Understanding Clinical Phenotypes and Collecting Biomarker Samples in C9ORF72 ALS

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

Summary

ID

NL-OMON45822

Source
ToetsingOnline

Brief title
Phenotypes and biomarkers in C9ORF72 ALS

Condition

- Neuromuscular disorders

Synonym
ALS, Amyotrophic lateral sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Washington University in St. Louis
Source(s) of monetary or material Support: ALS Association (ALSA),Washington University in St. Louis

Intervention

Keyword: ALS, Biomarkers, C9ORF72

Outcome measures

Primary outcome

The primary outcome measures will be the collection of clinical data (ALS Functional Rating Scale-Revised (ALS-FSR-R and slow vital capacity (SVC)) to determine rates of disease progression and collection of biomarkers samples (blood, cerebrospinal fluid (CSF) to be correlated with the clinical measures.

Secondary outcome

The secondary outcome measures include determination of the C9ORF72 hexanucleotide repeat expansion size and correlating this with the outcome measures of disease progression collected (ALSFRS-R/month, decrease in SVC/month and ALS Cognitive Screen) and determination of C9ORF72 ALS patients that may be available for a clinical trial.

Study description

Background summary

C9ORF72 repeat expansions were recently identified as a surprisingly common cause of ALS (30% of familial and 5-10% of sporadic ALS). Data collected to date suggest a toxic gain-of-function mechanism for the cause of neuronal loss, either by creating RNA-foci that sequester important RNA binding proteins or by translation of the repeat expansion into aggregation-prone dipeptides. This fact makes antisense oligonucleotide knock-down of C9ORF72 repeat RNA an attractive therapeutic strategy, which is already under development by several groups. Given a recently completed Phase I trial using antisense oligos (ASOs) targeted to SOD1, it is highly likely that a similar strategy will emerge for C9ORF72 in the near future. However, our understanding of clinical

characteristics and effect of the hexanucleotide repeat expansion size for C9ORF72 are not yet ready for such a clinical trial. Our collaborative effort proposed here will generate these important phenotype/genotype correlations.

We need to understand the natural history of C9ORF72 related ALS in terms of measures of rate of progression, and we need to understand how the size of the hexanucleotide repeat expansion influences these disease parameters. Although C9ORF72 is a relatively common genetic disorder, it only represents about 10% of all ALS, and thus for a C9ORF72-focused clinical trial, defining an accurate historical control population will be critical since there may not be enough subjects for a placebo controlled trial. To be ready for upcoming therapeutic trials, we need to start the detailed characterization of the C9ORF72 patients immediately.

Study objective

In order to define the natural history of C9ORF72 ALS and to understand how the size of the repeats correlates with disease progression, the six sites will:

1. Enroll a total of 60 C9ORF72 ALS participants with known mutation at time of enrollment
a. Each participant will have their C9 genetic mutation status confirmed by either UMASS (via a Screening Visit blood sample sent overnight to their lab) or a CLIA-approved testing laboratory report (FAX*ed to Dr. Timothy Miller for review and approval).
b. (Optional procedure): For each enrolled C9ORF72 ALS subject, a Caregiver will be invited to (1) enroll, (2) sign a consent form, and (3) complete a series of ALS Caregiver Behavioral Questionnaires during the course of the C9ORF72 ALS subject*s completion of his/her Screening Visit through Study Visit7.
2. Determine C9ORF72 hexanucleotide repeat expansion size in all subjects
3. Define ALS disease course in C9ORF72 ALS subjects
4. Determine to what degree the disease course correlates with expansion size
5. Collect biomarker samples including blood and CSF.
With the successful completion of these studies we will have carefully defined the genotype/phenotype correlations in C9ORF72 ALS subjects and thus conducted the necessary ground work to launching a clinical trial in C9ORF72 positive subjects.

Study design

The six sites participating in this study will have already defined and identified C9ORF72 ALS positive patients / carriers who will be approached for enrollment.
We will genotype a total of approximately 60 patients during the course of the study (two years of recruitment followed by approximately two years of

follow-up). These subjects will be enrolled (screened) into the study and then followed longitudinally.
(Optional): For each enrolled C9ORF72 ALS participant, a Caregiver will also be invited to enroll, sign a consent form, and complete a series of ALS Caregiver Behavioral Questionnaires during the C9ORF72 subject*s completion of: Screening Visit * Study Visit 7.

Determine Expansion Size
In the 60 subjects we identify with C9ORF72 ALS expansions, we will define the size of the repeat expansion in blood cells by Southern Blot. We will test expansion size from the DNA collected at the 3rd and 7th Study Visits to determine whether the expansion size changes over time.

Correlate Expansion Size with Phenotype
After we have collected 6 months* worth of phenotype data, we will begin to correlate phenotype with expansion size.

Study burden and risks

C9ORF2 Subject:

Blood draw:
Likely: There may be minimal discomfort associated with the blood draw and bleeding or bruising may occur. Some people become dizzy or feel faint.
Rare: There is a rare risk of infection at the site of the blood draw.

Lumbar Puncture (CSF Collection)
Likely/Common (Mild): Minor pain and/or pressure during the sampling procedure; Local bruising at the sampling sites; Local swelling at the sampling sites.
Less Likely/Less Common (Mild): All precautions will be taken to minimize this risk. The CSF sampling procedure will be conducted by experienced physicians specially trained to perform this technique. We are not aware that potential side effects are related to the volume of CSF being removed in this study. The risk of headache will be minimized by having the subject lie on their back for 30 minutes to one hour following the CSF collection procedure. Throughout the CSF sampling procedure, and following the 1 hour rest period, a nurse or physician will remain with the subject. If headaches occur during or following CSF removal, they usually are mild and last 0-2 days. They can, however, be quite severe and last up to a week if not treated with a local injection of blood (blood patch) which usually stops the headache within hours. If the subject has a severe headache after the study, we would recommend that s/he receives a patch to resolve the headache as soon as possible. We will provide for the patch at no charge. If the subject receives a patch or other medical care from another institution, we will not pay for any charges or be able to protect the subject*s confidentiality.
Rare: 1. Infection resulting from the sampling procedure. The risk of such an

infection is extremely low and is not greater than after blood is withdrawn from your arm. 2. Acquired intraspinal epidermoid tumor: This complication is extremely rare (and reports of epidermoid tumors in adults are rare) and represents a condition in which skin fragments are introduced (which then can grow) into the spinal canal at the time of the lumbar puncture. This complication usually arises because of the use of a spinal needle without stylette.
Our study uses spinal needles with stylette during the lumbar puncture procedure.

Caregiver (of C9ORFf72 subject) completing ALS Caregiver Behavioral Questionnaire:
Likely/Common/Mild: Questionnaire: The subject may find some of the questions personal or uncomfortable to answer.

Participation in the study has no direct benefit for the subject.

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. Age: 18 or older
2. Known positive C9ORF72 status upon enrollment (ALS or asymptomatic carrier)
3. Sporadic or familial ALS diagnosed as possible, laboratory-supported probable, probable, or definite as defined by revised El Escorial criteria, if the subject in included in the study as ALS patient.
4. Capable of providing informed consent and following study procedures.
(In the case that a ALS subject lacks the ability to provide informed consent, informed consent will be sought for the subject*s surrogate representative.)

Exclusion criteria

Negative for C9ORF72 gene mutation;Lumbar punctur (optional)
1.Medically unable to undergo lumbar puncture (LP) as determined by the investigator (i.e., bleeding disorder, a skin infection at or near the LP site, or evidence of high intracranial pressure).
2. Pregnant; breastfeeding
3. Any active dermatologic disease at the site of the puncture.
4. Any connective tissue disease including systemic lupus erythematous, Sjögren*s syndrome, scleroderma or mixed connective tissue disease.
5. Any known or suspected abnormal CSF pressure or intracranial/intraspinal tumors.
6. Use of anticoagulant medication (eg. warfarin, dalteparin, enoxaparin, rivaroxaban, fondaparinux, dabigatran) that cannot be safely withheld until coagulation parameters have normalized prior to lumbar puncture and for up to a week following the lumbar puncture.
7. Blood dyscrasia, abnormal bleeding diathesis, or the use of dialysis for renal failure.
8. Clinical judgment of the Site Investigator that the subject would be unable to undergo multiple lumbar punctures.

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):	01-04-2016
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO Date:	09-03-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-08-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-06-2017
Application type:	Amendment
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

No registrations found.

In other registers

Register	ID
CCMO	NL54797.041.16