Sjögren’s Syndrome: Diagnosis through Dysfunction

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ABSTRACT

Sjögren’s syndrome (SS) is characterized by keratoconjunctivitis sicca, xerostomia and rheumatoid arthritis. Salivary gland dysfunction is one of the key manifestations of this disease and thus it seems logical to use the dysfunction of these glands for its diagnosis. A growing number of researchers from various fields including dentistry are finding saliva as a useful diagnostic tool due to easy and noninvasive collection methods. The non-invasive nature of saliva makes it the most reliable and favored tool for diagnosis of SS. The ability to measure a wide range of molecular components in saliva and compare them with serum has made it feasible to study microbes, chemicals and immunological markers. This review article aims at summarizing the variable use of saliva as a diagnostic aid on a daily basis while treating patients with SS.

Keywords: Sialometry, Sialochemistry, Sjögren’s syndrome.

INTRODUCTION

Sjögren’s syndrome (SS) is a condition originally described by Henrik Sjögren in 1933 as a triad consisting of keratoconjunctivitis sicca, xerostomia and rheumatoid arthritis. The main etiologic factor for this disease is considered to be altered immunological response. Since, the etiopathogenesis of the diseases unclear, its diagnosis is still based on characteristics signs and symptoms. As a single diagnostic test does not detect changes pathognomic of SS, combinations of different tests are used. Salivary gland dysfunction in one of the key manifestations of this disease and thus it seems logical to use the dysfunction of these glands for its diagnosis.

Methods for assessing salivary gland dysfunction include the following:

- Sialometry—method for determining flow rate.
- Sialochemistry—chemical analysis of salivary composition.

Sialometry can be used as a diagnostic tool mainly in two ways:

Sialometry

A reduced rate of secretion of unstimulated whole saliva is currently considered to be of diagnostic value in SS. Various studies have showed reduced submandibular/sublingual (SM/SL) flow rate in SS. A possible explanation for this appreciably reduced flow rate is early involvement of SM/SL gland. In contrast, parotid flow rate may be decreased in SS negative patients also and hence measurement of parotid flow as a single test is of no use in diagnosing SS.

Sialochemistry

Sjögren’s syndrome patients showed elevated levels of Na⁺ and Cl⁻ levels. Normally Na⁺ act are extensively absorbed in the ductal system to produce hypotonic saliva, and in normal individuals, their concentrations decrease with decrease in flow rates. This phenomenon is not observed in SS patients and even patients with very low flow rates show a two fold or three fold increase in Na⁺ and Cl⁻ concentration. This could be due to impaired duct function by periductal lymphocytic infiltration that is present in major salivary glands in SS. Phosphate concentration was decreased in SS patients in unstimulated whole saliva and concentration was unaltered in stimulated saliva. The unaltered levels in stimulated saliva indicate a disease independent potassium secretion by duct cells or that potassium is secreted at other sites.

Proteins

Qualitative and quantitative changes of salivary protein content have been examined by means of electrophoresis and
isoelectric focusing on stimulated parotid secretion. Increased amount of anionic proteins was observed in SS patients.

**Lipids**

Salivary levels of phospholipids are increased and this may have diagnostic implications. Unsaturated fatty acids of salivary lipids were below normal, which may indicate an alteration in cell membrane function.

**Lactoferrin (L1)**

Tabak et al reported an increase in lactoferrin in stimulated parotid saliva with primary SS.

**Lysozyme**

In SS patients, the lysozyme levels, an antibacterial enzyme, were decreased which could be due to pronounced atrophy of epithelial cells.

**Amylase**

No significant difference in saliva of SS patients and healthy controls were reported, but in a group of patients with primary SS, a significantly decreased concentration in the nonsecreting patients as compared to nearly normal secreting patients were found. Amylase may be used as a marker/or acinar function.

**Kallikreins**

In SS patients, elevated levels especially in the morning were found in stimulated whole saliva compared with healthy controls. Salivary Kallikrein may serve as a marker for striated duct cell function and elevations found in SS may indicate damage to these cells.

**Albumin**

In SS albumin, levels in saliva are elevated indicating a certain loss of parenchymal integrity. These elevations reflect leakage and arc, therefore valuable in the assessment of extent of inflammatory changes present.

**B-2 Microglobulin (B2M)**

In majority of patients, the concentrations were higher than in serum, suggesting a local B2M production. Acinar cells and majority of lymphocytes stain for B2M in SS and intensity parallels the severity of inflammation.

Salivary B2M may therefore be a marker for the degree of inflammation in salivary glands in SS patients.

**Immunoglobulins**

- Immunoglobulin A (IgA): Increased concentration of secretory IgA has been found in SS patients in view of the lymphocytic glandular infiltration. Decreased in flow rate may also be partly responsible. Some studies have advocated the increase in salivary IgA, as a criterion for diagnosis of SS.
  - Immunoglobulin G (IgG): Marked elevation of IgG in SS patients were reported by several studies. The increase in salivary IgG is not influenced by diminution of salivary flow. The elevated levels are due to activated local synthesis which is supported by reports detecting increased number or IgG producing plasma cells in the lymphocytic infiltrate of minor salivary gland biopsy specimens in SS patients.
  - Immunoglobulin M (IgM): The presence of IgM in saliva of SS patients was inconsistent.

**Salivary Auto-Antibodies**

Both IgM and IgA-RF have been found in the saliva of primary SS.

IgA-anti SB autoantibodies are also synthesized locally in the diseased salivary glands and secreted into saliva of SS patients.

Horsfall et al reported the presence of salivary anti-La antibodies in SS patients by ELISA. Ben-Chitrit et al detected anti-Ro and anti-La antibodies in the saliva of patients with SS. Analysis of these antibodies showed that, although the serum contained mainly IgG and IgM antibodies, saliva contained antibodies of IgG and IgA classes only. SS anti-La antibodies were primarily found in the saliva of patients whose resting and stimulated whole saliva flow rates was extremely low. In some patients, this antibody was detected in whole saliva but not in serum, which suggested that the antibody is produced in the salivary glands. The deposition of this antibody within salivary gland tissue may contribute to the pathogenesis of SS.

**Other Markers of Inflammation**

Levels of salivary eicosanoids (PGE2 and TXB2), interleukin-6 and hyaluronic acid were elevated in SS patients compared with healthy controls.

**Early Salivary Manifestations in SS**

The following changes occurred almost exclusively in SS groups of relative shorter duration (less than 1 year) of oral symptoms:

- Sialometry showed normal flow rates, accompanied by considerably changed salivary composition, including Na⁺ and Cl⁻ concentration.
- Low stimulated flow rates from SM/SL glands accompanied by subnormal flow rate from parotid glands were

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1. Horsfall et al
2. Ben-Chitrit et al
3. U. Horsfall, personal communication
4. U. Horsfall, personal communication
5. U. Horsfall, personal communication
observed. These profiles are characteristics of early salivary manifestations of SS.

Late Salivary Manifestations of SS

Extremely low stimulated flow rates from all major salivary glands were observed and are characteristic of late salivary manifestations of SS.

Use of Sialochemistry in Differentiating from Other Lesions

Sjögren’s syndrome being a chronic inflammatory condition can be differentiated from acute inflammation of salivary glands by presence of much higher salivary protein concentration in acute inflammation resulting from protein leakage from the serum.

Also, the observed increase in potassium and amylase concentration indicated the presence of sialoadenosis and decreased in sodium concentration indicated patients with sodium retention dysfunction syndrome. Both of which are noninflammatory salivary gland disease. Thus, in addition to diagnostic potential of sialochemical changes in SS, the changes observed can also be useful in differential diagnosis of salivary gland diseases.

CONCLUSION

The diagnosis of primary SS is strongly suggested in patients who present with signs and symptoms of oral and ocular dryness and who test positive for antibodies to the anti-SS-A or anti-SS-B antigen, or who have a positive salivary gland biopsy.8,9 It should be noted that antibodies to the anti-SS-A and anti-SS-B antigens are not specific to SS; they may be present in persons with other diseases (e.g. lupus) and in healthy persons.9

Sjögren’s syndrome often has an insidious onset, a variable course, and a wide spectrum of clinical manifestations, making the diagnosis difficult or delayed. Early recognition of Sjögren’s syndrome may prevent complications, such as dental caries, corneal ulceration, chronic oral infection, and sialadenitis, and it allows for clinical surveillance for the development of serious extraglandular systemic manifestations.9,10

REFERENCES