Relation of pulp stones to the Ehlers-Danlos syndrome

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Abstract

Ehlers-Danlos Syndrome (EDS) are a group of connective tissue disorders with skin and joint manifestations. It results either from a new mutation occurring during early development or it may be inherited in an autosomal dominant. EDS is caused by a defect in the structure, production, or processing of collagen or protein that interact with collagen. Its symptoms include loose joints, stretchy skin, and abnormal scar formation. It has been classified into 10 specific types and also acknowledged that other extremely rare types existed. This paper will focus on the condition that have orofacial manifestations. Care should be taken during root canal treatment also pulp stone treatment procedures should be aware of for making correct diagnoses of such patients.

***Key words*:** Ehlers-Danlos syndrome, inherited disorders, connective tissue, denticles, oral cavity.

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Introduction:

Ehlers-Danlos syndrome is a group of inherited disorders that affect the connective tissues disorder primarily the skin, joints and blood vessel walls, it is with presentations that have been classified into several primary types (Pope,1991 pp321-349).

Figure 1 show (a) Normal collagen fibrils are of uniform size and spacing. Fibrils from a patient with dermatosparaxis (b) show dramatic alterations in fibril morphology with severe effects on tensile strength of connective tissues. Patients with classical EDS (c) show composite fibrils. Fibrils from a TNX-deficient patient (d) are uniform in size and no composite fibrils are seen. (e) Shows the TNX-null. (f) Fibrils are less densely packed and not as well aligned to neighboring fibrils.

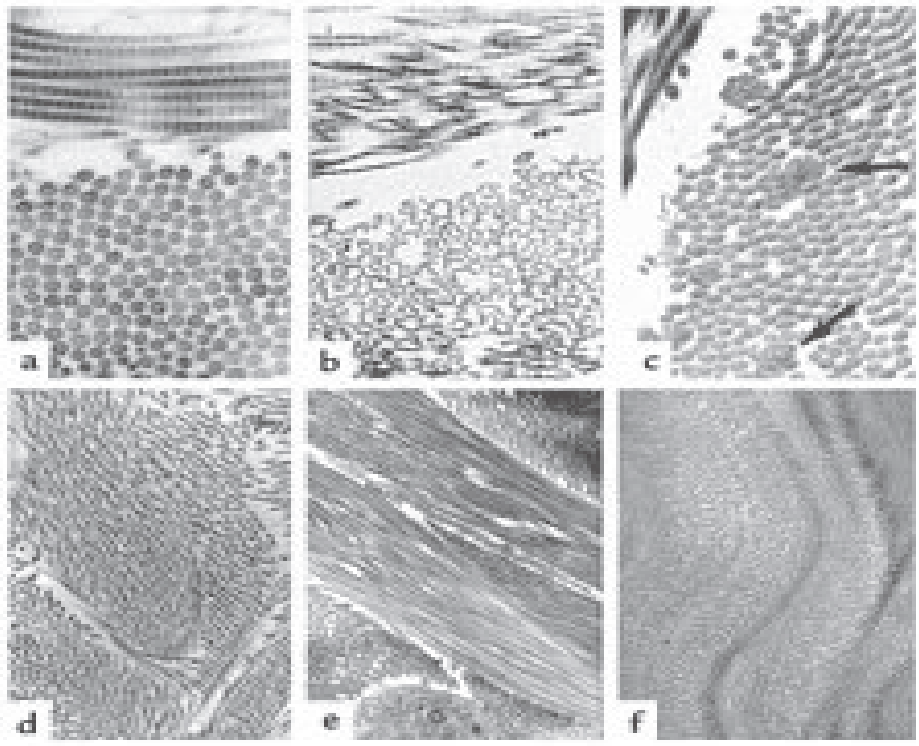

Figure 1 Primary types of Ehlers-Danlos syndrome

EDS is caused by a defect in the structure, production, or processing of collagen or proteinsthatinteractwithcollagen, such as mutations in the COL5A or COL3Agenes (Welbury, 1989 pp220-24). (This is the collagen of granulation

tissue, and isproducedquickly by young fibroblasts before the tougher type I collagenis synthesized. Commonly associated with keloid formation, reticularfiber, and found in arterywalls, skin, intestines and the uterus—COL3A1) (Ooshima et.al.1990 pp102-106).

History of EDS **:**

The features of EDS were first described by Hippocratesin 400 BC. The syndrome is named after two physicians, Edvard Ehlers from Denmark and Henri-Alexandre Danlos from France, whodescribeditat the turn of the 20th century. (Reichert et.al.1999, pp785-790). Up until 1997, the classification system for EDS included 10 specific types and also acknowledged that othe rextremely rare types existed. Atthis time, the classification system underwent an overhaul and was reduced to 6 majors types using descriptive titles (Gorlin et.al.,1990) Genetic specialists recognize that other types of this condition exist, but have only been documented in single families. Except for Hypermobility (type 3), none of the specific mutations involved have been identified and they can be precisely identified by genetictesting; this is valuable due to a great deal of variation in individual cases(Beighton,1990) .However, negative genetic test results do not rule out the diagnosis, since not all of the mutations have been discovered; therefore the clinical presentation is very important.[17]Although the classifications are well defined, itis rare for a case to fit neatly in a single category, and cross-over symptoms lead to under-diagnosis or misdiagnosis. Therefore, patients should not rely on the «fact» of having a certain type of EDS if cross-over symptoms are evident because of possibly life-threatening symptoms. For example, itis possible for an individual with Classical EDS to exhibit symptoms of Hypermobility or Vascular EDS (Kivirikko, 1993 pp113-116). Overall, research statistics of EDS show the prevalence as 1 in 2,500 to 1 in 5,000 people. Recent clinical experience suggests that this condition goesunder-diagnosed and the condition is more common than these ratios indicate. (Noël et.al.1993, pp 146-148)

Other types :

Forms of EDS in this category may present with soft, mildly stretchable skin, shortened bones, chronic diarrhea, joint hypermobility and dislocation, bladder rupture, or poor wound healing. Inheritance patterns in this group

include X-linked recessive, autosomal dominant, and autosomal recessive (Voermans et.al. 2009 pp687-697) .Examples of types of related syndromes other than those above reported in the medical literature include as seen in figure 2 and 3 below:

Figure 2 : Individualwith EDS displayinghypermobile joints

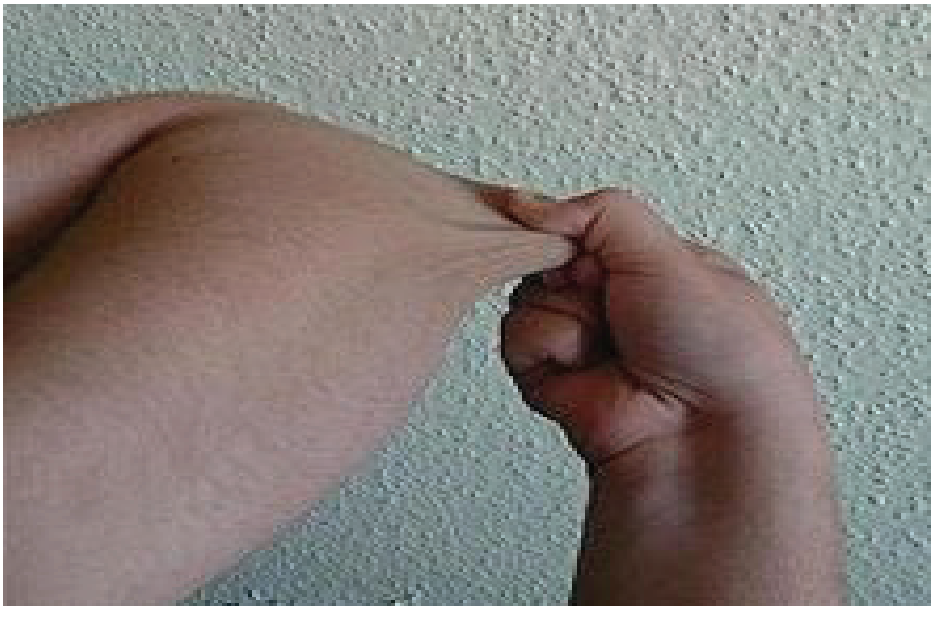

Figure 3 : Individualwith EDS displaying skin hyperelasticity

Signs vary widely based on which type of EDS the patient has. In each case, however, the signs are ultimately due to faulty or reduced amounts of collagen. EDS typically affects the joints, skin, and blood vessels. Following is a list of major signs and symptoms (Ozlece et.al. ,2015 pp116-117).

***Facial manifestations* :**

The oral and facial features of EDS vary with each type of disease. There have been few detailed studies of the orofacial manifestations of the rare and/or recently described types of EDS. In general the greater the laxity of the skin and mucosa the more likely that patients will have orofacial features. Similarly the haemorrhagic types are more likely than others to give rise to gingival (gum) bleeding (Castori 2012). The various Potential orofacial features of EDS are detailed below:

***Eyes*:**

Epicanthic folds: these are folds that extend from the nasal bridge to the upper eyelids and can give the appearance of a widened nasal bridge. These seem to be most common in classical and kyphoscoliosis EDS. Epicanthic folds may lessen with age or change to increased distance between the eyes, hence giving the appearance of wide spread eyes(Malfait et.al. ,2011, pp77-78)

Other ocular features of EDS include puffy or prominent upper eyelids, blue sclera (classical, kyphoscoliotic and arthrochalasic types), the ability to evert the upper eyelid (Meitenier›s sign, classical type), myopia (short-sightedness, classical Type) and strabismus (squint, classical Type). Patients with vascular type EDS may have large prominent «staring» eyes due to a lack of subcutaneous tissue. Kyphoscoliotic type EDS may give rise to down-staring palpebral fissures (Lumley et.al. ,1994 pp149-152)

Ears:

There may be a lack of ear lobes and the pinna of the ear may be firm (vascular type).

***Nose*:**

The bridge of the nose can be widened or flattened (classical and kypho-

scoliotic types) while in vascular type EDS the nose can appear pinched or sharp (Berglund et.al., 2010 pp 1-7).

Facial skin and appearance

The skin may be hyperelastic (very stretchy) and there may be 'cigarette-paper' scarring of the face and forehead (classical type). Individuals with vascular type disease have a distinct facial appearance of prominent eyes (see above), sharpened nose, thin lips and hollow cheeks, sometimes collectively termed 'acrogenic' facies (older appearance). Type VIIc disease may give rise to a small lower jaw (micrognathia) (Berglund and Gun, 2000 pp 111-118).

Oral cavity:

About 50% of individuals with EDS have the ability to touch the tip of the nose with their tongue (Gorlin's sign) - this is especially likely with classical and hypermobile EDS. The oral mucosa may be thin, easily tear and give rise to mouth ulcers (classical and hypermobile EDS). Individuals with these types may also lack labial and/or lingual fraenula (the folds of mucosa that are in the midline of the lips and beneath the tongue) (Myerson, 1994 pp22-27). Dislocation of the jaw joint (temporomandibular joint) is a possible feature of classical, hypermobile EDS and possibly some subtypes of the arthrochalasia EDS. A spectrum of dental anomalies have been described, particularly in classical and hypermobile including high cusps and deep fissures of premolars and molars, shortened or abnormally shaped roots with stones in the pulp of crowns, and enamel hypoplasia (under development) with microscopic evidence of various enamel and/or dentine defects. The enamel defects may predispose to easy loss of the tissue of crowns (attrition) and if these give rise to a loss of calicification of the enamel will increase the risk of caries. Multiple odontogenic keratocysts (that have the potential to cause local bony destruction of the jaws) have been described in vascular EDS (Narcisi and Ferguson 1994 pp 1617-1620). An increased liability to gum disease (gingivitis and periodontitis) have been described in Type VIII disease, this having the potential to cause early tooth loss in adults. Periodontal disease has also been suggested to arise in classical and vascular EDS (Levy 2004).

Implications for oral health care

EDS has the potential to lessen oral health by virtue of increasing the risk of dental decay (caries) as a consequence of the dental anomalies as these can trap food and dental plaque. Caries initially gives rise to painless white and darkened areas of the crowns, but without treatment will cause painful pulpitis ('toothache' with hot, cold and sweet foods) and later death of the tooth and painful abscess formation (periapical periodontitis). Additionally, patients with some types of EDS may have an increased liability to gum disease (especially periodontitis). Inflammation of the superficial gums (ginigivitis) causes swelling and bleeding, and may give rise to easy gingival bleeding, an unpleasant taste and oral malodour (halitosis). Inflammation of the deeper tissues (the periodontium) also causes bad taste and breath, but can also lead to mobility and migration of teeth, and potentially early loss of teeth. It must also be recalled that some patients with EDS may have gums that bleed more easily as part of their underlying connective tissue disorder. Prevention of tooth decay and gum disease is cardinal for all persons as this avoids the need for complex dental treatment and lessens the risk of loss of time from education or employment that would occur in having to have dental treatment. Furthermore, invasive dental procedures such as dental extractions or complex treatment of periodontal disease may be complicated by poor wound healing and possibly excess post-surgical bleeding. Thus there is a need for ALL individuals with EDS to have a diet that avoids the development of caries and maintain a high standard of oral hygiene that will lessen the risk of caries and gum disease. (Malfait et.al.2011, pp77-78)

Maintaining good oral health

The principles of sustaining good oral health are centred upon dietary restriction of sugars and maintaining a good oral hygiene regime.

Dietary considerations

Sugars increase the risk of tooth decay as plaque bacteria thrive on these and generate acids that can attack the teeth and cause caries. The simple measures that lessen acidic damage to the teeth are to avoid sticky sweet foods

(e.g. toffees etc) as these will not be easily dislodged with normal mouth action or saliva. Foods that contain sugar substitutes such as sorbitol are not as harmful as those that contain sucrose, glucose or fructose, but the sugar substitutes can cause gastrointestinal upset in some individuals (Melanie et.al.2015)

***Fluoride*:**

Fluoride hardens the surface enamel of teeth and lessens the risk of caries. Children living in a geographic region where the fluoride content of water is naturally or artificially at a level of one part per million will have enamel that has increased strength and greater resistance to dental decay. Fluoride in toothpastes and mouthwashes will lessen the resistance of decay of only the surface layer of enamel. Without doubt fluorides are thus of benefit and are recommended for all individuals with EDS. Twice daily use of a fluoride-containing toothpaste is thus recommended. Fluoride mouthwashes can also be helpful although are probably not required if a patient is already using a fluoridated toothpaste. Fluoride tablets are of no significant benefit to adults (as the teeth have already formed) although may be advantageous to children living in regions where the water is not fluoridated (Lawrence, 2005 pp 301-314).

***Risk of endodontics*:**

When teeth are extracted, bacteria from the gums pass into the bloodstream. In patients with cardiac valve abnormalities there is a risk that the bacteria will attach to the valve(s) and cause inflammation (endocarditis) that can affect cardiac function as well as give rise to systemic disease. It was previously advised that all patients with valvular defects required antibiotics before dental extractions to prevent possible endocarditis; however the National Institute for Clinical Excellence (NICE) has now concluded that the risk of endocarditis following dental extractions in the vast majority of patients with known cardiac valve disease is low and that antibiotics (antibiotic prophylaxis) are not indicated. Nevertheless not all cardiologists agree with this recommendation. It would thus seem sensible for a dentist to contact a patient›s cardiologist to determine if he/she wishes antibiotics to be prescribed for any

planned dental extractions. (Berglund and Gun, 2000 pp 111-118). If the dentist does not wish to prescribe antibiotics the specialist, if wishing them to be provided, will instead prescribe these and be medicolegally responsible for any adverse consequences (which is very unlikely).

***Root canal treatment*:**

Root canal treatment is required when a tooth dies (usually as a consequence of dental decay) or when an abscess forms at the base of the root. Endondontic therapy requires the root canal to be cleaned and filled (usually) with guttapercha. In EDS, endodontics may be complicated by the presence of pulp stones and/or the root having an unusual shape. In such instances endodontic therapy may be best undertaken by an appropriate specialist (an endodontist). Antibiotic prophylaxis is generally not warranted for endodontic treatment. (Narcisi and Ferguson 1994 pp 1617-1620)

***Diagnosis* :**

A diagnosis can be made by an evaluation of medical history and clinical observation. The Brighton criteria are widely used to assess the degree of joint hypermobility. DNA and biochemical studies can help identify affected individuals. Diagnostic tests include collagen gene mutation testing, collagen typing via skin biopsy, echocardiogram, and lysyl hydroxylase or oxidaseactivity. However, these tests are not able to confirm all cases, especially in instances of an unmapped mutation, so clinical evaluation by a geneticist remains essential (Erçöçen et.al. 1997 pp 128-130). If there are multiple affected individuals in a family, itmaybe possible to perform prenatal diagnosis using a NA information technique known as a linkage study.

Management :

There is no cure for Ehlers Danlos Syndrome. Treatment is palliative. Close monitoring of the cardiovascular system, physiotherapy, occupational therapy, and orthopedic instruments (e.g. wheelchairs, bracing, casting) maybehelpful. Orthopedic instruments are helpful for the prevention of further joint damage, especially for long distances, although itis advised that individuals not become entirely dependent on them until there are no other options

for mobility. One should avoid activities that cause the joint to lock or overextend (Mihorat et.al.2007 pp 601-609)

Surgery :

The instability of joints, leading to (sub)luxations and joint pain, often require surgical intervention in patients with Ehlers–Danlos syndrome. Instability of almost all joints canhappen but appearmostoften in the lower and upperextremities (figure 4), with the wrist, fingers, shoulder, knee, hip, and ankle being most common.[14]

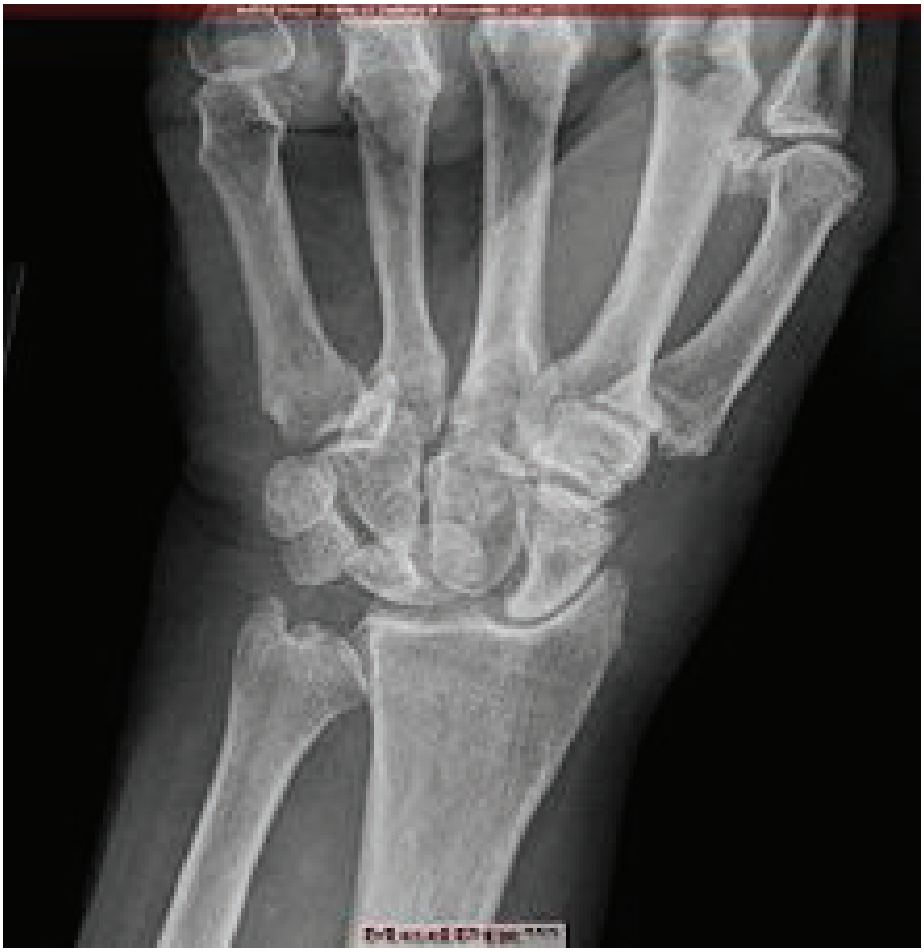

Figure 4 : X-ray of a wrist with midcarpalin stability

Prognosis :

The outlook for individualswith EDS depends on the type of EDS they have. Symptomsvary in severity, evenwithin one sub-type, and the frequency of complications changes individually. Some people have negligible symptoms while others are severely restricted in theirdaily life. Extreme joint instability, chronic musculoskeletal pain, degenerative joint disease, frequent injuries, and spinal deformities may limitmobility (Gedalia and Klein 1993 pp 494-494). Severe spinal deformities may affect breathing. In the case of extreme joint instability, dislocations may result from simple taskssuch as rolling over in bed or turning a doorknob. Secondary conditions such as autonomic dysfunction or cardiovascular problems, occurring in any type, can affect prognosis and quality of life. Severe mobility-related disability is seen more often in Hypermobility-type than in Classical-type or Vascular-type.

Although all types are potentially life-threatening, the majority of individuals will have a normal lifespan. However, those with blood vessel fragility have a high risk of fatal complication. Arterial rupture is the most common cause of sudden death in EDS. Spontaneous arterial rupture most oftenoccurs in the second or third decade, but can occur at any time. The median lifeexpectancy in the population with Vascular EDS is 48 years. (Dommerholt, 2013).

EDS is a lifelong condition. Affected individuals may face social obstacles related to their diseasedaily. Some people with EDS have reported living with fear of significant and painful ruptures, their condition worsening, becoming unemployed due to physical and emotional burdens, and social stigmatization in general.

Several articles describe the skin and joint problems linked to EDS, but very few describe the oral manifestations of the condition (Vigorita and Douglas 2008 pp 5-6). The purpose of this article is to review current knowledge about the syndrome, to present the case of a 12-year-old affected by hypermobility of the temporo-mandibular joint (TMJ) as well as vascular manifestations inherent to the syndrome, and the precautions to take when providing dental

treatment for EDS patients.

Epidemiology and Diagnosis:

The prevalence of the condition varies between 1:10,000 and 1:150,000 depending on the authors. The diagnosis of EDS depends primarily on clinical findings and family history, as it is an autosomal dominant hereditary disorder which presents in several ways. Only 4 types of EDS, namely types IV, VI, VII and Xcan are confirmed by biochemical and molecular tests. Since humans possess 19 types of collagen, it is especially difficult to establish a precise diagnosis. (Genetics home reference 2016) Even when there is a bleeding disorder associated with the syndrome, blood analyses are not diagnostically useful, in that no correlation has been made between the findings of such tests and the various types of EDS. The differential diagnosis of EDS includes Marfan's syndrome, generalized familial joint hypermobility syndrome, cutis laxa, pseudo xantho maelasticum and Larsen's syndrome

Characteristics of EDS:

The classic signs of EDS are joint hypermobility; hyperelasticity of skin, which is soft, thin and fragile; the presence of dystrophic scars; and a tendency to excessive bleeding manifested by bruises, ecchymoses and hematomas. At least 15 phenotypes of the syndromes have been catalogued to date, with 2 having recently been reclassified. We present a description of the first 8 of these phenotypes, but recommend that you read the works of Pope and Gorlin for further information.

Type I

In type I the skin is hyperelastic. Bony prominences such as the forehead, chin, elbows, knees and ankles are constantly lacerated. Given the limited healing power of the skin with this condition, pigmented and atrophic scars ("cigarette paper scar") are frequently found in these areas and they are accompanied at times by fibrous nodules caused by the fibrous transformation of subcutaneous hematomas.

The patient usually has a mesomorphic appearance with hands and feet

being slightly larger than average. Along with a generalized hypermobility of the joints there is usually an abnormal bleeding tendency. Occasionally the syndrome is accompanied by mitral valve prolapse. Over half of pregnant women with the condition give birth prematurely, following rupture of the fetal membranes.

Type II

Similar to type I, this form is less severe clinically. The scarring is less common, bleeding tendency is less pronounced and nodules are much smaller or totally absent. However, joint hypermobility is similar to that observed in type I and premature births are also a feature of type II, even if they are less common.

Type III

The patient with type III is usually tall and thin, as in Marfan's syndrome. The dominant features of this variation are joint hypermobility and hyperelasticity of the skin, which often feels velvety. Bruises and dystrophicscars are rarelyobserved.

Type IV

Type IV is characterized by a marked fragility of the vascular system. The individual is usually smaller than average. The skin of the hands and of the back appears to age prematurely (acrogeria). The eyes are widely spaced, the nose is narrow, the ear lobes are atrophied and the hair is thin. Aneurysms of the large and medium-sized arteries (axillary, femoral and carotid) are common. Frequently scar tissue appears to be hemorrhagic. Rupture of internal organs is common even at a young age, and perforation of the intestinal tract can be a problem. (Voermans et.al. 2009 pp 687-697). Joint hypermobility is usually limited to the small articulations of the hand, with acro-osteolysis of the distal phalanges. Mitral valve prolapse can also be present. Rupture of arteries and hollow organs such as the uterus and the intestine explains the high mortality rate (51% before age 40). Type IV is consequently, the most serious form of EDS.

Type V

Women are only carriers of this rare form, similar to types I and II, because transmission is associated with the X chromosome.

Type VI

This form resembles type I except for an ocular involvement with detached retina being a common feature. Severe scoliosis and vascular rupture are also features.

Type VII

This is a rare phenotype characterized by joint hypermobility, bilateral dislocation of the hips and a small stature.

Type VIII

First described by Stewart and others in 1977, type VIII is characterized by generalized early-onset periodontitis and by large patches of scar tissue on the shins, similar to diabetic ulcers or varicose veins. The periodontal problems appear at puberty and usually lead to loss of the teeth before age 30. Biesecker and others (Lumley et.at. 1994 pp149-152) describe a case of a man who became edentulous at age 16 as a result of severe periodontitis. Hoffman and others describe a case of EDS type VIII where a girl required splinting to treat mobile teeth. Type I (Hoffman) and type III (Lapière and Nusgens) anomalies of collagen have been linked to EDS type VIII.

Hyperelasticity of the skin and hypermobility of the joints are moderate in this phenotype. The facies can resemble that described in type IV — hypertelorism, widening of the root of the nose, a narrow curved nose, narrow face and scarring on the forehead and chin.

Clinical Manifestations of EDS

***Extraoral*:**

The extraoral manifestations of EDS are the presence of scarring on the chin and forehead, a history of repeated luxations of the TMJ, epicanthus, hypertelorism, a narrow curved nose, sparse hair and hyperelasticity of the skin.

***Intraoral*:**

The classic intraoral signs of EDS can point to the eventual diagnosis of

the condition.

Mucosa:

As fragile as the skin, the mucosa tears easily when touched by instruments. Sutures do not hold.

Periodontal tissue:

The fragility of the gingiva can be detected following treatments such as prophylaxis, periodontal surgery or extraction. Hemorrhage may be difficult to control during surgical procedures. Early-onset generalized periodontitis is one of the most significant oral manifestations of the syndrome. This can lead to the premature loss of deciduous and permanent teeth. (Myerson, 1994 pp22-27).

Teeth:

Hypoplasia of the enamel is commonly seen (Ozlece et.at.2015 pp 116-117). Premolar and molar teeth can present with deep fissures and long cusps. (Narcisi and Ferguson 1994 pp 1617-1620). The teeth seem to be fragile and microdontia is sometimes present. Radiographic examination often reveals pulp stones and roots that are short and deformed. Microscopic-level anomalies of the various dental tissues are described in detail by Barabas and Pope. One case of type III EDS with multiple supernumerary teeth has been reported in the literature. (Melanie et.al.2015).

Characters of pulp stones

The characters of pulp stones can be summarized in the following points, and figure 5 displys the pulp stones.

1. Asymptomatic, painless nodular calcified mass of dentin as radioopaque mass in X-ray film.
2. formed during tooth development or as an age change,
3. Leads to pulp atrophy will cause pressure on nerves.
4. Their chief significance is possible obstruction in root canal during root canal treatment.

5. not necessarily age-related, they are seen also in young person associated with the with the
6. Dental abnormalities (***Ehlers-Danols syndrome***).

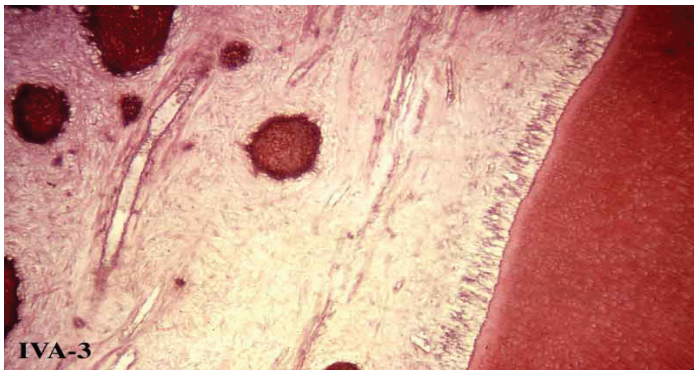

Figure 5 pulp stones

Formation of pulp stone during tooth development

The true denticle is formed due to the entrance of epithelial rests of Malassez into dental papilla during root formation, these cells considered as IEE which may influence the undifferentiated mesenchymal cells of dental papilla to differentiate to odontoblasts to form localized dentin inside the pulp tissue.

Formation of pulp stone during life

The false pulp stone (dystrophic mineralization) is formed by defect of nutrition at necrotic site of pulp tissue will result to mineralization of collagen fibers due to disturbance of pulp vascularity at necrotic site of pulp, it is not easy to seen by x-ray until it will be in sufficient size.

Classification of pulp stones

Figure 6 disply the different classifications of the pulp stones, these clasifocations categorized as following:

• according to their structure:

1- Truedenticles: is similar to dentin structure with dentinal tubules and odontoblastic process, they are rarely present, they are located at apical foramen, and they formed due to the remnants of H.R. sheath.

2- Falsedenticles: they are not same to the dentin structure, they are just

regular calcified mass found due to the necrotic and calcification of pulp cells.

3- Defusedenticles: they are irregular calcified tissue following collagen fibers or blood vesicles; they are located often at root canal.

• according to their location:

1- Free pulp stone: is completely surrounded by pulp tissue, it is located at apical portion.

2- Attached pulp stone: is partially fused with the wall of dentin.

3- Embedded pulp stone: is completely surrounded by secondary dentin.

• according to their morphology:

1- Nodular: as the true and false pulp stone.

2- Irregular: as in case of diffuse pulp stone

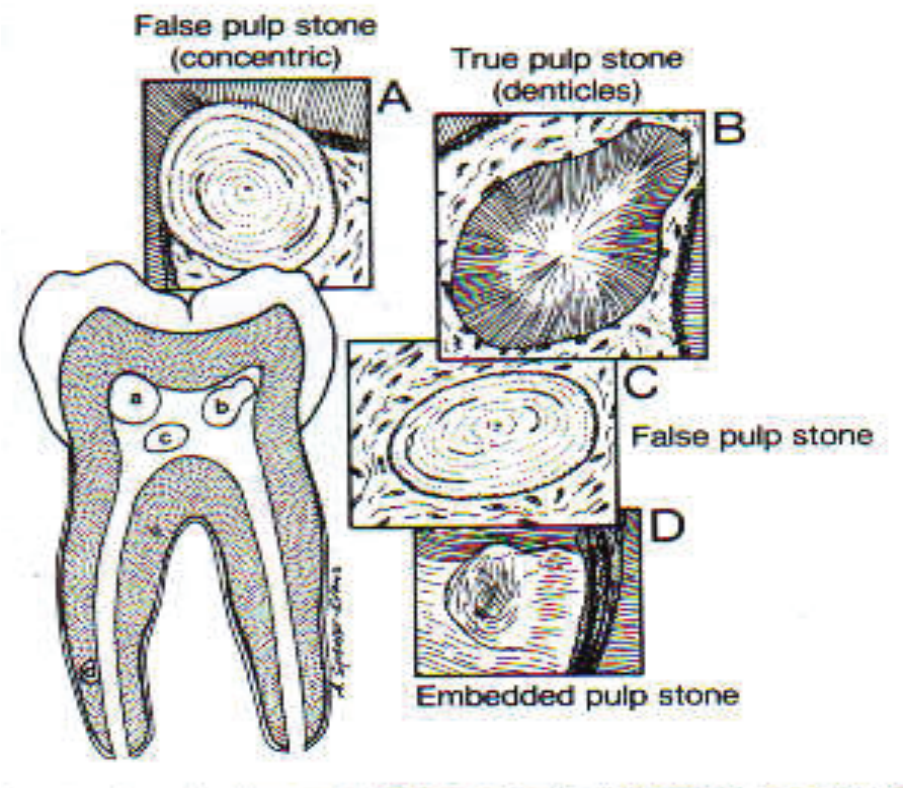

Figure 6 types of pulp stones

Tongue

The tongue is very supple. Approximately 50% of those with the syndrome can touch the end of their nose with their tongue (Gorlin's sign), compared to 8-10% of the population (Gorlin et.al.1990).

Clinical Precautions for the Dentist

The presence of mitral valve prolapse generally indicates that prophylactic antibiotics are indicated for relevant procedures (Lawrence 2005 pp301-314). Dental visits of short duration are preferable in order to avoid causing iatrogenic problems in the TMJs. Inferior alveolar nerve blocks should be given with great care to avoid causing hematoma. Root canal treatment should be done carfully, also pulp stone treatment procedurs should be aweard during treatment of (EDS) patients. Forces used in orthodontic treatment should be lighter than usual, given the fragility of the periodontal ligament. The teeth move rapidly with well-controlled forces, and root resorption does not seem to be a major problem (Noël et.al. 1993 pp146-148). Because relapse is frequent, a longer period of retention is necessary. The buccal mucosa is vulnerable to damage from orthodontic appliances [24]. Ideally, dental and maxillofacial surgery should be avoided. It is imperative to test blood coagulation values before proceeding with surgery. Sutures, which do not hold well, should be covered with acrylic dressings (Postgraduate medical jounal 2005).

Conclusion

Oral examination can be instrumental in establishing a diagnosis of EDS. The presence of the classic signs of the syndrome should prompt the clinician to arrange dermatology, genetics, rheumatology, cardiology and ophthalmology consults to confirm and type the diagnosis of EDS. The dentist should perform treatment observing precautions appropriate to this condition. Ehlers-Danlos syndrome can have a significant impact upon oral health and mouth function; however the majority of patients will probably only be liable to the common disorders of the teeth and gums (Wenstrup et al. 2001 pp 131-149). Dentistry is unlikely to be greatly compromised by EDS and similarly patients are unlikely to have significant complications as a consequence of routine oral health care. Certainly, patients who have complex oral needs must be managed by appropriate clinicians such as specialists in Special Care Dentistry, Oral Medicine and Oral and Maxillofacial Surgery (Berglund and Gun 2000 pp111-118).

References:

1) Pope FM. Ehlers-Danlos syndrome. *Baillieres ClinRheumatol* 1991; 5(2):321-49.

2) Welbury RR. Ehlers-Danlos syndrome: historical review, report of two cases in one family and treatment needs. *ASDC J Dent Child* 1989; 56(3):220-4.

3) Ooshima T, Abe K, Kohno H, Izumanitani A. Oral manifestations of Ehlers-Danlos syndrome type VII: histological examination of a primary tooth. *Pediatr Dent* 1990; 12(2):102-6.

4) Reichert S, Riemann D, Palschka B, Machulla HK. Early onset periodontitis in a patient with Ehlers-Danlos syndrome type III. *Quintessence Int* 1999; 30(11):785-90.

5) Gorlin RJ, Cohen MM, Levi LS. Syndrome of the head and neck, 3rd edition, Oxford, 1990.

6) Beighton P. McKusick's heritable disorder of connective tissue, 5th edition, Mosby, 1991

7) Kivirikko KI. Collagens and their abnormalities in a wide spectrum of diseases.*Ann Med* 1993; 25(2):113-26.

8) Noël SF, Chaillou P, Pistorius MA, Planchon B, Patra P. Syndrome d'Ehlers-Danlos de type IV révélé par un anévrisme disséquant primitif de l'artère sous-clavière gauche. *Journal des maladies vasculaires*. Masson 1993; 18:146-8.

9) Voermans, Nicol C.; van Alfen, Nens; Pillen, Sigrid; Lammens, Martin; Schalkwijk, Joost; Zwarts, Machiel J.; van Rooij, Iris A.; Hamel, Ben C. J.; van Engelen, Baziel G. *(2009). «Neuromusculari nvolvement in various types of Ehlers-Danlos syndrome». Annals of Neurology* ***65*** *(6): 687–97. doi:10.1002/ana.21643. PMID 19557868.*

10) Ozlece, HaticeKose; Ilik, Faik; Huseyinoglu, Nergiz (2015). "Coexistence of Ehlers-Danlos syndrome and multiple sclerosis". *Iranian Journal of Neurology* ***14*** *(2):116–117 doi:10.1177/1352458507083187 PMC 4449394. PMID 26056559.*

11) Castori, Marco (2012). "Ehlers-Danlos Syndrome, Hypermobility Type: An Under diagnosed Hereditary Connective Tissue Disorder with Mucocutaneous, Articular, and Systemic Manifestations". *ISRN Dermatology* ***2012****: 751768. doi:10.5402/2012/751768. PMC 3512326. PMID 23227356.*

12) Malfait, Fransiska; Wenstrup, Richard J; De Paepe, Anne (2011). "Reply to the letter to the editor by Marc Williams". Genetics in Medicine***13*** *(1): 77; author reply 77–8. doi:10.1097/GIM.0b013e318207bf8f. PMID 21217464.*

13) Lumley, Mark A.; Jordan, Margaret; Rubenstein, Ralph; Tsipouras, Petros; Evans, Mark I. (1994). "Psychosocial functioning in the Ehlers-Danlos syndrome». *American Journal of Medical Genetics****53*** *(2): 149–52. doi:10.1002/ajmg.1320530206. PMID 7856639.*

14) Berglund, Britta; Anne-Cathrine, Mattiasson; Randers, Ingrid (2010). "Dignity not fully upheld when seeking health care: Experiences expressed by individuals suffering from Ehlers–Danlos syndrome".*Disability and Rehabilitation****32*** *(1): 1–7. doi:10.3109/09638280903178407. PMID 19925271.*

15) Berglund, Britta; Nordström, Gun; Lützén, Kim (2000). "Living a restricted life with Ehlers-

Danlos Syndrome (EDS)". *International Journal of Nursing Studies* **37** *(2): 111–8*.

16) Myerson, Loreen (1994). "Clinical Versus Empathetic Encounters With Ehlers-Danlos Syndrome". *Anthropology of WorkReview* **15** *(2-3): 22–7. doi:10.1525/awr.1994.15.2-3.22*.

17) Narcisi P, Richards AJ, Ferguson SD, Pope FM (Sep 1994). *«A family with Ehlers-Danlos syndrome type III/articularhy permobility syndrome has a glycine 637 to serine substitution in type III collagen». Hum Mol Genet* **3** *(9): 1617–20. doi:10.1093/hmg/3.9.1617*. CS١ maint: Multiple names: authors list (link)

18) Levy, Howard (2004). "The EhlersDanlos Syndrome, Hypermobility Type." University of Washington: NIH. Retrievedfrom

19) Melanie G Pepin, MS, CGC, Mitzi L Murray, MD, MA, and Peter H Byers, MD. (September 2, 1999; Last Update: November 19, 2015.). *Vascular Ehlers-Danlos Syndrome. Gene Reviews*. Check date values in: |date= (help) CS1 maint: Multiple names: authors list (link)

20) Lawrence EJ (2005). "The clinical presentation of Ehlers–Danlos syndrome». *AdvNeonatal Care* **5** *(6): 301–14. doi:10.1016/j.adnc.2005.09.006. PMID 16338669*.

21) Erçöçen AR, Yenidünya MO, Yilmaz S, Ozbek MR (1997). "Dynamicswan neck deformity in a patient with Ehlers-Danlos syndrome». *J Hand SurgBr* **22** *(1): 128–30. doi:10.1016/S0266-7681(97)80039-3. PMID 9061548*. CS١ maint: Multiple names: authors list (link)

22) Milhorat TH, Bolognese PA, Nishikawa M, McDonnell NB, Francomano CA (December 2007). "Syndrome of occipitoatlantoaxialhy permobility, cranial settling, and chiari malformation type I in patients with hereditary disorders of connective tissue". *Journal of Neurosurgery. Spine* **7** *(6): 601–9. doi:10.3171/SPI-07/12/601. PMID 18074684*. CS١ maint: Multiple names: authors list (link)

23) Gedalia A, Press J, Klein *M, Buskila D (1993). «Joint hypermobility and fibromyalgia in school children». Annals of the Rheumatic Diseases* **52** *(7): 494–6. doi:10.1136/ard.52.7.494. PMC 1005086. PMID 8346976*. CS١ maint: Multiple names: authors list (link)

24) Dommerholt, Jan. "CSF EhlersDanlosColloquium, Dr Jan Dommerholt". *Chiari &Syringomyelia Foundation. Retrieved 10 June 2013*.

25) Vigorita, Vincent J; Mintz, *Douglas; Ghelman, Bernard (2008). Orthopaedic pathology (2nd ed.). Philadelphia: Lippincott Williams and Wilkins. pp. 5–6. ISBN 0781796709*.

26) "Ehlers-Danlos syndrome". *Genetics Home Reference. 2016-01-04. Retrieved 2016-01-06*.

27) "Unusualscars in a young female patient". *Postgraduate Medical Journal* **81** *(957): e5–e5. 2005-07-01. ISSN 1469-0756*.

28) Wenstrup, R.J; et al. (2001). The Ehlers–Danlos Syndromes*: Management of Genetic Syndromes. pp. 131–149*.