Following RVCL-S to Treatment (FORT) - A natural history study of Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic manifestations (RVCL-S)

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Congenital and hereditary disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON51098

Source
ToetsingOnline

Brief title
FORT

Condition

- Congenital and hereditary disorders NEC
- Eye disorders NEC
- Neurological disorders NEC

Synonym
Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic manifestations, RVCL-S

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Dioraphte;Hartstichting (Dekkerbeurs)

Intervention

Keyword: Biomarkers, Disease course, Hereditary, RVCL-S

Outcome measures

Primary outcome

1. Long-term disease course in RVCL-S

Long-term disease course will be determined by the occurrence of presumably RVCL-S related symptoms; by cognitive performance testing and by use of the modified Rankin Scale (mRS) and the Barthell Index. Standardised questionnaires will be used for screening for depression, anxiety and neuropsychiatric symptoms. Focal neurological symptoms will be evaluated by physical examination and 3T MRI. Ophthalmological examination will be performed for retinal involvement and organ involvement will be evaluated with venepuncture and urine examination (liver, kidney and thyroid function and blood count).

2. In vivo ocular and skin biomarkers

Eyes: ocular examination will be performed, including visual acuity, intraocular pressure and fundus photography. With Optical Coherence Tomography scans the retinal nerve fibre layer thickness will be measured. With OCT-angiography scans the vessel density at the retina and the size of foveal

avascular zone will be quantified. In patients with vascular retinopathy these scans will be combined with fluorescence angiography scans. Retinal oximetry is applied to calculate the oxygen saturation of the blood vessels of the retina.
Skin: vessels will be visualized by nailfold capillaroscopy. Four images (1*×*1* mm in size) from the nailfold in each finger will be evaluated. The modified Maricq criteria will be used for grading the capillary morphology, density and distribution.

3. Retinal angiogenesis

Optical Coherence Tomography Angiography (OCT-A) is a non-invasive technique that will be used to visualize the vascular structures of the retina and choroid three-dimensionally (without contrast).2 Quantitative assessment of vasculature of different segments and retinal layers, such as neovascularization or vascular dropout areas, and the creation of flow-density maps and calculations allows for comparison over time.

4. Long term progression of RVCL-S specific and common cerebral small vessels disease markers

Long term progression of RVCL-S specific and common MR-markers including i) *active* RVCL-S lesions (i.e. T2 hyperintensities with contrast enhancement and/or diffusion restriction, ii) brain (non-)lacunar infarcts, iii) white matter hyper intensities, iv) widened perivascular spaces, v) microbleeds, vi) permeability of the blood brain barrier, using both 3T and 7T MRI scanners.

5. Blood-brain-barrier dysfunction

To detect blood-brain-barrier (BBB) leakage, a late contrast leakage 7T MR imaging protocol will be performed. Blood-brain-barrier leakage rate will be adjusted for confounding variables in the gray matter, normal-appearing white matter, deep gray matter and cortex.

6. Store blood for biobanking purposes and future research.

If participants give permission for LUMC Biobank RVCL onder Neurologische Ziekten, blood samples will be stored for future (yet unknown) biomarker analysis.

Secondary outcome

Not applicable.

Study description

Background summary

Retinal Vasculopathy with Cerebral Leukoencephalopathy with Systemic manifestations (RVCL-S) is an autosomal dominant monogenic small vessel disease caused by mutations in the TREX1 gene. It manifests as a microangiopathy with retinal vasculopathy, focal and global neurological deficits and a wide range of systemic symptoms. Recently, our group conducted a large cross-sectional study (The RVCL-ID study, P13.286). However, the natural history of the disease, especially the early stages, remain to be identified. By identifying biomarkers predicting transition of the pre-symptomatic to symptomatic disease stage and progression of disease in RVCL-S we will be able to further unravel how TREX1 mutations cause disease. These findings will help define new treatment targets for this currently incurable disease. Furthermore, we aim to be able to give patients a more accurate prognosis. Additionally, as RVCL-S is a monogenic model for more common disorders, such as stroke, vascular dementia and migraine, we predict that our study will provide insights in the pathophysiology of other (neuro)vascular disorders as well.

Study objective

Our objective is to find predictive biomarkers for disease progression in RVCL-S, a monogenetic small vessel disease, and to dissect disease mechanism to identify new treatment targets to improve health for RVCL-S patients, which may also serve as biomarkers for patients suffering from associated disorders such as stroke, and vascular dementia and other cerebral hereditary angiopathies in the (near) future.
1. Perform an extensive clinical work-up using structured interviews, physical examinations and venepuncture and urine examination (for identifying organ dysfunction) during regular intervals to investigate long-term disease course in RVCL-S.
2. Studying ocular and skin biomarkers in vivo.
3. Studying retinal angiogenesis by using ocular techniques to visualize the retina in vivo.
4. Quantifying specific RVCL-S and common cerebral small vessel disease markers and evaluating their progression over time on 3T- and 7T-MRI.
5. Quantifying and localizing blood brain barrier dysfunction using MRI.
6. Store blood for biobanking purposes and future research.

Study design

Prospective follow-up study.

Study burden and risks

Contra-indications will be carefully investigated per subject for different parts of the study. If patients have contraindications for a part of the study (e.g. the MRI) they can still participate in the other parts of the study. Blood withdrawal is a routine procedure at the LUMC. MRI scans involve a negligible risk to the participants* health. The burden of the MRI scan will be kept at a minimum by using short protocols for the MRI study. Patients will be informed extensively about the potential risks of these procedures, after which written informed consent will be obtained. Relatives of RVCL-S patients who wish to remain unaware of their genetic status can participate on a research basis and test results will not be reported in the patients* hospital records or to treating physicians. Identifying possible biomarkers for recognizing (pre)clinical disease stages and for predicting outcome or future progression would be valuable for RVCL-S patients. Altogether we feel the advantages of this study outweigh the minimal risks.

Contacts

Public

Leids Universitair Medisch Centrum

Einthovenweg 20
Leiden 2333 ZC
NL
Scientific
Leids Universitair Medisch Centrum

Einthovenweg 20
Leiden 2333 ZC
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

(Pre-)symptomatic mutation carriers:
- Age: >= 18 years
- Proven TREX1 mutation
- Ability and willingness to provide written informed consent
Control subjects:
- Age: >= 18 years
- Not genetically related to an RVCL-S patient or genetic testing has ruled out TREX1 mutations
- Ability and willingness to provide written informed consent

Exclusion criteria

For all subjects:
- Subjects who do not want to be informed about unexpected findings that are considered serious, with prognostic or therapeutic consequences. This does not

concern genetic test results.
- Contra-indications for 3T/7T MRI as determined by the 7Tesla safety committee. (exclusion for a subpart of the study)
For controls:
- Presence of known (cerebro) vascular diseases such as overt manifestations of hypertensive/ atherosclerotic vascular disease, excessive anticoagulation (INR >3.0), CNS disorders, vascular malformation, vasculitis, blood dyscrasia, diabetes mellitus, severe clinical relevant carotid artery stenosis.

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:	Recruiting
Start date (anticipated):	12-09-2022
Enrollment:	80
Type:	Actual

Medical products/devices used

Generic name:	7Tesla MRI
Registration:	No

Ethics review

Approved WMO

Date:	29-09-2021

Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL77441.058.21