Clinical and molecular genetic aspects of idiopathic epilepsies

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(1) Identification of novel loci and genes in which mutations are responsible for the development of inherited epileptic syndromes. (2) Establishing genotype-phenotype correlations; defining the yield of mutation screenings in specific patient...

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

Summary

ID

NL-OMON35523

Source
ToetsingOnline

Brief title
genetics of idiopathic epilepsies

Condition

- Neurological disorders congenital
- Seizures (incl subtypes)

Synonym
epilepsy, seizures

Research involving
Human

Sponsors and support

Primary sponsor: Epilepsiecentrum Kempenhaeghe
Source(s) of monetary or material Support: Ministerie van OC&W,Het onderzoeksdeel dat uitgevoerd wordt in Belgie (meer bepaald moleculair genetisch deel) zal uitgevoerd worden met fondsen van Universiteit van Antwerpen en van Neurogenetica

Intervention

Keyword: Epilepsy, Genetics, Idiopathic

Outcome measures

Primary outcome

In this project we want to

1) describe new genes or loci

2) identify mutations in known epilepsy genes, but in a broader population than

the one in which the gene was originally described.

Secondary outcome

not applicable

Study description

Background summary

The epilepsies are a heterogenic group of common neurological disorders, affecting about 3% of the population at some point in their lives. Epilepsy can be caused by structural or metabolic brain defects, but more than 40 % of epilepsy patients have no underlying aetiology except for a genetic predisposition. These *idiopathic* epilepsy syndromes often have a complex inheritance pattern. In most cases several genetic factors, together with environmental factors, influence the development of the epileptic phenotype. Some cases are inherited in a Mendelian way in which case a mutation in 1 gene is responsible for the epileptic phenotype.
Careful clinical study of individuals and families combined with the powerful techniques of molecular genetic analyses has led to major breakthroughs in our understanding of epilepsy, particularly of the idiopathic variants. Initially the most significant advances in the domain of genetics of epilepsy have been made in extended multiplex families with autosomal dominant inheritance of the epileptic phenotype. However, recent technological advances have opened novel avenues to study patients with a presumably idiopathic form of epilepsy who lack a family history of similarly affected individuals. These patients often have a severe form of epilepsy that is difficult to control and often mental deterioration occurs leading to an epileptic encephalopathy. These catastrophic forms of epilepsy put a large burden on the well-being of the child and the

family. Apart from the care of the affected child, parents are often confronted with the uncertainty about the recurrence risk in case of later pregnancies.
To date about 40 loci and causal mutations in 15 genes have been identified for inherited forms of epilepsy but these findings only explain the epilepsy in a minority of idiopathic epilepsy patients underscoring the huge genetic heterogeneity of the idiopathic epilepsies and the urgent need for additional studies.

Study objective

(1) Identification of novel loci and genes in which mutations are responsible for the development of inherited epileptic syndromes.
(2) Establishing genotype-phenotype correlations; defining the yield of mutation screenings in specific patient cohorts; drawing guidelines for diagnostic mutation screening in the Dutch population of idiopathic epilepsy patients with a focus on severe idiopathic epilepsies with early onset.

To achieve this a collaboration will be started between the clinical team of the epilepsy centre Kempenhaeghe in the Netherlands (head of research Prof. P. Boon) and the research team of Neurogenetics of Prof. P. De Jonghe of the University of Antwerp in Belgium.

Collaboration is planned with het group of child neurologists of the azM Maastricht and the Neurogenetics group of Prof. D. Lindhout of the UMC Utrecht. When these collaborations will be formalized, an amendment will be submitted.

Study design

A. Collecting and clinical characterization of patient material
Blood samples and clinical data of Dutch families followed in Kempenhaeghe will be collected prospectively. Special attention will be dedicated to the collection of multiplex families, but also to smaller nuclear families with variable phenotypes for project B (cfr. infra) or to isolated patient with idiopathic epilepsies for project C (cfr. infra). To every patient or, in case of children or mentally retarded patients, to their legal representative informed consent will be asked and signed. Patients will always be allowed minimal two weeks of time to decide about their collaboration to the study.
In the research lab of Neurogenetics in Antwerp DNA samples of Belgian patients with idiopathic epilepsy have been collected during the last few years. Relevant samples will be selected for this project, and additional patients from Belgium will be included.

B. identification of new loci: delineation of candidate regions and gene identification
This part will be done in the first place in big muliplex families with an

epileptic phenotype that has a Mendelian inheritance. Within the epilepsy centre of Kempenhaeghe such families will be recruted, clinically described and blood will be drawn for analysis. Secondly in the Neurogenetics group of Prof. De Jonghe and in international literature several loci for epilepsy have been described in families. Often these are private loci that until now only have been described in a single family. To confirm these loci and to make them smaller so that the amount of positional en functional candidate genes is reduced, it's necessary that additional families are found that also link to these loci.
Besides the classical linkage analyses we will also perform Comparative Genome Hybridization (CGH) in patients with complex phenotypes in which epilepsy is an important part. The underlying hypothesis is that deletions and duplications of chromosomal regions with dosage-sensitive genes can be responsible for such complex disease phenotypes. For this subproject we will select patients with a combination of epilepsy, dysmorphia and mental retardation.

C. Mutation analysis in known epilepsy genes.
The analysis of mutations in known epilepsy genes will focus in this project on severe idiopathic epilepsies with early onset. In this population we will screen for STXBP1 (recently described in ohtahara syndrome), KCNQ2 and SCN2A mutation (responsible for BFNS and BFNIS, but apparently also present in atypical early onset epilepsy syndromes).
Performing these mutation analyses in cohorts of patients with a phenotype similar to the patients in which the gene was originally described will give us an idea of the relative frequency of these mutations. These data will make it possible to say something about the usefulness of diagnostic screening of this gene. The mutation analysis will also be extended to a broader phenotype to see if mutations in these genes are also responsible for other epileptic syndromes.
Finally we will screen for GLUT1-transporter mutations in patients on a ketogenic diet with epilepsy of unknown origin. The hypothesis is that in the group of patients that respond well several patients carry a mutation in this gene.

Study burden and risks

For this research project 1 blood sample has to be taken. Where possible this will be done at the moment an already planned blood test is done, so that this is actually not an extra procedure.
Performing a blood test can be unpleasant because it involves a puncture with a needle. There is a small risk of a hematome. There exists also a risk that participating in this study causes concerns about the heritability of the disease. If this is the fact the patient can contact the investigator who can refer the patient to a geneticist.

Minors and incapacitated adults will also be included in the study. This is necessary because:
1. In a very big subset of patients with a severe early onset epileptic

encephalopathy a genetic cause is suspected. Especially in this group the detection of an underlying genetic cause is important. This are patients in which genetic counselling (recurrence risk in siblings) is very important for parents. Furthermore a genetic diagnose makes that no more unnecessary investigations are planned, and that parents can be informed about prognosis. These patients often do not reach the adult age, and for this this study has to be done in minors.
2. Part of this study will be done with the technique CGH(comparitive genome hybridization) in which deletions/duplications are detected in patients with a "contiguous gene syndrome". These patients have a complex phenotype, consisting of mental retardation, dysmorphia and, in case of this study, epilepsy.

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

1. Patients with a familial history of epilepsy, with multiple (at least 4) family members affected
2. Patients with a severe form of epilepsy with onset in the first year of life in which no acquired cause can be detected.
3. patients with a combination of epilepsy, mental retardation and dysmorphia (=contiguous gene syndrome, probably caused by deletion/duplication of multiple genes and detectable by CGH)
4. Patients on a ketogenic diet with epilepsy of unknown origin
Theoretically there are no age restrictions. In case of severe epilepsy with early onset (cfr.2), cases with neonatal onset will also be included, but as DNA diagnostics in a genetic research setting only will be done after all other possible causes are excluded, inclusion in this study in actual practice will only be done after 2 months of life.

Exclusion criteria

Patients in which a acquired cause of epilepsy is suspected (for example perinatal brain damage, lesions visible on MRI,...)

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-01-2010
Enrollment:	300
Type:	Actual

Ethics review

Approved WMO Date:	23-12-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL28184.068.09