Elucidating the pathogenesis of Sjogren's syndrome: Analysis of lower lipbiopsies

Published: 19-05-2010
Last updated: 04-05-2024

To gain more insight into the pathogenetic processes involved in SS by analyzing the infiltrate and structural changes in salivary glands of SS patients and compare these findings to those in other (aspecific) inflammatory and non-inflammatory...

Ethical review	Approved WMO
Status	Pending
Health condition type	Autoimmune disorders
Study type	Observational invasive

Summary

ID

NL-OMON34623

Source
ToetsingOnline

Brief title
Analysis of lower lipbiopsies

Condition

- Autoimmune disorders

Synonym
dry mouth, Xerostomie

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Reumafonds

Intervention

Keyword: Lower lipbiopsie, Pathogenesis, Sjogren's syndrome

Outcome measures

Primary outcome

Obtained material will be used to elucidate primarily the B cel pathogenesis of Sjogren's syndrome. Using immunohistochemistry, RNA and protein analysis, the B cell receptor (BCR), T cell receptor (TCR), a B cell stimulating cytokine (A proliferation-inducing ligand, APRIL), and the interaction between different immune cell populations and cytokines will be studied.

Whenever enough patientmaterial is obtained, we are also be able to study different subpopulations, based on extra-glandular manisfestations and the severity of salivary gland inflammation.

Secondary outcome

Not applicable.

Study description

Background summary

Sjögren*s syndrome (SS) is a systemic autoimmune disorder of unknown etiology, characterized by mononuclear cell infiltration in exocrine glands, principally the lacrimal and salivary glands. Other organ systems are frequently involved and 5% of SS patients develop lymphoma. The inflammation of exocrine glands is most prominent, resulting in dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). The salivary gland dysfunction with associated difficulty in eating and swallowing is the major complaint of patients. SS may occur isolated, termed primary SS, or in association with another defined autoimmune disease, such as rheumatoid arthritis, termed secondary SS. Primary SS is one of the most common autoimmune diseases affecting 0.6% of the total population in the Netherlands with women being nine times more likely to be affected than men. Generally there are two age-peaks seen in primary SS patients, the first

between 20-30 years and the second around 50-60 years of age.
The exact pathogenesis of SS is unknown, but it is clearly multifactorial. The presence of multiple autoantibodies in the peripheral blood of patients with SS and the signs of chronic inflammation in the target organ, indicate an autoimmune response against the exocrine glands. This is supported by several findings at the histological level, such as the presence of large persistent mononuclear foci, consisting of both T lymphocytes (~80%) and B lymphocytes (~20%) in salivary and lacrimal glands in patients with SS. Evidence confirms that lymphocytic disturbances, including formation of ectopic germinal centers and aberrations of cellular signaling play a significant role, but still the exact function has to be elucidated. Variable degrees of acinar cell atrophy and progressing fibrosis can also be observed. Currently, there are different hypothetic models for the SS pathogenesis. The *classical* model to explain glandular hypofunction is tissue loss secondary to immune attack mediated by a combination apoptosis and cytotoxic cell death. In the *non-apoptotic* model glandular hypofunction follows immune-mediated inhibition of acinar secretory function.
While there is effective palliative therapy for lacrimal manifestations, no effective treatment exists for the salivary gland dysfunction. Current palliative treatment for salivary gland dysfunction includes artificial saliva, frequent dental prophylaxis, and/or stimulation by muscarinic agonists, such as pilocarpine and cevimeline, and the use of steroids and other immunomodulatory agents. However, systemic immunosuppressive and immunomodulatory therapies, including classical immunosuppressives and TNF-alpha inhibitors, are largely ineffective.
Since SS primarily involves the salivary and lacrimal glands, tissue analysis of the salivary gland is essential to gain more insight into the pathogenesis of the disease process. Therefore, descriptive studies of SS salivary glands may provide a better understanding of the events that take place in vivo and complement experimental animal studies and in vitro studies. Moreover, knowledge about the pathogenesis can be used for the identification of new targets and development of innovative therapies for SS.

To evaluate if the salivary gland infiltrate and structural changes are specific for SS, it is important to compare SS salivary gland tissue to that of other (aspecific) inflammatory and non-inflammatory salivary glands.

Study objective

To gain more insight into the pathogenetic processes involved in SS by analyzing the infiltrate and structural changes in salivary glands of SS patients and compare these findings to those in other (aspecific) inflammatory and non-inflammatory salivary gland diseases.

Study design

1.1 Patients:
Inclusion criteria:
Patients undergoing lower lip biopsies for diagnostic purposes.

1.2 Clinical evaluation and demographic measurements:
Individual patient information will be reported in a form (Case Report From (CRF). Recording of:
- Demographic data (date of birth, sex, and race)
- Medical history (sicca symptoms, arthralgia, medication)
- Diagnosis
- Disease duration
- Presence of autoantibodies in serum (anti-ENA, anti-SSA and anti-SSB)
- Histological evaluation of the salivary glands (focus score)

1.3 Collection of material:
Salivary gland (lower lip):
In all patients undergoing diagnostic lower lip biopsies, salivary gland tissue will be collected and processed using a standard protocol for formalin fixation to allow standard histological evaluation for diagnostic purposes. Samples will also be frozen in Tissue-Tek OCT compound for immunohistochemistry (IHC) or snap frozen for PCR, micro-array, T Cell Receptor (TCR) and B Cell Receptor (BCR) analysis, and protein expression analysis.

Serum and Peripheral Blood Mononuclear Cells (PBMC):
From all patients, 54 ml blood will be collected (6 heparine tubes of 9 ml each). Serum will be isolated for detection of immunoglobulins (Ig*s) and cytokine levels. Also, PBMC*s (± 54x10exp6) will be isolated and ribonucleicacid (RNA) will be extracted from these cells. PBMC RNA will be used in TCR and BCR analysis and compared to RNA samples from salivary glands. This will give us the opportunity to compare in parallel systemic versus tissue levels.

Study burden and risks

1-time blood withdrawal (54 ml).
1-time lower lipbiopsy: 1 extra lipbiopsy in patients having already a diagnostic biopsy in daily patient care.

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

Patients having a diagnostic lower lipbiopsie for evaluation xerostomia

Exclusion criteria

None

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:	Pending
Start date (anticipated):	01-11-2010
Enrollment:	200
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL30982.018.09