Review Article

Orofacial pain considerations in autoimmune disorders: narrative review

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Background and Objective: Autoimmune diseases (AD) affect significant proportion of patients worldwide and are major cause of morbidity and mortality. Several countries including the U.S. have reported a surge in the prevalence of AD in the past decade. Healthcare professionals including oral healthcare professionals (OHP) may frequently encounter patients with AD. The objective of the narrative review is to summarize the orofacial pain conditions and oral manifestations in key rheumatologic diseases and other systemic AD.

Methods: Comprehensive search was performed on the scientific research data base and all the literature reviewed for orofacial manifestations related to AD.

Key Content and Findings: Orofacial manifestations are common in the several AD and may constitute the preliminary signs of onset. Orofacial pain and orofacial manifestations may affect extraoral or intraoral sites. Orofacial pain conditions affecting extraoral facial sites include temporomandibular disorders (TMD), neuropathic pain (NP), headaches. Intra oral signs and symptoms include xerostomia, oral lesions, periodontal disease and others. The review also discusses the prevalence, salient clinical features, diagnosis, dental considerations related to orofacial region and treatments of important AD.

Conclusions: The identification of early signs and symptoms while performing comprehensive intraoral and extraoral examination by OHP can help in timely referrals and diagnosis. It also facilitates interdisciplinary collaboration between physicians, rheumatologists and OHP to provide comprehensive care to patients with AD. Understanding the underlying AD can enable comprehensive treatment planning, better pain management strategies and improve prognostic outcomes.

Keywords: Orofacial pain; autoimmune diseases (AD); temporomandibular disorders (TMD); Bechet's; Sjögren's syndrome (SS); arthritis; thyroid disease

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Immunity is an essential self-defensive mechanism comprised of biological structures and processes within an organism that protects it against invasive microorganism, viruses, malignancies and diseases (1,2). Malfunction of the immune system can cause the self-destruction of its own cells, tissues, and organs resulting in autoimmune diseases (AD) (2). Approximately, 5% of the population worldwide and 3% of US population suffer from AD imposing a significant burden of morbidity and mortality (1,3).

Scientific research and literatures have provided substantial advancements in our understanding of human autoimmunity that have led to improvements in classification, diagnosis and management of the diseases (1-3). Tissue damage in AD is an exaggerated responses of the immune system towards self-antigens (1). Evidence suggests that antigens released by bacteria, viruses, toxins, blood, and tissue can trigger an

autoimmune response (1). This may initiate a cascade of events leading to damage, malfunction, and delayed growth of tissues and organs (1). Exact etiology of AD is often unknown. However, known risk factors include, family history, microbiological, environmental, and psychosocial factors (2).

B and T cells are important players in the adaptive immune response of human body (4). B cells need help of T cells in productions of antibodies, antigen presenting ability and cytokines production (4). B cells are known to contribute in pathogenesis of ADs by autoantibody production (4). Cytokines released by B cells regulate the T cell function and inflammation (4). Therefore, B cells controls multiple aspects of humoral and cellular function in immune system and ADs (4).

AD can be categorized based on several criteria including a classification based on the location of the autoimmune attack (4,5). Based on this criterion, ADs are classified into systemic (which affects multiple affected organs and generalized autoantigens are expressed) or organ-specific where tissue-specific antigens are targeted (4,5).

The AD spectrum is complex, and the underlying pathophysiological mechanism is common with mostly overlapping signs and symptoms. In the AD spectrum, the presentation of the initial symptoms may vary as compared to the development of the disease (3-5). One of the major challenges in understanding the development of autoimmunity is delay in recognizing the early events of the diseases. Usually, the symptoms are obvious only once the disease has been initiated and phenotypic changes have occurred (3). The developmental process of AD can be segmented into four sections (I) susceptibility phase; (II) initiation phase; (III) propagation phase; (IV) regulation phase (4,5).

ADs incidences can be inherited, acquired, or both. Once initiated, an interplay of a series of events and complex pathways results in a sustained tissue injury. In the propagation phase, there is continued autoimmune tissue injury resulting in cell injury. The damaged cells act as a source of antigens for the cycle to continue (1-5).

Scientific evidence garnered through preclinical and clinical studies show strong association between genetic predisposition, environmental factors (chemical agents, pathogens), hormonal influences, gender (> females) and development of the autoimmune disorder (1-5). Multiple organs are affected in the AD but the signs and symptoms can also be presented in focused region or related organs or can appear all together. Signs and symptoms rarely present focused in the orofacial region.

"Mouth is the mirror that can reflect the overall health of the body"; and various AD manifest themselves in the oral cavity as a primary sign and precise, early diagnosis by an oral healthcare provider can be the key for improved prognosis and treatment outcomes (5,6). Complete understanding of the Orofacial signs and symptoms related to ADs can help oral healthcare professionals (OHP) to focus and identify the symptoms. Early detection of the symptoms can help in improving the quality of life. Also, management of the complex AD requires multidisciplinary approach that includes medical team and OHP to provide comprehensive oral health care. Therefore, the goal of this article is to summarize the most common systemic autoimmune and inflammatory conditions that manifest as orofacial pain conditions, the relevant diagnostic tools, implication on general and oral health, and treatment options. We present the following article in accordance with the Narrative Review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-115/rc).

Methods and procedures

A comprehensive review of the literature was performed from August 2020 to August 2021 by two independent researchers. The following search engines were used: PubMed, Embase, and Google Scholar. The goal was to review all prospective studies on autoimmune disorders with orofacial pain manifestations. In the first step, narrative, systematic, and meta-analytic studies from the Cochrane Collaboration review and the National Institutes of Health Research (NIHR) were reviewed. An additional search of the American Dental Association website was performed to find statistics on the prevalence of orofacial pain conditions. In step two, the PubMed database was searched using the following terms: "autoimmune disorders", "orofacial pain", "temporomandibular disorders", "headaches" and "neuropathic pain". All the studies from the search for keywords were identified and reviewed for orofacial pain and manifestations exclusively in autoimmune disorders. Finally, the reference lists of the studies found in the second step were reviewed.

Articles were retrieved for further evaluation by reviewing the titles and abstracts. The full texts of selected studies were then analyzed to ensure and extract information related to orofacial pain manifestations, prevalence and diagnosis in autoimmune disorders (*Table 1*).

Table 1 Methods and procedure

Items	Specification
Date of search	30 Aug 2021
Databases and other sources searched	PubMed, Embase, Google Scholar
Search terms used	Autoimmune disorders and orofacial pain manifestations
Timeframe	Aug 2020–Aug 2021
Inclusion and exclusion criteria	Included: literature review/case reports/studies on orofacial pain and AD/book chapters Excluded : any studies not relevant to orofacial pain manifestations and not in English language were excluded
Selection process	The initial search was performed by SS. The included articles were further reviewed by MK for confirming the eligibility

AD, autoimmune diseases.

Discussion

Type 1 diabetes

It is one of the most widespread chronic ADs affecting children. Prevalence of type 1 diabetes is estimated to be 9.5% while the incidence is reported to be 15 per 100,000; and the incidence is increasing at a startling rate of 3–5% every year (7-10). The condition is a consequence of an autoimmune process acting in concert with genetic and environmental factors in genetically predisposed individuals. The onset of type 1 diabetes occurs between ages of 6 to 13 years, close to puberty and slightly more prevalent males as compared to females (7-10). The autoimmunity targets pancreatic beta cells resulting in their destruction and subsequent insulin deficiency and organ damage. The autoimmunity in type 1 diabetes may also affect other organs resulting in additional AD such as hypothyroidism, celiac disease, rheumatoid arthritis (RA) (11).

Diabetes can itself manifests in the oral cavity and present with several orofacial pain signs and symptoms. Most common orofacial signs and symptoms presented in Diabetes includes burning mouth syndrome (BMS), which is presented in approximately 55.2% of patients. Other signs and symptoms include burning sensation intraorally (11.5–17.2%), xerostomia (38.5%), temporomandibular disorders (TMD), myofascial TMD (31%), impairment of smell and taste, periodontitis, and tooth loss (12). Burning mouth symptoms were more frequent in female type 1 diabetes patients exhibiting symptoms of peripheral neuropathy (13-15). Type 1 diabetes is also associated with poor sleep quality, obstructive sleep apnea, shorter sleep duration, increased risk of epilepsy, anxiety and depression (15-18).

Approximately (17.5%) type 1 diabetics exhibit symptoms of diabetic peripheral neuropathy (DPN) (19), DPN is more frequently encountered in elderly subjects and associated with longer duration of the disease (20). Quantitative Sensory testing (QST) has revealed abnormalities in the small diameter nerve function resulting in higher pain threshold, electrical, heat and cold threshold corresponding to higher glycemia and glycated haemoglobin (11). There is an altered intraoral somatosensory profile including increase of heat and electrical threshold in patients with DPN as compared to controls and in heat pain threshold in painful DPN as compared to non-painful DPN suggesting augmentation in trigeminal nociceptive processing (11). Studies have also reported lower intraoral nerve fibre length density (21) in patients with DPN.

Diagnosis and management

As an OHP when a patient presents with such symptoms, diabetes should be considered as differential diagnosis. Standard diagnostic tests such as fasting plasma glucose test (less than 5.6 mmol/L is considered normal) and hemoglobin A1C (HbA1C) (less than 5.7% is considered normal) can help diagnose diabetes type I (18) (*Table 2*).

Oral complications in patients with diabetes are considered major complications of the disease and can affect quality of life of an individual. Thus, prevention and management of oral complications requires close monitoring and routine care by dentist. The management of the oral manifestation is mainly symptomatic, preventive and prophylactic. Xerostomia, periodontal disease, and caries are a few of the common findings (22) (*Table 2*). These can be managed with routine dental care, fluoride tooth pastes, periodontal maintenance, Biotene mouthwashes and restorations

Table 2 Oral implication and diagnosis of AD

AD	Type of AD	Age group (years)	Gender female: male	Diagnostics	Oral implications
Type 1 diabetes	Organ specific	6–13[a]	1/1	Fasting plasma glucose test ≤5.6 mmol/L; hemoglobin A1C test ≤5.7%	Periodontal disease; caries; xerostomia; BMS; TMD
Hashimoto's	Organ specific	3 to 15[b]	2:1; 4–5:1	TSH (0.5–4.5 or 5.0 mIU/L), anti-thyroid antibodies tests, T4 (0.8–1.8 ng/dL), thyroid ultrasound	macroglossia, dysgeusia, delayed eruption, poor periodontal health, altered tooth morphology and delayed wound healing
Grave's disease	Organ specific	50–60		TSH—decreased; T3 and T4 elevated	Burning mouth syndrome, periodontal disease, TMD; tension type headaches; tinnitus
MS	Systemic brain/ white matter	20–40	2/1	MRI; spinal tap (lumbar puncture); blood test for MS bio markers; evoked potential tests	trigeminal neuralgia (tic douloureux), sensory neuropathy of the trigeminal nerve (paresthesia) and facial palsy
RA	Systemic/ connective tissue, IgG	44–55	2/1	RF: high levels (over 20 U/mL); anti-CCP: high levels (over 20 U/mL); ANA, or: the results are positive or negative; CBC; ESR; CRP	TMD; increased prevalence of periodontitis; symptoms related to SS
SS	Systemic/Salivary gland, liver, kidney, thyroid	40–50	9/1	ANA with SS-A or SS-B	Xerostomia; TMD
MCTD	Connective tissue			Clinical eval; anti-RNP	Trigeminal neuralgia-like pain, neuropathy, features suggestive of Sjögren's syndrome and lymphadenopathy; TMD
SLE	Systemic/DNA, nuclear protein, RBC and platelet membranes	30–50	9/1	CBC; ANA; antibody test (anti-dsDNA); anti-Sm	Xerostomia; ulcerative lesions with erythema on non-keratinized tissue or hard palate; xerostomia; TMD
GCA	Vasculitis	50 and above	5:1	ESR/CRP; ultrasound; biopsy	New headache; jaw claudication; vision loss
BD	Systemic		More in males than females	Clinical evaluation	Oral mucosa ulcers; arthritis and arthralgia
JIA	Systemic	16 years		Clinical exam and evaluation	Mandibular micrognathia, anterior open bite; restricted mouth opening, jaw pain and stiffness; TMD
APS	Systemic	30–40	Females	Anti-phospholipid autoantibodies	Migraine; retinal thrombosis; recurrent transient ischemic attacks; cerebral stroke; double vision; ocular pain; headaches; hearing loss

[a], Wang *et al. J Intern Med* 2015 (3); [b], Kyritsi EM and Kanaka-Gantenbein C. *Front Endocrinol (Lausanne)* 2020 (22). AD, autoimmune diseases; MS, multiple sclerosis; RA, rheumatoid arthritis; SS, Sjögren's syndrome; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematous; GCA, giant cell arteritis; BD, Bechet's disease; JIA, juvenile idiopathic arthritis; APS, antiphospholipid syndrome; IgG, immunoglobulin G; RBC, red blood cell; TSH, Thyroid stimulating hormone; mIU/L, milli-international units per liter; ng/dL, nanograms per deciliter; MRI, magnetic resonance imaging; RF, rheumatoid factor; Anti-CCP, anti-cyclic citrullinated peptide; ANA, anti-nuclear antibody; CBC, complete blood count; ESR, erythrocyte sedimentation rate; SS-A, anti-Ro-antibody; SS-B, anti-La-antibody; RNP, ribonucleoprotein; CRP, C-reactive protein; BMS, burning mouth syndrome; TMD, temporomandibular disorder.

of caries. For any surgical procedures like extractions, periodontal surgeries, implants etc., it's important to consider the fasting glucose levels as well as the HbA1C. Because delayed healing of wounds is very common in uncontrolled diabetics and prophylactic antibiotic medications and hygiene maintenance can manage the healing process (23).

Thyroid disorders

Primary hypothyroidism may be attributed to autoimmune conditions, surgery, and radiation therapy. It is estimated to affect 40 and 6 per 10,000 women and men respectively every year (24). Autoimmune thyroid disease is also referred to as Hashimoto's thyroiditis (HT) (24). The prevalence of HT ranges from 0.3% to 9.6%, with the highest predilection towards early pubertal adolescents. Females are generally more affected than males with studies reporting F-M ratio up to 9.7:1 (25). Usually, patients are asymptomatic but may present with goiter. So, a comprehensive clinical evaluation and timely laboratory investigation confirm the diagnosis (21,22). The blood tests include the thyroid hormones (T3 &4), thyroid stimulating hormone (TSH), and an antibody test [thyroid peroxidase (TPO) antibodies] (26). T3 and T4 are low but TSH is elevated and elevated thyroid autoantibodies are present (26). HT has been associated with a higher prevalence of TMD, widespread chronic pain and fibromyalgia (23,24). Autoimmune thyroiditis is an inflammatory degenerative condition affecting the thyroid. Subacute thyroiditis may also result in pain referral to the jaw (27).

Primary hypothyroidism may also have a negative effect on smell and taste and untreated primary hypothyroidism patients have lower smell identification, discrimination, threshold, bitter and sweet taste scores. Treatment helps in recovery of both senses. The negative effect on taste may lead to amplification of sensorial inputs to the trigeminal nerve. A study on patients with BMS suggested a significant proportion of patients had high levels on thyroid autoantibodies, evidence of hypothyroidism or changes indicative of thyroid nodularity (26-28).

There is uncertainty on association of thyroid disorders and headaches with some studies reporting no association and other studies reporting a higher prevalence of primary headache disorders such as migraine in patients with thyroid dysfunction; primarily hypothyroidism (29-32).

Grave's disease (GD), is very rare in children, with a prevalence of 1 in 10,000 in the US. GD has a strong predilection towards females and adolescents. Contrary to HT, GD has elevated levels of T3 and T 4 and decreased levels of TSH. Oral manifestations include BMS, periodontal disease, increased risk for caries, TMD's, tension type headaches and tinnitus (26-28).

Diagnosis and management

HT/GD

Understanding and obtaining information about thyroid dysfunction becomes critically important for a dentist in detecting early signs of thyroid symptoms and possibly avoiding dental complications related to thyroid disorders. Avoiding exposure of thyroid gland to X-rays while performing intraoral/extraoral radiographs by providing extra protective shields. Knowledge of adverse drug reactions and interactions and signs and symptoms of the conditions are of utmost importance to the oral health providers (33,34).

OHPs need to provide comprehensive dental care in terms prophylaxis, prevention of complications related to dry mouth and delayed wound healing. Dentists should be aware of drug interactions as patients can be sensitive to central nervous system depressants and barbiturates; hence these medications should be used with caution. Patients on propylthiouracil treatment must be monitored for possible agranulocytosis, hypoproteinemia or bleeding, and a complete blood count (CBC) including prothrombin time must be performed before doing any invasive procedures. Treatment modifications are indicated while providing comprehensive dental care for patients with hypothyroidism (Hashimoto's) (27).

Multiple sclerosis (MS)

MS is a chronic debilitating inflammatory disorder resulting in axonal degeneration and demyelination in the central nervous system (32). Although the exact pathogenesis is yet to be completely elucidated; immune mediated autoimmunity in concert with environmental and genetic factors may play an important role (35). MS can be diagnosed at an early age 20 and is more prevalent in females compared to males. Lhermitte's sign (36) (also known as Lhermitte's phenomenon and the barber chair phenomenon) a typical electric shock like pain extending down the spine, and/or extremities upon flexion of the neck, often a sequela of neurologic disease. A radiographical and laboratory test including new T2 and/or gadolinium (Gd)-enhanced magnetic resonance imaging (MRI) (with reference to a baseline scan), and presence of oligoclonal bands (OCB) in cerebrospinal fluid (CSF) confirm the diagnosis for MS (37).

Pain, neuropathic pain (NP), extremity pain, Lhermitte's sign, back pain, painful tonic spasms, and headache are commonly reported in patients with MS (36). Orofacial manifestations have been reported in 88.6% of MS patients (38). They include visual disorders (80.4%), TMDs (58.2–56.7%), dysphagia (26.6%), dysarthria (42.1%), facial palsy (19%), and trigeminal neuralgia (TN) (7.9%) (39). In addition, paraesthesias, hemifacial spasm, Charcot triad, facial pain, muscle weakness, tremor, unilateral or bilateral deafness or hyperacusis with normal sound audiometry, taste deficits, facial myokymia, myofascial and neck pain were also reported. Unusual initial signs prior to diagnosis include brachial pain, hypoglossal nerve palsy, ptosis, oculomotor nerve palsy, throat pain, peripheral facial palsy (40). MS significantly affects the ability of patients to perform routine activities affecting their quality of life, and anxiety, depression is frequently encountered in these patients (36-40).

NP affects approximately 86% of patients with MS (41). MS may affect the trigeminal nerve, glossopharyngeal nerve or occipital nerve causing respective neuralgia (41). Rarely nervus intermedius, retroauricular neuralgias have also been reported (41,42). Double crush mechanisms due to neurovascular contact and pressure from the demyelinating plaques are proposed to be the primary mechanism in these neuralgias. 1.9–4.9% of the patients with MS may be affected with TN and conversely MS is detected in 2–14% of the patients with TN (42). There is a 20-fold increased risk for TN in MS patients an there was no significant differences between different subtypes of MS (42). TN may precede symptoms the onset of MS in approximately 15% of the patients. Glossopharyngeal neuralgia occurs in 0.5% cases and currently there is lack of data on prevalence of ON in MS (43) (*Table 2*).

Headaches (68%) in MS may be present in the pre-symptomatic phase, at onset or during treatment (interferon beta, laquinimod) and course of MS (44,45). Among various headache conditions, migraine (up to 55%) [migraine with aura (16%), migraine without aura (10–39%)], tension type headache (20%), medication overuse headache (38%) was most common (46). Migraine MS patients were more symptomatic as compared to MS patients without migraine. In approximately 2/3rd of the patients' headaches precedes onset of MS symptoms and 80% of MS patients reported headaches after onset of treatment (23,35,46-48).

Diagnosis and management

Primary testing for MS to confirm the diagnosis is MRI for cranial, cervical and thoracic region, with intravenous contrast Gd. Another important test is lumbar puncture for CSF to study basic CSF biochemistry [glucose, protein, albumin, immunoglobulin G (IgG), and lactate levels], microbiological tests [cell count, and, if needed, other microbial and enzyme-linked immunosorbent assay (ELISA) tests], cytopathological evaluation (screening for malignant cells) and tests for intrathecal IgG synthesis, both quantitatively (IgG index) and qualitatively (OCB analysis). Blood tests that include anti-nuclear antibody (ANA) test, antiphospholipid antibodies (aPL), anti-ds DNA (40) (*Table 2*).

Orofacial region symptoms include TN, sensory neuropathy of the trigeminal nerve (paresthesia) and facial palsy (23). Management of MS symptoms requires the use of steroids, adrenocorticotropic hormone (ACTH), interferon and immunosuppressors. Secondary to medications oral side effects are cheilitis, gingivitis, stomatitis, xerostomia and candidiasis, dysgeusia or certain changes secondary to neutropenia and thrombocytopenia (42).

The focus of oral health care in MS is on prevention and/or reduction of dental or periodontal disease, maintenance of oral hygiene and facilitating access to stress free oral care. The OHP must be aware of potential interaction of drugs used in MS and commonly prescribed medications in oral health care (23). Particular care must be exercised while prescribing non-steroidal anti-inflammatory drugs, narcotics and acetaminophen where interactions between these drugs may result in hepatoxicity, cytotoxicity, alter the metabolism of certain drugs and/or amplify fatigue, myalgia and depression (41-45).

RA

These group of chronic inflammatory disorders are suspected to have a strong autoimmune component in their etiopathogenesis and occur in genetically predisposed individuals (49). RA is estimated to affect 1.16% females and 0.44% males (50). RA can start at any age, but most prevalent in fourth and sixth decades (49). The condition affects the articular surfaces, articular cartilage and subchondral bone causing synovial hyperplasia and bony destruction. Systemic RA involves symmetric small peripheral joints commonly and temporomandibular joint (TMJ) may be involved in 50% of the cases (49). A recent study suggested that TMJ pain, higher general pain, and crepitation were more commonly seen within 2 years of systemic RA disease onset and structural changes and pain related dysfunction were reported over a longer period (51) (*Table 2*). Otalgia and tinnitus are accompanying features.

Radiographic features include erosion and flattening of condylar head of TMJ (23).

Psoriatic arthritis (PA)

PA is a relatively rare chronic inflammatory disease with psoriasis. Psoriasis affects 0–8.5% of the population in the world and approximately 0.91% individuals in the U.S. and arthritis in these patients accounts for only 6% of the cases making it relatively rare condition (48,52). PA symptoms includes pain in joints, reduced joint movements, skin rashes and pain in ligaments & tendons.

Extraoral symptoms involves cutaneous lesions of vermilion border of lip that may present with diffused erythema, fissuring, scaly patches and occasional bleeding. Exudation, discomfort, and itching of the lesions may also be accompanied. Intraoral lesions are commonly found in palatal region, gingiva, and buccal mucosa. These lesions are mostly transient, migratory and pinpoint bleeding could be evident. In tongue lesions resembles benign migratory glossitis and fissured tongue is common in PA that can prompt the dentists (OHPs) to consider PA in differential diagnosis (53).

PA also affect the pain TMJ referring to ear and temporal headaches. Depending on the arthritic changes in the TMJ limitations in range of motion of jaw, myalgia, joint sounds, changes in occlusion and facial profile changes (54).

Ankylosing spondylitis (AS)

AS affects 0.1–1.4% of the population globally (55). In a majority of instance, it affects sacroiliac joint and vertebral column with the primary site being the point of insertion of ligaments and capsule into the bone. TMJ is affected in 4–35% of patients with AS (55). Tenderness on TMJ palpation, joint sounds, pain on muscle palpation, pain on jaw movements, restriction of mouth opening, preauricular swelling, occlusal changes such as anterior open bite, bony or fibrous ankylosis, restricted lateral excursions are frequently reported in RA, AS and PA (56). Subjective symptoms were more in patients with RA, PA as compared to AS (57). The conditions may also be associated with periods of remission.

Neuropsychiatric manifestations are common in these conditions and may be associated with the inflammatory process, diagnosis, alterations in bony components, neural compression, treatment related side effects (56). It is suggested that in patients with migraine there is a frequent association with systemic AD.

Diagnosis and management

The diagnosis of RA is made from haematological tests and imaging of joints and organs. Haematological findings include elevated erythrocyte sedimentation rate (ESR), rheumatic factor, anaemia, and anti-cyclic citrullinated peptide antibodies (50-52,55). MRI is considered as the gold standard for diagnosis and staging of RA (22) (*Table 2*).

TMJ signs and symptoms are common in RA and should be treated symptomatically to improve the quality of life. Jaw function and pain management can include medications, (including corticosteroids, non-steroidal anti-inflammatory drugs, and disease-modifying antirheumatic drugs), oral appliances, physical therapy, biobehavioral therapy or combinations of all (23). In cases where medical treatment is ineffective, surgical management is considered as the next choice of treatment (23).

RA has increased prevalence of periodontitis and SS like symptoms of xerostomia. These symptoms can be managed by prophylaxis and preventive measures. Good oral hygiene care, supportive oral rinse and frequent dental checkups can control the progression of peritonitis and related problems.

Sjögren's syndrome (SS)

SS is one of the common chronic auto-immune, inflammatory disease of the exocrine glands, affecting 0.5% to 5.0% of the general population. It is a multisystem AD with hypofunction of salivary and lacrimal glands (27). Prevalence in females is more (at a ratio of 9:1) and a mean age of incidence is the 4^{th} and 5^{th} decade. SS represents in two common clinical forms: (I) primary SS—a systemic disorder characterized by lymphocytic infiltration of exocrine glands and with extra glandular manifestations that can be present; (II) secondary SS—is diagnosed when there is at least one other concomitant AD (e.g., RA, systemic lupus erythematosus, or dermatomyositis) (27,55).

Oral manifestation in SS is due to hypofunction of salivary glands that results in reduction salivary flow as well changes its composition (23). The reduced saliva increases the risk of caries, gingivitis, periodontal disease, fungal infections, dysgeusia (an altered or impaired sense of taste), cheilitis, and glossitis (23).

Dermatological symptoms of SS include dry skin, itching, and burning sensation (23). Extra glandular symptoms might involve malaise, polyarthralgia, thyroid, neural, and psychological disturbances (23,27).

Around 15–90% of the patients suffering from SS develop musculoskeletal symptoms (23). Usually, the distribution of arthralgia is symmetrical and hands, wrists, ankles, feet, and TMJ are most frequently involved (23). Prevalence of TMDs is high in SS with pre-auricular pain in 54.2%, tinnitus and ear pain in 55.5%, jaw movement problems 44.4%, limited mouth opening 44.4%, and temporal headaches in 41.6% (23) (*Table 2*).

Distal symmetrical neuropathy is present in 10–20% of the cases with primary SS (23). In addition, cranial neuropathy, trigeminal neuropathy and optic neuritis are also reported in patients with SS. Trigeminal sensory neuropathy is slow progressing, unilateral or bilateral facial numbness or paresthesia, and occasionally with pain (23).

Diagnosis and management

Diagnosis of SS is made by clinical presentations and antinuclear antibody (ANA) test (22). Even though nonspecific markers of autoimmune disorders (e.g., elevated ANA, ESR, total protein levels, etc.) can help in initial diagnosis, anti-Ro-antibody (SS-A) and anti-La-antibody (SS-B) are specific markers of SS (22) (*Table 2*).

There is no definitive treatment of SS, however, palliative treatments such as salivary secretagogues and substitutes might help alleviate the oral symptoms (22). Muscarinic agonists (e.g., pilocarpine and cevimeline) act by increase in the salivary flow thereby improve dry mouth symptoms (22). Electrical stimulation of salivary flow has proven to be useful in dry mouth symptoms. Other products such as pseudo-pharmaceuticals and herbal supplements can help reduce xerostomia (22). Opportunistic fungal infections might be prevented or treated using topical and systemic antifungals (27). Dental caries needs routine dental care, good oral hygiene measures and topical application of fluoride can prevent caries (27).

Systemic lupus erythematous (SLE)

SLE is another group of AD which affects the connective tissues. SLE is a chronic disease that involves multisystem organs such as dermatologic, renal, central and peripheral nervous system. Annual incidence of SLE is approximately 1–10 per 100,000 and estimated prevalence is about 5 to 130 per 100,000. Females have a higher incidence rate compared to males and the 2^{nd}–5^{th} decade (58).

Oral manifestations are clinically important findings in SLE patients. Prevalence of oral lesions range from 9% to 45%. Oral lesions present in form of bullous-ulcerative lesions with erythema on non-keratinized tissue or patchy lesions in hard palate. The prevalence of candidiasis varies from 5% to 75%, dysphagia (11% to 75%) and xerostomia from (1% to 100%) (*Table 2*).

TMJ involvement has been reported in SLE patients, and approximately 22% of SLE patients will have some internal derangements within joint (23). Almost 30% of patients will have radiographic changes in the condyles of the joint like flattening of condyles or erosions, osteophytes and sclerosis (23). Trigeminal sensory neuropathy may present in SLE patients with clinical symptoms of facial numbness, paresthesia, dysesthesia and pain (23).

Diagnosis and management

Diagnosing SLE may be difficult as its early signs and symptoms are not specific that can overlap for other diseases (27). Comprehensive evaluation by rheumatologists is extremely important to diagnose SLE. Complete thorough examination, CBC, ANA test, testing for antibody to double-stranded DNA antigen (anti-dsDNA) and antibody to Sm nuclear antigen (anti-Sm) are important in diagnosis of SLE (27) (*Table 2*).

Multidisciplinary approach is required to manage the symptoms of SLE. Treatment modifications are required while managing patient for dental care. TMJ impairment can be managed, gingivitis, and systemic complications from dental infections can be treated symptomatically to improve the quality of life (23,27).

Mixed connective tissue disease (MCTD)

MCTD were first described in 1972 as an entity with overlapping clinical features of SLE, RA, polyarthralgias systemic sclerosis, Raynaud's phenomenon, polymyositis and mucosal lesions. MCTD has been reported both in children and adults over 89 years of age (59,60).

Oral manifestations include arthritis of TMJ and trigeminal sensory neuropathy that includes tooth pain and facial numbness. Mild to moderate neurovascular headaches has also been reported in MCTD (60). Masticatory system dysfunction has been reported in MCTD patients with TMJ tenderness, and jaw joint sounds like symptoms (59,60) (*Table 2*).

Diagnosis and management

A comprehensive clinical evaluation, medical history, clinical examination for characteristic findings and blood tests as diagnostic tool can help in diagnosing MCTD.

Specialized blood tests reveal abnormally high levels of antibodies to the U1 small nuclear ribonucleoprotein (anti-RNP) (60,61) (*Table 2*).

Goal of managing orofacial symptoms in MCTD is to improve quality of life. Pharmacological approach of managing the systemic symptoms includes analgesics [e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids] and anti-malarial drugs (e.g., hydroxychloroquine). Involvement of major systems warrants the use of immunosuppressive drugs such as cyclophosphamide. Along with supportive management for MCTD, TMDs and neuropathy symptoms are treated symptomatically. Other symptoms that need routine comprehensive dental care include trismus, taste alteration, fissured tongue, fungal infections, and increased dental caries (60,61).

Antiphospholipid syndrome (APS)

APS is an autoimmune systemic disorder characterized by thrombotic (venous, arterial and/or microvascular) and/or obstetric morbidity in the context of persistently positive aPL [lupus anticoagulant (LA), IgG and/or IgM anti-beta-2 glycoprotein-1 (aβ2GP1) and anticardiolipin antibodies [aCL)] (62). In the general population the prevalence of aPL is around 2–5% APS is reported alone or in association with SLE, or other connective tissue diseases or SS (63).

Migraine, retinal thrombosis, recurrent transient ischemic attacks (TIAs) and cerebral stroke are common clinical manifestations (64). History of headaches are very similar to teenage headaches that is associated with premenstrual days that diminish by 10–20 years of age and return back at age of 30–40 years of age (64). There is family history of migraines and migraines presents with aura, speech or visual impairments (65).

Involvement of the eyes results in a variety of symptoms including diplopia, pain, visual fields impairment, transient loss of vision. Sudden hearing loss can be one of a clinical manifestation due to reduced supply of blood (63). Both the eye and ear manifestations have presence of aCL antibodies (65) (*Table 2*).

Diagnosis and management

Proper diagnosis of APS includes medical history, physical examination, and blood tests. aPL tests are used to confirm clinical suspicion. ELISA detection of aCL is of high sensitivity and coagulation assays for LA test is of more specificity (65) (*Table 2*). Anticoagulants are used as preventive and long-term measures (64,65).

Giant cell arteritis (GCA)

GCA also known as temporal arteritis (TA) and Horton's disease (66). It is a, chronic systemic vasculitis of unknown cause, which involves medium and large arteries (23). It is the most common type of systemic vasculitis with a predilection towards individuals of 50 years or more age (23,66).

Almost half of the patients with GCA presents with pain and stiffness of neck, shoulder, and pelvic girdle (23). Symptoms of GCA involve severe temporal headaches, low-grade fever, malaise, visual changes, jaw claudication, depression, and weight loss (23). Some patients may present with dental pain, dysphagia, dysarthria, chronic cough and rarely necrosis of the lips and tongue. TA has similar presentations of polymyalgia rheumatica (PMR) like morning stiffness, pain in neck and shoulder or hips and biopsy reports of TA suggests 40–60% of PMR manifestations (66).

Complications of TA can result in cranial ischemia, visual loss and life-threatening manifestations can be myocardial infarction, ruptured aortic aneurysm, intestinal infarction, pulmonary embolism, renal insufficiency and TIAs and strokes (66).

Oral manifestation of TA is limited mouth opening (trismus), pain in masticatory muscles on chewing (jaw claudication), and odontogenic pain; 40% of TA patients presents with jaw claudication (23,64,66). This is one of the acute orofacial pain conditions presenting to a dentist due to oral manifestations and failure to promptly recognize and treat may result in morbidity and mortality (*Table 2*).

Diagnosis and management

GCA/TA is diagnosed on the basis of the combination of symptoms, clinical findings, laboratory results, and diagnostic imaging, laboratory investigations include ESR and C-reactive protein (CRP); elevated levels necessitate further investigations. High resolution MRI, Positron emission tomography or color-coded duplex sonography could be performed to further confirm the TA. Biopsy of temporal artery is gold standard diagnostic to confirm TA. The characteristic histological findings are patchy infiltration of lymphocytes, plasma cells, macrophages and occasional eosinophils in the lamina media of the artery (*Table 2*).

The delay in diagnosing TA can be fatal. So, it's critically important to diagnose TA and treat. The mainstay

treatment for TA steroid therapy.

Bechet's disease (BD)

It's a chronic rare multisystem disorder usually with recurrent inflammatory mucocutaneous lesions of the oral cavity, genitals, dermis, ocular, vascular, digestive and nervous system (66,67). Forty to seventy percent of the patients of BD presents with arthritis and arthralgia (66). BD is prominent in young adults between second and fourth decades. Rarely found in children and over 50 years of age. BD is predominant in males with male to female ratio of 0.73 (66). When the CNS is involved inflammation of the meninges often leads to headaches and stiffness of the neck (67) (*Table 2*).

Diagnosis and management

A diagnosis of BD is made when there are recurrent oral lesions along with any of the two following—recurrent skin, eye, or genital ulcer or a positive hypersensitivity skin reaction (67,68). Oral ulcers are typically managed by systemic immune suppressive and anti-tumour necrosis factor (TNF)-alpha therapies (67).

Juvenile idiopathic arthritis (JIA)

It is a self-limiting (typically 6 weeks) arthritis of teenagers with an unknown cause (68). It is an autoimmune disorder against the synovial tissues, which presents as chronic arthritis. TMJ is very commonly involved in JIA with prevalence reaching up to 96% (68). TMJ arthritis symptoms presents as mandibular micrognathia, anterior open bite, restricted mouth opening, jaw pain and stiffness (68) (*Table 2*). There is high prevalence of TMD in JIA as compared to RA (69).

Diagnosis and management

Chronic arthritis of one or more joints lasting 6 weeks or more in an adolescent under 16 years of age, which cannot be referred to any other cause is diagnosed as JIA (22,69). Complete medical history and physical evaluation is required. Laboratory blood tests includes ESR, ANA test, RF, HLA-B27 typing and CBC (69). MRI, or computerized tomography (CT) scan or cone beam computed tomography (CBCT) is also required to confirm the diagnoses (22,24). Treatment is symptomatic and includes medication, physical therapy, oral appliances, surgeries, biobehavioral management (23) (*Table 2*).

Conclusion and recommendations

Signs and symptoms of AD are complex and usually overlap with each other frequently resulting in misdiagnosis. However, oral signs and symptoms are most of the time associated in AD and as OHP, we can be first one to identify and provide efficient care. Understanding of signs and symptoms becomes essential for OHP so that while performing early detection of AD can be performed and treatment options can be planned. A multidisciplinary approach can enhance the success rate of treatment avoid fatal consequences and also improve quality of life.

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