RESEARCH REVIEW

Ehlers–Danlos Syndrome, Classical Type

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Classical EDS is a heritable disorder of connective tissue. Patients are affected with joint hypermobility, skin hyperextensibilty, and skin fragility leading to atrophic scarring and significant bruising. These clinical features suggest consideration of the diagnosis which then needs to be confirmed, preferably by genetic testing. The most recent criteria for the diagnosis of EDS were devised in Villefranche in 1997 [Beighton et al. (1998); Am J Med Genet 77:31-37].The aims set out in the Villefranche Criteria were: to enable diagnostic uniformity for clinical and research purposes, to understand the natural history of each subtype of EDS, to inform management and genetic counselling, and to identify potential areas of research. The authors recognized that the criteria would need updating, but viewed the Villefranche nosology as a good starting point. Since 1997, there have been major advances in the molecular understanding of classical EDS. Previous question marks over genetic heterogeneity have been largely surpassed by evidence that abnormalities in type V collagen are the cause. Advances in molecular testing have made it possible to identify the causative mutation in the majority of patients. This has aided the further clarification of this diagnosis. The aim of this literature review is to summarize the current knowledge and highlight areas for future research. © 2017 Wiley Periodicals, Inc.

KEY WORDS: Ehlers–Danlos syndrome; classical type; cEDS; joint hypermobility; skin fragility; skin hyperextensibility

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INTRODUCTION

The Committee met by phone throughout 2015 to discuss the Villefranche diagnostic criteria for classical Ehlers–Danlos Syndrome (classical EDS) and how they might be modified to improve specificity and sensitivity. A comprehensive review of the literature was conducted, led by two of the authors

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Marina Colombi is a full professor of Medical Genetics at the School of Medicine, University of Brescia, Italy. Her major interests are diverse heritable connective tissue disorders including Ehlers–Danlos syndromes, for which she has provided new insights in the molecular basis, phenotypic characterization, clinical spectrum, and pathogenesis.

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(Bowen and Sobey). The diagnostic criteria presented here represent the consensus of the group after review of the literature and considering the professional experience of each of the authors.

The committee agrees to retain the name "classical EDS."

METHODS

Each member of the committee carried out a literature search for classical EDS. The results were collated. All articles were reviewed for relevance and additional articles were identified from the literature. The articles were summarized and divided into themes. Themes that were suggested by the Steering Committee of the International Consortium on the Ehlers–Danlos syndromes were also included to assess where there were gaps in the literature. Each theme was written up to include the relevant literature in that area, focusing on information since the Villefranche nosology. The original list of articles was then reviewed to ensure all areas of the current literature had been covered.

Organ System Review

Musculoskeletal: Joint hypermobility is present. This will be evidenced by the presence of a Beighton score of 5 or greater, either on examination or historically. Joint instability complications may comprise sprains, dislocation/subluxation, temporomandibular joint dysfunction, pain and pes planus, dyspraxia, and early osteoarthritis. Mild muscle hypotonia, and some skeletal morphological alterations (scoliosis, pectus deformities, elbow/genus/hallux valgus) are regularly observed. Pre-menopausal osteopenia or an increased bone fragility in the presence of a bone mineral density within the range may occur [Mazziotti et al., 2016].

Skin: The skin involvement is key to establishing the diagnosis of classical EDS. Skin is hyperextensible and soft, with severe atrophic scarring and haemosiderin deposition over the shins and extensor surfaces. Easy bruising is also a hallmark of classical EDS.

Cardiovascular: While aortic root dilation and mitral valve prolapse are seen in classical EDS, they are rarely clinically significant. Arterial aneurysm and rupture have been reported in a few individuals and families with *COL5A1* mutations.

Gastrointestinal: Gastrointestinal complaints are more commonly described in the hypermobile type of EDS, although they can be present in patients with classical EDS and may include: dysphagia, dyspepsia, reflux disease with or without hiatal hernia, irritable-bowel disease-like symptoms, unspecified abdominal pain, defecatory dysfunctions (constipation, diarrhea), and rectocele [Ritelli et al., 2013; Nelson et al., 2015].

Neurologic: Pain is a common feature of EDS. One report suggests that pain intensity in classical EDS patients is mild and less frequent compared to hypermobile EDS.

Literature Review

The literature was divided into 8 themes: The history of classical EDS, the mechanism of disease, clinical description, testing strategy, management, differential diagnoses, genetic counselling, and gaps/future research.

THE HISTORY OF CLASSICAL EDS

Classical EDS (OMIM #130000) is a heritable disorder of connective tissue characterized by skin hyperextensibility, poor wound healing, and joint hypermobility. Classical EDS was first noted to be a distinct type of EDS in the 1960s when Beighton reviewed 100 patients and described a patient with distinct features which he termed EDS gravis [Beighton, 1968]. Patients were noted to have characteristic findings on electron microscopy, which helped to differentiate between EDS diagnoses [Vogel et al., 1979]. In 1988, gravis type was termed EDS type I and the milder, mitis type was labelled EDS type II [Beighton et al., 1988]. Type V collagen was implicated after mouse models with mutations in *COL5A2* showed features of the condition [Andrikopoulos et al., 1995]. This was shortly followed by the first reports of *COL5A1* mutations in patients with classical EDS [Nicholls et al., 1996; Wenstrup et al., 1996; De Paepe et al., 1997]. Linkage to *COL5A1* also suggested the EDS types I and II were phenotypic variation of the same condition [Burrows et al., 1996]. In 1996, a balanced translocation interrupting the *COL5A1* gene was identified and haploinsufficiency was suggested as the cause of the patient's EDS phenotype [Toriello et al., 1996]. The name classical EDS was given when the Villefranche nosology was written in 1997 [Beighton et al., 1998]. Initially other genes were thought to be involved, as *COL5A1* and *COL5A2* mutations were only found to account for around half of classical EDS patients [Schwarze et al., 2000; Malfait et al., 2005]. Advances in molecular testing have allowed more type V collagen abnormalities to be identified, and recent reports indicate that the majority of patients with classical EDS do have a mutation in either *COL5A1* or *COL5A2* [Symoens et al., 2012; Ritelli et al., 2013].

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THE MECHANISM OF DISEASE

Reduction in the amount of type V collagen is central to the pathogenesis of

classical EDS [Symoens et al., 2008; De Paepe and Malfait, 2012]. Type V collagen has a regulatory function in fibrillogenesis. The phenotype is caused by disturbance in the regulatory function of type V collagen [Symoens et al., 2012].

Type V collagen is a fibrillar collagen present in small amounts in a wide variety of tissues [Malfait and De Paepe, 2005]. It is mainly found in vertebrate tissues as the heterotrimer $\alpha1(V)_2\alpha2(V)$ [Viglio et al., 2008]. Type V collagen and type I collagen come together to form collagen fibrils. *COL5A1* haploinsufficiency is, therefore, a limiting factor for an adequate production of heterotrimers, hence compromising the regulatory role in fibrils assembly. Most of the $\alpha1(V)_2\alpha2$ (V) heterotrimer is embedded within the fibril, apart from the amino-terminal propeptide domain which remains exposed on the surface and has a role in fibril assembly and regulating fibril diameter [Birk, 2001].

The *COL5A1* gene encodes the $\alpha1$ chain and is located at 9q34.2-q34.3. The *COL5A2* gene encodes the $\alpha2$ chain and is located at 2q31. Both genes are large, comprising 66 and 52 exons, respectively. The majority of patients have mutations in *COL5A1*. A report of 93 gene positive patients found 73 had *COL5A1* mutations, 13 had *COL5A2* mutations, and in 7 cases the mutation could not be identified; however, *COL5* null allele testing confirmed the abnormality was in type V collagen [Symoens et al., 2012]. In this series two thirds of the mutations were found to be de novo. A series of 40 patients achieved a mutation detection rate of 93% [Ritelli et al., 2013]. Both studies confirmed that *COL5A1* and *COL5A2* are the major, if not the only genes involved.

The most common molecular defects result in nonsense mediated decay of the mutated *COL5A1* mRNA [Schwarze et al., 2000]. Whilst haploinsufficiency is seen most often, dominant-negative mutations are also reported [Wenstrup et al., 2000]. In general genotype–phenotype correlations are not found, but there are a couple of possible exceptions. Mutations in the highly conserved amino-terminal propeptide domain of $\alpha1(V)$ that cause atypical splicing outcomes have been associated with a more severe classical EDS phenotype with kyphoscoliosis and retinal detachment [Symoens et al., 2011]. There is one report that questions whether mutations involving glycine substitutions near the C-terminal end cause an increased arterial risk [Monroe et al., 2015]. Although numbers are still limited, *COL5A2* gene mutations are thought to result in a phenotype at the more severe end of classical EDS spectrum [Symoens et al., 2012].

CLINICAL DESCRIPTION

The Villefranche criteria list three major criteria for classical EDS [Beighton et al., 1998]:

(1) Skin hyperextensibility
(2) Widened atrophic scars (manifestation of tissue fragility)
(3) Joint hypermobility

In addition, there are a number of minor criteria which show less diagnostic specificity:

(1) Smooth velvety skin
(2) Molluscoid pseudotumours
(3) Subcutaneous spheroids/spherules
(4) Complications of joint hypermobility (e.g., sprains, dislocations/subluxations, pes planus)
(5) Muscle hypotonia, delayed gross motor development
(6) Easy bruising
(7) Manifestations of tissue extensibility and fragility (e.g., hiatus hernia, anal prolapse in childhood, cervical insufficiency)
(8) Surgical complications (postoperative hernias)
(9) Positive family history

The Villefranche criteria are still considered relevant for classical EDS. A study of 126 suspected classical EDS patients found that 93 out of the 102 that demonstrated all three major Villefranche criteria for classical EDS were found to have a type V collagen abnormality [Symoens et al., 2012]. They suggested making the diagnostic criteria more stringent as fulfilling all three major criteria was seen to be a reliable indicator of a type V collagen mutation. Another review of 40 patients also found that these three major criteria are considered to still be useful for clinical diagnoses in the majority of patients [Ritelli et al., 2013].

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There have been a number of typical case histories of classical EDS described. These suggest that investigations into childhood bruising are often the first presentation to medical professionals, and if skin hyperextensibility and joint hypermobility are noted at this time, the diagnosis is generally made [De Paepe and Malfait, 2012; Byers, 2013; Morais et al., 2013; Sobey, 2014]. Bruising is generally a feature seen when children start to crawl and walk, with the characteristic scarring becoming apparent after knocks and bumps around the same time. Hypermobility may delay motor development, but intellectual development is unaffected.

Skin Features

Skin hyperextensibility has been shown to be a reliable and reproducible feature of classical EDS [Remvig et al., 2010]. This group confirmed that patients with classical EDS show extensibility beyond the normal range (Fig. 1). However, they found skin consistency to be an unreliable test and concluded that skin consistency should not be included in the diagnostic criteria for classical EDS.

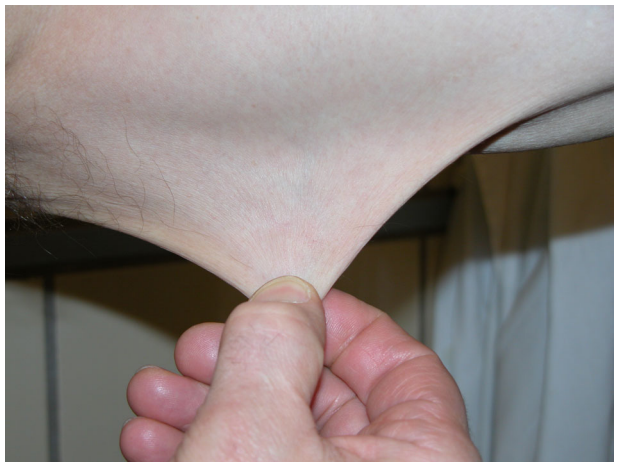

Figure 1. Hyperextensible skin in Classical Ehlers-Danlos Syndrome.

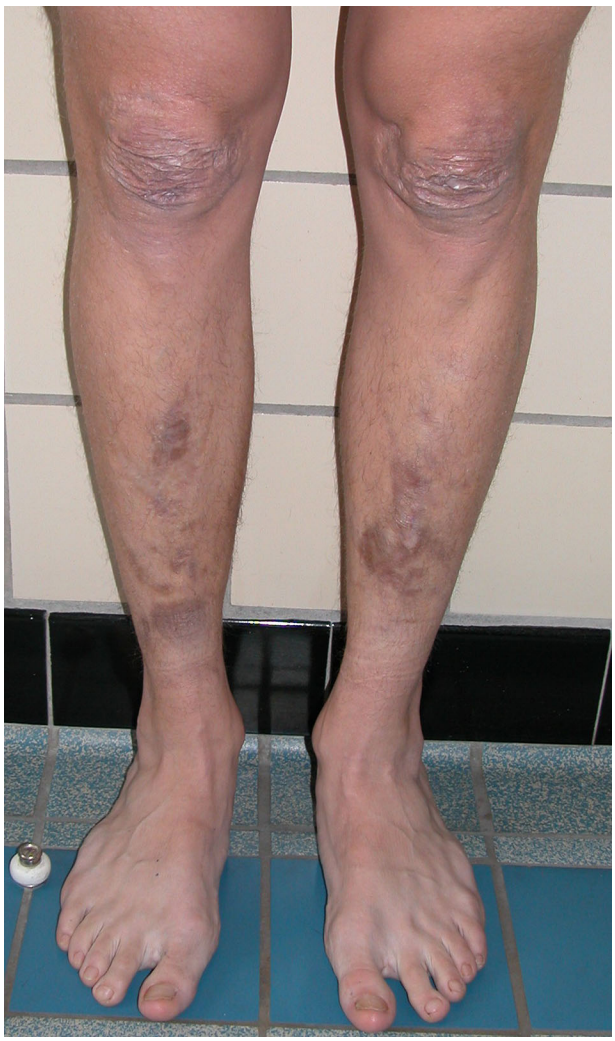

Figure 2. Typical scarring in classical EDS.

Other reports have also found skin hyperextensibility to be a good indicator for classical EDS, as it quite specific to this diagnosis [Heidbreder et al., 2008; Catala-Pétavy et al., 2009] Skin fragility with atrophic scarring and poor wound healing is a hallmark of the classical type of EDS [Beighton et al., 1998] (Fig. 2).

Cardiovascular Involvement

Nine patients (three in one family) have been reported to have molecularly confirmed classical EDS and vascular events [Monroe et al., 2015]. To determine whether there is any reporting bias it is helpful to compare these cases to the larger patient series that have been reported. Twenty-five patients with proven type V collagen abnormalities showed no vascular events at the time of writing [Malfait et al., 2005]. A series of 102 patients, 93 with collagen type V abnormalities, had two patients with vascular complications which included aneurysm and dissection of medium sized artery [Symoens et al., 2012]. They reported that severe or progressive cardiac-valvular disease was absent in their cohort. A report of 40 patients showed no patients with type V collagen abnormalities that had severe cardiovascular involvement [Ritelli et al., 2013].

The family of three are two brothers and their mother who were given a clinical diagnosis of vascular EDS [Monroe et al., 2015]. One brother died age 43 due to a subarachnoid bleed, after previously having a ruptured left subclavian artery age 15 years and a coeliac artery aneurysm was resected age 18 years with significant bleeding. His mother had died at age 28 while under anaesthesia for dental extraction; the post mortem revealed a renal artery tear. The other brother died age 34 following a right iliac artery rupture; his tissues were compared to rice paper in the operating theatre. They were all shown to have a *COL5A1* p.(Gly1537Val) mutation. This family represents the only report of familial vascular events with a *COL5A1* mutation. The authors wondered about modifying genes in the family or whether there could be a genotype–phenotype correlation. They speculated there could be increased arterial risk in cases involving glycine substitutions near the C-terminal end.

Another report of a patient with a glycine substitution at the C-terminal end of the triple helix domain had a symptomatic superior mesenteric artery aneurysm age at 9 years [de Leeuw et al., 2012]. This patient was said to fit clinically with a classical EDS diagnosis and was found to have a *COL5A1* p.(Gly1564Asp) mutation. Two further vascular events have been reported at young ages. One report is of a 13-year-old girl with classical EDS who had a superior mesenteric artery rupture and was found to have a *COL5A1* missense mutation c.1532G>T p.(Gly511Val) [Yasuda et al., 2013]. Another patient with a *COL5A1* p.(Gly922Asp) mutation was diagnosed with classical EDS at 4 years of age and presented at age 11 with a superior mesenteric artery aneurysm with thrombosis [Karaa and Stoler, 2013]. This patient was treated with anticoagulation, and a week later he ruptured his inferior mesenteric artery.

Two patients with classical EDS and hypertension have been reported following vascular events. A patient with a *COL5A1* mutation c.3184C>T p.(Arg1062*) who already had a clinical diagnosis of classical EDS went on to have a left common iliac artery rupture at age 42 years [Borck et al., 2010]. This patient had been diagnosed with hypertension at 40 and treated with clonidine, metoprolol and valsartan/hypochlorothiazide. The authors felt they could not exclude a chance association between the classical EDS diagnosis and the rupture, but felt a causal relationship was more likely. They considered whether the concurrent hypertension might have played a part, causing a second hit. However, their view was that a systematic counselling of the risk of arterial rupture in classical EDS should await confirmation of this association in larger series. Another patient with chronic hypertension (although well controlled) with a *COL5A1* nonsense mutation c2185C>T p.(Gln729*) had an iliac artery dissection whilst resistance training [Mehta et al., 2012]. This time the authors considered a triple hit effect; chronic hypertension, elevated vascular stress from resistance training, and his underlying weakened collagen matrix due to classical EDS. They suggested avoiding intense resistance training and/or tighter control of blood pressure.

Aortic root dilation has been reported in classical EDS [Wenstrup et al., 2002; McDonnell et al., 2006; Atzinger et al., 2011]. It appears to be more common in young patients and rarely progresses [Atzinger et al., 2011]. Mitral valve prolapse can occur in up to 6% of cases but tends to be of little clinical significance [Atzinger et al., 2011].

Newly recognized features

Features not mentioned in the Villefranche criteria that arise in the literature include premature rupture of fetal membranes, characteristic facial features, absence of striae, scoliosis, cardiac and blood vessel fragility. Premature rupture of fetal membranes can result in prematurity and this was reported to affect half of classical EDS patients, but is now thought not to be so common [Wenstrup et al., 2000]. The characteristic facial features described are; epicanthic folds, excess skin on eyelids, a prematurely aged appearance, and scars on the forehead and chin [Malfait and De Paepe, 2005]. Absence of striae has been noted in classical EDS patients [Sobey, 2014], although some patients with confirmed classical EDS have been seen to have striae. Three patients out of 40 were reported to have striae in one study [Ritelli et al., 2013]. Dual-energy X-ray absorptiometry (DXA) and quantitative vertebral morphometry were performed in 12 unrelated adult patients with classical EDS which showed bone mineral density below the expected range for age (osteopenia) in about 33.3% of patients and pre-menopausal osteoporosis in one patient. Giant bladder diverticula have been described in four cases, all male [Burrows et al., 1998]. In two reports the subtype of EDS was not given but the descriptions were compatible with classical EDS.

Gastrointestinal findings

Gastrointestinal (GI) manifestations were analyzed among a cohort of 73

unrelated adult patients with classical EDS. The most common upper GI symptoms were nausea (46.5%), vomiting (30.2%), and gastroesophageal reflux (30.2%); the most common lower GI symptom was chronic constipation (37.2%) [Nelson et al., 2015]. Gastroesophageal reflux and defecatory dysfunctions (i.e., chronic constipation) were also described in the cohort of 39 classical EDS patients reported in Ritelli et al. [2013].

Oral findings

Overall periodontal status in EDS is poor. One case of abnormal pulp shape and seven with pulp calcification were seen out of nine classical EDS patients examined [De Coster et al., 2005a]. It has been suggested that the absence of the inferior labial and lingual frenulae is a helpful marker for hypermobile and classical EDS, but the total numbers of classical EDS patients reported to date are too small to conclude that this is useful sign in this subtype [De Felice et al., 2001]. Pierro et al. [2006] reported on ligneous periodontitis in Ehlers-Danlos syndrome. Temporomandibular joint dysfunction is a common feature and a frequent cause of secondary headache in classical EDS patients with generalized joint laxity [De Coster et al., 2005b].

Ocular findings

Macro- and microstructural changes of the cornea were found in classical EDS patients [Villani et al., 2013]. Classical EDS patients have been shown to have thin, steep and transparent corneas as well as floppy eyelids [Segev et al., 2006; Villani et al., 2013]. Both studies found that these changes did not cause an increase in refractory errors (including astigmatism) nor an increase in keratoconus. This supports the lack of correlation between corneal thickness and refractive error. Villani et al. [2013] also found that the patients reported no complaints of ocular surface symptoms, despite having abnormal ocular surface symptoms and reduced tear secretion when compared to controls. One caveat concerning the report by Villani et al. [2013] is that the diagnosis of classical EDS was not supported by molecular testing in the reported population.

Pain and Neurological Features

Pain is considered a common feature in EDS patients, but it has been shown to be more prevalent and more severe in patients with hypermobile EDS than in those with classical or vascular EDS [Voermans et al., 2010]. The authors correlate pain intensity with the degree of joint hypermobility, dislocations, and previous surgery. A decrease in quality of life has been reported but found not to be significantly different between classical and hypermobile patients, provided they have been diagnosed and are under multidisciplinary management [Castori et al., 2010]. When compared to patients with vascular EDS and patients with homozygous and heterozygous TNXB mutations, the patients with classical EDS reported the most neuromuscular complaints [Voermans et al., 2009]. This study found mild, moderate or severe muscle weakness on examination of all of 10 classical EDS patients. They suggest that the neuromuscular involvement is due to the abnormal extracellular matrix within muscle and peripheral nerve. This is an alternative explanation to the view that it is exercise avoidance, for fear of dislocations and sprains, which leads to muscle weakness and fatigue. Rowe et al. [1999] reported an association between orthostatic intolerance, chronic fatigue, and Ehlers-Danlos syndrome. Autonomic burden has been reported to be lower in classical EDS than in hypermobile EDS, and classical EDS patients had levels more comparable to those reported by vascular EDS patients [De Wandele et al., 2014].

TESTING STRATEGY

The diagnosis of classical EDS can be confirmed by identifying the pathogenic causative mutation in COL5A1 or COL5A2. As the number of identifiable mutations has increased, molecular testing has been the main route for classical EDS testing. Testing strategies generally start with COL5A1 sequencing. If COL5A1 is negative, sequence COL5A2 and proceed to Multiplex Ligation-dependent Probe Amplification (MLPA) for COL5A1 [De Paepe and Malfait, 2012; Ritelli et al., 2013]. If the causative mutation is not identified, COL1A1 sequencing should be considered, at least in a subset of patients with vascular and/or valvular involvement, or history thereof [Ritelli et al., 2013; Colombi et al., 2016] (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).

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Molecular investigations identify mutations in the majority, but currently not all, patients with the diagnosis [Symoens et al., 2012]. Pathogenicity must be determined and there is a registry of reported collagen gene variants [Dalgleish, 1998].

The pathogenicity of one reported variant remains unclear. The p.(Gly530Ser) variant in COL5A1 is reported to be potentially disease modifying in the heterozygous state and disease causing in the homozygous state [Giunta and Steinmann, 2000; Giunta et al., 2002]. However, there is still some uncertainty about whether this variant is disease causing, due to its frequency in the general population and the fact that not all molecular causes of classical EDS can currently be identified. Another study found the frequency of the

p.(Gly530Ser) variant to be similar in patients with classical EDS, vascular EDS, osteogenesis imperfecta (OI), and the three control groups they used as comparison [Mitchell et al., 2009]. They state that if homozygosity of this variant did cause classical EDS, 1 in 400 people would be affected. This is much higher than the current suspected frequency of classical EDS. Hence, they consider homozygosity of this variant is unlikely to cause classical EDS.

When a pathogenic mutation cannot be found, type V collagen abnormality can be sometimes be demonstrated by the COL5A1 null allele test [Greenspan and Pasquinelli, 1994; Schwarze et al., 2000; Mitchell et al., 2009; De Paepe and Malfait, 2012; Symoens et al., 2012]. The patient must be heterozygous for a polymorphic marker in COL5A1 gDNA. cDNA from a skin biopsy is then tested to look for the presence of one or both markers. If a marker is not expressed that allele is assumed not to be functional, that is, "null" [Malfait and De Paepe, 2005].

Typical frequent collagen flowers on electron microscopy (EM) of skin can be a helpful diagnostic tool for classical EDS, however collagen flowers are not unique to this condition. Electron microscopy of a skin biopsy can be used to direct testing [Sobey, 2015], and electron microscopy can aid diagnosis [Vogel et al., 1979; Hausser and Anton-Lamprecht, 1994]. The absence of typical collagen flowers would go against the diagnosis, as there are no reports of patients with type V collagen abnormalities without collagen flowers on EM [de Moraes et al., 2000; Proske et al., 2006; Symoens et al., 2012]. However, collagen flowers are not specific to classical EDS and have been reported in other connective tissue disorders including OI and Ullrich congenital muscular dystrophy (UCMD) [Kirschner et al., 2005; Hermanns-Lê and Piérard, 2007; Balasubramanian et al., 2015]. Collagen flowers on EM should be an indicator to look for COL1A1 mutations, when clinical features of classical EDS are present in the absence of a COL5 abnormality.

Collagen protein analysis of cultured fibroblasts is not an effective diagnostic tool for classical EDS as type V collagen is only synthesized at low levels [Malfait et al., 2010]. This analysis may be used to exclude alternative diagnoses in the absence of genetic confirmation and may be helpful for the confirmation of the mutation effect, that is, recognition of splice site mutations.

MANAGEMENT

The key management advice is fairly consistent and focuses on the skin and joints [Steinmann et al., 2002; Proske et al., 2006; Malfait et al., 2010; Sobey, 2014].

The advice on managing the skin is to:

Avoid undue trauma. Children are particularly prone to injury and benefit from protective pads and bandages. Custom made shin pads can be obtained from local appliance departments. Contact sports should be avoided.

Wounds should be expertly closed via sutures without tension. Patients should be known to their local plastic surgeons to enable access in emergencies. Stitches should be applied generously, in layers and left in place twice as long as usual. Tape can also help prevent stretching of the scar, but needs careful removal.

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Ascorbic acid (2 g/day for adults) may reduce bruising, but does not affect the basic clinical picture.

Surgery may be difficult due to tissue fragility and original problem may reoccur, for example, hernia.

Deamino-Delta-D-Arginine Vasopressin (DDAVP) may be useful to normalize bleeding time. Although bleeding is related to tissue and capillary fragility rather than clotting time, it may be beneficial in case of bruising, epistaxis or before procedures such as dental extractions.

Avoid excessive sun exposure to reduce the risk of premature skin aging.

Plastic surgery to remove molluscoid pseudotumors may be considered in presence of psychological/aesthetic issues.

The musculoskeletal management advice is:

Physiotherapy is beneficial for children with hypotonia and delayed motor development.

Light, non-weightbearing, muscle strengthening exercise such as isometric training and swimming are beneficial for hypermobile joints and pain management.

Competitive activities, such as gymnastics, repetitive heavy lifting, and sports that cause heavy joint stress, are not advisable. Mild strength training has shown benefit in joint stabilization and hypotonia.

Avoid "showing off" hypermobility and excessive stretching of the hypermobile joints.

Joint hypermobility is best managed by Rheumatology, Physiatry and Sports Medicine, together with physiotherapy, proprioception exercises, and occupational therapy (OT).

Ring splints, carefully considered bracing, and orthotics may be beneficial.

Skin fragility, muscle hypotonia, joint instability, and pain are key aspects of the condition and should be recognized and discussed with the patient. Lifestyle and professional choices may need to be adapted.

There are several articles giving contradictory advice on resistance exercise. One report found heavy

resistance training was both feasible and safe, although their numbers were small they saw an improvement in musculotendinous function and a reduction in fatigue [Møller et al., 2014]. Another report describes a case of iliac artery dissection following vigorous physical exercise [Mehta et al., 2012]. Schroeder and Lavallee [2006] offer guidance for athletes with EDS of all types.

The advice on pain management includes:

Anti-inflammatory drugs and pain medications using narcotics only as a very last resort.

Neurological assessment in patients with symptoms suggestive of neuropathic pain/compression neuropathy.

Regular, light, non-weightbearing exercise.

Relaxation techniques including mindfulness-based stress reduction and biofeedback.

Counselling support including cognitive behavioral therapy. See also "Pain Management in Ehlers-Danlos Syndrome" by Chopra et al., this issue.

Cardiac Management

Cardiac assessment including echocardiography to look for aortic root dilation and mitral valve prolapse. Mitral valve prolapse may need management. Aortic root size and mitral valve prolapse are increased in patients with classical EDS, but they tend to be of little clinical significance. Echocardiography may be warranted, but in symptom-free adults frequency can be reduced [Atzinger et al., 2011]. If this is normal in adulthood no follow up is required [Malfait et al., 2010].

Consider vascular imaging/use of blood pressure medication if the patient has a glycine substitution identified near the C-terminal end of the triple helix, or on the basis of their family history [Monroe et al., 2015].

Gastrointestinal Management

Endoscopy and colonoscopy should be performed with care due to a possibly increased risk of mucosal bleeding and tissue fragility.

Pregnancy Management

Follow up throughout pregnancy is warranted.

Preterm delivery is more likely when the fetus is affected and is mainly due to premature rupture of the membranes.

Breech presentation is more common if the baby is affected.

After delivery, extension of episiotomy incisions and pelvic prolapse leading to urinary/faecal incontinence may occur due to tissue fragility and extensibility. Treatment of symptomatic pelvic prolapse remains problematic in classical EDS.

DIFFERENTIAL DIAGNOSIS

There are a large number of conditions reported to be amongst the differentials when a diagnosis of classical EDS is being considered. One paper specifically on classical EDS gives a detailed description of 18 differential diagnoses [Malfait et al., 2010]. Another highlights the need to distinguish hyperelastic skin from the redundant skin seen in cutis laxa syndromes and Menkes disease [Malfait and De Paepe, 2005].

A paper describing the differential diagnoses for connective tissue diseases in general, mentions features similar to those of classical EDS in four other conditions [Murphy-Ryan et al., 2010]:

(1) Cardiac-valvular EDS—In this condition, patients sometimes present with the skin and joints of classical EDS but have an increased risk of cardiac valvular complications and autosomal recessive inheritance (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).
(2) Classical-like EDS due to complete tenascin X deficiency—can present with a phenotype similar to classical EDS but without the typical scarring, and with autosomal recessive inheritance (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).
(3) Spondylodysplastic EDS due to SLC39A13 mutations—a rare recessive condition caused by mutations in SLC39A13, which presents with atrophic scarring similar to that seen in classical EDS, in addition to fragile skin which appears prematurely aged on hands and feet. Muscle atrophy, pes plans, postnatal growth deficiency, and small joint contractures are also characteristic [Giunta et al., 2008] (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).
(4) Loeys–Dietz syndrome—which can present with a whole spectrum of features including the translucent and velvety skin and joint laxity seen in classical EDS, but also craniofacial features and vascular tortuosity not typical of cEDS.

A review on the differential diagnoses of joint hypermobility syndrome (JHS)/EDS hypermobile type (hEDS) includes classical EDS [Colombi et al., 2015]. In a small number of cases, patients with classical EDS and those with JHS/hEDS can present similarly. In one study, two adult patients with confirmed classical EDS were reported to have no atrophic scars [Ritelli et al., 2013]. Another study reported hEDS patients with hyperextensible skin [Castori et al., 2015].

Also to be included in the differential diagnosis of classical EDS is the dermatosporatic type of EDS, which is an autosomal recessive disorder characterized by extreme skin fragility with congenital or post-natal skin tears. Typically the skin is redundant, with excessive palmar wrinkling and severe bruisability with a risk of subcutaneous hematomas and haemorrhage Postnatal growth retardation with short limbs, hand and feet, which are not typically features of cEDS, are seen in the dermatosporatic type (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).

A review of case reports and patient series reveals a number of incidences where a clinical diagnosis of classical EDS was altered after genetic testing identified an alternative diagnosis. In all cases, they all involved mutations in type I collagen.

There are currently three reported forms of type I collagen abnormality that can present with EDS features:

(1) Cardiac valvular EDS—an autosomal recessive condition caused by total absence of α2(1) collagen chain [De Paepe and Malfait, 2012]. The condition was named because three patients were reported to have aortic or mitral valve requiring replacement surgery in adulthood [Schwarze et al., 2004]. A review of all reported cases concludes that loss of function mutations result in a phenotype similar to hEDS or classical EDS but with cardiac valve disease in adulthood while gain of function mutations lead to a severe OI phenotype [Malfait et al., 2006] (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).
(2) "Classic EDS-like with a propensity for arterial rupture"/"vascular-like classical EDS" are two names that have been used for the condition caused by COL1A1 mutations involving substitutions of arginine for cysteine. This condition can present as classical EDS with an increased risk for arterial dissection [Malfait et al., 2007; Ritelli et al., 2013; Gaines et al., 2015]. Three patients were described who had arginine to cysteine substitutions in the pro-alpha (l) collagen chain and one had presented as classical EDS [Malfait et al., 2007]. They suggest that this shows the need to differentiate COL1 patients (given the phenotypic similarity) as there is vessel fragility in patients with COL1A1 arginine to cysteine mutations. The molecular characterization of 40 patients with classical EDS showed that one patient had a COL1A1 p.(Arg312Cys) mutation [Ritelli et al., 2013]. This patient was reported to be similar to the other classical EDS patients except that he had vascular involvement (see also "Ehlers–Danlos Syndromes, Rare Subtypes" by Brady et al., this issue).
(3) OI/EDS overlap syndrome.

Patients with mutations at the N-terminal end of both COL1A1 and COL1A2, which are seen to affect the processing of the N-propeptide, can present phenotypically as EDS rather than OI [Malfait et al., 2013]. This is in contrast to patients with mutations in the same region who do not show delayed type I procollagen N-propeptide processing on SDS–PAGE analysis, who present with an OI phenotype. The potential risk for vascular rupture associated with these mutations means they need to be diagnosed correctly, particularly given the clinical overlap. This again highlights the need to consider type I collagen in patients presenting with EDS features. The authors recognized that the further work was needed to fully characterize this phenotype, but suggest being aware of the potential for vascular aneurysm or rupture at a young age and recommend caution and consideration of the risk of vascular fragility in event of surgical or other invasive procedures.

GENETIC COUNSELING

Classical EDS is inherited in an autosomal dominant pattern. Affected individuals have a 50% chance of passing on the condition in each pregnancy. For siblings of an affected person it will depend on whether one of the patents is also affected. If a parent is affected the other children will have a 50% chance of being affected. Intrafamilial variability has been reported [Burrows et al., 1996]. About 50% of cases are thought to be de novo [Malfait et al., 2010]. If the parents are unaffected there is a theoretical risk to the other children due to gonadal mosaicism, however, this has not yet been reported [Malfait et al., 2010].

Once the molecular cause is known for a patient, cascade testing is possible to confirm or exclude the diagnosis in relatives who may have a milder phenotype [Ritelli et al., 2013]. Prenatal testing and preimplantation genetic diagnosis are possible once the mutation is known; however, requests for these are not common for conditions that do not affect intellect or life span [Malfait et al., 2010].

Diagnostic Criteria

After review of the literature, and considering the clinical experience of the authors, we recommend the following diagnostic criteria:

Major criteria

(1) Significant skin hyperextensibility and atrophic scarring.
(2) Generalized joint hypermobility.

Minor criteria

(1) Easy bruising.
(2) Soft, doughy skin.
(3) Skin fragility (or traumatic splitting).
(4) Molluscoid pseudotumours.
(5) Subcutaneous spheroids.
(6) Hernia (or history thereof).
(7) Epicanthal folds.
(8) Complications of joint hypermobility (e.g., sprains, dislocation/subluxation, pain, pes planus).
(9) Family history of a first degree relative who meets clinical criteria.

Minimal criteria suggestive for a diagnosis of classical EDS

Major criteria (1)—Skin hyperextensibility and atrophic scarring

Plus

Either: Major criteria (2)—generalized joint hypermobility

Or: three of the nine minor criteria

Comments

Skin is hyperextensible if it can be stretched over a standardized cut off in the following areas: 1.5 cm for the distal part of the forearms and the dorsum of the hands; 3 cm for neck, elbow and knees; 1 cm on the volar surface of the hand (palm).

Abnormal scarring can range in severity. Most patients have extensive atrophic scars at a number of sites. A minority of patients are more mildly affected. The relevance of surgical scars should be considered with caution in classical EDS, they can appear normal in patients with classical EDS if well managed. Atrophic surgical scars can be found in the general population due to mechanical factors and site of the incision.

Joint hypermobility (JHM) is evaluated according to the Beighton score; a

Beighton score of >5 is considered positive for the presence of generalized joint hypermobility. Since joint hypermobility decreases with age, patients with a Beighton score <5/9 may be considered positive based on their historical observations.

Easy bruising can occur anywhere on the body, including unusual sites. The pretibial area often remains stained with hemosiderin from previous bruises.

Subjective abnormality of the skin texture is appreciable by touching the skin.

Molluscoid pseudotumors are fleshy lesions associated with scars, found over pressure points (e.g., elbow, fingers).

Subcutaneous spheroids are small spherical hard bodies, frequently mobile and palpable, on the forearms and shins. Spheroids may be calcified and detectable radiologically.

Epicanthal folds are often seen in childhood but may also be seen in adults.

Verification of clinical diagnosis

Confirmatory analysis is recommended for any patient meeting the above clinical criteria.

Molecular analysis of COL5A1 and COL5A2 genes identifies a causal mutation in more than 90% of the patients [Symoens et al., 2012; Ritelli et al., 2013]. Molecular screening by means of targeted resequencing of a gene panel that includes at least the *COL5A1*, *COL5A2*, and *COL1A1* gene, or by WES or WGS is indicated. When no mutation is identified, this approach should be complemented with a copy number variant (CNV) detection strategy to identify large deletions or duplications.

If genetic testing is not available, electron microscopy findings of collagen flowers on skin biopsy can support the clinical diagnosis.

Absence of these confirmatory findings does not exclude the diagnosis; however, alternative diagnoses should be considered in the absence of a type V collagen gene mutation or electron microscopy findings.

GAPS/FUTURE RESEARCH

A study of the management of vascular complications in EDS described 15 patients with clinical diagnoses of classical EDS with two having thoracic aortic aneurysm repair and two having abdominal aortic aneurysm repair [Brooke et al., 2010]. The authors recognized that they were limited by reliance on clinical criteria for diagnosis when biochemical and genetic testing is more accurate. The evidence that COL1 mutations have an increased vascular risk raises this particular question for these patients. This highlights the benefit of molecular confirmation of patients for research purposes.

A large proportion of the current literature on patients that have had molecular testing focuses on confirming the diagnosis, while the literature on clinical features and management is often not based on molecularly characterized populations. Further studies of associated features in confirmed classical EDS patients is warranted. There are some recent large patient reviews that have helped to develop the understanding of classical EDS. There is huge potential for research using these large patient groups with molecularly confirmed diagnoses.

Mutations in COL5A2 account for a relatively small number of cases. As more mutation analysis is carried out, genotype-phenotype correlations may become more apparent.

Large scale studies on vascular risk and cardiac features would aid management. A few cases studies may be skewing the data and further clarification of this would be helpful for patients with type V collagen mutations. However, it is clear that in the absence of molecular testing, the potential for a type I collagen mutation with an increased risk of arterial rupture cannot be ruled out.

Another question that would benefit from further research is whether a lack of striae can be used as a good indicator for classical EDS and help to direct molecular testing.

Literature is lacking on the frequency of dysautonomia, chronic fatigue syndrome, gastrointestinal involvement, Chiari and cranio-cervical instability in this patient population.

Pregnancy and delivery in classical EDS is another area that would benefit from clear management guidelines.

More data are needed in regard to mild, persistent strength training in relation to the treatment of the hypotonia seen in some cases of classical EDS. The role of fitness, exercise, and rehabilitation in the functional ability and quality of life measure in those with classical EDS is an area for further investigation.

Finally, there is a lack of good prevalence and natural history data for classical EDS.

SUMMARY

A diagnosis of classical EDS is indicated by the well-described triad of hyperextensible skin, atrophic scarring, and hypermobile joints. Although a set of clinical criteria has predominated diagnosis, other conditions do present similarly. Confirmation of diagnosis informs management and is vital for research purposes. Much of the early literature on classical EDS is limited by the lack of laboratory confirmation of diagnoses.

The diagnosis of classical EDS can be confirmed by identifying the pathogenic causative mutation in COL5A1 or COL5A2. Molecular investigations identify mutations in the majority, but currently not all patients with a clinical picture compatible with the diagnosis. Where genetic confirmation has not been possible, a type V collagen abnormality can sometimes be demonstrated by the COL5A1 null allele test. Typical frequent collagen flowers on electron microscopy (EM) of skin can be a helpful diagnostic tool for classical EDS, however, collagen flowers are not unique to this condition. Collagen flowers on EM should be an indicator to test COL1A1 and COL1A2 when clinical features of classical EDS are present in the absence of a COL5 abnormality. Patients with a type 1 collagen abnormality can present with a similar initial clinical appearance to classical EDS, but they have a higher risk of vascular events and need appropriate management.

The management advice for classical EDS has remained consistent over a number of years. There are now a large number of patients with molecularly confirmed classical EDS and these provide a basis for further research on management. Further evidence on cardiac risks, skin care management, exercise potential, and associated features would aid the understanding and management of the condition.

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