Metabolic state and survival in patients with amyotrophic lateral sclerosis

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Primary Objective: To study alterations in metabolic balance in ALS patients and their impact on disease progression and survival.Secondary Objective(s): 1. To evaluate and compare the metabolic balance in patients with ALS and neurological control...

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

Summary

ID

NL-OMON50744

Source
ToetsingOnline

Brief title
MEASURE

Condition

- Neuromuscular disorders

Synonym
amyotrophic lateral sclerosis (ALS), motor neuron disease (MND)

Research involving
Human

Sponsors and support

Primary sponsor: Afdeling Neurologie
Source(s) of monetary or material Support: Ministerie van OC&W,ALS Stichting Nederland

Intervention

Keyword: ALS, Energy expenditure, Metabolism, Survival

Outcome measures

Primary outcome

The main endpoint in the study will be disease progression, expressed as change from baseline on the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R)

Secondary outcome

• Survival, defined as death of any cause and/or permanent respiratory support.

• Lung function, analyzed as change from baseline and expressed as forced vital capacity (FVC).

• The metabolic state will be evaluated as energy expenditure (expressed in VO2/kg consumption and estimated kilocalories/day) and respiratory exchange ratio (RER).

• The body composition is evaluated by % fat mass, % fat free mass, body volume (liters) and body density (kg/L)

• The dietary intake will be evaluated by average caloric intake/day. Subdivision of caloric intake in percentage protein, fat (saturated, unsaturated) and carbohydrates. Specific substrates will be registered and expressed as average daily intake in grams: Alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), cholesterol, fibers, alcohol, calcium (mg), vitamin B2, C&E (mg), lycopene, flavonoids, glutamate and phytoestrogens

Study description

Background summary

Amyotrophic lateral sclerosis (ALS) is a lethal neurodegenerative disease without a cure. Besides solely focusing on a cure, it is important to develop strategies that alleviate or slow the progression of the disease. ALS is considered as a purely neurological disease, however a metabolic component seems to underpin disease progression and prognosis: an increased metabolism, reduced body mass index (BMI) and malnutrition contribute to earlier death (Kasarskis, Berryman et al. 1996, Desport, Preux et al. 1999). Along the course of ALS, the metabolic balance is distorted and hyperbolism is observed in both familial as sporadic ALS patients (Desport, Torny et al. 2005, Funalot, Desport et al. 2009). This in combination with the fact that ALS patients only consume 84% of the recommended daily calorie intake, disease progression will eventually lead to weight loss (Funalot, Desport et al. 2009). The weight loss and accompanying decline in BMI is of clinical importance due to its influence on clinical outcomes (Kasarskis, Berryman et al. 1996, Shimizu, Nagaoka et al. 2012, Gallo, Wark et al. 2013, Reich-Slotky, Andrews et al. 2013, Ahmed, Mioshi et al. 2014). First, a lower BMI in early life has an increased risk of ALS mortality (Gallo, Wark et al. 2013). Second, patients with a higher BMI prior to diagnosis have better scores on the ALS functional rating scale (ALSFRS-R) (Reich-Slotky, Andrews et al. 2013). Moreover, a fast decline in BMI throughout the course of disease is highly correlated with a shortened disease duration and overall survival (Shimizu, Nagaoka et al. 2012). While BMI depends on both muscle and fat mass, a significant relationship has been found between patient survival and their subcutaneous fat mass (Lindauer, Dupuis et al. 2013). Additionally, a positive correlation was found between increased survival and elevated serum triglyceride and cholesterol in ALS patients (Dupuis, Corcia et al. 2008, Dorst, Kühnlein et al. 2010). The loss of total fat mass and hypermetabolism were confirmed in the SOD1G86R mice model (Dupuis, Oudart et al. 2004). These findings suggest that the body fat mass and an altered metabolic profile are factors that influence disease progression and thus the prognosis of ALS patients. Recent results from our workgroup reveal that patients with the C9orf72 mutation have a lower BMI during life and during the course of disease compared to ALS patients without the mutation. Moreover, asymptomatic carriers of the C9orf72 mutation have a lower BMI during life compared to non-carriers (Westeneng, van den Berg, unpublished data). These results may be indicative that a genetic background correlates the metabolic function and ALS symptomology.
Metabolic profile and body composition are heavily influenced by food intake and therefore dietary intervention might have therapeutic potential in ALS patients. In animal studies, a high-fat diet improved symptoms and extended the survival of SOD1G93A and SOD1G86R mice (Dupuis, Oudart et al. 2004, Mattson, Cutler et al. 2007). Moreover, by reversing the metabolic imbalance, metabolic

function was improved and delayed the onset of neuromuscular denervation (Palamiuc, Schlagowski et al. 2015). Recent studies in ALS patients report that supplementation with protein, carbohydrates, fats and nutriceuticals have some benefit on body weight, clinical outcomes and survival (Veldink, Kalmijn et al. 2006, Silva, Mourão et al. 2010, Dorst, Cypionka et al. 2013, Wills, Hubbard et al. 2014). A recent phase 2 placebo-controlled clinical trial assessed nutritional intervention in ALS patients and found favorable results in the hypercaloric intake groups. The authors recommend that dietary approaches should be studied in larger trials at an earlier disease stage (Wills, Hubbard et al. 2014).
Unfortunately, not all patients will tolerate dietary intervention (Dorst, Cypionka et al. 2013, Wills, Hubbard et al. 2014). Relatively high drop-out rates have been reported which indicate that dietary regimens might be unpleasant or unsustainable (Dorst, Cypionka et al. 2013). Sustaining adequate dietary supplementation in ALS becomes a greater challenge as disease progresses. Eventually, ALS will lead to the patients* inability to control their diet (i.e. by loss of fine motor control and weakness of the hand musculature) and patients are at increasing risk to develop complications due to dysphagia. Moreover, it remains unknown if the improved outcomes in response to dietary intervention are due to the surplus of calories or due to availability of specific dietary substrates. Therefore there is a need to comprehensively assess the metabolic needs in ALS patients and their dietary intake. Identifying dietary components that are associated with an improved ability to sustain energy requirements provides vital information about the mechanisms that underlie the increased energy needs in ALS. Moreover, the association between metabolic balance, dietary intake and disease progression can be used in future, more efficient and tolerable strategies. These strategies can in turn assist the body with providing optimal energy needs and potentially improve the prognosis of ALS patients.

The UMC Utrecht and the Royal Brisbane and Women*s Hospital in Brisbane, Australia, initiated a close collaboration in 2015. In June 2017, we jointly analysed preliminary data of the Australian group who initiated a similar study two years earlier. Data of 58 patients with ALS were matched with 58 controls on BMI, gender and age and is currently not yet published. Hypermetabolism, defined as a metabolic rate of 120% or higher of the predicted metabolic rate, was present in 41% of the ALS patients and in 12% of the healthy controls (adjusted odd ratio of 5.4, $p < 0.001$). Subsequently, we compared ALS patients with and without hypermetabolism. We looked at preliminary survival data of the hyper- and normometabolic patients (figure), which showed a remarkable difference in overall survival ($p = 0.0006$). 18-month survival after assessment was 94.4% in normometabolic patients (CI: 84.4% - 100.0%) vs 32.6% in hypermetabolic patients (CI: 11.4% - 93.1%). These results indicate that hypermetabolism is a strong prognostic factor and may help in guiding medical decision making and counseling.

Interestingly, hypermetabolic patients showed a faster rate of functional

decline (p = 0.028) and had more lower motor neuron involvement (p = 0.030). Moreover, 29% of the hypermetabolic patients had a familial form of ALS, whereas this was only 3% in normometabolic ALS patients (p = 0.013). Of the familial patients (N = 8), 7 were hypermetabolic (88%). This indicates a strong genetic link with the presence of hypermetabolism. At the moment, genetic information (C9orf72 repeat expansion) of these patients are analysed in the UMC Utrecht and are not yet available. Combined with our presymptomatic weight loss and alteration in body composition for C9orf72-cases, it would be worthwhile to assess asymptomatic C9orf72 carriers and determine whether hypermetabolism is related to C9orf72 mutation. It would be worthwhile to assess other genes related to ALS as well, to compare the different genetic links with the presence of hypermetabolism.

Study objective

Primary Objective:
To study alterations in metabolic balance in ALS patients and their impact on disease progression and survival.

Secondary Objective(s):
1. To evaluate and compare the metabolic balance in patients with ALS and neurological control subjects
2. To evaluate and compare the metabolic balance in asymptomatic C9orf72-carriers and neurological control subjects
3. To evaluate and compare the metabolic balance in family members of familial ALS (fALS) patients (carriers and non-carriers)
4. To study the association between alterations in metabolic balance and the rate of disease progression and total survival time
5. To identify dietary components associated with the ability to sustain energy requirements
6. To study the change in body composition and metabolic state over time as ALS progresses
7. To study the relationship between dietary components and metabolic balance, body composition, clinical parameters and disease progression
8. To determine if the improved outcomes in response to dietary intervention are due to the surplus of calories or due to the availability of specific dietary substrates
9. To improve and optimize future dietary interventions in ALS patients
10. To study if single or a combination of metabolic blood products, muscle proteins and/or cholesterol products can serve as an prognostic or surrogate biomarker for disease progression in ALS
11. To study the change in nutritional status, indicated by PG-SGA, over time in patients with ALS
12. To study the relationship between nutritional status, indicated by PG-SGA, and disease progression and overall survival

Study design

Design: cross-sectional case-control and prospective cohort study. The first part of the study consists of a cross-sectional case-control study with ALS patients, and neurological controls and asymptomatic carriers of ALS related genes matched on gender, age and BMI. The ALS patients of the first part will be followed up longitudinally.
Duration: follow-up period of two years
Setting: The study will be carried out at the premises of the University Medical Center Utrecht (UMCU) the Netherlands. The sample size calculated for this study is 234 subjects, of which 78 ALS patients and 78 neurological age-gender-BMI matched controls. Additionally, we will include 39 asymptomatic carriers and 39 families of ALS patients (carriers and non-carriers).
Procedures: baseline measurements for both control and ALS-patients consisting of evaluation of dietary intake, clinical progression, energy expenditure, metabolic state and body composition. Survival data will be gathered for all patients. ALS patients are (optionally) followed-up at 3-monthly intervals (window of four weeks) and evaluated at the clinic for energy expenditure, metabolic state, body composition, dietary intake and clinical progression. Daily activity will be measured using the ActiGraph, an accelerometer to estimate the Metabolic Equivalent of Task (MET) scores in kcal/kg x hour. The ActiGraph GT9X Link (ActiGraph LLC, Pensacola, FL), is a small (.5 × 3.5 × 1 cm), lightweight (14 g) tri-axial accelerometer. The ActiGraph will be worn on the right hip in the anterior axillary line using a belt clip during waking hours for 7 days. The ActiGraph reduces the burden for patients by removing the need to keep an activity diary. We validated the ActiGraph in 42 patients with ALS (unpublished) in a recent study.
The ActiGraph will be handed over after completing the study visit. Participants will be asked to return the ActiGraph by mail.

Study burden and risks

The energy metabolism and body composition are assessed using non-invasive methods such as respiratory calorimetry and air-displacement plethysmography. Metabolic blood products can be determined by venous blood tests with a minimal risk of complications. Patients (controls once) are required to visit the hospital nine times in two years, each visit lasting one morning. But it is possible for patients as well to visit the hospital only once. Furthermore, patients and controls are asked to register their daily food intake. Collation of data between patient and neurological controls will provide essential knowledge to help characterise the altered metabolic profile in ALS and ascertain associated changes in energy intake, storage and metabolism.

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

For patients only (N = 78): meeting the El Escorial criteria for definite, probable, probable laboratory supported or possible ALS, For controls only (N = 78): diagnosis with neurological syndrome within the range of peripheral polyneuropathies with sensorimotor or motor fiber involvement. Or other motor neuron disease (primary lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy or pseudobulbar palsy) , Asymptomatic carriers and family members (N = 2x39): absence of any neurological symptom associated with ALS., For family members, non-carriers and carriers, of any related gene to ALS: absence of any neurological symtpoms associated with ALS. , All subjects: >= 18 years of age

Exclusion criteria

All subjects:
1.2. Participants < 18 years of age
2.3. Participants are not able to lay down for at least one hour, without any difficulties of swallowing or breathing.
3.4. Participants with tracheostomy or other assisted ventilation in the preceding 3 months., Neurological Controls, asymptomatic carriers, carriers of any other gene related to ALS and family members of ALS patients with a suspected genetic background of ALS (familial ALS):
7.6. Patients with peripheral polyneuropathy with only sensory fiber involvement (i.e. human immunodeficiency virus or vitamin B5 toxicity)
8.7. Patients with peripheral mononeuropathy (i.e. compression or entrapment neuropathies)

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-03-2017
Enrollment:	234
Type:	Actual

Ethics review

Approved WMO

Date:	13-04-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-02-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-09-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-04-2020
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	NL54833.041.15