Assessing ion-channel dysfunction in ALS using surface-EMG and high-resolution ultrasound

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

Summary

ID

NL-OMON55763

Source
ToetsingOnline

Brief title
Ion-channel dysfunction in ALS

Condition

- Neuromuscular disorders

Synonym
amyotrophic lateral sclerosis, neuromuscular diseases

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ALS Stichting Nederland

Intervention

Keyword: Amyotrophic lateral sclerosis, EMG, Neuromuscular diseases, Ultrasound

Outcome measures

Primary outcome

1. Axonal excitability-variables of the median nerve motor axons at the wrist to determine ion channel dysfunction. Each excitability test consists of 4 subtests, including: (i) Latent addition and strength-duration time constant (SDTC) reflects activation of persistent Na-channels, (ii) threshold electrotonus reflects resting membrane potential, (iii) current-voltage (I/V) relationship reflects activity of slow K-channels and HCN-channels, (iv) recovery cycle reflects transient Na-channel inactivation.

2. Clinical parameters of functional state (ALSFRS-R questionnaire), survival and/or time to assisted ventilation.

Secondary outcome

1. Sonographic variables (amount of fasciculations - in median nerve innervated muscles, and nerve size - cross-sectional area of median nerve at forearm and upper arm level) on ultrasound imaging.

2. Demographic data and patient characteristics (age, gender, weight, medical history, disease duration), and results from routine genetic testing (sporadic or familial ALS with genetic mutations e.g. C9orf72).

3. Data from routine EMG and CMAP scan based examination (electromyographic features of lower motor neurone involvement).

Study description

Background summary

Amyotrophic lateral sclerosis (ALS) is a devastating disorder characterized by the progressive degeneration of upper and lower motor neurons. Survival varies considerably between patients due to different genetic and pathophysiological mechanisms contributing to the disease. A major challenge is to identify these mechanisms, and find sensitive biomarkers to measure treatment efficacy in humans directly. A promising target for disease-modifying treatment involves ion channels of which their dysfunction has been associated with motor neuron degeneration in ALS.

Human peripheral nerve excitability studies indicate that changes in axonal excitability of lower motor neurons induced by the altered functioning of ion channels are an important early mechanism in ALS, that precedes the clinical dysfunction and deterioration. Up till now, most nerve excitability studies have been conducted after the diagnosis has been made. These studies, therefore, do not involve treatment-naive patients, which may mask highly relevant, but subtle differences in ion channel dysfunction. Furthermore, the diagnostic phase provides the opportunity to capture their dysfunction as early as possible in muscles without clinical symptoms. Ion channel dysfunction has further been suggested to facilitate fasciculations, a clinical hallmark in ALS. High resolution ultrasound has become an emerging tool into the diagnostic phase of ALS to assess presence of fasciculations. Compared to standard invasive needle-EMG to assess presence of fasciculations, high-resolution ultrasound has the benefit to be non-invasive and to cover a large portion of the investigated muscle avoiding patient discomfort and mitigating sampling bias. Next to assessing lower motor neurons fasciculations, it also forms a practical, bedside tool that enables capturing morphological consequences of motor neuron degeneration along the neural axis. It may therefore be an additional relevant diagnostic tool, complementary to current clinical electrodiagnostic studies.

This project aims to identify ion channel dysfunction in axons of lower motor neurons of individual ALS patients, that contributes to loss of these axons, together with techniques that enables quantification of their loss, function and morphology. This is important since currently available drugs can modify ion channel dysfunction in such a way that the death of these nerves may be delayed or avoided. Assessment in a large group of individual patients is necessary because molecular biological mechanisms may differ between patients, and which may therefore also have different practical implications in the diagnosis of these patients.

Study objective

Main objective is to identify ion-channel dysfunction in motor nerve cells of individual ALS patients, that contributes to their death, by assessing the association between ion-channel function tests in lower motor neurons and survival of patients with ALS using nerve excitability testing.

Secondary objectives:
1. To determine unique features of ion channel dysfunction that can help to further dissect pathophysiologic processes of ALS.
2. To explore the potential diagnostic value of excitability testing and high-resolution ultrasound in patients with suspected ALS, based on assessing distinctive profiles of ion channel dysfunction that can help to accurately identify ALS patients early in their disease course.
3. Based on the most discriminative markers, we will define an optimized protocol that can be easily implemented in future clinical trials and also performed in routine clinical practice.

Study design

It concerns an observational single-center study. The study will be performed in the Department of Neuromuscular Disorders of the University Medical Center Utrecht, The Netherlands. The duration depends on the inclusion rate with current estimates it is set at 3 years.

Study burden and risks

All applied recordings are non-invasive and form an extension of routine clinical diagnostic examination. There are no known risks for the recordings based on the literature and on our experience in previous high-resolution ultrasound, excitability and nerve conduction studies. The main burden concerns the time investment on part of the participants. Slight physical discomfort due to electrical stimulation and brief local skin reddening due to skin electrode adhesive gel may occur. Patients will benefit indirectly from the study because more will be known about pathogenic mechanisms in ALS which, in turn, may potentially lead to development of treatment strategies aimed at motor neuronal protection. Especially for family members of ALS patients, we anticipate that being asked to participate in a study investigating neural alterations in asymptomatic family members may raise questions. In such instances, participants will be informed that - may they have such questions - they can be referred to the Department of Medical Genetics for adequate counselling and information.

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

- Age >= 18 years
- Written informed consent
- Patients with suspected MND and who are referred for an EMG, healthy controls and family
members of patients with MND who have an established genetic mutation

Exclusion criteria

- Age < 18 years
- Signs for other neuropathy than MND including carpal tunnel syndrome (CTS) and polyneuropathy
- Any physical, psychological, familial, sociological or geographical condition potentially hampering
compliance with the study protocol. Judgment is up to the investigators

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	27-07-2020
Enrollment:	400
Type:	Actual

Ethics review

Approved WMO Date:	11-12-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	31-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-07-2023
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	NL69267.041.19