Novel genetic markers of surgical candidacy in refractory epilepsy: Whole Exome Sequencing in historical cohorts of patients

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Primary Objective: Our overall aim is to improve selection of patients for epilepsy surgery and predict surgical candidacy with use of genetic test results as a biomarker. The specific objective is:Cohort 1. perform trio-WES in MRI-negative patients...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON52626

Source
ToetsingOnline

Brief title
Genetics & epilepsy surgery 2 / GENES 2

Condition

- Other condition

Synonym
Focal epilepsy; Epilepsy

Health condition

Hersenaandoeningen; Epilepsie

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMw,MING fonds

Intervention

Keyword: Epilepsy surgery, Focal epilepsy, Genetics, MRI-negative

Outcome measures

Primary outcome

We will select all de novo mutations that are predicted to be pathogenic and causally related to the epilepsy and are absent in available control databases. Surgical outcome is collected from the databases and electronic medical patient files. Genetic findings will be compared between both groups, and related with seizure outcome. Genetic biomarkers for seizure outcome will be determined, functionally validated and rapidly transferred to the clinical implementation phase (separate application).

Secondary outcome

n.a.

Study description

Background summary

Epilepsy surgery is the only treatment that can fully cure patients from their seizures without the need for lifelong medication. During surgery, the epileptogenic zone is removed or disconnected with sparing of surrounding normal functional tissue. The chance of postoperative seizure-freedom is maximized when the epileptogenic lesion is completely removed/disconnected. Whereas in the past only patients with visible structural MRI- lesions (considered causative for the seizures) were considered surgical candidates, we

now increasingly evaluate people with refractory epilepsy and normal imaging. Currently 60-70% of these MRI-negative (but presumed lesional/structural) patients are rejected for surgery, often after extensive and invasive source-localizing diagnostics. Operated MRI-negative patients have a lower chance of reaching seizure freedom. Furthermore, the absence of a histopathological abnormality (~8% of all operated patients) is a major predictor of poor outcome. When evaluating MRI-negative patients with refractory focal seizures for surgical candidacy, the epilepsy is either caused by an *invisible* microstructural lesion or malformation of cortical development -probably implying a high chance of postoperative seizure-freedom-, by a genetic syndrome without an identifiable lesion -probably reflecting a low chance of surgical success -, or by a combination of the two (e.g. tuberous sclerosis). The crucial differentiation between people with operable and non-operable epilepsy (i.e. between a presumed lesional and non-lesional cause of seizures) requires new and reliable biomarkers. Pathogenic variants in novel and known epilepsy genes are such biomarkers that are currently not routinely implemented in the presurgical evaluation. This project will will extend the scope of genetic biomarkers in a more experimental phase to find novel biomarkers of focal epilepsy that will be functionally validated and rapidly transferred to the clinical presurgical evaluation phase.

Study objective

Primary Objective:
Our overall aim is to improve selection of patients for epilepsy surgery and predict surgical candidacy with use of genetic test results as a biomarker. The specific objective is:

Cohort
1. perform trio-WES in MRI-negative patients who were shown to be poor surgical candidates (cohort I) and patients who proved to be good surgical candidates (cohort II) to discover new genetic variants that can serve as new biomarkers to predict surgical candidacy in patients with refractory focal epilepsy.

Hypothesis
We hypothesize that by discovery of new pathogenic variants and functional validation, we will expand the diagnostic utility and validity of genetic screening. We hypothesize that routine testing for germline epilepsy gene mutations in MRI-negative
patients with refractory epilepsy can improve the differentiation between good surgical candidates (i.e. those with a focal structural cause of seizures) and those who
are less eligible for epilepsy surgery (particularly those with non-lesional genetic epilepsy
syndromes), ultimately improving the rate of seizure-freedom after surgery and preventing unnecessary invasive source localization techniques. In addition, we hypothesize that the detection of somatic mutations in resected tissue can

improve post-surgery diagnosis, outcome prediction and postsurgical AED regimens. Furthermore, we assume that detection of somatic mosaicism gene mutations in saliva of operated patients with use of ultra-deep targeted sequencing could improve the diagnostic yield of genetic testing during the presurgical evaluation phase. This could ultimately improve the presurgical differentiation between good ** presumed lesional focal epilepsy patients ** and poor surgical candidates.

Overall approach
In this study we will extend the scope of genetic biomarkers in a more experimental phase to find novel biomarkers of focal epilepsy that will be functionally validated and rapidly transferred to the clinical presurgical evaluation phase. In a parallel study, we start with the clinical presurgical evaluation phase in which we apply routine genetic testing in MRI-negative patients and in resected tissue, demonstrate proof-of-concept, and evaluate the effect of detecting genetic biomarkers on surgical decision-making, lesion characterization, and outcome prediction. For this parallel study, a separate application for ethical approval will be submitted.

General relevance
Seizure control is not reached in ~30% of all patients 12 months after epilepsy surgery. Those with normal MRI scans have an even higher chance of poor surgical outcome up to ~50%, because the preoperative differentiation between patients with either focal lesional (structural) epilepsy, or with focal genetic non-lesional epilepsy has proven to be difficult. It is of crucial importance to improve the selection of suitable surgical candidates, and to reduce the risk of unnecessary (deemed unsuccessful) invasive diagnostics and resective surgery. We hypothesize that routine testing for the recently discovered genetic causes of epilepsy in MRI-negative patients can improve the recognition of poor surgical candidates and prevent further presurgical and invasive diagnostics. Vice versa, demonstration of a genetic abnormality that is likely to underlie a structural cause (such as FCD or mMCD) may improve the recognition of patients who are good candidates for surgery, despite normal MRI. Most importantly, in patients with refractory focal non-lesional epilepsy, in whom semiology and ictal EEG findings are not concordant with other functional imaging techniques to localize the epileptogenic zone (such as MEG, PET, and SPECT), the demonstration of a genetic underlying cause of the epilepsy syndrome should prevent invasive and expensive (further) presurgical diagnostics, such as grid or SEEG monitoring. Currently, genetic studies have presented the prelude for personalized medicine by demonstrating the potential relevance of genetic mutations for focal epilepsy, yet these fundamental discoveries have not been translated to improved care and clinical utility. Our proposal will accelerate the implementation of genetic discoveries into the epilepsy surgery program, by immediately implementing genetic testing in MRI-negative patents that are enrolled for surgery. By implementing genetic screening in clinical practice, and assessing prospectively and retrospectively the impact on presurgical evaluation, we aim to provide the evidence needed for

long term application. The combination of basic and applied studies from at least two different institutions, in collaboration with at least two renowned foreign centers, will provide the clinical evidence needed to implement molecular diagnostics in epilepsy surgery.

Study design

We will perform trio-(both parents and affected child) WES in a retrospective cohort of 50 patients (and their parents) who were shown to be poor surgical candidates, defined as: a) MRI-negative, stereo-EEG (SEEG) no focus, rejected for surgery, or b) MRI-negative, resected, pathology-negative and poor seizure outcome. Furthermore, we will screen 50 MRI-negative and pathology-negative surgical patients (in particular FCD) that reached seizure freedom. We will functionally validate the mutations in genes previously unknown to be related to FE in this study. Patients will be selected from the epilepsy surgery databases of the three participating centers (UMC Utrecht, Netherlands; UCL Great Ormond Street Institute of Child Health & Great Ormond Street Hospital for Children, London, UK).

Sequencing results will be analysed and interpreted by a collaborative team of bioinformaticians. We will select all de novo mutations that are predicted to be damaging and are absent in available control databases. Surgical outcome is collected from the databases and electronic medical patient files. Genetic findings will be compared between both groups, and related with seizure outcome. Furthermore, we will share results with our international partners through several genetic consortia that are aimed at identifying epilepsy genes. By sharing our results we will increase the likelihood of finding similar patients with mutations in the same gene, which is necessary evidence for causality.

Study burden and risks

The current proposal aims to describe the implications of genetic testing in patients with refractory epilepsy who received a clinical assessment for epilepsy surgery, and to confirm the as well as elucidate the association between different subtypes of gene mutations and surgical candidacy, and to discover new genetic pathogenic variants. The burden of patients in both cohort studies is minimal and consists of drawing one tube of blood for the purpose of the study.
All in all, the overall burden of participation in this study is low, while the associated risk is negligible (vene puncture for DNA blood draw). There is no clear benefit associated with this study, however knowledge obtained from this study will contribute to the decision making and outcome prediction in future patients with focal refractory epilepsy who are evaluated for epilepsy surgery. The inclusion of minors in the current study is required and justified; meaningful results can only be acquired through this group-related design.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

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

Cohort I
o The patient has a history of refractory focal epilepsy
o The patient was operated in one of the participating centers, was MRI and pathology negative and had poor surgical outcome (not seizure free), or: the patient underwent presurgical evaluation, was MRI and SEEG negative and was rejected for surgery
o The patients* parents are both available, give consent and are willing to participate in the study (trio WES, thus DNA of parents necessary for validation of variants), Cohort II

o The patient has a history of refractory focal epilepsy
o The patient was operated in one of the participating centers, was MRI-negative and pathology-negative and had good surgical outcome (seizure free)
o The patients* parents are both available, give consent and are willing to participate in the study (trio WES, thus DNA of parents necessary for validation of variants)

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
o No age exclusion criteria
o Known genetic disorders at entry that are directly related to the patient*s epilepsy; genetic disorders not related to the epilepsy are not a reason for exclusion, however such conditions will be noted in the participant*s research file.
o The patient*s parents have a condition (e.g. focal epilepsy) or known genetic disorder that that is related to the patient*s epilepsy

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-06-2018
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	04-04-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-07-2022
Application type:	Amendment
Review commission:	METC NedMec

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	NL64439.041.17