An investigator-initiated prospective, longitudinal, single center, observational study to investigate biomarkers of TDP-43 and oxidized lipid metabolism in Amyotrophic Lateral Sclerosis (ALS).

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Primary Objective: To characterise longitudinal changes in biomarkers of TDP-43 pathology and oxidized lipid metabolism in ALS patients. Secondary Objective: To characterize the relationship of longitudinal changes in these biomarkers to changes in…

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

Summary

ID

NL-OMON56755

Source
ToetsingOnline

Brief title
ALS-Biomarker Study

Condition

- Neuromuscular disorders

Synonym
ALS, Lou Gehrig Disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Subsidie vanuit VectorY Therapeutics,VectorY

Intervention

Keyword: Amyotrophic Lateral Sclerosis, Biomarkers, Oxidative stress, TDP-43

Outcome measures

Primary outcome

Biomarker levels of oxidized lipid metabolism and TDP-43 pathology in blood at

time 0, 4,8 and 12 months and CSF at time 0 and 12 months, and changes of

biomarker levels of oxidized lipid metabolism and TDP-43 over time.

Secondary outcome

Association of biomarker levels with phenotypical characteristics over time,

e.g. time from onset of symptoms, ALSFRS-R, MiToS stage, site of onset

(Limb/Bulbar), respiratory function, time to ventilation/death.

Study description

Background summary

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disorder characterized by the degeneration of motor neurons in the brain and spinal cord leading to muscle weakness, paralysis, and ultimately death. The exact cause of ALS is not fully understood. Developing biomarkers in ALS is crucial.
Biomarkers can aid diagnosis, track disease progression, and monitor treatment response. Biomarkers can also offer insights into ALS's molecular and cellular pathways, aiding in new therapeutic developments.
Protein aggregation and inclusion body formation are hallmarks of neurodegenerative diseases, including ALS. The common proteinopathy in sporadic ALS (sALS) is the aggregation of wild-type TDP-43. Aggregation is mediated by both the loss of function and the gain of toxic function of the TDP-43 protein. Additionally, recent studies have shown that ALS spinal motor neurons have

altered lipid metabolism, with an upregulation of pathways related to glycerophospholipid metabolism and a specific increase of phosphatidylcholines (PC). Oxidative stress potentiates the oxidation of PCs at the cellular membrane, generating phosphatidylcholines (OxPC), which have been linked to many pathologies.
Identifying biomarkers associated with TDP-43 and OxPC levels in CSF and blood samples of ALS patients could aid to the development of new therapeutic approaches targeting TDP-43 and OxPC toxicity in the early stages of the disease. Neurofilament light (NfL) is identified as a significant biomarker of neuronal damage and has been found to correlate with disease progression and severity in ALS patients, its potential as a pharmacodynamic biomarker is noted.

Study objective

Primary Objective: To characterise longitudinal changes in biomarkers of TDP-43 pathology and oxidized lipid metabolism in ALS patients.
Secondary Objective: To characterize the relationship of longitudinal changes in these biomarkers to changes in the phenotypical characteristics of the disease.

Study design

Observational, single center, longitudinal, cohort study. biospecimens: blood will be collected at 4-monthly intervals during a 12-month observation period and cerebrospinal fluid (CSF) will be collected at baseline and at 12 months.

Study burden and risks

This is an observational study. Four study visits take please, at month 0, 4, 8 and 12, including blood sampling (month 0, 4, 8, 12) and lumbar puncture (month 0 and 12). The frequency of lumber punctures is determined by the natural history of ALS and the changes anticipated over a 12-month interval. 6 ml of CSF and a maximum of 20 ml blood will be collected on each occasion. Subjects will be closely monitored up to discharge and are free to withdraw from the study at any stage and for any reason. Participants may opt to participate at only the baseline visit or at any of the subsequent follow-up visits. Lumbar puncture is generally considered a safe procedure when performed by a skilled clinician, and any discomfort or side effects are usually temporary.
Post-lumbar puncture headache is the most common side effect of lumbar puncture occurring in 25% of the patients.
Analysis of the CSF can provide insight into the disease processes in ALS that cannot be obtained by other procedures. The hypothesis of this study is that identifying biomarkers associated with TDP-43 and OxPC levels in CSF and blood samples of ALS patients could aid to the development of new therapeutic approaches targeting TDP-43 and OxPC toxicity in the early stages of the

disease.
Given these considerations, the potential scientific benefits of performing a lumbar puncture in an observational study are likely to outweigh the risks, provided the procedure is carried out correctly and ethically, and informed consent is obtained.
All procedures are not part of regular care and are additional assessments.

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

- Signed informed consent
- Age above 18 years

- Diagnosis ALS

Exclusion criteria

- Fulfilling the criteria for respiratory insufficiency (non-invasive ventilation use >23 hours per day for 10 consecutive days or having a tracheostomy)
- MiToS stage 2, 3 or 4
- confirmed FUS or SOD1 mutation
- Contraindication to lumbar puncture
- Any of the following medically significant conditions:
1. Neurological impairment/dysfunction or unstable psychiatric illness that in the investigator*s opinion is likely to interfere with assessment of ALS disease progression.
2. Clinically significant unstable medical condition other than ALS, which would present a risk to a patient to participate in the study
3. Presence of dementia that impairs the ability of the subject to provide informed consent, according to the PI decision.
4. Cancer that is currently under active treatment or is likely to require treatment during the study that may alter the subject*s function and thereby interfere with assessment of ALS disease progression.
5. Any other condition that in the investigator*s opinion would present a risk to a patient to participate in the study, interfere with the assessment of safety or has an increased risk of causing death during the study.

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):	13-06-2024
Enrollment:	70

Type:	Actual

Ethics review

Approved WMO Date:	16-05-2024
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-02-2025
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	NL83842.041.24