ARTICLE

Oral and Mandibular Manifestations in the Ehlers–Danlos Syndromes

JOHN MITAKIDES* AND BRAD T. TINKLE

The Ehlers–Danlos syndromes (EDS) are hereditary disorders that affect the connective tissue and collagen structures in the body. Several types of EDS have been identified. Oral and mandibular structures, which include oral soft tissue, dentition, facial and head pain, and the functioning of the temporomandibular joint (TMJ), are variably affected in the various types of EDS. These various manifestations of EDS have been noted for many years, but newer diagnostic techniques and studies are shedding additional light on the challenges faced by EDS patients in the area of oral and mandibular disorders. Further, the impact of temporomandibular disorder (TMD) on musculoskeletal dysfunction and vice versa, make this an important feature to recognize. Oral and mandibular hypermobility of the TMJ with associated consequences of EDS are noted. These features, diagnostic parameters and treatment procedures are presented.

KEY WORDS: Ehlers-Danlos syndrome; temporomandibular dysfunction; temporomandibular joint; oral manifestations; hypermobility

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INTRODUCTION

Oral and mandibular manifestations have been observed in all types of EDS patients. Collagen defects compromise oral health including vascularity, bone, teeth, gum tissue, nerve tissue, as well as the tendons and ligaments that retain maxillofacial structures in position in addition to the temporomandibular joint (TMJ) [Norton and Assael, 1997; Abel and Carrasco, 2006]. These oromandibular manifestations in EDS are often poorly recognized by healthcare providers but are commonly reported by patients and impact pain, functionality as well as quality of life [Conti et al., 2012]. Here, we describe the oral and mandibular manifestations of EDS, diagnostic techniques, and treatment modalities.

ORAL SOFT TISSUE MANIFESTATIONS

The structural collagen(s) and its function is altered in all types of EDS. The mucosal tissue is often thin [Ferré et al., 2012]. Mucosal fragility is also commonplace [Nelson and Assael, 1997]. Easy wounding occurs with oral appliances. Poor wound healing and excessive hemorrhaging is common with incidental injury as well as dental procedures.

Early onset periodontitis is seen in a variety of EDS patients, especially type VIII, the periodontal type [Reinstein et al., 2013]. The structural defects in collagen or collagen-related proteins as part of the innate immune system may increase susceptibility to degradation by bacterial pathogens. Functional consequences of altered collagen could also affect oxygen and nutrient delivery to the tissue affecting the overall health but this may also be affected in a pro-inflammatory state. Alterations of the extracellular matrix would also likely affect diffusion of not only nutrients but other small molecules and may be an important aspect of the observation resistance to local anesthesia [Hakim et al., 2005].

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system may increase susceptibility to degradation by bacterial pathogens.

The lack of lingual and inferior labial frenula has been noted in several studies. De Felice et al. [2001] studied 12 patients with EDS, 4 of whom were classified as classic EDS and the remaining eight as hypermobile (hEDS). All patients were clinically characterized and included "significant" skin hyperlaxity. All 12 patients had an absent inferior labial frenulum (between the lower lip and gum line) whereas only nine also had absence of the (sub)lingual frenulum. Although a small sample size, both sites were significantly distinct from the appropriate control group. However, such observations were not reproduced in two subsequent studies [Bohm et al., 2001; Shankar et al., 2006].

Machet et al. [2010] evaluated patients of classic (n = 4), hypermobile (n = 19), and vascular (n = 20) types of EDS. As a subgroup (classic and hypermobile), the sensitivities of the absence of the inferior labial frenulum was 42% and 53.5% for the lingual frenulum with specificities of 99% and 98%, respectively. In vascular EDS, sensitivity was 65% with 97% specificity with an odds ratio of 72. Celletti et al. [2011] evaluated 32 patients with clinically characterized hEDS. Using a variation of assessment, the investigators did not find complete absence of the lower labial frenulum in any subject. However, the lingual frenulum was not visualized in 23 patients and 13 controls by one method but only four patients and one control by another method. Both methods produced significant results but demonstrated that the methodology could widely change the prevalence of and therefore usefulness of such a sign. It has also been noted that up to 50% of EDS patients are able to touch their tongue to their nose (Gorlin sign) but it is unclear if the absence of the lingual frenulum has an impact on the presence of this sign [Tanwar et al., 2014; Awal et al., 2015].

BONE STRUCTURE AND DENTITION

In the EDS patient tooth mobility has been noted which may accelerate the periodontal recession [Norton and Assael, 1997; Abel and Carrasco, 2006]. Orthodontia therapy is rapid due to accelerated tooth movement in the EDS patient and is usually accomplished in 1 year or less. Unfortunately, rapid but mild relapses and tooth movement are noted usually by 18 months. Tooth retention will be a lifelong necessity [Fridrich et al., 1990].

Several tooth abnormalities have been noted among EDS patients in one study [Table I; Norton and Assael, 1997]. Posterior teeth are reported to have high cusps and deep fissures. The roots may be abnormally shaped, fused and/or elongated. Pulp stones are seen in some. Congenital absence of teeth and microdontia have been also noted [Norton and Assael, 1997; Létourneau et al., 2001].

THE TEMPOROMANDIBULAR JOINT

The anatomy of the TMJ is complex. The joint is classified as a ginglymoarthrodial joint and may be better described as a sliding ball and socket joint. The muscles of mastication allow function and motion of the TMJ and mandible. Bilaterally, they are the temporalis (anterior, middle, and posterior), the masseter (superficial and deep), the internal pterygoid, and the external pterygoid muscles. Muscles of the inferior border of the mandible, anterior and posterior neck, and suboccipital triangles can also be affected by temporomandibular dysfunction (TMD). Included are the anterior belly of digastric, superior pharyngeal constrictor, middle pharyngeal constrictor, and the omohyoid muscles. It should also be noted that the TMJ and its muscles and functions are intimately associated with cervical and pharyngeal functions of the head and neck. Therefore, the general anatomy of the head and neck well beyond the TMJ must also be considered.

TMJ hypermobility and TMD have been linked to systemic joint hypermobility in several studies [Harinstein et al., 1988; Buckingham et al., 1991; Westling and Mattiasson, 1991; Westling, 1992; De Coster et al., 2005; Kavuncu et al., 2006; Hirsch et al., 2008] with fewer linking to hEDS [Diep et al., 2016]. Much like any joint in EDS, the TMJ often is hypermobile, subluxes and can dislocate [Norton and Assael, 1997; Wincour et al., 2000; Pasinato et al., 2011]. TMJ dislocation is noted to occur more often in women in the general population which mirrors that of EDS

TABLE I. Dental Manifestations of EDS

Soft tissue
• Fragile oral mucosa
• Early onset of periodontal defects
Dentition
• High cusps and deep fissures on the crowns of teeth
• Higher incidence of enamel and dental fractures
• Stunted roots or dilacerations
• Coronal pulp stones
• Aberrant dentinal tubules
• Pulpal vascular lesions and denticles
• Ready movement of teeth in response to orthodontic forces
• Easier accomplishment of orthodontic retention
Temporomandibular joint
• Hypermobile TMJ with high incidence of subluxation/dislocation
• TMD

[Nosouhian et al., 2015]. The TMJ can relocate once hyperextended but cause the cartilaginous disc to stay dislocated resulting in pain, bony destruction, and limited mobility. The muscles of mastication can be overused, spasm, and cause referred face, head, and neck pain thus resulting in decrease functionality and quality of life [Hagberg et al., 2004; Berglund and Björck, 2012].

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EXAMINATION AND DIAGNOSIS OF TMD

The tracking of opening and chewing motions can be diagnostic of TMD. Common symptoms of TMD include: (i) deflection of the jaw to the affected side; (ii) limitation of opening; (iii) inability to chew; (iv) pain in front of the ear; (v) headaches in the temples or lateral side of the jaw; (vi) tooth pain; (vii) inability to turn the head and/or neck; (viii) inability to get the posterior teeth together; (ix) fullness, itching or pain in the ear(s); (x) "popping" or crepitus with movement of the TMJ.

The mouth opening for the first 33 mm is unstressed pure rotation. Opening beyond the 33 mm involves translation of the condyle and the meniscus down the articular surface. The meniscus should remain interposed between surfaces. If it becomes dislodged anteriorly, the motion of translation is blocked and mouth opening is limited to approximately 33 mm or less. If the meniscus is dislodged posteriorly, the patient will not be able to close their mouth, occlude their teeth, or chew on the affected side. Patients with hypermobile TMJ will often display increased maximal mouth opening often well-beyond the normal range of 40–55 mm [Norton and Assael, 1997; Hirsch et al., 2008].

It is not uncommon that the hypermobile patient suddenly dislocates within the TMJ and thereafter has a limited mouth opening of 20–33 mm. This may be due to injury or stress such as: (i) prolonged opening of the mouth (i.e., dental work or intubation); (ii) blow to the head, face, or jaw; (iii) "whiplash" type injury; (iv) hyperopening; (v) hypermobile joints with increase range of motion; (vi) degenerative breakdown of TMJ articular surfaces; (vii) unbalanced occlusion; (viii) habits such as nail biting or gum chewing; (ix) bruxing or clenching the teeth and jaws. Of all of these possible causes, the most common is the bruxing of the teeth and/or clenching of the jaws. When these habits are combined with EDS or other hypermobility syndromes, the effects are substantially amplified, particularly in craniocervical instability patients [Inês et al., 2008].

In an initial examination for TMD, it is important to observe the typical tissues of the oral cavity and the head and the neck, but also the function of the TMJ, cervical, pharyngeal, and tonsillar areas. Excessive translation of the mandible may be associated with pharyngeal collapse which could be related to sleep-disordered breathing in EDS patients [Guilleminault et al., 2013].

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Muscles of mastication positions, action, tenor (especially spasms), and health should be noted. The muscles of mastication are the temporalis, masseter, internal pterygoid, and external pterygoid muscles. Palpation of these muscles will delineate fasciculation and tender areas that generate myofascial pain referral patterns. Traditionally the temporalis muscle refers pain to the upper teeth, and the masseter refers pain to the lower molars. It is not uncommon, however, to have all of the teeth in a quadrant be percussive; teeth may be sensitive to biting pressure and/or produce an aberrant vitality test. Nociceptive pain may also be present.

THE RELATIONSHIP AND UNDERLYING CAUSES OF THE TMD IN EDS

Several studies have addressed TMJ hypermobility, generalized joint hypermobility, and TMD with various conclusions. The studies reported between 40% in one study and up to 100% in another, of patients presenting with multiple types of headache and/or unilateral or bilateral TMJ pain [Castori and Voermans, 2014].

In a recent study of 114 EDS patients comprising several types with an equal number of controls, a higher proportion of the EDS patients experienced hypermobile joints during extreme mouth opening, poor mouth opening ability when biting into thick food, clicking, crepitation, and permanent locking of the jaw open and closed. Many of the EDS patents reported decreased hypermobility of the joint with age [Abel and Carrasco, 2006].

Understanding the relationship between the head, neck, and mandible structures ultimately provides a key to pain management. The classic TMD headache has been deemed to be caused by muscle spasms triggered by stress, clenching of the jaws, ischemia, osteoclastic and compression degeneration, and/or neurological input to the trigeminal nerve, which is a potential TMD input source of migrainous head pain [Shankland, 1998]. Inflammation of TMJ structures also occurs due to meniscal displacement and/or condylar displacement. Muscle spasticity and postural disorders also impact TMD [Ciancaglini et al., 1999]. An additional, less widely recognized significant trigger

of TMD pain is displacement of the cervical vertebrae [De Laat et al., 1998; von Piekartz and Lüdtke, 2011].

CRANIOCERVICAL INSTABILITY, CERVICAL SPINE DISORDERS, AND TMD

As early as 1934, researchers noted the relationship between craniocervical instability (CCI), craniomandibular disorder, and headaches [Costen, 1997]. De Laat et al. [1998] found 71% of cervical spine disorders (CSD) in the TMD group with 40% in the non-TMD group. Similar findings had been described previously by de Wijer et al. [1996], abeit using a smaller group. More recently, Inês et al. [2008] examined the effect of TMD and positioning of the skull over the cervical region. The authors found that 90% of the patients with cervical pain had TMD, and, thus, concluded that the position of the cervical spine (postural) impacted TMJ function. As the neck and especially the upper cervical spine are often involved in EDS patients, the interaction, recognition, and potential co-management should be considered.

MANAGEMENT

Soft Tissue

Dental visits should be minimal in length to avoid causing problems related to the TMJs. All injections should be given with care to preclude hematomas especially the inferior alveolar nerves. An orthodontic appliance for a patient with EDS should be smooth and relatively simple in spring design, so that the tongue and buccal mucosa are not abraded.

The periodontal ligaments are fragile which requires the orthodontic forces to be less than usual. The teeth will move rapidly due to the fragility of the periodontal ligament and relapse quickly. Longer periods of tooth retention is recommended. Dental and oral surgeries should be avoided if possible. If surgery is necessary, blood coagulation tests should be evaluated before proceeding. Suturing should be done with extreme care due to the fragility of the tissues and oral mucosa.

TREATMENT OF TMD

Years of study of TMD, as well as advanced imaging techniques, have led to a deeper understanding of the syndrome, its causes, and treatment. Yet, while proper diagnosis and precise treatment of TMD is always complex, it is far more so in the EDS patient. Even practitioners highly trained in the area of TMD can face unexpected challenges in diagnosing and treating an EDS patient if they do not have an in-depth understanding of EDS. Some symptoms are obvious to the practitioner familiar with the disorder, and some are very subtle.

Yet, while proper diagnosis and precise treatment of TMD is always complex, it is far more so in the EDS patient. Even practitioners highly trained in the area of TMD can face unexpected challenges in diagnosing and treating an EDS patient if they do not have an in-depth understanding of EDS.

Assuming TMJ hypermobility and generalized joint hypermobility increases the prevalence of TMD, all EDS patients should be treated prophylactically. Prevention of TMJ injury should be paramount. Postural alignment as well as upper back and cervical issues need to be addressed. Lifestyle changes can include alteration of chewing patterns, diet, stress reduction techniques, and management of physical activities.

Multiple treatments are available for management of pain and TMD-associated problems, depending on the source and type of symptoms. Because all musculature in the body is susceptible to spasm and contracture, eliminating or minimizing muscle spasms is often the first step in reducing pain, and offers conservative treatment options which are appropriate for the EDS patient. With the multiple manifestations of EDS, it is important that TMD care be conservative, focused and highly informed. The following techniques are helpful:

- Deep heat has the ability to relax muscle fibers and decrease spasms. The usual protocol is 10-3-10: 10 min of warm, followed by 3 min of cold, and 10 min of warm.
- Cold laser (Superpulsed Low Level Laser Therapy) has been shown to be effective in pain management of TMD [Marini et al., 2010].
- Friction muscle massage stretches and relaxes the muscle fibers. A muscle is relaxed when it is a full length.
- Custom splints to stabilize the TMD have proven effective over time. Such appliances, when carefully created to target appropriate anterior repositioning, provide stabilization, limit joint injury, and help maintain physiological posture.
- Prolotherapy, also called regenerative injection therapy, is a non-surgical alternative medicine treatment for ligament and tendon reconstruction. Injections of a combination of dextrose and local anesthetic have proven promising [Hakala, 2005].
- Medications offer a variety of options, such as muscle relaxants, mood elevators, anti-inflammatories, and pain medications. In the EDS patient, care must be taken to consider other medications and possible additional effects of any medication.
- Botulinum toxin to relax muscle or at trigger points can provide almost immediate relief for some patients. Botulinum toxin is injected into specific trigger points, particularly for the purposes of relieving migraines, muscle spasms, involuntary positional motions, and structural physicality.
- Physical therapy can assist with muscle integrity, posture, and can maintain

ranges of motion and physiological structural position for function. It is vital that the physical therapist understand the special needs of the EDS patient, including the attendant increased fragility.

- Surgical options should be limited to extreme cases, such as physical damage to the TMJ. EDS patients in particular face unique surgical challenges, making them less than ideal candidates for surgical TMJ stabilization. Surgical repairs heal slowly and often with unpredictable results.

FUTURE DIRECTIONS

Oral mandibular manifestations are commonly encountered in the EDS patient but their true prevalence and significance should be studied to establish the relationship between EDS and TMD. Additional study could also be informative regarding diagnosis and treatment, particularly in the area of craniofacial pain. Most importantly, the relationship of cervical spine disorders to TMD in EDS patients requires further study. While the "mechanics" of a malfunctioning TMJ are well established, the question remains: in addition to obvious factors such as trauma or bruxism, what causes malfunctioning of the joint? Could cervical spine disorders and craniocervical instability be an underlying causative factors?

The increased fragility and friability of the oral tissues are an indication of the friability of other mucosal-based tissues in the body. The presence of the concerning signs of EDS should be an indication to the practitioner to consider further consultations including rheumatology, dermatology, and/or genetics to confirm and establish the potential type of EDS.

EDS patients face a variety of quality of life issues, often including sleep disturbances related to chronic pain [Voermans et al., 2010]. It is important that practitioners not overlook additional issues that could affect sleep. The previously discussed relationship between head, neck, and mandibular structures, in combination with EDS-type changes in soft tissue and cartilaginous structures, might also be a contributing factor for sleep-disruptive manifestations. EDS tissue laxity and lack of tonicity may cause constriction and in some cases, collapse of the nasal and pharyngeal spaces. Mandibular structure, function, and motion all dictate the position of the actions of the origins and insertions of the musculature that allow pharyngeal structure and function in the action of breathing.

Recent studies have suggested a link between sleep-disordered breathing (SBD) and EDS, "which is commonly unrecognized, and is responsible for daytime fatigue and poor sleep," [Guilleminault et al., 2013]. Additionally, the study concluded, "ED[S] patients are at particular risk for SDB due to genetically related cartilage defects causing these patients to develop facial structures known to cause SDB."

While the relationship between bruxism, including sleep-related bruxism, and TMJ remains unclear [Manfredini and Lobbezoo, 2010] given the prevalence of TMJ disorders and soft tissue impairment in the EDS patient, practitioners should be cognizant of the possibility of an affected airway, which can best be determined by a formal sleep study. The subject of sleep-disordered breathing in the Ehlers–Danlos patient is one that requires additional study.

Additionally, further studies to document the prevalence of the absence/hypoplasia of the oral frenula in the various types of EDS with specific emphasis on consistency of the evaluation. Further studies on the prevalence of Gorlin sign in the various EDS types and the relationship to the lingual frenulum could prove helpful to dental practitioners in the recognition of EDS.

SUMMARY

Research has confirmed a variety of oral and mandibular manifestations associated with EDS. TMD and pain resulting from a malfunctioning oral and mandibular structure appear to be highly prevalent in the EDS patient population. This relationship is logical given the nature of EDS and its effects on the multiple oral structures and collagen. The exact nature of this relationship merits further study. Additionally, the relationship between TMD, myofascial pain, and CCI presents an opportunity for meaningful research, with the goal of providing more effective treatment.

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