Characterizing Rate of progression in USHer syndrome type 2 (CRUSH) study

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Main objective: To map the natural course of the visual and hearing deterioration in Usher Syndrome type 2 for upcoming genetic therapy studies.Secondary Objective 1): To determine a. the necessary type of (combined) examinations, b. the sample size...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Ear and labyrinthine disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON46184

Source
ToetsingOnline

Brief title
CRUSH

Condition

- Ear and labyrinthine disorders congenital
- Hearing disorders
- Retina, choroid and vitreous haemorrhages and vascular disorders

Synonym
progression of the hearing and vision loss in Usher syndrome, Usher syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Stichting Ushersyndroom

Intervention

Keyword: hearing impairment, natural history study, retinitis pigmentosa, Usher syndrome

Outcome measures

Primary outcome

- Visual field sensitivity measured by static perimetry with topographic

analysis (Hill of Vision)

- Best corrected E-ETDRS visual acuity

- Mean retinal sensitivity as measured by fundus-guided microperimetry

- EZ area as measured by SD-OCT

- Rod- and cone-mediated retinal function as measured by FST

- Retinal function using full-field ERG amplitudes and timing in response to

rod- and cone-specific stimuli

- Hearing function and perception of sounds and words

- Vestibular function

Secondary outcome

None

Study description

Background summary

Usher syndrome is the most common form of congenital deafblindness. Patients with Usher syndrome are hearing impaired or profoundly deaf from birth and can be rehabilitated with hearing aids or a cochlear implant. Furthermore, these patients develop retinitis pigmentosa (RP), a slowly progressive type of retinal degeneration that usually starts in the first or second decade of life. This leads in the majority of patients to severe visual impairment or blindness around the 50th-60th year of life. There are no treatment options for the retinal degeneration. The hearing impairment is treated with hearing aids and

later cochlear implantation.
Usher syndrome is an autosomal recessively inherited disorder and is known to be genetically heterogeneous. Currently, 10 Usher syndrome genes have been identified. Research nowadays is, however, shifting from gene identification and functional analysis of encoded Usher syndrome proteins towards development of (genetic) therapies to treat Usher syndrome-related blindness. For Usher syndrome type 1b, the first phase I/II clinical studies already started using UshStat®.[1] As the retinal symptoms manifest during the first or second decade of life, there is a window of opportunity to stop the progression before onset of symptoms or in an early stage of the disease.
Usher syndrome leads to reduced mobility and social isolation. In addition, studies in the United States indicate that healthcare costs for patients with Usher syndrome are $7,000 higher per person per year than for the average population. In the Netherlands, there are an estimated 850 individuals with Usher syndrome.

To measure the effect of a (genetic) therapy, it is crucial to know the detailed natural course of the clinical deterioration over time. Several genetic therapy studies for other disorders are currently delayed because the natural history has not been studied in detail previously. It is therefore essential to start natural history studies as early as possible.
Our previous phenotype studies of the past decades were retrospectively performed and are not suitable and extensive enough to reconstruct a thorough view on the natural course of clinical deterioration in Usher syndrome. A novel prospective study that very thoroughly examines visual deterioration in Usher syndrome over time is therefore essential to establish the natural course of visual deterioration.
By performing detailed visual examinations that are repeated at regular intervals and by combining the acquired data, we will be able to capture the gradual decline. This study will not only provide us with knowledge on the natural history of clinicaldeterioration in Usher syndrome type 2, but more importantly also helps us to determine 1. the necessary type of (combined) examinations, 2. the sample size and 3. length of studies (in years) that are essential to evaluate (future) genetic therapy in Usher syndrome type 2
A sophisticated database that is suitable for (inter)national collaboration will be developed to store data anonymously. The data collection mainly focuses on evaluation of visual function and to a lesser degree also on auditory and vestibular function. In our previous studies on the auditory phenotype a lot of variability in hearing impairment was observed. This variability cannot be explained by genetic factors only. We aim to identify the additional etiological factors by adding questionnaires and psychophysical audiometric tests. In addition, the vestibular phenotype was never thoroughly evaluated in Usher syndrome type 2 patients and is therefore an interesting additional research topic that is included in this study. Finally, we also want to evaluate the impact of the disease on quality of life and psychosocial and general well-being by using validated questionnaires.

Study objective

Main objective: To map the natural course of the visual and hearing deterioration in Usher Syndrome type 2 for upcoming genetic therapy studies.

Secondary Objective 1): To determine a. the necessary type of (combined) examinations, b. the sample size and c. length of studies (in years) essential to evaluate future genetic therapy in Usher syndrome.
Secondary objective 2): To counsel patients with Usher syndrome type 2 with detailed information on the prognosis of Usher syndrome type 2.
Secondary Objective 3): We aim to identify additional etiological factors that explain variability in hearing impairment by adding questionnaires and psychophysical audiometric tests; and to assess the vestibular phenotype in Usher syndrome type 2 patients.

Study design

Longitudinal, prospective natural history study of Usher syndrome patients with a one-year follow up for a total of four years. As, to date, no treatments are available for Usher syndrome patients, they have not been followed up on a regular basis, and therefore detailed information on disease progression is lacking. This observational study will provide reliable data on the natural history of Usher syndrome.

Study burden and risks

Participants do not benefit, risks are considered negligible and procedures are non-invasive.

Most of the study procedures are considered part of standard care. There are no known risks beyond those involved in standard clinical care. The risks and discomforts that may be involved in the usual care of the patients during the period of time of prospective data collection:

- Visual acuity testing, (micro)perimetry, ERG and questionnaires require time and concentration of the patient, which might cause frustration, but no lasting adverse effects are associated with these non-invasive tests.
- Dilating eye drops will be used prior to fundus photography, OCT, FAF, ERG, FST, and microperimetry. Dilating eye drops cause a blurry vision for a few hours, and may sting, cause light-sensitivity, or an allergic reaction. There is a very small risk of inducing a narrow-angle glaucoma attack from the pupil dilation. Since all participants will have had prior pupil dilation usually on multiple occasions, the odds of the event in these patients are even smaller. If glaucoma occurs, treatment is available. Participants are instructed to contact our department in the extremely unlikely event of eye drop-induced glaucoma.

- IOP measurement and ERG: In rare instances, the cornea may be scratched during measurement of intra-ocular pressure or use of a contact lens electrode. An abrasion like this may be painful, but it heals quickly with no lasting effects. In the event that a participant experiences a corneal abrasion, antibiotic ointment will be administered and an eye patch may be placed over the eye.
- The audiometric tests require time and concentration of the patient, which might cause frustration and tiredness, but also no lasting adverse effects are associated with these non-invasive tests.
- The caloric measurement and rotational chair tests (part of vestibular exam) can cause minor dizziness and discomfort, which will be of short duration. The other vestibular tests do not cause these complaints.

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

- clinically diagnosed with rod-cone degeneration and congenital hearing loss, and at least two; pathogenic or likely pathogenic mutations in one of the Usher type 2 genes;
- Willing and able to complete the informed consent process;
- Ability to return for all study visits over 48 months;
- Age >= 18 years.;Both eyes must meet all of the following:
- Clinical diagnosis of a rod-cone degeneration;
- Clear ocular media and adequate pupil dilation to permit good quality photographic imaging;
- Ability to perform kinetic and static perimetry reliably;
- Baseline visual acuity ETDRS letter score of 54 or more [approximate Snellen equivalent 20/80 or better];
- Stable fixation ;
- Clinically determined [on Octopus 900 Pro] kinetic visual field III4e area 10° or more in the study

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Mutations in genes that cause autosomal dominant RP, X-linked RP, or presence of biallelic mutations in autosomal recessive RP/retinal dystrophy genes other than the Usher gene
- Expected to enter experimental treatment trial at any time during this study
- History of more than 1 year of cumulative treatment, at any time, with an agent associated with pigmentary retinopathy (including hydroxychloroquine, chloroquine, thioridazine, and deferoxamine);If either eye has any of the following, the patient is not eligible:
- Current vitreous hemorrhage
- Current or any history of rhegmatogenous retinal detachment
- Current or any history of (e.g., prior to cataract or refractive surgery) spherical equivalent of the refractive error worse than -8 Diopters of myopia
- History of intraocular surgery (e.g., cataract surgery, vitrectomy, penetrating keratoplasty, or LASIK) within the last 3 months
- Current or any history of confirmed diagnosis of glaucoma (e.g., based on glaucoma visual field, nerve changes, or glaucoma filtering surgery)
- Current or any history of retinal vascular occlusion or proliferative diabetic retinopathy
- Expected to have cataract removal surgery during the study
- History or current evidence of ocular disease that, in the opinion of the investigator, may confound assessment of visual function
- History of treatment for retinitis pigmentosa that could affect the progression of retinal degeneration (including participation in a clinical trial within the last year or a retained drug delivery device);If either ear has any of the following, the patient is not eligible:
- The audiometric PTA(1-2-4kHz) for the best hearing ear should not exceed 75dB HL. Patients with (bilateral) cochlear implants cannot participate in the study.

- A planned cochlear implantation during the study.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-02-2019
Enrollment:	50
Type:	Actual

Medical products/devices used

Generic name:	Octopus 900 Pro
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	05-12-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL67258.091.18