Primary Sjögren’s Syndrome
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Sjögren’s syndrome (SS) is a systemic autoimmune disease, second to rheumatoid arthritis, with an estimated prevalence of 0.05% in the general population. SS commonly affects the exocrine glands, in particular the salivary and lacrimal glands, resulting in a sensation of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). SS can be distinguished in primary Sjögren’s syndrome (pSS), in case no other autoimmune disease is present, and secondary Sjögren’s syndrome (sSS), in case additional connective tissue diseases are present.

Recently, the accuracy of ultrasonography to evaluate the involvement of the major salivary glands as well as its suitability to be used as an alternative to or replacement of other diagnostic tests used to classify pSS gained a lot of interest. The true diagnostic properties of salivary gland ultrasonography remain, however, vastly unknown.

With regard to treatment of pSS, for many decades this was mainly symptomatic and aimed to, e.g., reduce the feeling of dryness and provide comfort to the patients. With the advent of disease-modifying antirheumatic drugs’ (DMARDS) the possibilities for treating pSS have considerably expanded. DMARDS not only aim to reduce the symptoms, but are also aimed to have a systemic effect. There is, however, so far no agreement on which pSS patients are susceptible to a treatment with DMARDS.

Finally, as far as patient education is concerned, persons experiencing xerostomia or being diagnosed with pSS and undergoing treatment, like any other online health information seeker, may search the Internet for background knowledge. However, the diversity of authorship and the lack of peer-review process have led to dissemination of inaccurate and misleading information on the Internet.

Taking into account the abovementioned open issues regarding the diagnosis, treatment and patient education of patients with pSS, the overall aim of the research described in this PhD-thesis was to assess new challenges and trends in the diagnosis, treatment and e-education of pSS patients (Chapter 1).

The study described in Chapter 2 reviews the three major causes of xerostomia, viz. side-effects of medication, radiotherapy in the head and neck area and SS. With regard to medication, certain classes of drugs are known to induce hyposalivation and/or xerostomia by, e.g., targeting neurotransmitters and receptors. As far as head and neck radiotherapy is concerned, the administration of high radiation doses to the major salivary glands leads to progressive loss of glandular function and a diminished salivary output. Reduction of the dose and the volume of the radiated salivary gland tissue by advanced radiotherapy techniques was shown to be highly beneficial for patients. As mentioned before, SS affects the exocrine glands, the salivary and lacrimal glands in particular. The pathogenesis underlying SS involves systemic B-cell hyperactivity and T-cell lymphocytes targeting glandular epithelial cells.

Diagnosis

Chapter 3A presents a meta-analysis on studies examining the properties of ultrasonography of major salivary glands (SGUS) for diagnosing pSS, a tool that is more frequently used in the diagnostic work-up of SS. This meta-analysis demonstrated that SGUS has a sensitivity, specificity and diagnostic odds ratio of 69%, 92% and 33.89, respectively, to diagnose pSS according to the ultrasonographic characteristics of the major salivary glands. Based on the results of this meta-analysis, it was concluded that SGUS has the potential to evolve into a viable alternative in the diagnostic work-up of the major salivary glands in patients with pSS. In the study described in chapter Chapter 3B, concerns were expressed regarding a similar meta-analysis performed by other authors, as discrepancies were detected between the data shown in that study and the data presented by the source studies.

With respect to the reproducibility of SGUS, the study presented in Chapter 3C showed that the intra- and inter-observer reliability of SGUS ranged from good to excellent. The results of this study also showed that scoring the severity of the ultrasonographic findings is less consistent between observers. Thus, when monitoring patients over time, the observed change might not be only attributed to the progression of the disease or to the effect of medication, but might also be partly due to the discrepancy in scoring between the different observers.

In order to investigate the validity, i.e. the ability of SGUS to indicate which individuals have pSS and which do not, SGUS results were compared to the results of the parotid and labial gland biopsy, as well as to the performance of the classification criteria in patients who were clinically suspected with pSS (Chapter 3D). We learned from this study that the agreement between SGUS and parotid or labial gland biopsy outcomes was good and moderate, respectively, but also that SGUS cannot replace salivary gland biopsy. One of the most important findings of this study is that when combining positive SGUS with presence of anti-SSA antibodies, 94, 97 and 97% of the patients fulfilled the AECG, ACR and ACR-EULAR criteria, respectively.

The pilot study described in Chapter 3E addressed a major issue detected in the meta-analysis presented in Chapter 3A, viz. none of the studies included in the meta-analysis had recruited as controls patients with sarcoidosis, amyloidosis, human immunodeficiency virus infection or hepatitis C virus infection. These are all diseases that can mimic pSS. Therefore, a pilot study was performed to assess the performance of SGUS in these patient groups. It was shown that SGUS is a potentially accurate imaging technique in diagnosing pSS and in differentiating pSS from these systemic diseases.
Treatment

The study described in Chapter 4A revealed that treatment with rituximab (RTX) significantly reduced the overall lymphocytic infiltrate with a major loss of the B-cell component and number of germinal centers/mm² of parotid gland parenchyma in pSS patients. In addition, a major reduction of the quantity and severity of lymphoepithelial lesions was apparent. These findings clearly show that RTX treatment results in significant restoration of the salivary gland parenchyma of patients with pSS. The study described in this chapter showed also that clinical responders to treatment with RTX had a higher number of CD20⁺ B-cells/mm² of parenchyma of parotid gland tissue at pre-treatment (baseline) compared to non-responders. The baseline number of B-cells/mm² of parenchyma of parotid gland may thus predict the patients’ response to RTX and may be considered as a biomarker for a more personalized treatment approach.

The same conclusion as mentioned above could be drawn when baseline proportions of B-cells in the parotid gland tissue were used and thus not absolute numbers of these cells (Chapter 4B). The observations described in Chapter 4C further stressed the need for standardized guidelines to assess the histopathological characteristics of the salivary gland tissue of patients with pSS. Consensus guidelines will assist researchers to better identify and quantify histopathological parameters in pSS and thus contribute to a more accurate prediction of disease progression and targeted personalized treatment.

e-Patient education

In Chapter 5A an e-search was performed using four popular search engines: Google™, Bing™, YAHOO!® and Ask®. The terms ‘dry mouth’ and ‘xerostomia’ were entered individually to mimic a common, i.e., a search performed by a layperson, online search. It was found that the bulk of the Web information related to xerostomia was written in a fairly difficult to very difficult understandable mode and language. Furthermore, medium accessibility and a considerably low reliability were detected for the sites under investigation, with implications for site transparency, expertise authorship, review procedures and update frequency. These findings have raised concerns about the susceptibility of patients to misinformation.

In addition to the information available on Web sites, we also showed that approximately 50% of YouTube videos relevant to pSS were deemed useful (Chapter 5B) and thus may have the power to positively modify patient-doctor relationship, by encouraging patients in the management of their health through a more shared decision making approach. At the same time, incomplete information on the etiology of pSS and drugs of unknown ingredients were posted by the misleading videos. Videos were evaluated with the global quality score (GQS), a 5-point scale, which assesses the quality of the information and how useful the reviewer assumed the particular video would be to a patient. In terms of GQS, reliability and comprehensiveness of information, government/news agencies appeared to be the most creditable contributors. On the other hand, university channels/professional organizations presented as high GQS as government/news agencies, while none video was classified as misleading. Therefore, to increase the chances of accessing high quality information on pSS, YouTube users should seek for videos of reliable origin.

Conclusion

The research described in this thesis has shown that SGUS is a reliable imaging technique in the diagnostic process of patients suspected with pSS, but should be used with caution when following up patients longitudinally for assessing disease progression or treatment evaluation. Combining a positive SGUS with the presence of anti-SSA antibodies is highly predictive whether a patient might fulfill the classification criteria. As far as treatment is concerned, baseline histopathological characteristics of a parotid gland biopsy may strongly contribute to a more personalized treatment approach to pSS patients with RTX. Last but not least, the currently available online patient information on xerostomia and pSS exhibits a variable quality and therefore should be approached with caution.