A flexible electrophysiological protocol for assessing novel quantitative biomarkers in amyotrophic lateral sclerosis

Published: 18-03-2025
Last updated: 04-04-2025

Primary objective: To longitudinally characterize alterations in electrophysiological biomarkers in ALS of peripheral excitability in relation to neurodegeneration. Secundary objectives:1. To determine the value of multi-muscle CMAP-scan outcomes as...

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

Summary

ID

NL-OMON57379

Source
ToetsingOnline

Brief title
EPHALS

Condition

- Neuromuscular disorders

Synonym
Lou Gehrig's disease, Motor neuron disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: ALS Stichting Nederland

Intervention

Keyword: ALS, CMAP-scans, Electrophysiology, Excitability

Outcome measures

Primary outcome

Primary endpoints:

• Measures derived directly from CMAP-scans pertaining to motor neuron loss (MUNE, D50, CMAP-max, etc.)

• Measures derived directly from peripheral excitability tests (SDTC, superexcitability, etc.)

Secondary outcome

Secondary endpoints: measures derived directly from cortical excitability tests and RNS tests, clinical parameters of functional state (ALSFRS-R questionnaire, neurological examination), genetic data, survival and/or time to assisted ventilation

Study description

Background summary

Rationale: Amyotrophic lateral sclerosis (ALS) is a deadly neurodegenerative disorder marked by motor neuron loss. The disease*s variability complicates diagnosis and treatment development. Recent understanding of ALS pathophysiology has shifted the focus from a one-size-fits-all approach to personalized treatments, resulting in promising experimental therapies including Tofersen for patients with the SOD-1 mutation and lithium for those with the UNC13A/CC polymorphism. Despite these advances, there is a critical need for quantitative biomarkers to track disease progression, reflecting ALS's inherent heterogeneity.

Electrophysiological techniques have emerged as valuable tools for monitoring ALS. The compound muscle action potential (CMAP) scan can is a quick and practical bedside test that can provide valuable biomarkers to monitor disease progression, enhancing the efficiency of clinical trials. Techniques to track changes in peripheral and cortical motor neuron excitability, predictive of disease progression and survival, could yield promising prognostic and pharmacodynamic biomarkers. Combining these novel techniques could produce novel insights into the pathology and pathogenesis of disease, and help in the development and testing of novel treatments. However, gaps in knowledge persist, particularly in applying these techniques across multiple muscles and genetic mutations.

To address this, a flexible electrophysiological protocol is proposed, consisting of a fixed (or critical) sequence of test to which additional tests can be added depending on specific genetic subgroups or practical constraints. This approach allows us to efficiently evaluate and integrate non-invasive electrophysiological biomarkers into clinical practice and trials.

Study objective

Primary objective:
To longitudinally characterize alterations in electrophysiological biomarkers in ALS of peripheral excitability in relation to neurodegeneration.

Secundary objectives:
1. To determine the value of multi-muscle CMAP-scan outcomes as biomarkers for monitoring disease progression in clinical trials

2. To longitudinally characterize alterations in electrophysiological biomarkers of cortical excitability and neuromuscular transmission in relation to peripheral excitability and neurodegeneration.

3. To determine whether genetic factors contribute to a unique series of electrophysiological changes that could be of relevance for deep-phenotyping and precision medicine approaches

Study design

Observational study, cross-sectional and longitudinal design

Study burden and risks

All applied recordings are non-invasive and form an extension of tests performed during routine clinical diagnostic examinations. There are no known risks for the recordings based on the literature and on our experience in previous CMAP-scan, peripheral nerve excitability and nerve conduction studies

in which RNS is performed. The most serious adverse event during cortical excitability testing is a seizure. However, the reported incidence is very low (2 in 100.000) and is, therefore, considered to be extremely unlikely. Due to the severity of this AE, a short procedure has been included in the protocol describing the steps the research team needs to take to ensure the safety of participants. Ultimately, 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.

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

Inclusion criteria

1. Age >= 18 years at the time of screening
2. capable of providing informed consent and complying with the study procedures;
3. Belong to one of the following population bases:
a) Diagnosis of ALS according to the revised El Escorial criteria (possible, probable-laboratory supported, probable or definite), PMA or PLS
b) Healthy controls with: no history of nerve entrapment syndromes (such as carpal tunnel syndrome); no active neurological, neuropsychiatric or neuromuscular conditions.
c) Family members from patients with a history of ALS in the family (regardless of the presence of gene mutation status or knowledge thereof), with: no history of nerve entrapment syndromes (such as carpal tunnel syndrome); no active neurological, neuropsychiatric or neuromuscular conditions.

Exclusion criteria

1. Pregnancy
2. Alcohol dependence syndrome, current regular use of neuroleptic or psychoactive medication
3. The presence of frontotemporal dementia (FTD) with a degree of severity that could potentially hamper compliance with the study protocol. Judgment is up to the investigators.

Further exclusion criteria for patients: patients with frontotemporal dementia may initially be able to comply with the study procedures. These participants may be excluded from follow-up recordings, if they lose the ability to adequately follow and adhere to the examiner*s instructions.

Further exclusion criteria for participants of cortical excitability studies: although cortical excitability testing is not incorporated in the two base sequences A-B (see section 5.3), these may be added later. For these specific tests we will follow the expert guidelines for safety and recommendations for TMS, excluding individuals with (a history of) epilepsy or metallic implants (e.g. pacemakers or deep-brain stimulators).

Study design

Design

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

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2025
Enrollment:	640
Type:	Anticipated

Ethics review

Approved WMO

Date:	18-03-2025
Application type:	First submission
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	NL88002.041.24