Developmental recapitulation of spinocerebellar ataxia

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

Summary

ID

NL-OMON40742

Source
ToetsingOnline

Brief title
Spinocerebellar ataxia recapitulation/ORSA

Condition

- Neurological disorders congenital
- Movement disorders (incl parkinsonism)

Synonym
Ataxia, SCA

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Ataxia, Cerebellum, Development, IPS

Outcome measures

Primary outcome

1. The molecular and electrophysiological profile of probands and their family

members

2. Clinical characterization of the probands and their family members

Secondary outcome

Not applicable

Study description

Background summary

Spinocerebellar ataxias:
Patients with spinocerebellar ataxia (SCA) experience a gradual loss of physical control while maintaining full mental capacity due to progressive neurodegeneration of the cerebellum. This genetic disorder has 60 variants, of which only 12 can be diagnosed with a blood test. As there is currently no cure for SCAs, therapeutic rehabilitation of patients is used for alleviating some of its symptoms such as, poor coordination of: gait, eye, speech and hand movements. There are 29 gene mutations responsible for SCA which are classified into autosomal dominant, autosomal recessive or X-linked. The SCA mutant genes lead to neuron degeneration, specifically Purkinje neurons in almost all SCAs, which undergo at least one of the following: iron stress (Anheim et al. 2012), oxidative stress (Guo et al. 2010), mitochondrial dysfunction (Rugarli and Langer 2012) or protein aggregation (Orr 2012). While the gene mutations of SCA are categorized, the SCA pathology is still unclear with respect to whether transcription regulation, import of proteins to nucleus, RNA splicing and ubiquitination are causes or effects of SCA (Orr 2012). Mouse models cannot completely reproduce the human disease because of their relatively short life span as most SCAs in humans have an onset several decades into life. Another factor to consider in mouse models is the expression of the mutant transgene in all neurons vs. specific populations of neurons such as Purkinje neurons, which more closely resembles the human disease. What is clear until now is that the full complexity of the human disease has not been possible to be repeated in

mice (Ingram et al. 2012). Because neurons in culture have a shorter lifetime than the lifetime of a mouse, we would use the cultures to identify the molecular and electrophysiological events that precede the onset of Ataxia. Thus, we do not expect to fully recapitulate the neurodegeneration in vitro, we do however expect to replay some of the progression of the neuropathology.

From cerebellar development to spinocerebellar ataxia disease models:
While Purkinje cells of mouse models of SCA display alterations in innervations (Barnes et al. 2011) and intrinsic firing rates (Shakkottai et al. 2011), it is not clear which developmental stages lead to these phenotypes and which molecular events precede them. In this study, we propose to recapitulate cerebellar development to obtain adult cerebellar neurons through differentiation of the induced pluripotent stem (IPS) cells of probands. Thus far, human IPS cells have been differentiated into neurons for the purpose of studying the molecular events that result in Ataxia telangectiasia (Carlessi et al. 2013), which is the second most common autosomal recessive SCA. Differentiation protocols of human IPS cells with or without the ataxia telangiectasia gene have yielded GABAergic and glutamatergic (De Filippis et al. 2007) and dopaminergic (Donato et al. 2007) neurons to study in vitro the molecular onset of the disease (Carlessi et al. 2013). However, the current challenge is to obtain specialized neurons from IPS cells; such as, Purkinje neurons because these are particularly sensitive to mutant SCA genes. In this regard, mouse embryonic stem cells have been successfully differentiated into Purkinje neurons (Muguruma et al. 2010). Therefore, we would adapt this protocol with embryonic stem cells (Muguruma et al. 2010) for the neuronal differentiation of human IPS cells summarized in these three steps: IPS culture, neuronal differentiation with fibroblast growth factor-2 (FGF2), Insulin and cyclopamine, and adult neuron co-culture.

Because many ataxias are misdiagnosed or go years without knowing the exact type, recapitulation of development of specialized neurons can yield a molecular and electrophysiological profiling of healthy and diseased phenotypes that is not possible to achieve in mouse models. For example, rapid developments in microarray technologies would provide new opportunities to correlate the molecular pathways stimulated in diseased neurons with their electrophysiological phenotype.

Study objective

1. We will recruit 6 probands who experience cerebellar movement disorders with spinocerebellar ataxia features such as uncoordinated movement (i.e. asthenia, asynergy, delayed reaction time and dyschronometria) in limbs and organs such as the eyes. A skin biopsy and DNA from blood drawn would be used for the generation of induced pluripotent stem (IPS) cells. It will be assessed if cerebellar neurons can be obtained in vitro from the IPS cells of these probands. If cerebellar neurons are produced, their biology will be evaluated through immunohistochemistry with known markers of cerebellum physiology and

neurodegeneration and patch clamp techniques for electrophysiology.

2. We will recruit up to 5 first-, second-, or third degree biological relatives of these probands who may or may not be affected with cerebellar movement disorders. These subjects will also be clinically assessed with blood drawn and a skin biopsy for the generation of cerebellar neurons. Cerebellar development and neurodegeneration markers and electrophysiology of cerebellar neurons will also be evaluated in these probands.

Study design

Definition of Subject Groups:

1. Probands (N = 6). These individuals who meet spinocerebellar ataxia inclusion criteria for a cerebellar movement disorder will be fully clinically assessed and have blood samples taken for the extraction of DNA and a skin biopsy (4 mm).

2. Relatives of probands (N = 5). Available first-, second-, or third degree biological relatives (both affected and unaffected) will be asked to contribute a blood specimen for DNA testing. In addition, they will receive the same clinical assessments as the probands. These family members will help elucidate heritability patterns and to evaluate whether potentially pathological genetic variants identified in this investigation co-segregate with the complex phenotype in certain families.

Recruitment:
Probands: Recruitment is performed by a member of the research group and will be done through referral by clinicians of the Erasmus MC department of neuroscience. Referral can also be done by a family member or by confidential screening of records with subsequent contact by a clinician. The investigator (G. A. Higuera) will explain the study fully to the patient and provide an information sheet to the patient. The patient will be able to read and retain the details of the study (see informed consent sheet). After the patients have time to consider the information fully and have been encouraged to ask questions, they will be asked to give informed consent by signing and dating a consent form. All consent forms should be signed and dated by the investigator. Access to the patient notes for verification and auditing purposes will be required and permission must be obtained as part of the consent process. Consent forms will be reviewed at the trial center and retained in the patient*s dossier by the investigator. A copy of the signed consent form will be given to the patient. A separate log will include all patients (initials and date of birth) screened for inclusion for the study. The principal investigators will meet regularly with the clinicians to supervise recruitment and selection of appropriate cases.

Family members: If the proband has signed his/her consent form, We will ask the

proband to explain to interested family members his or her own participation in this study and give the family members the information letter and the research team*s request to include them in the study. If this is not feasible, the members of the research team will help wherever possible to track and contact family members in order to explain to them the study, give them the information letter and ask for their participation. Contacting family members of the proband will be done only after having obtained permission from the proband. Should the family members agree to participate after reading the information letter, we will obtain their informed consent before receiving blood, clinical or family history information.

Study burden and risks

Risks:
We expect no serious adverse events in this study. Peripheral venous blood sampling (max. 30 mL) is a routine minimally-invasive procedure which will be performed only by highly experienced and certified nurses and phlebotomists. Further, our neuropsychological assessments are highly structured and have been extensively tested, without any known serious adverse events.

Adverse events may include minor bruising or local tenderness at the site of venous blood sampling. All patients will be monitored to ensure proper hemostasis. During interviews and neuropsychological testing, the patient will be fully aware of his/her right to terminate the testing at any time and for any reason.

The Erasmus MC medical ethical committee has waived the obligation of insurance for the participants in this study because it believes that this research has little or no risk involved.

Compensation:
Probands and family members will be compensated for any travel costs incurred. For the clinical assessment and blood sample, participants will be remunerated with ¤50,- for their time and effort. For donating the skin biopsy, participants will be remunerated with ¤50,- as well.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. All subjects must give signed, informed consent.
2. Probands must have a cerebellar movement disorder or a disorder with spinocerebellar ataxia features such as uncoordinated movement (i.e. asthenia, asynergy, delayed reaction time and dyschronometria) in limbs and organs such as the eyes.
3. Subjects must be over 18 years of age at interview, male or female.

Exclusion criteria

1. Unable to give informed consent to all aspects of the study.
2. Unable to speak and be interviewed in Dutch or English (to ensure validity of the interviews).
3. Cerebellar movement disorder is deemed secondary to substance use by the consensus diagnostic procedure because uncoordinated movement symptoms are limited to periods of likely intoxication or withdrawal.
4. The cerebellar movement disorder is deemed secondary to causative factors, such as, head injury, or alcohol withdrawal.
5. Subjects with severe mental retardation.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-08-2015
Enrollment:	11
Type:	Actual

Ethics review

Approved WMO Date:	27-11-2014
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

No registrations found.

In other registers

Register	ID
CCMO	NL49151.078.14