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Labial gland biopsy: shared care, medico-legal and surgical considerations

Running Title: Labial Gland Biopsy Considerations

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Abstract

Aim: To give the surgeon an overview of Primary Sjögren's Syndrome, its pathophysiology, diagnosis and management thus giving insight into why labial gland biopsies are required. The authors also aim to make the operating surgeon aware of their role, responsibility and medicolegal factors to be considered prior to undertaking a labial gland biopsy.

Materials and Methods: A literature search of PubMed (MEDLINE), Cochrane and EMBASE electronic databases using the search terms "Primary Sjögren's Syndrome", "Diagnostic Criteria for Sjögren's Syndrome", "Labial Gland Biopsy", "Labial Gland Biopsy Complications", "Diagnostic Imaging for Sjögren's Syndrome", and "Medicolegal Responsibility of Surgeons". Title and then abstract were reviewed to determine relevance. Widely used guidelines were identified, indications for biopsy and the risks posed by surgery considered. Medicolegal advice was formally sought via a medical/dental defence union.

Results: The authors considered the available evidence and medicolegal advice and applied this knowledge to the clinical setting. A preoperative checklist for consideration prior to labial gland biopsy was developed.

Conclusions: Labial gland biopsy is an invasive procedure with potential to cause postoperative complications. The operator assumes ultimate responsibility for the procedure. Every surgeon aims to ensure safe surgical practice, in the best interest of the patient. Here we consolidate recent evidence and propose a checklist to facilitate the process for oral surgeons.

Clinical Relevance

Rationale for Study: This paper came about due to the difficulties a colleague faced after performing a labial gland biopsy on a patient who subsequently experienced paraesthesia.

Principle Findings: Labial gland biopsy is a procedure with potential to cause complications. Current medicolegal advice is that the surgeon assumes ultimate responsibility for the procedure itself and must be cognisant with the underpinning rationale and current evidence relevant to the potential diagnostic value of this invasive procedure.

Practical Implications: We have developed a tool to use prior to performing a labial gland biopsy to facilitate the necessary checks.

Introduction

Sjögren's Syndrome (SS) is a chronic inflammatory multisystem, progressive, autoimmune exocrinopathy. It mainly manifests in abnormal ocular and salivary gland function; however other organs can be affected in more than 30% of patients[1]. The pathogenesis of SS is not fully understood. Nevertheless, it is known to be an autoimmune disease with anti-nuclear antibodies produced targeting Ro and La found in many cases[2]. SS associated with an underlying condition is classified as secondary SS and when presenting in the absence of other related pathology as primary Sjögren's Syndrome (pSS)[3]. Here we focus on the role of the labial gland biopsy (LgBx) in the diagnosis and future management of pSS.

pSS is still a complex and often misunderstood disease with significant quality of life implications for the patients. It can manifest in different ways, affecting salivary and lacrimal flow but also causing major salivary gland swelling and associated pain, cutaneous and genital dryness, fatigue, arthralgia and myalgia[4]. Thus, the prompt diagnosis and management of the disease is imperative but can be hindered by the spectrum of signs and symptoms experienced by individual patients.

Diagnosis of pSS

Diagnosis of Sjögren's involves a multidisciplinary approach often involving rheumatologists, ophthalmologists, oral surgeons and oral physicians.

Diagnostic Criteria

Over the last two decades, three main sets of validated criteria have been published. In 2002 the America-European Consensus Group (AECG) diagnostic criteria for pSS[5] were published (see Table 1 below).

Table 1

In 2012 the American College for Rheumatology (ACR) proposed new diagnostic criteria which were aimed at selection of patients prior to enrolment into clinical trials[6]. However, these criteria have not yet been validated by epidemiological studies. Whilst there are differences between the AECG and ACR criteria, concordance is high[7]. More recently the 2016 ACR/European League Against Rheumatism (EULAR) criteria were published consequent to collaboration between the AECG and ACR/ Sjögren's International Collaborative Clinical Alliance (SICCA)[8]. Oral surgeons should be aware that a labial gland biopsy is a component of diagnosis in all three systems and that individual rheumatologists may refer to any of the above-mentioned criteria in establishing a diagnosis of pSS. Hence it is important that the surgeon is aware of the relevant criteria utilised to consider the potential diagnostic yield of a labial gland biopsy in individual patients. If there is any confusion, clarification of the specific criteria should be sought. Considering the multiple criteria in clinical use, for purposes of this paper we will henceforth refer solely to the most recent 2016 ACR/EULAR criteria[8] (Table 2).

The 2016 ACR/EULAR criteria[8] require that patients initially must meet inclusion criteria set out in Table 2 below. They must thereafter have positive results to a threshold of the diagnostic investigations to establish a diagnosis of pSS.

Table 2

To be able to give a diagnosis the patient must score 4 or more when the weights of each individual criteria are considered to fulfil the 2016 ACR/EULAR classification[8] (Table 2). Thus, if a patient had a positive anti SSA/Ro extractable nuclear antigens (ENA) (heavily weighted by the criteria and given a score of 3) and positive Schirmer's Test (reduced lacrimal flow) they would fulfil the criteria for having pSS, not requiring further tests to prove it. The labial gland biopsy is another heavily weighted criterion to that also scores 3 in this classification and can therefore be utilised by clinicians to establish a diagnosis of SS.

To add further complexity to the diagnostic process, advances in ultrasonography have resulted in this imaging modality being considered to replace radiation modality dependent imaging modalities such as sialography or scintography[9]. Within Oral Medicine Specialist practice in the UK ultrasonography is becoming the prime imaging modality utilized, in preference to radiation dependent modalities. In the future an ultrasound may be deemed to satisfy the AECG imaging criterion without need of recourse to radiation dependent investigations. Whilst there are no current criteria set for the utilisation of an imaging modality in the current ACR/EULAR 2016 guidelines, provision for future adoption has been referred to by the group[8].

Chairside investigations:

There are common chairside and laboratory investigations for pSS, these are testing lacrimal function, salivary flow and ANA and ENA analysis. A Schirmer's test is a simple chairside test that can measure lacrimal function. A graduated strip of filter paper with specially shaped ends is inserted into the conjunctival fornix of the eye and after 5 minutes the length of fluid tracking along the paper is recorded (<5mm tear wetting track indicates abnormal lacrimal activity)[10]. Unstimulated whole saliva flow rate measurement described by Navazesh and Kumar[11] is measured by passively collecting the patient's saliva in a calibrated tube over a 15-minute period (<1.5mL indicates an abnormal result). This test has an important role in differentiating between patient reported dry mouth and clinically demonstrated hyposalivation. The presence of anti SSA/Ro antibodies is assessed via sending an appropriate blood sample to the immunology laboratory.

Investigations through referral:

Suspected cases of pSS are often referred from primary care to ophthalmology and/or rheumatology departments. Ocular staining scores are usually accessed via a referral to ophthalmology. Corneal integrity is assessed using Fluorescein and conjunctival health is visualised using Rose Bengal or lissamine green[12]. Rheumatology departments routinely manage Sjögren's disease. Their input is required when treatment provided in primary care is not managing patient symptoms and systemic complications are suspected. They will carry out basic chairside investigations listed above and may enlist input from ophthalmologists and potentially oral surgeons or oral physicians for the provision of a biopsy of labial gland tissue.

Labial Gland Biopsy

Procedure

Due to accessibility, avoidance of skin incision, ease of anaesthesia, lack of complicating structures and the presence of many minor salivary glands; the lower lip is the anatomical position of choice for salivary gland biopsy[13,14]. The procedure is normally carried out under local anaesthesia. A 1-1.5cm superficial incision is made lateral to the midline (as this area holds the most glands), blunt dissection is used to arrive deep to the mucous membrane and superficial to the orbicularis oris muscle. Vertical or horizontal incision can be made and there is no conclusive evidence to suggest one technique is better than the other. However, vertical incision is less likely to transect the mental nerve, though this should be unlikely due to the superficial nature of the initial incision. A sample of 6-8 glands is sent in formalin solution for histopathological analysis. The sample will be mounted in wax then stained with haematoxylin and eosin (H&E) to assess focal lymphocytic sialadenitis (FLS). The request to the pathologist should include asking for the focus score, the presence or absence of germinal centre-like structures and IgG4 staining[15].

A focus is defined as an aggregate of 50 or more lymphocytes per 4 mm^2 glandular tissue adjacent to normal mucous acini[16]. Daniels *et al* (as part of the Sjögren's International Collaborative Clinical Alliance (SICCA)) studied the histopathological results of a large cohort of 1726 patients with signs or symptoms linked to primary or secondary Sjögren's syndrome. They found that a diagnosis of focal lymphocytic sialadenitis with a focal score (FS) of greater than or equal to 1 per 4mm^2 versus a FS of less than 1 with non-specific or sclerosing chronic sialadenitis was strongly associated with the ocular and serological components of Sjögren's syndrome and reflects Sjögren's syndrome autoimmunity[17]. Depending on the pSS diagnostic criteria being used, a focus score cutoff of either "1" or "greater than 1" is considered positive for Sjögren's syndrome[18] (Table 3).

Table 3

Complications

As with any minor oral surgery procedure there are risks involved. Post-operative concerns include bleeding, bruising, swelling and pain. Reported complications range from these routine transient issues to damage to adjacent minor salivary glands and permanent paraesthesia of the mental nerve. Anatomical dissection of the lower lip has shown patterns of neurological fibres in the lower lip indicating that there is no completely safe anatomical space for minor oral procedures to the inner mucosal aspect of the lower lip[19].

Colella et al performed a systematic review of the literature between January 1990 and January 2010 that included 21 studies of minor salivary gland biopsy. Within these studies patients reported disorders of lip sensitivity for up to 6 months occurring as frequently as 11%[13]. Patients reported neurological complications lasting between 7-14 days and one patient over 2 years. While short term neurological complications may occur, the long term risk will be of importance to patients. *Pijpe* reported in a 2006 study a permanent sensory loss of 6%[20]. In 2014 *Centelles et al* performed a meta-analysis of cases looking at the incidence of neurological complication in relation to the type of incision and found an initial incidence of 11.7%, this can persist in up to 6% of patients beyond 6 months[21,22]. In these persistent cases the paraesthesia was reported to be permanent. Thorough knowledge of the possible postoperative complications is required to gain fully informed consent. It would be reasonable to discuss the above studies with patients and give them an estimate of 12% chance of developing altered sensation of the mental nerve that may persist beyond 6 months and be permanent in 6% of biopsies performed. These risks are summarised in Table 4, below.

Table 4

Sensitivity and Specificity

In addition to the risk of complications there is also the risk of a LgBx providing in an inconclusive outcome. Focus scores of 2 to 6 have been detected in biopsies from 15% of healthy volunteers with no sicca symptoms in one study of 54 participants[23]. False negative results were found in 20 to 40% of biopsies taken in another study[24] and in a further study revisiting the analysis of biopsy samples resulted in the change of diagnoses in 32 out of 60 patients' cases[25]. This difficulty and variability of interpretation of lip gland biopsies between pathologists is recognised as part of recent consensus reports and cohort studies[26,27,28]. The need for standardisation of interpretation of histopathological results between histopathologists has been acknowledged by rheumatologists[29]. However, as demonstrated in the aforementioned studies general pathologists have a much higher variation in reporting of biopsy results than the specialist head and neck pathologists that checked the results. The potential inconsistency of sensitivity and specificity should be relayed to the patient when discussing the benefits and drawbacks of the procedure as another part of an informed consent process, but reassurance given if it is known that a specialist pathologist will be available. Patients consenting to this surgical procedure also need to be aware of the difficulties in biopsy interpretation that may preclude a definitive diagnostic outcome.

Management of pSS

Management of pSS is dependent on the individual disease characteristics experienced by each patient. Dryness of the mouth and eyes (known collectively as Sicca Syndrome) are the most common complaints by patients diagnosed with pSS, occurring individually in 98% and in combination in 89% of patients in a large (6110 patient) case series[11]. Chronic eye irritation, difficulty eating and speaking and dental disease all ensue from lack of lacrimal

and salivary fluids[15]. If detected early these can be treated with topical lubrication, but disease progression can result in permanent visual disturbance and potentially tooth loss due to caries and periodontal disease. The awareness of and monitoring by ophthalmologists and dental practitioners is essential.

Exocrine glandular swelling due to focal, mononuclear cell infiltrate accumulating around ducts, encompassing and replacing secretory cells results in acute and chronic inflammation occurring recurrently in pSS[30]. Glandular enlargement, especially if recent onset and unilateral should be investigated for underlying pathology. In a UK-based study of 152 patients with pSS 28.3% developed malignancy over a 25-year follow-up period, 1.72 cases per year equating to an incidence rate of 1.1%. The majority of those patients developing non-Hodgkin lymphoma[30]. There is ongoing research into the predictive value of LgBx on the progression of pSS to lymphoma. A recent review by *Kroese et al* suggests that more research and further consensus on the interpretation of the labial gland biopsy is required before this can be considered a reproducible and reliable test[31]. Other severe systemic manifestations can arise affecting the skin, lungs, kidneys and peripheral and central nervous systems[15]. Treatments for pSS can range from topical eye drops and salivary substitutes for sicca symptoms to systemic steroids and disease modifying anti-rheumatic drugs (DMARDs)[32]. However, some pSS patients have limited symptoms and require no medical intervention. Considering the spectrum of disease and its management, pSS diagnosis will have different levels of significance on a case by case basis.

Medicolegal Implications and Consent

Medicolegal input was formally sought via a medical/dental defence union regarding the legal-standing of the surgeon performing a LgBx. The Senior Dento-legal Advisor concluded that if a patient is referred to a practitioner for an investigative procedure or for treatment, the practitioner accepting the referral has a professional and legal obligation to make every reasonable effort to determine whether that procedure or treatment is appropriate and necessary for the individual patient, hence in the patient's best interest. To simply carry out the requested treatment without question would render the practitioner open to justifiable criticism as indicated by the below citation from the GDC's document *Standards for the Dental Team*[33] (Table 5).

Table 5

A labial gland biopsy can be requested by referral from a non-dental specialty. Clearly, an oral surgeon cannot be expected to possess the same specialist knowledge of disease management regarding this specific subject matter compared with a referring consultant rheumatologist or an oral medicine specialist. Nevertheless, the oral surgeon accepting a referral must have sufficient knowledge of the indications for the procedure or treatment requested by the referring practitioner such that they can assess whether it is appropriate, in the correct sequence of the investigation pathway, necessary for the individual patient, and thus in the patient's best interest.

Consent is not a one-off event but an ongoing process and will start with the referring practitioner explaining to the patient about their condition, the options for investigation and treatment, and their pros, cons and risks, and the reason for the referral. That dialogue will continue when the patient attends the oral surgeon accepting the referral. Whilst responsibility

for obtaining consent is a shared responsibility between the referrer and the operating surgeon, it rests predominantly with the practitioner accepting the referral. The inference is that the oral surgeon must therefore have sufficient knowledge of the indications and underpinning rationale including the ability to balance the diagnostic gain against the potential harms whilst respecting the patient's views. This is critical in terms of obtaining informed consent in line with the Montgomery judgement[34].

If the practitioner accepting the referral is of the opinion the treatment requested by the referring practitioner is inappropriate, unnecessary, and not in the patient's best interest, then in line with paragraph 6.4.2 of the GDC's Standards for the Dental Team[33], they should contact the referring practitioner and seek to resolve the concern. If they cannot satisfactorily resolve their concern, they should decline to carry out the procedure or treatment as per paragraph 6.4.2 of the GDC's Standards for the Dental Team[33], explaining to both patient and referring practitioner their reasons for so declining. It is a fundamental clinical principle that a dental or medical professional should not be compelled to carry out an investigative procedure or a treatment with which they disagree because they do not consider it is appropriate, necessary, in the patient's best interest, and in line with current accepted practice and teaching as would be supported by a responsible body of clinical opinion[33].

Shared Care Decision Making

Expert input from a medical/dental defence union and the General Dental Council (discussed previously) dictate that a surgeon on accepting a referral needs to be appropriately satisfied that the investigation is required, and that consent derived from the patient does not restrict itself to that of potential complications but also to indications for such a procedure. They must also be able to evaluate what the potential impact (or otherwise) to the condition the diagnostic yield of the LgBx would have. The expectation is that oral surgeons who, as part of their clinical responsibilities are performing labial gland biopsies, need to be familiar with the most widely utilised AECG criteria and generally with the current literature around pSS as a multi-system disease, as well as current developments in the management of this condition.

The authors have developed a checklist to guide oral surgeons in their assessment of patients. However, each patient must be treated as an individual and assessed on a case-by case basis. A thorough knowledge of the current literature and the background of patients being referred in for surgical investigations is required for labial gland biopsies and other interventions with associated morbidity. Though these patients may have been referred by specialists, the operating surgeon must appreciate the indications for and the risks and benefits of any procedure undertaken.

Using the literature, expert opinion and recent developments we have established our own checklist when considering performing a LgBx:

Pre-Consent Checklist:

- Has the referrer outlined the clinical justification for this investigation?
- Has the referrer outlined how the potential diagnostic yield from this investigation will change the patient's management?
- Has the referrer exhausted all non-invasive investigations that can be utilised?
- Has the patient understood the reason for this investigation?
- Has the patient understood the implications of a positive or negative diagnosis within the context of their future management?
- Has the patient been informed of the short-term and long-term complications of the surgical procedure?

The authors suggest that the referring practitioner has informed the clinician requested to take a LgBx of the diagnostic criteria that they are using prior to referral. If a clinician wishes to implement a checklist like the one above, they may wish to inform the referring team and possibly involve them in adaptation of the list to any specific local departmental needs.

Discussion

LgBx remains a key investigative modality in both the AECG and the 2016 ACR/ EULAR criteria for diagnosis of pSS. Consequently, oral surgeons in receipt of referrals from other medical specialties (such as rheumatology) asking for labial gland biopsies to be carried out will find that negotiating the differing stipulated requirements of each of these criteria might be challenging. If not included in the referral, and if there is any ambiguity, it would be advisable to enquire as to the criteria used by the referrer.

It is possible that a positive LgBx will not result in confirmation of a diagnosis of pSS if the AECG criteria are referred to but will do so with the 2016 ACR/ EULAR criteria. It is reasonable, in our opinion, for an oral surgeon to consider a LgBx referral with due critical consideration as it is an invasive investigation with potential significant complications. The diagnostic yield will need to be considered as part of the decision-making process to be discussed with patient. This will vary for example in a case where systemic treatment with potentially harmful side-effects are being considered should the diagnosis of pSS be confirmed. In the latter case the significance of a formal confirmation of pSS may outweigh the potential surgical risks. Another scenario where a diagnosis will not result in a change to the patient's management and hence have no functional benefit to the patient may result in a consideration that the surgical risks are not in the patient's best interest. pSS is a long-term condition that will require long-term follow up and management. Its signs and symptoms can fluctuate over time. A specific diagnosis may be of benefit in the long term as treatment options change and in giving the patient reassurance to the underlying cause of their ailments. The patient's views are key to this shared care decision making approach. Hence it is reasonable to assume that an oral surgeon follows the following principles (as outlined in the checklist):

- **Has the referrer outlined the clinical justification for this investigation?**
- **Has the referrer outlined how the potential diagnostic yield from this investigation will change the patient's management?**

Will the result influence the patient's management? Across the disease spectrum of pSS management strategies may range from simply managing xerophthalmia and xerostomia related symptoms to consideration of disease-modifying anti-rheumatic drugs (DMARDs) to manage systemic symptoms. It is reasonable to consider that a rheumatologist planning the introduction of a DMARD may wish to exhaust all potential avenues to obtain evidence to substantiate a diagnosis. As indicated above there are groups of patients who may have the range of signs and symptoms of pSS but lack investigation-based evidence to substantiate a diagnosis according to the AECG or ACR criteria. In such cases the Rheumatologist is placed in challenging position to treat the condition without the benefit of a formal diagnosis and hence may request a LgBx reasonably in our opinion even in situations where a positive LgBx investigation will not result in a formal diagnosis of pSS according to the AECG or ACR criteria. Within this context the validity of such indications will be based upon the diagnostic yield that may be derived from this investigation and how this diagnostic yield may potentially influence patient management.

- **Has the referrer exhausted all non-invasive investigations that can be utilised?**

Have the relatively non-invasive investigations such as blood-based investigation and imaging have been performed before proceeding to LgBx? Depending on the facilities available at particular institutions there may also be an opportunity to utilize non-invasive investigations such as ultrasound imaging.

- **Has the patient understood the reason for this investigation?**

- **Has the patient understood the implications of a positive or negative diagnosis within the context of their future management?**

Patients' views are critical within the required shared care decision making approach underpinning a decision to proceed with LgBx. For example, some patients may indicate that a quest for a formal diagnosis is important to them whilst for others establishing a formal diagnosis is only considered as critical if the actual management of the condition may potentially change with confirmation of a formal diagnosis.

- **Has the patient been informed of the short term and long-term complications of the surgical procedure?**

Post-operative surgical considerations to discuss include; pain, swelling, bleeding, bruising, infection and temporary or permanent numbness to the lower lip and chin. The patient should be informed that paraesthesia has been reported in one study with an incidence of up to 11.7% at 6 months post LgBx, and that there is around a 6% chance that the altered sensation could be permanent, as reported in another, separate study.

We have provided examples of clinical scenarios to illustrate the complexity around the decision-making process required to inform the decision concerned (Table 6).

Table 6

Conclusion

The decision to proceed to performing a LgBx to aid in the diagnosis of pSS is not a straightforward one. Due to the anatomical position of the labial glands, biopsy in this region has the potential to cause postoperative complications. The analysis of the resulting tissue can occasionally be unreliable and there are ongoing studies that evaluate and aim to solve this issue[26,29].

The oral surgeon in receipt of a referral to perform a LgBx must be familiar with the rationale and current evidence relevant to the potential diagnostic value of this procedure and have in depth knowledge of potential complications, enough to discuss this in detail with the patient and inform the consent process. The decision to perform the biopsy must be considered on an individual patient basis and with input from multiple specialties in a shared care decision making process.

Follow-up work could include evaluation of the use of the checklist on clinic prior to listing a patient for a LgBx and its influence on the frequency of LgBx's being carried out.

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