REVIEW

Recent Perspectives and Advances in Obstructive Salivary Gland Diseases

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Abstract

Salivary gland disorders have been recognized for centuries, with early studies focusing primarily on tumors. The discovery of salivary ducts expanded this knowledge, leading to the identification of obstructive diseases as a significant yet often misunderstood subset of salivary gland pathology. Obstructive salivary gland disorders (OSGD) affect a substantial number of individuals each year and arise from various causes, including sialolithiasis, mucous plugs, ductal strictures, stenosis, radioiodine-induced sialadenitis, and autoimmune conditions like Sjögren's syndrome. These obstructions disrupt normal glandular function, resulting in inflammation and associated complications. This paper explores the etiopathogenesis, histological features, and available treatment options for OSGD. By enhancing our understanding of these disorders, we aim to contribute to improved diagnostic and therapeutic strategies, ultimately leading to better patient care.

Keywords: Obstructive diseases, Obstructive salivary gland disorders, Sjögren's syndrome, sialolithiasis, mucous plugs, ductal strictures, stenosis, radioiodine-induced sialadenitis

Introduction

Mankind has been aware of the existence of salivary glands and associated pathologies for centuries. Initially, our knowledge was restricted to tumours, later on with the discovery of the ducts, it expanded to include obstructive diseases. Obstructive salivary gland disorders (OSGD) are a major subset of salivary gland disorders that affect a significant portion of the population annually, yet is poorly understood. Various pathological processes such as sialoliths, mucous plugs, strictures, ductal stenosis, radio iodine induced sialadenitis and autoimmune diseases (Sjögren's syndrome), can be attributed to the obstruction of the salivary ductal system and ultimately inflammation of the parenchyma.[1]

This paper aims to provide an elaborate report on the etiopathogenesis, histological characteristics and treatment options of various obstructive salivary gland diseases. The overarching objective is to draw valuable insights that can enhance our comprehension of these conditions, paving the way for better treatment modalities for the management of obstructive salivary gland disorders.

Architecture of Salivary Glands:

Salivary glands are tubulo-acinar exocrine glands, consisting of a terminal acinar unit (serous, mucous or mixed) and an elaborate ductal system (intercalated duct, striated duct and excretory duct). The major salivary glands (the parotid, submandibular and sublingual glands) produce 90% of the whole saliva and the remaining 10% is produced by the minor salivary glands present in the oral cavity. The parotid, located at the periauricular region, is the largest salivary gland. This is followed by the submandibular gland which is located below the angle of the mandible and between the two bellies of the digastric muscle. The gland is divided into a small anterior lobe and a larger posterior/deep lobe by the mylohyoid muscle. The smallest of the major salivary glands is the sublingual salivary gland. It is an almond shaped gland that lies in the submucosal plane of the floor of the mouth, above the mylohyoid muscle and medial to the sublingual fossa of the mandible. While the parotid gland mainly se-

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cretes serous saliva, the submandibular gland and sublingual gland, both secrete predominantly mucinous saliva.[2] The saliva secreted by the acini undergoes several modifications as it passes through the intercalated duct, striated duct and is finally emptied into the oral cavity via the excretory duct. The excretory duct of the parotid gland, also called the Stenson's duct drains in the maxillary vestibule opposite the second molar, the Wharton's duct (submandibular salivary duct) drains into the frenulum linguae at the sublingual caruncula.[3] The excretory ductal system of the sublingual gland is complex. The gland can be subdivided into two segments, an anterior and a posterior, which are both drained separately. The posterior segment drains it's saliva into the floor of the mouth at the crest of sublingual folds, through a collection of 8-20 small ducts called the duct of Rivinus.[4] The excretory ductal system of the anterior segment shows 3 major anatomic variations. The major duct of this segment is called the Bartholin's duct and can be seen to fuse with the mid portion of the Wharton's duct and drain at the sublingual caruncula in majority of the cases (40%). To a lesser degree, it can also empty directly into the floor of the mouth via small ducts (36.7%). In 23.3% of individuals the Bartholin's duct was noted to open independently at the sublingual caruncula.[5] Salivary gland obstructions can be seen in any portion of the ducto- acinar unit but, are most common in the hilum/ proximal duct of submandibular salivary gland.[6]

Sialoliths:

Nearly 60-70% of the reported cases of OSGD are associated with the presence of Sialoliths.[1] Sialoliths are intermittent in growth and morphologically diverse, hence produce a range of symptoms depending on their location and extent of occlusion of the gland. The symptoms of sialolithiasis typically manifest before or during mealtime and include pain, a foul-tasting discharge, and enlargement of the obstructed gland. It is commonly seen in the fourth to fifth decade of life.[7] Salivary stones primarily affect the major salivary glands with 80-90% seen in association with the submandibular salivary gland and the Wharton's duct.[6] The physical characteristics of the salivary stones varies over a wide range depending on the site of occurrence and duration. Sialoliths are yellow to yellow- brown in colour, round to oval in shape, measuring between 2.1mm to 10mm in diameter and weight an average of 300mg (Fig 1a). Larger liths (>15mm) are found within the glandular parenchyma and are called giant Sialoliths.[8] Generally, salivary stones occur as single stones. However, stones occurring in the parotid gland can be multiple in number. Radiologically, around 80% of the Sialoliths are radio opaque.[9] However, diagnosis and treatment of Sialoliths is rather challenging owing to the varied biochemical composition of the stones.

Mucous plugs:

Mucous plug formation is the accumulation of mucin within the salivary duct which in turn causes obstruction of the salivary gland (Fig 1b). Since the submandibular glands mainly produce mucin rich saliva, they are more prone to create obstructive mucous plugs than the parotid glands. Salivary gland obstruction due to mucous plugs are classified into two types- Primary mucous obstruction, where mucous plug is the only obstructive factor and Secondary mucous obstruction, where mucous plugs are found in addition to another obstructive process, like a stricture or sialolith.[10]

Strictures and Ductal stenosis:

A stricture is characterised by a short stretch of intraluminal scar or adhesion that blocks the duct almost entirely, leaving a very narrow lumen (Fig 1c). A long section of circumferential narrowing of the ductal lumen is referred to as a stenosis. They preferentially affect women in the fourth to sixth decade of life and are more typically discovered in the parotid duct (70–75%).[10] Within the stenson's duct, strictures were most often found involving the middle and proximal third of the duct, while in the wharton's duct they are commonly associated with the posterior third of the duct.[11]

ETIOPATHOGENESIS OF VARIOUS OBSTRUCTIVE SALIVARY GLAND DISEASES:

Sialoliths:

Sialolithiasis is a multifactorial disease, with several local and systemic factors contributing to lithogenesis. The predisposing factors are broadly categorized as: factors affecting the glandular structure and factors that alter the biochemistry of the saliva produced.[12]

Anatomic Variations:

Nearly 80-90% of the Sialoliths are found in association with the submandibular salivary glands. The obvious preference of the disease for the submandibular gland has been attributed to the long and tortuous path of the Wharton's duct.[6] Ductal alterations such as, presence of strictures, stenosis and ductal diverticulitis, cause stasis of salivary flow and make these areas very conducive for sailolith formation.[12]

Biochemical Variations:

Salivary stones may develop more frequently in those with altered salivary composition. Studies have shown a significant correlation between sialolithiasis and the presence of saliva that is highly viscous with increased concentrations of proteins and calcium ions. Salivary analysis of these patients also showed a marked reduction in the amount of crystallisation inhibitors phytate, citrate, and magnesium, making them more prone to stone formation. Hyposalivation caused due to dehydration of polypharmacy has also been attributed as a risk factor for the development of salivary stones. Gout is the only systemic illness proven to alter the composition of the saliva and predispose them to the development of uric acid rich Sialoliths.[6]

Although many factors have been attributed, the precise pathogenesis of salivary stone formation is still poorly understood. Various theories have been proposed including, Inflammation, Organic core theory, Sialmicrolith theory, Mucoepidermoid gel theory, Retrograde migration theory, Role of biofilms, and Neutrophil Extracellular traps.[12,13,14]

Organic Core Theory:

According to this theory, calcification and growth of a Sialolith occurs around an organic nidus such as exfoliated cells and bacteria. Recent studies examining the microstructure of the Sialolith identified the presence of inflammatory exosomes produced in response to bacteria at the core of the calculi. These inflammatory exosomes contain cytokines and other enzymes that can aid in the mineralisation of calcium apatite crystals.

The peripheral layers of the stones also demonstrated the presence of numerous exfoliated salivary epithelial cells that may help in the growth of the Sialolith by deposition of salivary particles and their mineralisation.[15]

Mucoepidermoid Gel Theory:

In areas of salivary stasis and high mucin content, the salivary mucin (muc 5b and muc 7) condense together to form a gel matrix called a mucous plug.(16) Mucous plugs cause the obstruction of salivary flow and have been suggested to act as a framework for the deposition of calcium salts and Sialolithogenesis.[15]

Sialomicroliths:

The sialomicrolith is a small amalgamation of granular organic secretory material, necrotic cell remnants, calcium and phosphorus crystals found in the salivary glands. In healthy salivary glands, sialomicroliths often form in autophagosomes, reach the lumen, and exit the gland via saliva, undetected.[6] It was hypothesised that, secretory inactivity in the salivary gland could lead to the accumulation of sialomicroliths resulting in a micro obstruction. This obstruction in turn results in obstructive atrophy, inflammation, and compression of the surrounding parenchyma, which stagnates saliva and sets up the conditions for calcium to accumulate on the phospholipid membrane, resulting in the formation of sialoliths.[17]

Retrograde Migration Theory:

Several case reports showed the presence of foreign bodies such as hair follicle, plant and cellular debris at the core of the Sialoliths. Based on these findings it was proposed that organic substances, bacteria or cellular debris from the oral cavity might migrate into the salivary ductal system and later serve as a nidus for calcification. It is hypothesised that an easier retrograde migration of oral materials may be caused by a variant a sphincter-like mechanism found within the first 3cm of the Wharton's salivary duct.[18]

Role of Biofilms:

According to this theory, the nidus for sialolithiasis is formed by the establishment of biofilms around bacteria that enter the salivary duct through retrograde migration and its interaction with host immunity and calcium nanoparticles. Bacterial biofilms have several characteristics that are conducive to Sialolith formation. Primarily, biofilm infections are chronic and persistent in nature and hence, trigger a strong inflammatory response from both the innate and adaptive immune system, resulting in collateral tissue damage to the surrounding ductal lining. Furthermore, biofilms also demonstrate a high concentration of calcium within the extracellular polymeric substance (EPS) and microscale electric gradients that alter the local pH, creating a favorable microenvironment for the deposition and crystallization of calcium.[14]

Neutrophil Extracellular Traps (NETs):

Neutrophils recruited to sites of inflammation form web-like structures called neutrophil Extracellular traps which act as physical and chemical barriers against pathogens.[19] Though a pivotal defense structure, it is a double edged sword as excessive NET formation leads to aggregated NETs that can occlude vessels and ductal structures causing tissue damage.[20] Presence of neutrophilic enolase activity associated with a high prevalence of extracellular DNA in a salivary calculi and the high bicarbonate content in the saliva, points to NETs as nidus for the formation of sialoliths. The interaction between neutrophils and the precipitated particulate matter is presumed to aid in the growth of the salivary stone.[12]

Mucous plugs:

Salivary mucous is mainly composed of 95% water and 5% mucins. Numerous factors affect mucous elasticity and adhesion, including physical factors such as pH and ionic forces, and pathological conditions such as, autoimmune diseases affecting the glands and diabetes. These factors cause saliva's pH to drop below the reference value of 7.1, leading to the loss of spinnbarkeit, viscosity and thickness of the salivary mucous and indirectly mucous plug formation.[21]

Mucous plug formation mainly depends on two conditions: salivary stasis and supersaturation of saliva with mucins. Salivary stasis or stagnation can be attributed to multiple reasons such as hyposalivation, anatomical variation or polypharmacy.[10] Oral microorganisms have been associated with mucous plug formations in salivary ducts during the infectious process. The mucins can undergo an action of lysis or damage by the oral microbiome, which causes them to disassociate from the salivary suspension and precipitate within the duct, giving rise to the mucous plug. The phenomenon is aggravated by the decrease in the pH of saliva during infection.[22]

Ductal Strictures and Stenosis:

The exact etiopathogenesis for the development of salivary ductal stenosis is largely unknown. Although recent studies have made significant correlations between various salivary

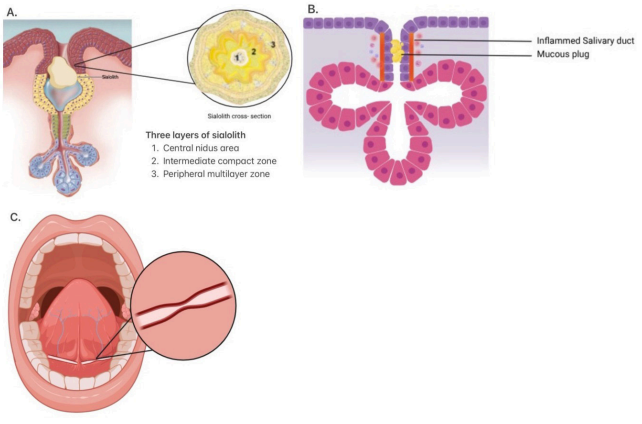

Figure 1: a) Sialolith, b) Mucous Plug and, c) Ductal stricture

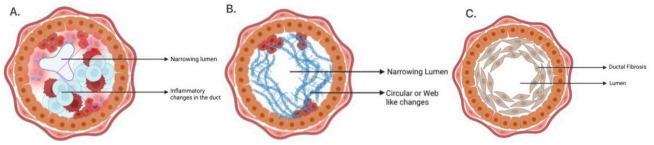

Figure 2: a) Type 1: "Inflammatory changes" in the stenosis region of the duct. b) Type 2: Abnormal ductal structure showing "circular or web-like changes" and "megaducts". c) Type 3: The stenosis appears "purely fibrotic" in nature.

diseases such sialadenitis, sialolithiasis, trauma, radiation exposure, and inflammatory conditions such as Sjogren's syndrome.[11,23] Chronic recurrent parotitis is the most common cause associated with stenson's duct stenosis.[24] The chronic inflammation within the ductal structure leads to fibrosis and partial obstruction of the duct which in turn aggravates the symptoms of sialadinitis.[25]

HISTOLOGY OF OBSTRUCTIVE SALIVARY GLAND DISEASES:

Sialoliths:

Histologically, obstruction of the ductal system initially presents as an abnormal dilation of ducts, also called as sialectasis.[25] Recurrence or persistence of the obstruction results in sialadenitis, which can be evidenced by the presence of ductal dilation along with obstructive factor, chronic inflammatory infiltrate, and fibrosis. Failure to treat the condition finally causes the atrophy of the ductal and acinar structures around the obstruction and shows peritubular and intralobular fibrosis.[26]

Ground section analysis of the structure of a Sialolith resembles that of an onion skin with concentric laminations that alternate between being highly mineralised and organic. On histopathologic examination, it appears as alternating eosinophilic and basophilic zones or globular calcified zones. The degree of eosinophilia corresponds to the level of mineralization, with the basophilic zone indicating a heavily mineralized area. Numerous bacteria, cellular debris and mucoid material are seen dispersed throughout the matrix, that may help in the growth of the Sialolith by deposition of salivary particles and their mineralisation.[27]

Micro-CT and SEM analysis show that the Sialolith is made up of three distinctive zones: the central nidus or the nucleus, an intermediate circular compact zone and a peripheral multilayered zone (Fig 1a).[27] The nucleus is usually homogeneous and is composed of poorly calcified organoid materials including numerous bacteria in haphazardly arranged calcium apatite matrix, inflammatory exosomes and saliva. The intermediate zone is highly mineralised, primarily composed of calcium apatite crystals. Lastly, the peripheral multilayered zone consists of concentric lamellated layers which can either be homogeneous or irregular owing to the intermittent nature of Sialolith formation.[6] Microstructure analysis using TEM revealed layers of amorphous material, known as "aspidinic" hydroxyapatite layers, which are abundant in the micro structure of salivary hydroxyapatite calculi, similar to the renal hydroxyapatite calculi.[28] The surface of submandibular calculi revealed pyramidal, granular, globular or coarse crystalline structures with a diameter of 5–15 μm, similar to the crystalline structure of struvite stones of the kidney and vascular thrombi. There have also been reports of hexagon-shaped, and plate-shaped crystals on the surface of sialoliths, comparable with the appearance of the cystine urinary stones.[6,29] Well- crystallised areas of calcium hydroxyapatite show highly defined needle- shaped nanocrystalline arrangements, whereas areas rich in whitlockite and in the initial stages of mineralisation show a more rectangular-shaped arrangement.[30]

Crystallography studies of Sialoliths demonstrate that the primary inorganic component of Sialoliths, in both the inner and outer regions, is calcium apatite. The second most prevalent component, whitlockite, is more frequently found in the nucleus. Brushite and whitelockite were found in the sialolith's growth layer.[31] Sialoliths also show trace amounts of Mg, K, Na, Cl, Al, Fe, Pb, Ti, and Zn ions. Few studies have found that the concentration of Mg was slightly higher than expected, leading us to the conclusion that struvite may also be found in the stones.[32]

Study of the organic matrix of the Sialolith, using liquid chromatography-mass spectrometry showed the presence of 116-419 proteins, neutral lipids and to a lesser extent, phospholipids and glycolipids.[6,32] Solubilised submandibular Sialoliths demonstrate presence of calcium binding proteins such as, high- molecular weight glycoproteins and low- molecular weight statherin and acidic proline-rich protein.[6] The calculi also demonstrated Extracellular exosomes, blood microproteins, and Alpha-1-microglobulin/bikunic precursor (AMBP) proteins. The exosomes appear to be a location for the deposition of amorphous mineral microcrystals and are a constituent of the extracellular matrix. They are hypothesised to create three-dimensional globular formation that render the Sialoliths variable in organisation and texture.[32] Immunologic proteins such as, lactoferrin, lysozyme and s-IgA are also found in the matrix of a few salivary calculi. Lysozyme also has high affinity for calcium phosphate, leading to its accumulation within the forming stone.

Amino acid estimation of submandibular sialoliths exhibited comparatively high quantities of alanine, leucine, glutamine, aspartic acid, valine, and glycine.[33]

Mucous plugs:

Mucous Plugs have been classified endoscopically as mucous, fibrinous, or fiber-like.

They have been found associated with inflammatory stenoses. Histologically, they contain inflammatory cells, desquamated parenchymal cells, and albuminous coagulum. This coagulum is the result of plasma proteins seepage into the ductal lumen during inflammation.[17]

Ductal strictures and stenosis:

Koch and Iro classified ductal strictures into three categories using endoscopy:

Type 1: Shows "inflammatory changes" in the stenosis region of the duct. Some studies suggest that type 1 stenosis is a precursor for type 3 stenosis (Fig 2a).

Type 2: Characterized by abnormal ductal structure showing "circular or web-like changes" and "mega-ducts". This type of stenosis is more commonly seen in cases with multiple stenosis (Fig 2b).

Type 3: The stenosis appears "purely fibrotic" in nature with diffuse involvement of the ductal wall. When compared to other types of stenosis, type 3 causes a greater degree of luminal narrowing (Fig 2c).[23]

On microscopic examination, the inflammatory response was most severe at the location of the stenosis and appears to spread proximally. The salivary gland and ductal tissue distal to the stenosis were not affected.[25]

COMPARISON OF SIALOLITH WITH OTHER ECTOPIC

CALCIFICATIONS:

Nephroliths have been extensively studied and are shown to commonly affect individuals with a diet high in oxalates, bacterial infection or gout. Hypersaturation of urine with calcium oxalate results in its deposition within the renal tubules forming a nidus for further calcifications. The stones are primarily composed of calcium oxalate crystals (80%) followed by struvite and uric acid crystals.[29] Gallbladder stones, on the other hand, are majorly cholesterol-based, and hence are commonly seen among obese patients. Microenvironments with a high pH, increased calcium and carbonate concentration and supersaturated cholesterol crystals create the perfect conditions for the development of cholelithes.[34] Vascular calcifications encompass mineral deposits, predominantly calcium phosphate, over atherosclerotic plaques, contributing to arterial stiffness and cardiovascular complications.[35] However, the sialoliths formation is multifactorial in nature and consist of a combination of organic components (mucin and proteins) as well as inorganic compounds (hydroxyapatite).[6] While each of these conditions are unique, they are all ectopic calcifications that start in tubular microenvironments inside hollow tissue structures (such as the salivary duct and kidney tubule), suggesting that there may be some similar variables that affect Calcium crystal deposits occurring and results in the formation of stones.[35] An in-depth comparative analysis of their disease processes can help us develop better treatment strategies.

TREATMENT:

Sialolithiasis, the most common OSGD, has been managed traditionally by the following techniques:

1. Medical management – antibiotics & analgesics
2. Occasional expression of the stone through the papilla,
3. Marsupialisation of the ductal opening and removal. – Transoral sialolithotomy
4. Gland excision

Sialendoscopy:

Sialendoscopy is being preferred for most surgical procedures nowadays with the intent to reduce recovery time and complications of open procedures as well as facilitate early return to function. Sialoliths occurring in either the submandibular or the parotid are managed similarly albeit with slight differences.

Calculi with diameters of 3-4mm are ideal for endoscopic retrieval. In these cases, they can be entrapped and retrieved by use of a wire or dormier basket, or dragged to the punctal opening where a small retro papillary may be required to facilitate removal.

Larger stones require a combined approach, which as the name suggests combines the use of the endoscope to identify and locate the sialolith along with an appropriate open technique to retrieve the stone.

In the submandibular duct, it would entail an incision and dissection of the floor of the mouth where the sialolith is located, whereas for the parotid duct it would be either a preauricular incision and raising of the Surgical musculoaponeurotic system flap to approach posterior/proximal stones or a transcutaneous approach for stones anterior to the masseter muscle.

Apart from sialothiasis, Sialendoscopy is most commonly used in the management of various other obstructive salivary gland diseases such as:

1. Strictures/stenosis or narrowing of the duct wall either within the duct or at the opening
2. Mucous plugs which is essentially thickened saliva – leading to obstruction
3. Retrograde bacterial infection
4. Foreign bodies – which can also get calcified over time
5. Radio Iodine induced Sialadenitis.
6. Autoimmune conditions such as Juvenille Recurrent Parotitis and Sjogren's Syndrome.

Ductal strictures which may be secondary to calculi or those at the papilla opening can be managed via serial dilatation with sialendoscopes of increasing diameter. Balloons are also an effective mode of widening narrow sections of the duct. For strictures at the opening, hollow bougie dilators – serially increasing may also be used to dilate that area of the duct.

Autoimmune conditions as well as radio iodine sialadenitis usually present with strictures and are consequently, managed similarly.

While Sialendoscopy offers a minimally invasive path to manage obstructive salivary gland disease, it naturally has its share of restrictions. It is a technically challenging procedure with a shallow learning curve. For the same reason, procedural time is high, especially in the early stages of practice. The armamentarium required is specific, extensive and delicate. Being specialized and comparatively not as commonly practiced across the globe, it still is very expensive.

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