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Three-dimensional cone-beam computed tomographic sialography in the diagnosis and management of primary Sjögren syndrome: Report of 3 cases

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ABSTRACT

Sjögren syndrome is a chronic autoimmune inflammatory disease characterized by lymphocytic infiltration of exocrine glands, predominantly the parotid and lacrimal glands, thereby resulting in oral and ocular dryness. It has been reported to occur most frequently in women between 40 and 50 years of age. Sjögren syndrome has an insidious onset, is slowly progressive, and presents a wide range of clinical manifestations, leading to delays or challenges in the diagnosis. Early diagnosis of this condition is essential to prevent the associated complications that affect patients' quality of life. This report presents 3 cases of Sjögren syndrome in female patients aged between 40 and 75 years who presented with complaints of persistent dry mouth and burning sensation. The cases highlight the diagnostic value of 3-dimensional cone-beam computed tomographic sialography in the detection of salivary gland pathologies at an early stage. ***(Imaging Sci Dent 2021; 51: 209-16)***

KEY WORDS: Cone-Beam Computed Tomography; Diagnosis; Sialography; Sjögren Syndrome; Xerostomia

Sjögren syndrome is a chronic autoimmune disease characterized by immunologically mediated destruction of exocrine glands, mainly the salivary and lacrimal glands. This condition results in dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca). Its primary form involves exocrine glands, while its secondary form is associated with other autoimmune disorders.[1] The prevalence of Sjögren syndrome in the general population has been estimated to be 0.5% to 4.8%, it commonly occurs in middle-aged women between 40 and 50 years of age, and its male-to-female ratio has been reported to be 1 : 9.[2] The etiopathogenesis of this syndrome remains elusive, but the adaptive immune system has been documented to play an important role in the onset of Sjögren syndrome, as demonstrated by the presence of autoreactive T and B lymphocytes, abnormal regulation of apoptosis, production of autoantibodies to ribonucleoprotein particles (anti-SSA/Ro and anti-SSB/La), and lymphocytic infiltration of glandular tissues; these processes eventually interfere with glandular function and result in impaired secretory activity, particularly of the salivary and lacrimal glands.[3]

Sjögren syndrome has variable clinical presentations, ranging from local exocrinopathy to the involvement of multiple organs, and affected individuals have an increased risk of B cell non-Hodgkin lymphoma. Studies have reported the presence of autoantibodies to ribonucleoprotein particles (anti-SSA/Ro and anti-SSB/La) in the majority of Sjögren syndrome patients. The diagnosis is often delayed for years in many patients because the clinical symptoms of Sjögren syndrome mimic those of other medical conditions such as xerostomia due to diabetes mellitus, psychotropic

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drugs, sialadenosis, and viral infections.[3] The diagnosis becomes even more challenging for the clinician if the patient presents with persistent symptoms and without any detectable bilateral parotid gland swelling; therefore, it is essential to establish a proper diagnosis at an early stage to prevent complications and to achieve better treatment outcomes.

Numerous standards have been proposed for the diagnosis of Sjögren syndrome, of which the most widely accepted is the American and European Group (AECG) criteria, according to which the diagnosis should be based on 6 parameters: 1) the presence of ocular symptoms; 2) oral symptoms of hyposalivation, 3) positive ocular signs assessed by the Schirmer and Rose Bengal dye test; 4) biopsies of minor salivary glands and/or lacrimal glands; 5) abnormal oral signs such as unstimulated whole salivary flow (<1.5 mL in 15 minutes), abnormal parotid sialography and salivary scintigraphy findings; and 6) assays for anti-SSA/Ro or anti-SSB/La antibodies (Table 1).[4-9] For a definitive diagnosis of primary Sjögren syndrome, at least 4 of the 6 criteria should be met, including positive results for the minor salivary gland biopsy or antibody test.[4] In addition, the severity of oral dryness can be quantified by the Xerostomia Inventory and Challacombe scales of clinical oral dryness.[9] The Xerostomia Inventory scale consists of 11 items, each on a 5-point Likert scale (Table 2), whereas the Challacombe scale is a 10-point scale in which an additive score of 1-3 indicates mild dryness, 4-6 moderate dryness and 7-10 severe dryness, as depicted in Table 3.

Table 1. Revised American-European Consensus Criteria for Sjögren syndrome[4]

1) Ocular symptoms (at least one present)
Symptoms of dry eyes for at least 3 months
A foreign body sensation in the eyes
Use of artificial tears 3 or more times per day
2) Oral symptoms (at least one present)
Symptoms of dry mouth for at least 3 months
Recurrent or persistently swollen salivary glands
Need for liquids to swallow dry foods
3) Objective ocular signs (at least one present)
Abnormal Schirmer's test (without anaesthesia; ≤ 5 mm/5 minutes)
Positive vital dye staining of the eye surface
4) Histopathology
Lip biopsy showing focal lymphocytic sialoadenitis (focus score ≥ 1 per 4 mm^2)
5) Oral signs (at least one present)
Unstimulated whole salivary flow (≤ 1.5 mL in 15 minutes)
Abnormal parotid sialography
Abnormal salivary scintigraphy
6) Autoantibodies (at least one present)
Anti-SSA (Ro) or Anti-SSB (La), or both

Various imaging techniques such as conventional radiography, computed tomography (CT), cone-beam CT (CBCT), sialoendoscopy, ultrasonography, and magnetic resonance (MR) imaging are used to complement the diagnosis of Sjögren syndrome. Sialography, which is one of the most widely used techniques, enhances visualization of the ductal architecture and gland parenchyma following an injection of radiopaque contrast media.[5] One of the typical sialographic appearances of Sjögren syndrome, as described by Rubin and Holt, is "sialodochiectasis or sialectasis," which can manifest as punctate, globular, cavitary, and destructive patterns on sialograms.[6] Three-dimensional (3D) CT, CBCT, and MR sialography are recently introduced imaging modalities that provide 3D images of the salivary gland ductal architecture, unlike other modalities.[7] This paper emphasizes the diagnostic value of 3D CBCT sialography in 3 cases of primary Sjögren syndrome.

Case Report

Case 1

A 44-year-old female patient was referred to Department of Oral Medicine and Radiology due to a complaint of dry mouth and recurrent episodes of swelling in the left parotid region for 5 years. She also complained of multiple decayed teeth. Her past dental history revealed that she had visited many private clinics and otolaryngologists for the same problem, for which only medications were given. The patient's medical, family, and drug history were nonremarkable. On an extraoral examination, no abnormality was seen, and the right and left parotid glands were normal in shape and size. An intraoral examination showed signs of

Table 2. The series of questions assessed by the Xerostomia Inventory subjective scale for oral dryness[8]

– I sip liquids to aid in swallowing food.
– My mouth feels dry when eating a meal.
– I get up at night to drink.
– My mouth feels dry.
– I have difficulty in eating dry foods.
– I suck sweets or cough lollies to relieve dry mouth.
– I have difficulties swallowing certain foods.
– The skin of my face feels dry.
– My eyes feel dry.
– My lips feel dry.
– The inside of my nose feels dry.

Response options: 1: never, 2: hardly, 3: occasionally, 4: fairly often, 5: very often.

dryness of the oral mucosa, with the mouth mirror sticking to the right and left buccal mucosa and dorsum of the tongue. Cervical caries of the upper and lower anterior teeth, as well as mild depapillation of the dorsum of the tongue, were observed (Fig. 1). Additive scores of 51 in the Xerostomia Inventory scale[8] and 4 in the Challacombe scale of clinical oral dryness[9] were suggestive of moderate dryness of the oral mucosa. Milking of the bilateral parotid glands revealed reduced salivary flow through the ducts (Tables 2 and 3).

Case 2

A 65-year-old female patient was referred to the Department of Oral Medicine and Radiology for a complaint of dry mouth and recurrent episodes of swelling and pain in the right and left parotid regions for the last 6 years. She had visited many otolaryngologists for the same complaint, and antibiotics and analgesics for swelling and pain were given. No further investigations or treatment was done. The patient's medical, family, and drug history were non-contributory. On an extraoral examination, no abnormality was detected; the right and left parotid glands were normal in shape and size. An intraoral examination showed dryness of the oral mucosa, with the mouth mirror sticking to the right and left buccal mucosa and dorsum of the tongue. Cervical caries of the upper and lower anterior teeth, no pooling of saliva in the floor of the mouth, and mild depapillation of the dorsum of the tongue were observed. Additive scores of 38 in the Xerostomia Inventory scale and 5 in the Challacombe scale of clinical oral dryness were suggestive of moderate dryness of the oral mucosa. Milking of the bilateral parotid glands revealed reduced salivary flow through the ducts (Tables 2 and 3).

Case 3

A 75-year-old female patient presented to the Department of Oral Medicine and Radiology with a chief complaint of dry mouth and burning sensation in the mouth while consuming hot and spicy foods. She was initially diagnosed with oral candidiasis at our department, but her complaint of dryness persisted even after treatment with antifungal therapy. The patient had a known history of diabetes and hypertension in the past 8 years and was taking medication. Extraorally, no abnormality was seen, the right and left parotid glands were normal in shape and size. On an intraoral examination, there was dryness of the oral mucosa, with the mouth mirror sticking to the right and left buccal mucosa and dorsum of the tongue. Cervical caries of the upper and lower anterior teeth, no pooling of saliva in the floor of the mouth, severe depapillation and lobulations of the dorsum of the tongue, and altered gingival architecture were observed. Additive scores of 54 in the Xerostomia Inventory scale and 7 in the Challacombe scale of clinical oral dryness were suggestive of severe dryness of the oral mucosa. Milking of the bilateral parotid glands revealed severely reduced salivary flow through the ducts (Tables 2 and 3).

Investigations

Conventional plain film radiography did not demonstrate any significant findings; therefore, all 3 patients underwent 3D CBCT sialography. Informed consent was obtained from the patients after explaining the procedure. Thereafter, the parotid duct orifice of the right and left parotid glands for each patient were located, scout views were obtained, and 4 mL of iodinated contrast medium (iohexol; Omnipaque-350, Shanghai, China) was injected into the efferent parotid duct bilaterally under aseptic conditions using a lacrimal cannula until the patient felt fullness. Image acquisition was performed by CBCT (Carestream CS9300 Premium, Carestream Health, Rochester, NY, USA), using the following operational parameters: 17 × 13.5 cm field of view, 70 kVp tube voltage, a tube current of 6.3 mA, and an exposure

Table 3. Challacombe scale of clinical oral dryness[9]

Additive score	Clinical signs	Treatment
1-3, Mild dryness	Mirror sticks to buccal mucosa, tongue and frothy saliva	May not need treatment. Sugar-free chewing gum for 15 minutes twice daily, hydration and routine check-up monitoring required
4-6, Moderate dryness	No saliva pooling in floor of mouth, tongue shows mild depapillation, and altered gingival architecture	Sugar-free chewing gum or sialagogues, saliva substitutes and topical fluorides, and monitoring at regular intervals
7-10, Severe dryness	Glassy appearance of oral mucosa, tongue fissured/lobulated, cervical caries in more than two teeth, and debris on palate or sticking to teeth	Saliva substitutes and topical fluorides, cause of hyposalivation needs to be ascertained and monitoring at regular intervals

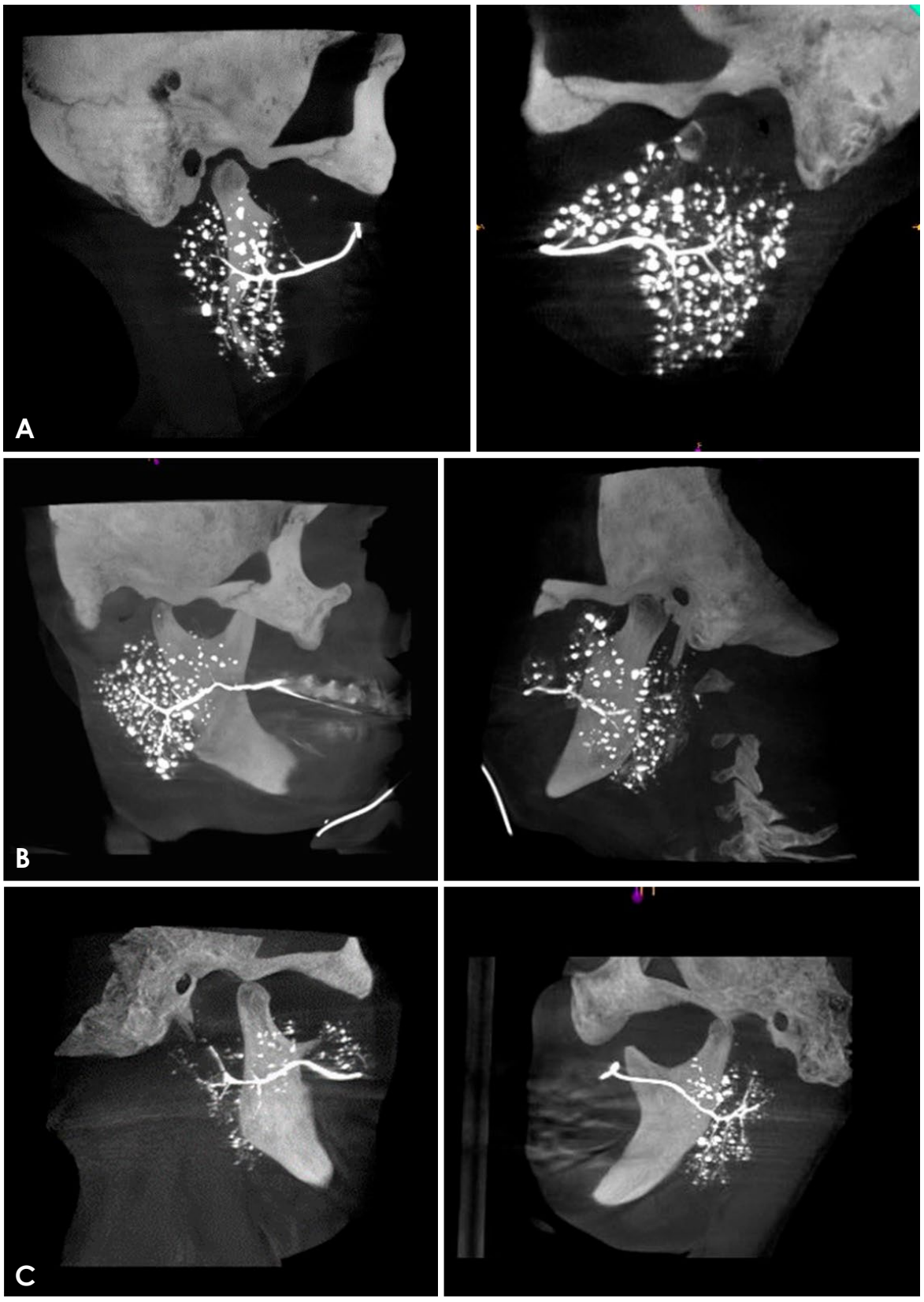

Fig. 1. Three-dimensional cone-beam computed tomography sialographic images of 3 cases depict the multiple globular type of sialectasis within the glandular architecture giving a characteristic "cherry blossom" radiographic appearance of both the right and left parotid glands. Preoperative, filling, and emptying phase times for case 1: 2 minutes, 4 minutes and $\geq$2 hours, respectively (A), case 2: 3 minutes, 4 minutes and $\geq$2 hours (B), and case 3: 3 minutes, 5 minutes and $\geq$2 hours (C).

time adjusted based on scout views. The data acquisition time for the scan was 9.0 seconds. Images were analysed on a 19-inch liquid crystal display with a resolution of 1,280 × 1,024 pixels (Dell, Round Rock, TX, USA) at the Department of Radiology, Faculty of Dental Sciences, Ramaiah University of Applied Sciences, Bangalore, India. Images were adjusted for contrast and brightness by software tools and reconstructed into 3D images. The multiple globular type of sialectasis within the glandular architecture, giving a "cherry blossom" radiographic appearance characteristic of Sjögren syndrome, was observed (Fig. 1). Table 4 shows the time taken for the 3 phases of sialography (preoperative filling, filling, and emptying). Based on the 3D sialographic findings, the working diagnosis of primary Sjögren syndrome was made.

Further investigations were performed to confirm the diagnosis of primary Sjögren syndrome. In a quantitative assessment of the salivary flow rate, unstimulated whole salivary flow rate was found to be < 1.5 mL/15 minutes, suggestive of reduced saliva production as per the AECG criteria (Table 1). The patients were positive for the Schirmer test, indicating insufficient tear production bilaterally (Table 4). The anti-SSA/Ro autoantibody test was positive and antinuclear antibodies (ANA) produced a speckled pattern on an indirect immunofluorescence assay. Based on the above investigatory findings, the absence of extraglandular symptoms, and the presence of 5 of the 6 AECG criteria,[4] the final diagnosis of primary Sjögren syndrome was given.

Treatment plan

Patients were advised to take small sips of water while eating dry food, avoid speaking continuously, to chew or suck on sugar-free gum, candies, or lemon slices to stimulate salivation, and to use artificial tear substitutes. Continuous milking of the glands was done through external pressure to ensure that any blockage present within the ducts was removed. One patient, aged 75 years, was advised to consult with her physician to check whether the antihypertensive and antidiabetic medications she was taking may have been the cause of oral dryness. Intraglandular saline lavage of right and left parotid glands was done for each patient by injecting isotonic saline within the glands, which helps to flush the glands by removing any mucous plugs within the ducts and prevents the formation of sialoliths. This procedure was done for the bilateral parotid glands of each patient every day for 4 weeks.

Table 4. Three-dimensional cone-beam computed tomography (CBCT) sialography and Schirmer test findings

	Case 1	Case 2	Case 3
Phases of CBCT sialography			
Preoperative phase (minutes)	2	3	3
Filling phase (minutes)	4	4	5
Emptying phase (hours)	≥2	≥2	≥2
Schirmer test results	<10/5 minutes (positive)	<15/5 minutes (positive)	<10/5 minutes (positive)

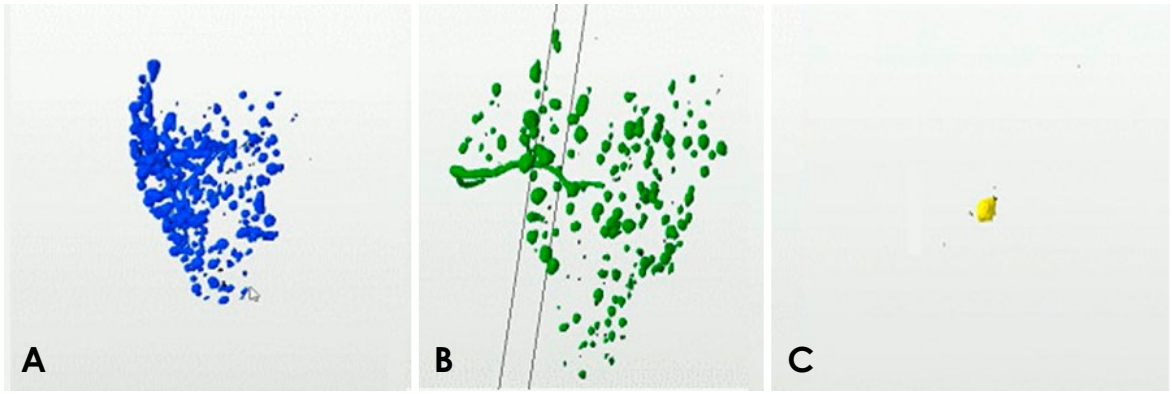

Fig. 2. After 4 months, computational dynamic images taken with 3D Slicer open software version 4.10.2 show the dye evacuation time at 0 (blue color; A), 30 (green color; B), and 60 minutes (yellow color; C), respectively, after 3D CBCT sialography, suggestive of improved functional activity of the parotid glands.

Table 5. Follow-up (at 4 months post-treatment) scores of the Xerostomia Inventory and Challacombe scales

Scale	Case 1		Case 2		Case 3	
	Before	After	Before	After	Before	After
Xerostomia Inventory (subjective)	51	30	38	14	53	42
Challacombe scale (objective)	4	2	5	2	7	4

Each of our patients also underwent transcutaneous electrical nerve stimulation (TENS), involving the application of adhesive electrode pads over the right and left parotid region for 15 minutes every day for 4 weeks. Patients were followed up for 4 months every 15 days to assess their treatment response. After 4 months, milking of the bilateral parotid glands of each patient showed improvements in the salivary flow rate. Computational dynamic images taken with 3D Slicer open software version 4.10.2 (http://www.slicer.org) revealed that the dye evacuation time had decreased to 1 hour, from 2 hours at the initial visit, suggestive of improved functional activity of the parotid glands after 3D CBCT sialography (Fig. 2 and Table 5).

Discussion

Sjögren syndrome is a slowly progressive chronic autoimmune disorder characterized by symptoms of dry mouth and eyes, referred to as "sicca symptoms."[1,2] In some cases, recurrent swelling in the parotid gland leads patients to consult multiple specialists without any symptomatic relief; furthermore, diagnosing the underlying cause of xerostomia that persists for >3 months is a challenge for dental professionals.[10,11] Early diagnosis is mandatory to achieve better clinical outcomes and prevent the complications associated with Sjögren syndrome. Unfortunately, reaching a diagnosis can often be difficult and has been reported to take an average of 3 years from the onset of symptoms. It is well established that no single investigation can rule out Sjögren syndrome. Most often, this condition is diagnosed by rheumatologists and immunologists at a later stage by using an expensive diagnostic test. In our cases, anti-SSA/Ro autoantibody was found to be positive and ANA produced a typical "speckled pattern" on an indirect immunofluorescence assay; these findings play an important role in the differentiation of sicca symptoms due to other causes than autoimmune diseases. In addition to clinical examinations, we established the working diagnosis of primary SS at an early stage by performing 3D CBCT sialography.

Sialography was first mentioned by Carpy in 1902 has since been considered the gold standard for demonstrating fine gland ductal structures. Moreover, functional assessment of salivary glands is possible by observing the rate of excretion of contrast medium from the ducts.[12,13] Plain imaging has been extensively used with sialography to identify ductal inflammatory and degenerative diseases, including sialoliths, sialectasis, fistulae, ductal strictures, and tumours. Sialectasis is a typical radiographic appearance of both Sjögren syndrome and sialadenitis, and manifests as dots and blobs of contrast agent within the gland on sialograms. It is characterized by a patent, non-dilated main duct with uniform punctate or globular collections of contrast medium throughout the gland, which represent the extravasation of contrast medium outside the duct lumen through weakened duct walls. Although multiple globular sialectasia could lead to the diagnosis of primary Sjögren syndrome, this condition should be differentiated from chronic parotid sialadenitis. The underlying disease process allowing the collection of contrast medium in form of dots or blobs is different; in Sjögren syndrome, the epithelium lining the intercalated ductule becomes weakened, whereas in sialadenitis, the acinus becomes dilated and eventually results in extravasation of contrast medium out of the duct.[1,2] The sialographic staging of sialectasia seen in Sjögren syndrome is based on the criteria of Rubin and Holt,[6] which divide it into 5 categories: normal, punctate (smooth oval ≤ 1 mm), globular (smooth oval 1-2 mm), cavitary (smooth oval >2 mm) and destructive (irregular >2 mm). Cavitary and destructive sialectasis are more prevalent in advanced cases, and punctate foci of calcifications in major salivary glands and multiple cystic or solid intraglandular masses in a miliary pattern are occasionally seen in Sjögren syndrome patients.[14]

However, two-dimensional (2D) images offer low contrast resolution, therefore, sialography has been combined with CT, but CT has the disadvantage of a high radiation dose and anisotropic voxel resolution obscures the fine anatomy of ductal structures.[5] Moreover, as Sjögren syndrome progresses, fatty degeneration or cystic changes indicative of destruction of gland in advanced stages are not well appreciable on 2D images. As a recently introduced technique,

MR sialography has been shown to have higher sensitivity and specificity than conventional sialography in demonstrating non-calcified sialoliths and globular sialectasis associated with chronic sialadenitis and Sjögren syndrome.[5] In addition, MR sialography is non-invasive and could be performed in acutely inflamed glands in which CT images fail to reveal any relevant findings. High signal foci measuring between 1-2 mm or >2 mm on T2-weighted MR images in comparison to the surrounding muscle are suggestive of Sjögren syndrome, but the high cost of MR imaging restricts its routine clinical application. 3D CBCT sialography is becoming popular over conventional sialography as it is non-invasive, reliable and provides 3D images of the ductal system and intraglandular structures with high spatial resolution.[14] In our patients, 3D sialograms revealed multiple areas of globular sialectasia with a "cherry blossom appearance" or "branchless fruit laden tree," highly suggestive of Sjögren syndrome, and the procedure was well tolerated by the patients. Moreover, due to high resolution of CBCT sialography, the image is not affected by metallic restoration; this technique enables more accurate mapping of salivary gland ducts to detect sites of stenosis, dilatation, and the presence of salivary stones than is possible with CBCT alone.

To our best knowledge, this is the first attempt to evaluate the diagnostic performance of 3D CBCT sialography in Sjögren syndrome patients. The literature contains a paucity of studies emphasizing the diagnostic capability of CBCT sialography in the detection of sialodochitis or ductal sialadenitis, sialoliths, and abnormal glands with chronic inflammatory changes. Bertin et al.[15] examined 27 patients with parotid and submandibular salivary symptoms using 3D CBCT sialography and suggested that this technique enabled a precise analysis of the ductal system in cases of non-tumorous chronic inflammatory salivary gland pathologies. The main lesions found were lithiasis and mucous plugs in 29.6% of patients, evidenced by duct filling defects and chronic salivary injuries that presented a "dead tree appearance" in 25.9% of patients. Jadu and Lam[16] found that 3D sialography outperformed 2D sialography with respect to visualization of the gland parenchyma ($P<0.001$) and identification of sialoliths ($P=0.02$). They reported that it had high sensitivity in the detection of abnormal glands with inflammatory changes. Kroll et al.[17] reported that 3D CBCT sialography allowed 3D visualization of the salivary gland ductal system up to the sixth branch (i.e., the peripheral ducts) and considered it to be a promising adjunctive tool for diagnosing conditions of the intraglandular ductal system and establishing the causes of recurrent salivary gland swelling. The high diagnostic accuracy is attributed to the isotropic voxel resolution offered by CBCT in comparison to other imaging modalities.[2]

Three-dimensional CBCT sialographic images could assist the clinician in the formulation of a proper treatment plan and in timely initiation of therapeutic intervention. Symptomatic treatment forms the mainstay of the management of Sjögren syndrome. Izumi et al. evaluated the efficacy of corticosteroid and saline lavage of parotid glands in relieving xerostomia in patients with Sjögren syndrome and found that salivary flow significantly improved.[18] Studies have also reported using TENS for the symptomatic improvement of xerostomia in patients with radiotherapy.[19,20] In 2015, Aggarwal et al.[19] showed that TENS significantly improved the whole salivary flow rate with little or minimal side effects. In the present study, all the patients were treated with saline lavage and TENS for a period of 4 weeks. The patients were followed up for 4 months every 15 days and were found to have reduced subjective and objective oral symptoms as estimated by the Xerostomia Inventory and Challacombe scale, as well as improved glandular function as assessed through 3D CBCT sialography.

To conclude, oral physicians play a prime role in identifying and managing Sjögren syndrome with a multifactorial etiology. Many Sjögren syndrome patients go undiagnosed or are left untreated and seek multiple consultations due to the overlapping symptoms of oral and ocular dryness with other conditions. Proper diagnosis of Sjögren syndrome at an early stage can greatly improve patients' quality of life. Three-dimensional sialography has been found to be a promising noninvasive imaging modality for detecting salivary gland pathologies in peripheral ducts that provides clinicians with high-quality 3D images of the intraglandular ductal system. Future case studies should be conducted to validate the diagnostic accuracy of this method in patients with salivary gland diseases.

Conflicts of Interest: None

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