NEW characterizing rate of progression in USHer syndrome (NEW-USH) study a natural history study in patients with Usher syndrome

Published: 27-01-2025
Last updated: 08-02-2025

The study will help us to determine 1. the necessary type of (combined) examinations and 2. the sample size that is essential to evaluate (future) genetic therapy in Usher syndrome type 2 and USH2A associated nsRP.

Ethical review	Approved WMO
Status	Pending
Health condition type	Eye disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON57255

Source
ToetsingOnline

Brief title
NEW-USH

Condition

- Eye disorders congenital
- Congenital eye disorders (excl glaucoma)

Synonym
Retinitis pigmentosa-deafness 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: natural history study, retinitis pigmentosa, Usher syndrome

Outcome measures

Primary outcome

The main study endpoints will be as follows:

- Visual field sensitivity measured by static perimetry with topographic

analysis (Hill of Vi-sion)

- Best corrected 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

- Cone density rates measured by Adaptive Optics Flood Illumination

- PROM: patient reported outcome measures (questionnaire)

Secondary outcome

Not applicable

Study description

Background summary

Mutations in USH2A give rise to two phenotypes: Usher syndrome type IIa (USH2A) and nonsyndromic RP (USH2A associated nsRP). 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. Patients with USH2A associated nsRP do not suffer

from early onset hearing loss. However a study by Hartel et al. showed us that in half of the studied patients a (subclinical) mild hearing impairment is present[1]. The study by Iannaccone et al. showed us similar results. Both USH2A and USH2A associated nsRP are most importantly characterized by the development of retinitis pigmentosa (RP), a slowly progressive type of retinal degeneration that usually starts in the first to third decade of life. This leads, in the majority of patients, to become visually impaired between the ages of 40-50. There are no treatment options for the retinal degeneration. The hearing impairment is treated with hearing aids and later cochlear implantation. 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 than for the average population. In the Netherlands, there are an estimated 600-850 individuals with this syndrome. 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 and hearing loss. As the retinal symptoms manifest during the first to third 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.

Radboudumc and Usher syndrome
The Dutch Ministry of Health has awarded the Radboud university medical center as center of expertise for Usher syndrome. Usher syndrome has been one of the main research topics of the departments of Otolaryngology and Ophthalmology at the Radboud university medical center in Nijmegen for more than 3 decades. Over these decades, numerous phenotype studies on the auditory and visual phenotype in Usher syndrome have been performed in our center. Based on the interaction with patients in clinic and the creation of multiple national platforms (ushersyndroom.nl, SWODB and the contact group for Usher patients of the Oogvereniging) for Usher syndrome that create awareness for the disease, we are now in contact with more than half of the estimated patients with Usher syndrome in the Netherlands. Over the past decades, genetic research on Usher syndrome in our center mainly focused on the identification of genes, related functions of encoded proteins and more recently the development of gene therapy. Many papers on these subjects have been published. Recently, in addition to the first three subtypes of the disease, a fourth subtype of Usher syndrome has been identified by the genetic research group at the Radboudumc. Furthermore, has the connection between sleep quality and Usher syndrome been made by this research team.
More recently, research in Ophthalmology is shifting towards detailed natural history studies using advanced and state-of-the art imaging modalities because of its importance to allow identification of treatment effect in genetic therapy studies.

Natural history studies of visual function in Usher syndrome are the basis for

evaluating future genetic therapy
To measure the interventional effect of a (genetic) therapy, it is crucial to know the detailed natural course of the visual deterioration over time. Several genetic therapy studies for other retinal disorders are currently delayed because the natural history has not been studied in depth. 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 visual deterioration in Usher syndrome. To address that problem, in 2018 the Characterizing Rate of progression in USHer syndrome (CRUSH) study was initiated at the Radboudumc.

Over a period of four years, we collected a substantial amount of data from patients with Usher syndrome type 2. Although this study was concluded in October 2024, we aim to gather additional data to gain deeper insights into the progression of the disease. We want to continue the follow-up of these patients to gain a better insight in disease progression and use additional state-of-the-art imaging techniques that allow for more detailed structure and function correlations. Therefore, not all tests from the original CRUSH study will be repeated; we will focus solely on those that demonstrated disease progression and show potential as endpoints in future clinical trials and we will add the newest, non-invasive state-of-the-art imaging techniques. Taken into account that the international Rate of Progression in USH2A-Related Retinal Degeneration (RUSH2A) study indicated the same tests showing potential as future clinical trial endpoints, it is of major importance to gain further data on these measurements[36]. Further information is needed on these tests to determine whether they can effectively track disease progression for upcoming clinical studies. By conducting this study, we aim to demonstrate either the validation or refutation of the potentially useful measurements.
Throughout the CRUSH study, new imaging technologies like Adaptive Optics(AO) have been developed that allow for more detailed information on structure-function correlations than for example the regular OCT images. These structure and function correlations are of major importance and provide comprehensive information on the retinal site of interest; namely, they allow for the identification of the exact location where retinal cells are on the verge of apoptosis. In other words, the position where treatment effect can likely be best observed. We want to add this Adaptive Optics as a test in our study, to determine whether this test can be used as a future clinical endpoint in a genetic therapy trial, as was stated in several studies.

Study objective

The study will help us to determine 1. the necessary type of (combined) examinations and 2. the sample size that is essential to evaluate (future) genetic therapy in Usher syndrome type 2 and USH2A associated nsRP.

Study design

Longitudinal, prospective natural history study of Usher syndrome or USH2A associated nsRP patients with a one-year follow up for a total of two years. This observational study will provide reliable data on the natural history of Usher syndrome and USH2A associated nsRP.

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 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, 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: In rare instances, the cornea may be scratched during measurement of intra-ocular pressure. 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, an eye patch may be placed over the eye.

Contacts

Public
Radboud Universitair Medisch Centrum

Geert Grooteplein Zuid 10
Nijmegen 6525 GA
NL
Scientific
Radboud Universitair Medisch Centrum

Geert Grooteplein Zuid 10
Nijmegen 6525 GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Clinically diagnosed with rod-cone degeneration and at least two; pathogenic or likely path-ogenic 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 imag-ing;
- Ability to perform 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] static visual field of 7,5 degrees, in at least one eye

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 biallel-ic mutations in autosomal recessive RP/retinal dystrophy genes other than Usher genes
- 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 de-generation (including participation in a clinical trial within the last year or a retained drug de-livery device)

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	02-02-2025
Enrollment:	50
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	27-01-2025
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	NL88309.091.24