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Problems in the orofacial region associated with Ehlers-Danlos and Marfan syndromes: a case series

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Abstract

Ehlers-Danlos syndrome (EDS) and Marfan syndrome (MFS) are characterised by hypermobility of joints and cardiovascular morbidity, and typical orofacial signs and symptoms are associated with both. Basic knowledge of these should prevent late-stage diagnosis and enable adequate management. This case series comprises all EDS and MFS patients who consulted the Department of Oral and Maxillofacial Surgery at University Hospitals Leuven between 2005 and 2017. Thirty patients had EDS or MFS, and in seven the diagnosis was made based on temporomandibular dysfunction or craniofacial dysmorphism. Non-facial symptoms led to diagnosis in the remaining patients. Twenty-five interventions were followed by two infections and one haemorrhage. One patient developed trismus. No major complications were reported. The complications we observed did not seem to differ from those often seen in patients who did not have EDS or MFS, possibly as a result of our strictly applied precautions and postoperative instructions. However, our study of relevant publications shows that patients with EDS and MFS are a vulnerable group.

Keywords: Ehlers-Danlos syndrome; Marfan syndrome; orofacial manifestation; joint hypermobility; bleeding tendency

Introduction

Ehlers-Danlos syndrome

The combined prevalence of the different subtypes of Ehlers-Danlos syndrome (EDS) is estimated to be 1/5000, with 1/20 000 to 1/5000 people having the hypermobile EDS subtype. The prevalence of the classic subtype ranges from 1/40 000 to 1/20 000. The remaining subtypes are extremely rare.[1]

Hypermobile EDS (hEDS) is characterised by generalised hypermobility of joints and skin involvement. Additional clinical signs are limited. Inheritance is autosomal dominant, but the causal mutation remains unknown.[2] In contrast, classic EDS (cEDS) is caused by a mutation in type V collagen. Patients usually present with hypermobility of joints and an increased bleeding tendency. Hyperextensibility of skin and delayed wound healing are seen, and scars are typically atrophic.[3] The oral mucosa may be vulnerable, resulting in multiple intraoral ulcers. Epicanthal folds, palpebral ptosis, and a pale, prematurely-aged face may be present. Mandibular retrognathia, low implanted ears, hypoplastic earlobes, and a wide philtrum have also been described. As inheritance of cEDS is autosomal dominant, there is a family history in most cases. In addition, molecular research can confirm the final diagnosis; point mutations or intragenic variants of *COL5A1* or *COL5A2* are found in more than 90% of patients with cEDS.[4]

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Vascular EDS (vEDS) is caused by a mutation in type III collagen and has a prevalence of 1/90 000.[5] Easy and excessive bruising is often the first symptom. During the course of the disease, the fragile walls of the mid-sized abdominal arteries or sigmoid colon may rupture, followed by sudden death. Because of these complications, the life span of vEDS patients is reduced to 51 years.[6] The cutaneous signs are rather limited. The skin may be translucent, exposing a prominent venous pattern over the hands and feet. A pointed nose, narrow lips, lobeless ears, prominent eyes, and hollow cheeks may also be present. Gingival recessions are common.[5] Inheritance is autosomal dominant. Because of the clinical overlap with Marfan syndrome, Loeys-Dietz syndrome, and familial arterial aneurysms and dissection syndromes, the diagnosis of vEDS must always be confirmed by sequence analysis of *COL3A1*, as the underlying pathogenic variant is identified in more than 98% of affected people.[7]

Rare variants of EDS include the arthrochalasia type, kyphoscoliosis type, and dermatosparaxis type, all of which are caused by mutations in type I collagen.[2] In dermatosparaxis-type vascular malformations, teeth deformities and dysfunction of the temporomandibular joint (TMJ) are often present. Epicanthic folds, down-slanting palpebral fissures, blue sclera, micrognathia, and facial scars are common.[6]

Marfan syndrome

Marfan syndrome (MFS) has a prevalence of 3/10 000 and is caused by a mutation in the FBN1 gene.[8] The main characteristic of MFS is cardiovascular involvement. Aneurysms of the ascending aorta can lead to life-threatening events at a young adult age.[9] The presence of an ectopic lens, which is seen in approximately 60% of patients, combined with an aortic aneurysm, is sufficient to diagnose MFS. In the absence of ectopia lentis, other systemic signs and symptoms can contribute to the diagnosis. Patients typically present with a slender build and disproportionately long limbs. Scoliosis and pectus carinatum are common. Hypermobile joints and dermal striae are often present. Mitral valve prolapse is frequent and should be investigated. Patients with MFS regularly present for dental treatment at a young age, as they are at an appreciably higher risk of caries, tooth root deformities, and gingivitis.[10] Severe periodontitis and alveolar bone loss are common.[11] In addition, these patients present with typical facial features: the skull is dolichocephalic and narrow, leading to maxillary constriction and overlapping teeth.[12] Mandibular retrognathia may be present. Enophthalmia occurs and the palpebral fissures are typically downslanting.[13] A narrow nasal airway with compensatory open mouth-breathing can lead to the development of a typical adenoid face.[14] Because the syndrome is inherited in an autosomal dominant fashion, a family history can contribute to the diagnosis. When a clinical diagnosis cannot be made, FBN1 mutation should be investigated and will confirm the diagnosis in more than 95% of cases.[9]

Material and methods

From their medical records we investigated the complaints of all patients diagnosed with EDS or MFS who presented to the Department of Oral and Maxillofacial Surgery at Leuven University Hospitals between 2005 and 2017, and recorded how the diagnosis of one or both syndromes was made. We studied the general postoperative course and wound healing and examined whether they developed perioperative complications. The study protocol was approved by the Ethics Committee for Research UZ/KU Leuven (MP005479).

Results

Our investigation yielded a total of 41 patients, 21 of whom were diagnosed with EDS, and nine with MFS. In the remaining 12 patients, a connective tissue disorder was suspected based on orofacial symptoms, but the diagnosis of MFS or EDS has not been confirmed to date.

Ehlers-Danlos syndrome

A total of 21 patients (3 men and 18 women) were diagnosed with EDS. In six of the patients, the diagnosis was made based on craniomaxillofacial symptoms. Five patients had disorders of the TMJ; the remaining patient presented with craniofacial dysmorphism, including an Angle class III malocclusion and macrocrania (Fig. 1).

Eighteen patients had symptoms of disorders of the TMJ, which in general responded well to a conservative approach. This consisted of the detection and unlearning of jaw clenching and other parafunctional habits, which were present in nine patients. Local application of heat and massage also relieved the symptoms. Physiotherapy was considered valuable. An inadequate response to conservative treatment was seen in two patients. One patient had persistent pain in the masticator space and a tendency to luxation of the TMJ at extremes of mouth opening. This was treated by arthroscopic discopexy of the TMJ, and successfully reduced its hypermobility and relieved the pain. A second patient had arthrocentesis of the TMJ because of recurrent acute closed locking of the joint associated with restriction of mouth opening and pain. No postoperative complications were reported.

Six patients came in for extraction of terminally decayed teeth, and two additional patients needed to have their third molars removed. A total of 15 teeth were extracted. Postoperative trismus occurred once, and no other complications were recorded.

Two patients were operated on to correct a functionally disruptive malocclusion, and both responded to combined orthodontic-orthognathic treatment. One patient presented with an Angle class III malocclusion, for which surgically-assisted rapid palatal expansion (SARPE) distraction osteogenesis and a Le Fort I osteotomy were

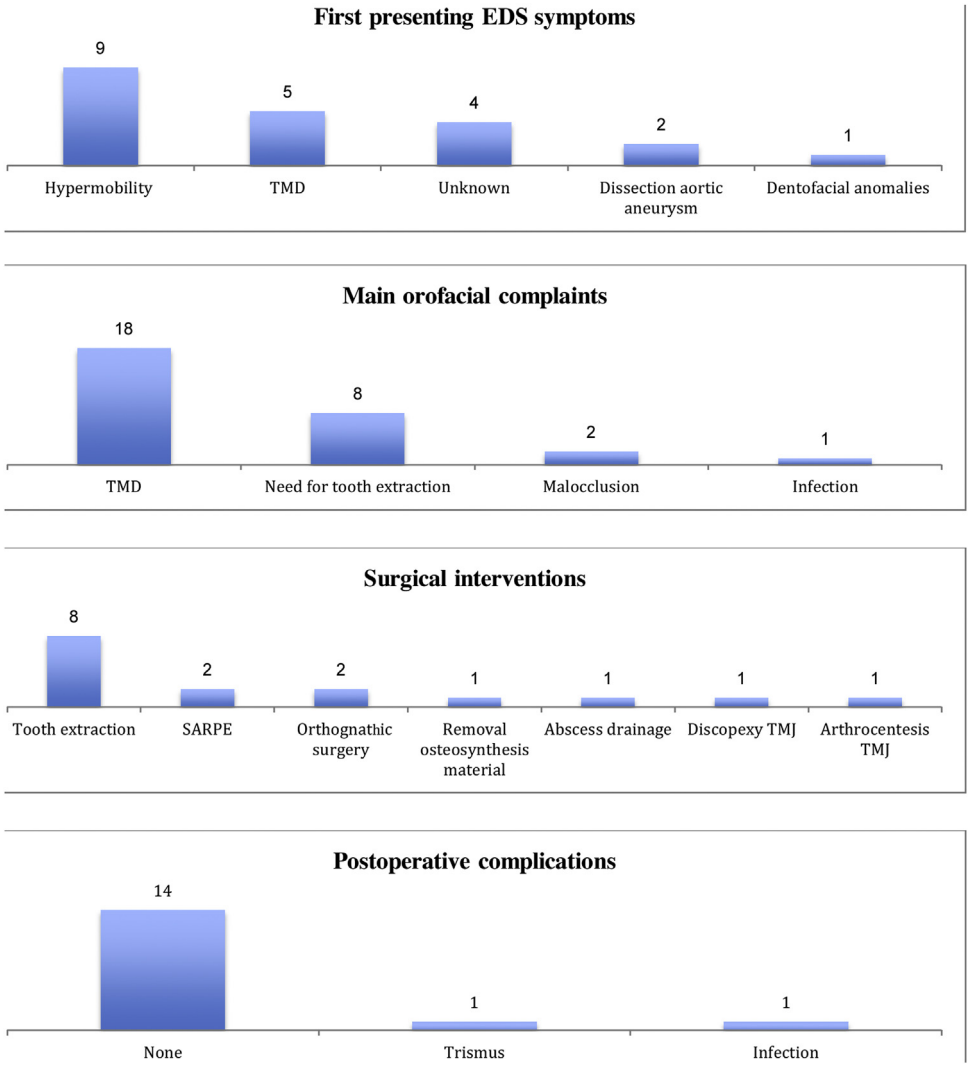

Fig. 1. First presenting symptoms, main complaints, surgical interventions, and postoperative complications in 21 patients with Ehlers-Danlos syndrome.

successful. The second patient had an Angle class II malocclusion. SARPE and bilateral sagittal split osteotomy (BSSO) with genioplasty sequentially. Five days postoperatively, the patient reported pronounced pain at the left TMJ and a disturbing feeling in the mental area, all of which are considered normal in the initial postoperative course and are often seen in patients who do not have EDS. At the medical check-up three months postoperatively, we found limited mouth opening, poor occlusion, and persistent pain at the left TMJ. Infection of the osteosynthesis plates was suspected and they were removed.

An abscess of the infraorbital space that emerged after dental treatment of a maxillary second molar was incised in one patient with EDS.

Marfan syndrome

Nine patients (4 men and 5 women) had MFS, and in one, the presence of a disorder of the TMJ led to the diagnosis of MFS (Fig. 2). Sixteen teeth were extracted in five different patients. In one patient, an oroantral communication developed during the extraction of a molar and was closed by a local Rehrmann flap. Healing was favourable, as in patients who did not have MFS. A second patient developed a postoperative haemorrhage that led to nausea, vomiting, and syncope, for which he consulted the emergency department. Application of tranexamic acid stopped the bleeding and volume resuscitation was not needed.

Two patients had pain and functional problems in the TMJ. Reduced mouth opening was the main problem in one patient, and the second patient had recurrent condylar luxations. Two patients were operated on to correct a skeletal and dental malocclusion; they both had chewing problems. One patient also reported mild speech impairment. Both patients were treated with combined orthodontic-orthognathic treatment with SARPE before the orthognathic procedure. One patient presented with an Angle class III malocclusion, which was treated by Le Fort I advancement. BSSO advancement was

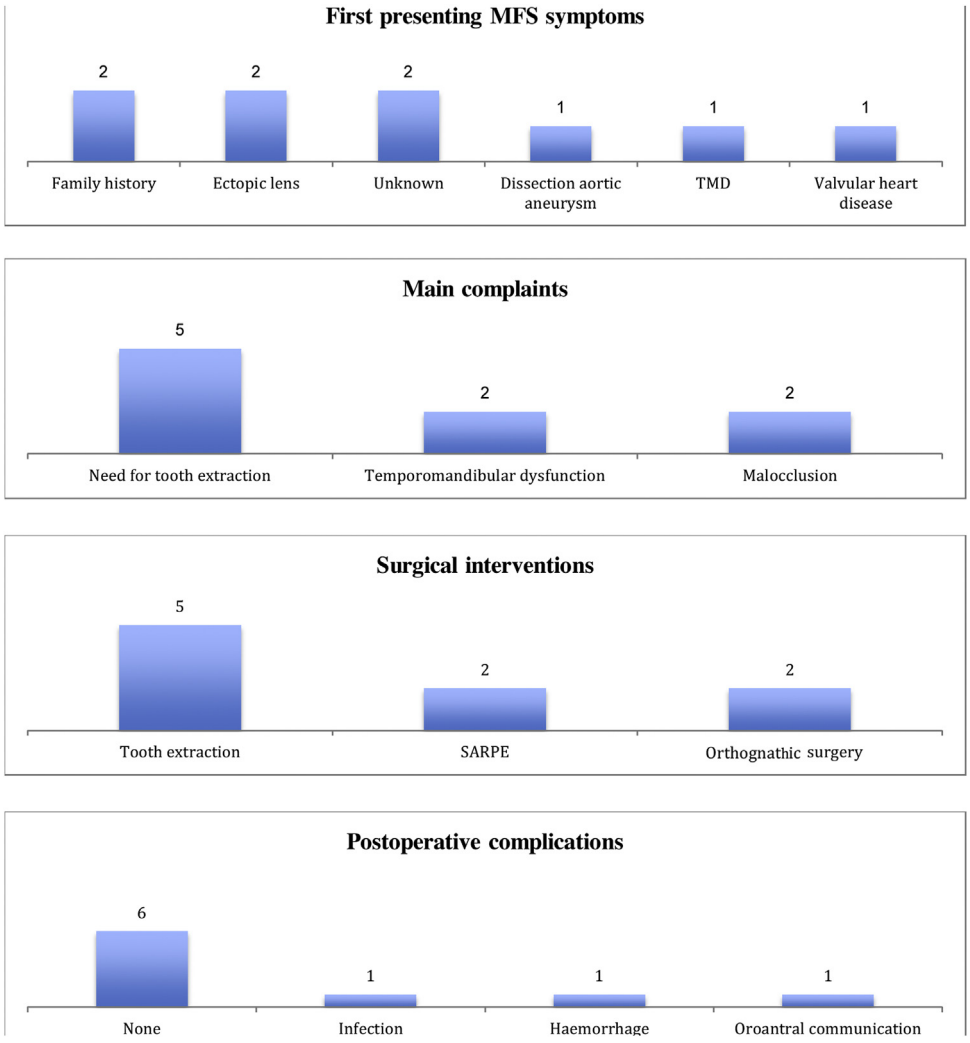

Fig. 2. First presenting symptoms, main complaints, surgical interventions, and postoperative complications in nine patients with Marfan syndrome.

used for the second patient who presented with an Angle class II malocclusion. One patient developed an infection after distraction osteogenesis, which resolved rapidly with antibiotic treatment. The postoperative course after orthognathic surgery was favourable in both patients.

Discussion

Currently, no treatment is available for EDS or MFS. Lifestyle changes, regular follow-up, and precautions in case operation is required ensure the best possible prognosis. Guidelines for the management of patients with EDS or MFS are not available, but are really needed.

Ehlers-Danlos syndrome

Increased intraoral mucosal fragility and trismus can interfere with good brushing habits and severely compromise oral hygiene in patients with EDS. Caries are more common in this group, and periodontitis is present in up to 62% of patients,[15] so the importance of good oral hygiene cannot be sufficiently underlined. Brushing teeth twice daily with fluoride-containing toothpaste should prevent caries. The daily use of antibacterial mouthwashes based on chlorhexidine 0.05% is recommended for the prevention and treatment of gingivitis, periodontitis, and halitosis, even with six-month follow-up at the dentist.[6] Dentists should take precautions when treating patients with EDS to prevent subluxation of the TMJ or trismus. When proposing endodontic treatment, one has to take into account that the root canals may be an abnormal shape, and pulpal calcifications are common, which can adversely influence the result.[16] Apical root resorption, gingival recession, and alveolar bone loss have been described as a result of orthodontic treatment in these patients.[15]

An increased bleeding tendency, from gingival bleeding after teeth brushing to perioperative haemorrhages, has been described in all subtypes of EDS,[5,17] and these are secondary to the poor support of the blood vessels by connective tissue and direct involvement of the vessel wall, rather than

an intrinsic dysfunction of platelets or defect of coagulation. Laboratory evaluations of coagulation are usually within the normal ranges.[18]

A less prolonged effect and a lack of analgesic effect of local anaesthetics have been described. In addition, caution with injections is required given the increased risk of haematoma. For dental procedures, articaine hydrochloride with epinephrine is the preferred choice.[19]

Tooth extractions should be as atraumatic as possible. Haemostatic gauzes can be used postoperatively to promote haemostasis, as well as mouthwashes that contain tranexamic acid.[19] Non-steroidal anti-inflammatory drugs should be avoided. Endocarditis prophylaxis is not recommended for invasive dental procedures in patients with prolapse of the mitral valve.[20]

Elective surgical interventions should be avoided in patients with vEDS. If operation is essential, soft tissues must be manipulated gently to prevent haemorrhages. The blood group must be ascertained preoperatively and adequate peripheral intravenous access ensured.[21] In the other subtypes of EDS, the decision for intervention should be made with great care. Surgical treatment of disorders of the TMJ is rarely indicated because an increased risk of persistent pain, reduced mouth opening, and ankylosis of the TMJ have been reported.[22] When operation is unavoidable, a thorough preoperative check-up must be made.

The use of desmopressin can contribute to good control of bleeding during operation in patients with vEDS or cEDS.[22] Wounds should be closed without traction in all subtypes. Numerous subcutaneous sutures must be applied, and the distance between the transcutaneous sutures must be reduced. Non-resorbable sutures should stay in place twice as long as in patients who do not have EDS. Additional fixation of the adjacent wound edges with adhesive tape to prevent stretching the scar is recommended.[16,21]

Postoperatively, thorough monitoring of the wounds is necessary because of an increased risk of haematoma, delayed wound healing, and infection. Wound dehiscence is common, particularly in vEDS.

Marfan syndrome

The guidelines applying to patients with MFS are similar to those for patients with EDS, and cardiac monitoring by serial echocardiography is indicated in all of them. In the case of aortic dilatation, adequate monitoring of blood pressure is recommended. The primary treatment is with both losartan and doxycycline, which results in a decreased volume in the dilated aorta. Consequently the risk of dissection or rupture decreases, as well as the associated morbidity and mortality.[23–25] We know of no data yet that illustrate the beneficial effect of losartan and doxycycline in primary prevention. Surgical treatment of aortic aneurysms is recommended in certain cases, but the indications are not within the scope of this paper.

Regarding oral prophylaxis, the same measures apply as for patients with EDS. Teeth extractions should be atraumatic, and the use of haemostasis-promoting agents is recommended. For dental procedures under local anaesthesia, mepivacaine 3% is the preferred anaesthetic. Those that contain epinephrine are contraindicated given the precarious cardiac condition of most patients with MFS. In case of extensive dental treatment, preference is given to sedation or general anaesthesia to avoid giving multiple injections of short-acting local anaesthetics.[10,11,26,27] Endocarditis prophylaxis is not recommended in the case of mitral valve prolapse or aortic dilatation.[20]

The same measures apply before, during, and after operation as for patients with EDS. A preoperative cardiac evaluation must be made for each patient.

Conclusion

Both EDS and MFS can present with distinct dental and maxillofacial signs and symptoms.

In six of our 21 patients with EDS the diagnosis was made based on orofacial characteristics. Dysfunction of the TMJ may be the first symptom, particularly in hEDS. As in MFS, systemic involvement is generally more pronounced than orofacial symptoms, and the latter led to the diagnosis in only one patient.

The problems we encountered in our patients with these syndromes seem not to differ from common complications in patients who do not have them, possibly because we strictly applied precautions and postoperative instructions. No major complications were reported. However, our study of relevant publications shows that patients with the syndromes are a vulnerable group with multiple points of attention in daily life, as well as in dental treatments and surgical interventions. Knowledge of the clinical presentation of both syndromes is essential for the management of affected patients, so a multidisciplinary approach is essential.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

The study protocol was approved by the Ethics Committee for Research UZ/KU Leuven (MP005479). Patients' permission was not required.

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