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Associations between immune and genetic imbalances and risk factors in patients with chronic rhinosinusitis

Submission date 17/12/2024	**Recruitment status** Recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 24/12/2024	**Overall study status** Ongoing	
Last Edited 24/12/2024	**Condition category** Ear, Nose and Throat	

Plain English summary of protocol

Background and study aims

As we learn more about chronic rhinosinusitis (CRS), it's clear that managing the inflammation in the nasal area is key to treating it effectively. Both local and overall immune system responses are important for how CRS develops. To improve treatment and quality of life for patients, we need to look at not just the obvious symptoms but also what's going on inside the respiratory system. Categorizing CRS by different types and causes will help to find the right treatment for each patient.

This study will dive into how immune and genetic factors relate to disease progression and management in CRS patients. It will check the links between inflammatory markers found in nasal polyps and in the blood to simplify diagnostics and monitor changes for different patient profiles.

Around 4% of people worldwide have CRS, with about 10.9% of the population in Europe affected. This condition takes a toll on quality of life and comes with hefty medical expenses. Right now, many patients take various medications that often just address the symptoms instead of the root causes, and some might need surgery if treatments aren't effective. Understanding the genetic and functional aspects of CRS is crucial for creating tailored treatment plans that could lead to full control of the condition or even complete recovery.

Who can participate?

Patients diagnosed with chronic rhinosinusitis (CRS) are invited to participate in a biomedical study. Eligible participants include those scheduled for routine surgical treatments for therapeutic and diagnostic purposes. This also includes patients undergoing surgery for non-CRS-related conditions, such as a deviated nasal septum, nasal deformities, chronic inflammation of the tear ducts (dacryocystitis), orbital pathologies, skull base lesions, nasal septum defects, and nasal bone fractures.

What does the study involve?

Participants will be asked for permission to collect venous blood samples (a total of 10 ml) for this study. These samples will be used to analyze blood for specific immunological markers and to conduct gene polymorphism testing. During the patient’s scheduled surgery, the researchers

will also request permission to collect a small postoperative nasal mucosa sample (2 x 3 mm). Participants will complete a questionnaire which addresses various aspects of health and quality of life, including physical problems, functional limitations, and the emotional impact of the disease. All collected samples and information will be coded to protect identity, and medical records will remain confidential.

What are the possible benefits and risks of participating?
Participating in biomedical studies will benefit patients by contributing to scientific progress; however, these studies will not directly benefit their current treatment. In the future, treatment guidelines will be developed based on the results obtained from the studies and after analyzing the data.
Participants will be able to learn about potential risk factors associated with their disease that could lead to earlier recurrence. They will also receive additional information that may help delay a possible recurrence. This approach aims to enhance opportunities for more personalized treatment.
Patients may encounter some inconveniences while participating in this study. These may include the need to familiarize themselves with the biomedical study information, signing the Informed Consent Form for participation in biomedical research, signing the Informed Consent Form for genetic testing, answering questionnaire questions, and providing venous blood samples. The estimated time required for these activities is approximately 30 minutes.
The blood sample procedure may cause unpleasant sensations, such as minor temporary discomfort.
Additionally, due to unforeseen circumstances, confidential information may become accessible to third parties without your consent.

Where is the study run from?
Lithuanian University of Health Sciences (Lithuania)

When is the study starting, and how long is it expected to run?
May 2023 to May 2028

Who is funding the study?
Lithuanian University of Health Sciences (Lithuania)

Who is the main contact?
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Clinical Trials Information System (CTIS)
2024-520038-31-00

Protocol serial number
LRS 1.4

Study information

Scientific Title
Associations between phenotypic and endotypic groups, risk factors, immune imbalances, and genetic alterations in patients with chronic rhinosinusitis

Acronym
CRSwNp, CRSsNP

Study objectives
Patients suffering from chronic rhinosinusitis (CRS) are typically treated with steroid medications that can produce both local and systemic effects. However, these medications primarily address symptoms rather than the underlying causes of the condition. When medications are ineffective, surgery may be considered. It is crucial to acknowledge that each case of CRS is unique; some individuals achieve complete control of their disease through medication alone, while others may require a combination of surgery and medication. Despite exploring various treatment strategies, some patients continue to struggle to achieve satisfactory therapeutic outcomes.

Given the variability in responses to treatment, it is essential to investigate the genetic, functional, and pathobiological processes—both local and systemic—that could enable more personalized treatment approaches. The ultimate goal is to help patients fully control their condition or even achieve complete resolution. The molecular mechanisms behind the inhibition of biologically active immune substances released from the respiratory epithelium are not yet fully understood, but these mechanisms play a critical role in the effectiveness of the local immune response.

Studying the clinical trajectory, inflammatory response, and specific biomarkers of CRS is vital not only from a scientific standpoint but also for practical application. This research can guide the personalization of treatment for CRS patients. Furthermore, patients' existing comorbidities can influence the strength of the nasal mucosal immune response. For instance, the immune response can vary between individuals with allergic and non-allergic rhinitis, and exposure to cigarette smoke can significantly increase the risk of respiratory inflammation. Cigarette smoke can provoke physiological reactions in the nasal passages, leading to increased airflow resistance, irritation, congestion, and excessive mucus production.

Evaluating these risk factors is crucial for understanding the pathogenesis of CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). Research shows a strong correlation between CRS and bronchial asthma across all age groups. Notably, a stronger association between asthma and CRS is observed in patients with diagnosed allergic rhinitis, while CRS without allergic rhinitis is often linked to late-onset asthma.

The relationship between allergies and CRS remains a topic of debate, particularly in distinguishing between CRSwNP and CRSsNP. Several potential pathophysiological mechanisms have been proposed to link allergies to CRS, but clinical data is inconsistent. Allergies are often associated with type 2 inflammation, characterized by the activation of IL-4, IL-5, and IL-13

cytokines. Improvements in clinical symptoms following treatment are closely tied to these interleukins, highlighting the impact of allergies on CRS, especially in cases involving allergic fungal rhinosinusitis or atopic diseases.

Advancing biomedical research will significantly enhance the multidisciplinary study of CRS by examining the relationships between immune and genetic imbalances and various risk factors. Although this research may not yield immediate benefits for participants, it will generate valuable clinical and experimental data that deepens our understanding of CRS. Ultimately, these findings will be crucial in developing individualized treatment strategies, guidelines for endotype differentiation, disease management, treatment efficacy, and prognosis for CRS patients.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 03/05/2023, Kaunas Regional Biomedical Research Ethics Committee (A. Mickevičiaus g. 9, Kaunas, 44307, Lithuania; +370 (0)614 83823; kaunorbtek@lsmuni.lt), ref: BE-2-10

Study design
Observational case-control study

Primary study design
Observational

Study type(s)
Diagnostic, Quality of life, Screening

Health condition(s) or problem(s) studied
Chronic rhinosinusitis

Interventions
The study will include patients diagnosed with CRS (chronic rhinosinusitis) based on the 2020 EPOS criteria. These patients will be divided into two phenotypic groups: CRSwNP (chronic rhinosinusitis with nasal polyps) and CRSsNP (chronic rhinosinusitis without nasal polyps). The control group will consist of patients consulted for reasons unrelated to CRS, such as skull base lesions, lacrimal sac or orbital pathologies, or nasal septum defects.

The standardized SNOT-22 questionnaire, validated in Lithuania, will be used to assess the clinical course of CRS and the severity of symptoms. A mucosal biopsy and nasal cytology will be collected during endonasal sinus surgery under general endotracheal anesthesia as part of the planned surgical treatment.

In blood samples collected preoperatively and in nasal mucosal epithelial biopsies, the concentrations of IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, IL-21, IL-22, IFN-γ, and TNF-α (in pg/ml) will be determined using flow cytometry, enabling simultaneous measurement of all markers.

Genetic polymorphism analysis will be performed for the following genes: IL-10 (rs1800629), IL-1A (4845G and 4845T), IL-1β (rs16944), TNF-α (rs1800629), IL-33 (rs3939286), IL-6 (rs1800793), IL-22RA1 (rs4292900, rs16829225, and rs4292900), CD14 (rs2569190), MMP1 (rs160701G/2G),

lactoferrin (LF) (140A/G), IL-4 (rs2243250), and MET (tyrosine kinase receptor) (14C/G). These analyses will use allele-specific primers based on the KASP (competitive allele-specific PCR) methodology. A KASP genotyping kit and real-time PCR system will be used for the genotyping.

Total RNA extraction kits and real-time PCR with primer plates will be utilized for gene expression analysis.

Intervention Type
Other

Primary outcome(s)
Measured on the day of surgery:
1. The concentrations of IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, IL-21, IL-22, IFN-γ, and TNF-α (in pg/ml) will be measured in tissue and serum samples using the flow cytometry-based Luminex method, which allows simultaneous detection of all investigated marker concentrations.
2. Gene polymorphism analysis in blood samples will use allele-specific primers based on the competitive allele-specific PCR (KASP) reaction methodology.
The polymerase chain reaction (PCR) method will be used to determine differences in the gene expression of miRNA in plasma, TGF-β, and Wnt signaling pathways, extracellular matrix proteins, and their regulatory molecules in postoperative tissue samples.

Key secondary outcome(s))
Measured on the day of surgery:
1. Complete blood count test
2. Histology of biopsy material
3. Citology tests
4. Assessing the quality of life using the SNOT-22 questionnaire

Completion date
01/05/2028

Eligibility

Key inclusion criteria
Patients with CRS:
1. Based on the 2020 EPOS criteria, a CRS diagnosis was established, and the patient underwent endonasal sinus surgery.
2. Presence of two or more symptoms: nasal obstruction/difficulty breathing through the nose, nasal discharge/postnasal drip, and/or facial pain or pressure, and/or loss or reduction of the sense of smell.
3. Endoscopic findings (polyps, mucopurulent discharge in the middle nasal meatus, mucosal swelling—edema causing obstruction, primarily in the middle nasal meatus); changes visible in computed tomography scans (bony canal and ostiomeatal complex changes and/or sinus mucosal changes).

Healthy (Control) Participants:
1. Individuals without CRS received treatment for conditions not related to CRS, such as skull base lesions, lacrimal sac or orbital issues, and nasal septum defects.

General Criteria:
1. Individuals who are 18 or older and meet the criteria mentioned above.
2. Participants are willing to take part in the study voluntarily.
3. Individuals who have read and signed the informed consent form and the genetic testing consent form.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
80 years

Sex
All

Key exclusion criteria
1. Individuals under 18 years of age
2. Individuals for whom venous puncture is contraindicated or poses a risk of complications
3. Individuals who have not read or signed the informed consent form
4. Pregnant women
5. Individuals with autoimmune diseases
6. Individuals with diabetes mellitus
7. Individuals with chronic lung diseases, such as cystic fibrosis, chronic obstructive pulmonary disease (COPD), or similar conditions
8. Individuals with Wegener's granulomatosis

Date of first enrolment
26/10/2023

Date of final enrolment
01/05/2028

Locations

Countries of recruitment
Lithuania

Study participating centre

Lithuanian University of Health Sciences, Kaunas Clinics
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Sponsor information

Organisation
Lithuanian University of Health Sciences, LSMU

Funder(s)

Funder type
Government

Funder Name
Lietuvos Sveikatos Mokslų Universitetas

Alternative Name(s)
Lithuanian University of Health Sciences, LSMU

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
Lithuania

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publicly available repository.
The datasets generated during and/or analysed during the current study will be available upon request from principal investigator Prof. Saulius Vaitkus, saulius.vaitkus@lsmuni.lt.
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication.

Regulatory authorities, such as the State Medicines Control Agency and biomedical research ethics committees, along with authorized individuals overseeing the study on behalf of the sponsor, the Lithuanian University of Health Sciences, will have access to all information collected about participants in this study. Other individuals or institutions will only receive coded data that does not allow for the direct identification of participants. "Coded" means that the patient’s name and surname will not appear in any documents; instead, a unique number will be assigned, which only the investigator can link back.

The researchers will use the collected data exclusively for this clinical study. The sponsor may use coded health data to conduct research, submit applications to validate scientific findings or develop diagnostic and/or medical tools.

Coded patient samples will be processed and stored until the study is completed. They will be analyzed in the Microbiology Laboratory of the Laboratory Medicine Clinic at LSMUL KK.

IPD sharing plan summary

Stored in non-publicly available repository, Available on request, Published as a supplement to the results publication