Systemic inflammation in ALSP patients and the effect of an allogenic hematopoietic stem cell transplantation on the inflammation

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The aims of this study are to examine the degree of systemic inflammation in ALSP patients, and whether there is a change in the degree of systemic inflammation after treatment with an allogeneic HCT.Primary research questions:1. Are cytokine...

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

Summary

ID

NL-OMON49611

Source
ToetsingOnline

Brief title
Systemic inflammation in ALSP patients

Condition

- Neurological disorders congenital

Synonym
Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia, hereditary white matter disorder

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: De Hersenstichting of een ander (inter)nationaal fonds

Intervention

Keyword: ALSP, Biomarkers, Inflammation, Stem Cell Transplantation

Outcome measures

Primary outcome

The primary outcomes of objective 1 are cytokine profiles in blood before HCT, expressed in Normalized Protein eXpression (NPX) in Log2 scale, and cytokine profiles in blood over time.

Secondary outcome

Secondary endpoints will be the association of cytokine profiles with clinical outcomes after treatment.

Study description

Background summary

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a progressive neurodegenerative white matter disease (leukodystrophy), which primarily affects adults between 30 and 50 years. The disease often starts with neuropsychiatric features, followed by progressive motor and gait disturbances, incontinence, speech and swallowing problems, epilepsy, and premature death with a median survival of 6.8 years after onset of symptoms. The disease is caused by dominant mutations in the gene CSF1R, encoding colony stimulating factor-1 receptor (CSF-1R). CSF-1R acts as a receptor for cytokines, including CSF-1 and IL-34. These cytokines regulate the production, differentiation and function of various immune cells in the blood and brain, such as macrophages and microglia. In addition, the microglia homeostasis is dependent on CSF-1R. The disease is therefore characterized by microglia loss, resulting in demyelination, axonal loss and inflammation in the central nervous system.

At present, ALSP patients are treated with an allogeneic hematopoietic stem cell transplantation (HCT), if diagnosed rather early in the disease course. The theory behind allogenic HCT is that hematopoietic stem cells from bone marrow, peripheral blood or umbilical cord blood of a healthy donor are able to cross the blood-brain barrier, and differentiate into healthy macrophages/microglia to replace the (diseased) patient microglia. There is increasing evidence that HCT may halt disease progression in ALSP patients, but the long-term therapeutic effects are still unknown. The treatment has been proven to be safe and halt disease progression if applied early in the disease in several other leukodystrophies, including metachromatic leukodystrophy and adrenoleukodystrophy, if stable engraftment following HCT has been accomplished. In addition, there is growing recognition that a significant part of the therapeutic effect of HCT in leukodystrophy patients comes from reducing inflammation in the central nervous system, and that HCT also reduces systemic inflammation in patients with a metabolic disorders with or without central nervous system involvement. We expect that the anti-inflammatory effects of HCT in ALSP patients might be even greater since the disease affects in particular microglia, the immune cells of the central nervous system, and results in loss of one of the most prevalent cytokine receptors present on immune cells in blood of healthy humans. Nevertheless, scientific data on systemic inflammation and in cytokine profiles in ALSP patients are currently lacking. Therefore, the aims of this study are to examine the degree of systemic inflammation in ALSP patients before and after HCT. The results could inform the pathophysiology and treatment of ALSP, and might also be used for patient monitoring before and after treatment, and to evaluate treatment effects. In addition, results of this study could also inform the pathophysiology and treatment of other metabolic neurodegenerative diseases, such as Krabbe disease and Gaucher disease.

Study objective

The aims of this study are to examine the degree of systemic inflammation in ALSP patients, and whether there is a change in the degree of systemic inflammation after treatment with an allogeneic HCT.

Primary research questions:
1. Are cytokine profiles in blood of ALSP patients before HCT different from cytokine profiles in blood of healthy individuals?
2. How do cytokine profiles in blood of ALSP patients change over time after treatment with HCT?

Secondary research questions:
1. Are changes in cytokine profiles in blood after treatment with HCT related to clinical outcomes?

Study design

The study uses a longitudinal cohort study design. It is a multi-center study that will be performed at the Department of Child Neurology in the Amsterdam UMC, location VU medical center (VUmc) (primary site) and in the Emma Children*s Hospital, Amsterdam UMC, location Amsterdam Medical Center (AMC), Amsterdam, The Netherlands. Since most Dutch ALSP patients are referred to us to discuss their disease prognosis and treatment possibilities, the ALSP patients will be recruited during a hospital visit to the VUmc or AMC. Sample collection from patients will take place during a period of 5 years (6 times in total) at moment of venous blood sampling for standard clinical care. Reference samples will be acquired via the mini donor bank in the UMC Utrecht.

Study burden and risks

The procedure includes collection of ±15ml extra venous blood at the moment of venous blood sampling for standard clinical care. There is no direct benefit for the patients; there is only benefit for the ALSP patient population by increased knowledge. Risks and burdens of the study will be minimized by collecting blood samples only during venous blood sampling in the context of standard care.

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

- Diagnosis of ALSP confirmed by a pathogenic CSF1R mutation
- Aged 18 years or older
- Capable of giving informed consent

Exclusion criteria

- No informed consent given by the patient
- Cognitive capabilities are too low at inclusion of the study to give informed consent

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):	03-02-2021
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO Date:	09-12-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL74275.029.20