Dravet syndrome, epileptic encephalopathy, Severe Myoclonic Epilepsy in Infancy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Vrienden WKZ namens de Stichting Panta

Rhei

Intervention

Keyword: Dravet syndrome, epileptic encephalopathy, SCN1A

Outcome measures

Primary outcome

Classification of developmental outcome, rated independently by a child neurologist, neuropsychologist, and clinical geneticist. Developmental outcome will be rated on a four-point Likert scale (1= no or mild learning disability, 2=moderate learning disability, 3 = severe learning disability, 4= profound learning disability) based on available data on IQ, school functioning, motor skills, communication and adaptive behaviour, and adjusted for age at assessment. The neurologist, neuropsychologist and clinical geneticist will be blinded for the results of genotyping. In case of disagreement about classification, a consensus meeting will be held among the three.

Secondary outcome

1. The intelligence quotient over time, adjusted for age at assessment

2. Epilepsy syndrome classification; Classified as: febrile seizures; GEFS+; DS; other epilepsy syndrome

3. Mobility:

-Functional Mobility Scale (FMS), completed by parents

-Gait analysis

For gait analysis parents will be asked to make videos of their child walking

barefoot, with and without walking aids, watching the child form different positions (sideways, forward and backward). Parents will send the videos through a secure internet connection to the study team. The link to the video will only be accessible for the investigators. The file will be saved on a secured computer after which the online link will be deleted. Gait pattern will be classified for each patient as: 1. normal gait; 2. mild gait abnormalities 3. severe gait abnormalities 4. unable to walk.

4. Quality of life, using the Pediatric Quality of Life Inventory (PedsQL). For adult patients, the adult version will be used.

5. Behavioural difficulties, using the child behaviour checklist (CBCL). For adult patients, the adult version of the CBCL will be used.

Study description

Background summary

Dravet syndrome (DS) is a severe neurological disorder of childhood, of which the first symptoms usually occur within the first year of life. Its frequency is about 1 in 20,000 - 40,000 children. The disorder usually starts with generalized or unilateral clonic seizures associated with fever, illness or vaccination. At a later stage, other seizure types occur as well and patients may have prolonged status epilepticus. Psychomotor development is initially normal, but slows down in the second year of life. In addition, other neurological symptoms may appear, like pyramidal tract signs. Many patients with DS also have behavioural problems. Outcome is poor, with intellectual disability in most patients and ongoing seizures. Intellectual impairment varies from severe in 50% of the patients, to moderate and mild intellectual disability each accounting for 25% of cases. Rare patients have normal

intellect. Gait studies have shown that in many patients with DS walking deteriorates and patients may gradually develop a crouch pattern.

In about 75% of children with DS, a mutation is found in the SCN1A gene, which is encoding for the *-subunit of a neuronal sodium channel, Nav1.1. In 95% of the cases, it represents a de novo mutation in the affected child.
Certain anti-epileptic drugs might worsen seizures in patients with Dravet syndrome. A positive SCN1A test therefore influences treatment choice and may thereby have a beneficial effect on clinical course and cognitive outcome, especially in the very young. Therefore early genetic testing may be beneficial, and might be considered in each infant under age 12 months with a febrile seizure or a seizure after vaccination, or even as part of neonatal screening programmes.

However, SCN1A-mutations are also identified in patients with febrile seizures and in patients with the milder epilepsy syndrome GEFS+ (Genetic Epilepsy Febrile Seizures Plus). Moreover, in patients with DS there is a wide phenotypic variability, with on the one end of the phenotypic spectrum patients with ongoing seizures who are institutionalized and severely disabled, and on the other end patients who live independent lives. One of the prerequisites for early genetic testing would be that the clinical course of a patient could be accurately predicted according to the genotype. Genetic testing by mutation analysis of SCN1A only, would not allow a reliable prognosis.

Mutations causing truncation of the SCN1A protein and missense mutations affecting the voltage and/or ion-pore regions of the protein are more frequent in DS than in GEFS+. However, no positive correlation has been found between a specific mutation and a specific phenotype, and variable phenotypes have been associated with the same mutation. Mosaicism for the SCN1A mutation and the percentage of mosaicism may contribute to the variable clinical expression. In addition, variants in other genes, like the SCN9A-gene and CACNA1A-gene, may modulate the phenotype in SCN1A-related DS. Since DS is caused by decreased levels of Nav1.1, variants in the SCN1A promoter region and in 5*- and 3* untranslated exons may affect phenotype as well, by modulating SCN1A-expression.

Study objective

The objective of the study is to investigate if it is possible to predict the clinical outcome of a patient with SCN1A related epilepsy based on the findings of advanced genotyping.

We aim to answer the following questions:

1. Can clinical outcome in SCN1A-related febrile seizures / epilepsy be predicted based on *advanced genotyping*?
a. Is the degree of somatic mosaicism for the SCN1A mutation associated with

disease severity?
b. Are DNA-variants in the promoter region and/or the 5*- and 3*untranslated exons of SCN1A, and other variations than the pathogenic mutation in the coding regions of SCN1A associated with disease severity?
c. Are mutations in modifier genes associated with disease severity?

2. Does an early genetic diagnosis have a beneficial effect on clinical course and outcome in patients with SCN1A-related febrile seizure(s)/ epilepsy?

Study design

a. Approach of possible study participants
The parents / caretakers / legal representatives (from here called: *parents*) of potential participants will be contacted by the physician who had requested analysis of the SCN1A-gene, or by the neurologist, or, if the medical genetics department has been visited before, by the clinical geneticist.

b. Informed consent procedure
Patients and their parents who fulfil the criteria for inclusion will receive oral and written information about the study.
The written information includes three informed consent forms: one for participation of the patient with SCN1A-related febrile seizures / epilepsy, and one for each of the parents.
For patients with Dravet syndrome with intellectual disability, both parents will be asked to give written consent. For participation of normally intelligent children aged 12-18 years, both the parents and the child will be asked for written informed consent.

Patients and their parents will be asked for permission:
* to obtain data from medical records of the patient
* to undergo a telephone interview
* to respond to questionnaires on mobility, quality of life and behavior
* to make videos of the patient for gait analysis
* to use their DNA stored at the UMC Utrecht laboratory for genome diagnostics
* to have the laboratory test performed for the detection of: somatic mosaicism; variants in the promoter region and /or 5*- and 3* untranslated region; additional variants in the coding region of SCN1A; and, variants in modifier genes.

c. Medical data collection
When informed consent has been obtained the following medical data will be collected:
- date of birth
- gender
- gestational age, birth weight, head circumference at birth, Apgar scores, perinatal complications
- age at clinical and at molecular diagnosis

- calendar year of clinical and molecular diagnosis
- age at onset per seizure type
- frequency and type of seizures
- fever sensitivity
- anticonvulsive treatment that has been / is being used
- response to treatment
- the results of neurological examination
- the results of EEG and MRI
- use of walking aids and procedures that the child underwent to improve walking ability
- comorbidity
- psychomotor development; including early developmental milestones
- school performance
- results of neuropsychological examination, including instruments that have been used and date of assessment
- behavioral abnormalities, autism, attention deficit (hyperactivity) disorder, aggression
- family history
- age of the parents at the time of conception

In case these data are not available in the patient*s records, additional information will be collected during a telephone interview with patient or parents.

d. Questionnaires
To evaluate clinical outcomes, we will interview parents by phone about mobility, quality of life, and behavioral problems using short standardized questionnaires. Parents receive the questionnaires in advance by mail.

e. Laboratory methods

Mosaicism
To establish whether the patient is mosaic for the pathogenic SCN1A mutation, and if so, at what grade, high coverage massive parallel sequencing of the DNA will used. After initial validation of the procedure using mixtures of DNA, the ratio of reads carrying the mutation relative to those carrying the wildtype can be used to establish the degree of mosaicism.

Regulatory variants
Variants in the promoter region, the 5*UTRs and the 3*UTRs of the gene SCN1A may affect expression of the gene. Additional non-pathogenic variants in the gene may affect the protein function or splicing. Presence of such variants will be established by massive parallel sequencing. Follow-up of identified variants will depend on the type of variant. In addition to bioinformatics prediction, cell culture experiments may be used to get better idea of the effect of the variant on SCN1A expression.

Modifier genes
To identify variants in modifier genes, again massive parallel sequencing will be used. Establishing a list of possible modifier genes and filtering strategies for possible modifier variants will be part of this project.

Study burden and risks

The only potential risk of participating in this study is related to a venous puncture in parents from whom no DNA is available yet. These risks include hematomas and local infection on the site of puncture, and for some patients a vasovagal response on the venous puncture.

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

patients with SCN1A related febrile seizures and/or epilepsy and their parents

Exclusion criteria

patients with a variant of unknown significance (class III) in the SCN1A gene

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-06-2015
Enrollment:	600
Type:	Actual

Ethics review

Approved WMO

Date:	31-03-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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: 27611
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL50984.041.14
OMON	NL-OMON27611