The skin microbiome in X-linked recessive ichthyosis and autosomal recessive congenital ichthyosis

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Primary Objective:Our main objective is to analyse if the microbiota composition of the affected skin is different from the non-affected skin in XRI and ARCI. Secondary Objectives:(1) To investigate the composition of the skin microbiota of patients...

Ethical review	Approved WMO
Status	Pending
Health condition type	Skin and subcutaneous tissue disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON51264

Source
ToetsingOnline

Brief title
Skin microbiome in XRI and ARCI / MIXA

Condition

- Skin and subcutaneous tissue disorders congenital
- Cornification and dystrophic skin disorders

Synonym
X-linked recessive ichthyosis and autosomal recessive congenital ichthyosis/fish skin disease

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: ARCI, Ichthyosis, Skin microbiota, XRI

Outcome measures

Primary outcome

The main endpoint will be to create an overview of the relative presence of the different bacterial genera in affected and non-affected skin of patients with XRI and ARCI.

Secondary outcome

The secondary parameters are:

1) Overview of the different bacterial genera in XRI and ARCI, and in different clinical phenotypes of ARCI.

(2) Skin microbiota composition of XRI and ARCI patients compared with healthy individuals and patients with AE and/or IV.

(3) Identification and isolation of specific clinical XRI and ARCI bacterial species for future follow-up studies regarding the pathogenesis of ichthyosis.

Study description

Background summary

Ichthyosis is a group of hereditary, chronic skin diseases in which the keratinization process of the skin is disturbed. These can be classified as ichthyosis vulgaris (IV), X-linked recessive ichthyosis (XRI), autosomal recessive congenital ichthyosis (ARCI), epidermolytic ichthyosis (EI) and syndromic ichthyosis. In the group of ARCI, patients are also traditionally subdivided by clinical phenotype, namely lamellar ichthyosis (LI; generalized,

thick, brown flakes), congenital ichthyosiform erythroderma (CIE; generalized erythema with fine white flakes) and the rare harlequin ichthyosis (premature neonate with very rigid collodion membrane, high risk of complications and mortality).
The treatment options for ichthyosis are limited and often insufficiently effective (Mazereeuw-Hautier et al., 2019). Quality of life depends on disease severity, which can vary from mild to severe in IV and XRI and from moderate to severe in ARCI. Studies show that all forms of ichthyosis give a clearly decreased quality of life (Troiano et al., 2020).
The pathophysiology of ichthyosis has not yet been fully elucidated. All forms of ichthyosis lead to abnormal epidermal differentiation and desquamation of the skin. Atopic eczema (AE) is strongly associated with IV, the most common form of ichthyosis (Oji et al., 2010). The Th2 axis plays an important role in AE, with IL-4 and IL-13 dominating the inflammatory profile. Initial research results on other variants of ichthyosis show an IL-17 predominant immune profile (Paller et al., 2010; Czarnowicki et al., 2018).
In common skin diseases, skin microbiota, and in particular changes in their composition (i.e.: dysbiosis), have been associated with the pathogenesis of these diseases. This dysbiosis can be the result of a changed bacterial composition, a disturbed immune response to them, or both. This could be a driving factor in inflammatory skin diseases such as AE and psoriasis (Zeeuwen et al., 2013). However, research results on the skin microbiome of psoriasis patients are contradictory and have not led to identification of a psoriasis-specific microbiome (Alekseyenko et al., 2013; Assarsson et al., 2018; Fahlen et al., 2012; Gao et al., 2008; Loesche et al., 2018; Tett et al., 2017).
In the case of AE, clear differences are found in the skin microbiome compared to healthy volunteers, namely decrease in microbial diversity, decrease in commensal bacteria and overgrowth of Staphylococcus aureus (Fyhrquist et al., 2019; Kong et al., 2012). However, it is still unclear whether this dysbiosis of the skin microbiome leads to disease, or whether the changed skin conditions (lesions) are the cause of the changed microbiota composition of the skin. Influencing the skin microbiome in patients with AE can lead to an improvement of the disease severity. It has been reported that treatment with diluted bleaching baths in these patients inhibits the colonization of Staphylococcus aureus and reduces the severity of AE (Huang et al., 2009). Furthermore, use of corticosteroids and immunosuppressants has been shown to reduce the dermatitis and Staphylococcus aureus colonization in AE (Gonzalez et al., 2016; Hung et al., 2007). Recently, it has been found that treatment with coal tar leads to a decrease in the amount of Staphylococcus species and an increase in the amount of Cutibacterium species, indicating a shift in microbiota composition towards healthy controls (Smits et al., 2020). In vivo modulation of cutaneous microbiota through skin microbiota transplantation and topical application of pre- and probiotics is also finding its way into research applications (Myles et al., 2018).
With respect to ichthyosis, only one study in human subjects has been published so far. It showed that filaggrin deficiency affects the microbiota composition

of non-eczematous skin in IV patients compared to healthy controls. In particular, IV skin displayed a reduced amount of Gram-positive anaerobic cocci (GPAC) (Zeeuwen et al., 2017). In the current project we aim to complement the knowledge of the skin microbiome in XRI and ARCI patients, and possibly also create a new therapeutic entrance.

Study objective

Primary Objective:
Our main objective is to analyse if the microbiota composition of the affected skin is different from the non-affected skin in XRI and ARCI.

Secondary Objectives:
(1) To investigate the composition of the skin microbiota of patients with XRI and ARCI and to investigate whether we can make a distinction between the different clinical phenotypes of ARCI based on the skin microbiota composition.

(2) To compare the microbiota composition of XRI and ARCI patients with (already existing data of) healthy individuals and patients with AE and/or IV.

(3) For future follow-up studies regarding the pathogenesis of ichthyosis, we want to explore if specific clinical XRI and ARCI bacterial isolates can be identified.

Study design

We will perform an transverse study with an exploratory character on a population of patients with XRI and ARCI. Expected study duration is 24 months and it will be performed in the Maastricht University Medical Center+.
Initially, we will study photo documentation of 20 XRI and 20 ARCI patients from the MUMC+ database to identify the most and least affected skin locations. For each patient, we will assess anatomical locations such as lower leg, thigh, etc, using the investigator global assessment score (0-4) (Vahlquist et al., 2013) and in this way select the average most and least affected area in this patient group. The sampling site is thus made uniform for all patients.Two samples will be taken from the most affected skin site and two samples of the least affected skin site in these patients, i.e. 4 samples per patient, in a total of 60 patients. From every skin location one sample is used for microbiota analysis (V3-V4 16S rRNA marker gene Illumina Sequencing). This will create insight into the bacterial taxa and their relative abundance. The other sample is used for bacterial culture on blood agar plates under aerobic and anaerobic conditions. Bacterial colonies will be selected (on morphology, color, size) and stored at -80°C for future experiments.

Study burden and risks

The procedure will be a swab of the skin. This will only touch the skin and will not hurt or penetrate the skin any deeper. This will have minimal to no risks for the patient. Furthermore, the procedure will take place during a regular clinic visit, so there is no additional time burden.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Patient group:
Patients >= 16 years old with a clinically and via Sanger, molecular inversion probes and/or whole exome sequencing genetically confirmed form of:
- X-linked recessive ichthyosis: with a mutation in or deletion of the STS gene.
- autosomal recessive congenital ichthyosis: with mutations in the ABCA12, ALOX12B, ALOXE3, CERS3, CYP4F22, LIPN, NIPAL4, PNPLA1, SDR9C7, SLC27A4, SULT2B1, ST14 or TGM1 gene.

Control groups:
Skin microbiome data from healthy individuals and patients with AD and/or IV >= 18 and <= 65 years old, who gave consent to use their data for future scientific research.
These subjects were already recruited in another study approved by the CMO region Arnhem-Nijmegen (registration number NL41569.091.12). Dr. P.L.J.M. Zeeuwen, who is part of our research team, was one of the principal investigators. This previous study compared skin microbiome data between healthy individuals, atopic dermatitis and ichthyosis vulgaris (published in Zeeuwen et al., 2016). The goal of our current study is in line with the consent given by these subjects, as we will use these data to compare to the obtained skin microbiome data from our patients with X-linked recessive ichthyosis and autosomal recessive congenital ichthyosis.

Exclusion criteria

- Body Mass Index greater than or equal to 35 or less than or equal to 18.
- Use of any of the following drugs within the last 6 months:
o systemic antibiotics (intravenous, intramuscular, or oral);
o oral, intravenous, intramuscular, nasal or inhaled corticosteroids;
o cytokines;
o methotrexate or immunosuppressive cytotoxic agents;
o large doses of commercial probiotics consumed (greater than or equal to 108 CFU or organisms per day) - includes tablets, capsules, lozenges, chewing gum or powders in which probiotic is a primary component. Ordinary dietary components such as fermented beverages/milks, yogurts, foods do not apply.
- Use of topical antibiotics, antifungal or topical steroids within the previous 7 days.
- Any confirmed or suspected condition/state of immunosuppression or immunodeficiency (primary or acquired) including HIV infection
- History of active uncontrolled gastrointestinal disorders or diseases including:
o inflammatory bowel disease (IBD) including ulcerative colitis (mild-moderate-severe), Crohn's disease (mild-moderate-severe), or indeterminate colitis;
o irritable bowel syndrome (IBS) (moderate-severe);
o persistent, infectious gastroenteritis, colitis or gastritis, persistent or chronic diarrhea of unknown etiology, Clostridium difficile infection (recurrent) or Helicobacter pylori infection (untreated);
o chronic constipation.
- Female who is pregnant or lactating.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2021
Enrollment:	80
Type:	Anticipated

Ethics review

Approved WMO

Date:	06-08-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL76168.068.21