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Ehlers-Danlos Syndrome: Primary Care Clinical Guidelines for Diagnosis and Disease Management

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Abstract

In pediatric genetic practice, the follow-up and treatment of some chronic diseases such as Ehlers-Danlos Syndrome (EDS) is of particular importance. EDS is a heterogeneous group of inherited diseases with joint hypermobility, skin hyperextensibility, and tissue fragility. There is no specific treatment for EDS. Follow-up and cure treatment continue to prevent severe compositions and to treat symptoms. Correct management may be vital for these children, as well as for increasing their quality of life.

Keywords: Ehlers-Danlos Syndrome; Connective tissue; Hypermobility; Quality of life.

Keynotes: The incidence of rare diseases such as EDS is increasing day by day. Proper management of the problems that these children are at risk of encountering is of great importance in terms of public health. Correct timing may be vital for these children, as well as for increasing their quality of life.

Introduction

Ehlers-Danlos Syndrome (EDS) is a group of inherited connective tissue disorders caused by abnormalities in the structure, production, and processing of collagen and some related proteins [1]. According to the new classification published by the International EDS Consortium in 2017 to replace the Villefranche classification, 13 EDS subtypes have been defined [2]. A new type was subsequently reported, bringing the number to 14 [3]. Signs and symptoms can range from mildly loose joints to life-threatening complications. Features shared by many subgroups include joint hypermobility and the presence of supple, soft, velvety skin that can easily bruise. There are 20 known genes associated with EDS. In order to appropriately plan the follow-up and treatment of patients with this disease group, it is first necessary to be familiar with the clinical findings.

Classification through Clinical Criteria

In addition to the heterogeneous clinical features of EDS subtypes, the new classification offers the possibility of validation with molecular data for all subtypes except the "hypermobile type" (Table 1) [2,3,4]. The characteristics of the rare types are also presented in Table 1.

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Table 1: General characteristics of rare EDS types and responsible genes.

TYPE	GENE(S) RESPONSIBLE	INHERITANCE PATTERN
Classic (cEDS)	**COL5A1, COL5A2, rarely COL1A1**	**AD**
Hypermobile (hEDS)	**?**	**AD**
Vascular (vEDS)	**COL3A1, rarely COL1A1**	**AD**
Classical-like (cllEDS)	**TNXB**	**AR**
Characterized by velvety skin texture and excessive laxity of the skin, generalized joint hypermobility (GJH) with or without recurrent dislocations (mostly shoulder and ankle), and easily bruised skin or spontaneous ecchymoses (discoloration). Atrophic scars are not observed.		
Cardiac-valvular (cvEDS)	**COL1A2**	**AR**
Characterized by severe progressive cardiac-valve problem, skin problems (hyperextensibility, atrophic scars, thin skin, easy bruising), and joint hypermobility (generalized or limited to small joints).		
Arthrocalazik (aEDS)	**COL1A1, COL1A2**	**AD**
Characterized by severe generalized joint hypermobility, moderate skin involvement, and osteopenia. Especially the presence of congenital hip dislocation should suggest aEDS.		
Dermatosparaxis (dEDS)	**ADAMTS2**	**AR**
Loose fragile skin, hernias and dysmorphic findings characterize it.		
Kyphoscoliotic (kEDS)	**PLOD1, FKBP14**	**AR**
Characterized by severe muscular hypotonia, progressive kyphoscoliosis, marfanoid habitus, osteopenia, and rarely rupture of the great vessels or the eyeball, which may become noticeable soon after birth. The joints are severely hypermobile. They can be misdiagnosed as neurologic diseases because of hypotonia. Aneurysmal dilatation and tortoise arteries may be seen. Other common features include a "marfanoid habitus" characterized by long, thin fingers (arachnodactyly), unusually long extremities, and "pectus excavatum" or "pectus carinatum".		
Brittle Cornea Syndrome	**ZNF469, PRDM5**	**AR**
It is characterized by a thin cornea, blue sclera, and early onset of progressive keratoglobus.		
Spondylodysplastic (spEDS)	**B4GALT7, B3GALT6, SLC39A13**	**AR**
They are hypotonic children with short height. Congenital contractures may be observed. It is misdiagnosed with OI because of multiple spontaneous fractures due to increased bone fragility. There are skeletal dysplasia findings in long bones and vertebrae.		
Musculocontractural (mcEDS)	**CHST14, DSE**	**AR**
Musculocontracture-type congenital contractures are present. In addition, specific ocular findings such as characteristic facial appearance, colonic diverticula (risk of severe perforation), renal anomalies, cryptorchidism, and severe glaucoma are observed. Skin hyperextensibility, easily bruised atrophic scars, increased palmar wrinkles.		
Myopathic (mEDS)	**COL12A1**	**AD, AR**
Congenital hypotonia, proximal joint contractures (knee, hip, and elbow joints), and hypermobility of distal joints (ankles, wrists, feet, and joints of the hands) are observed.		
Periodontal (pEDS)	**C1R, C1S**	**AD**
In addition to findings such as blue sclera, Hafik joint laxity, thin skin, and delayed wound healing, patients with gingival disorders and periodontitis that cause early loss of teeth are included in this group.		
Classical-like - 2 (cll2EDS)	**AEBP1**	**AR**
Flexible skin, delayed wound healing, easy bruising, atrophic scars, and markedly loose, sagging, thin translucent skin appear. Generalized joint laxity, multiple joint luxations/subluxations (especially hip and shoulder), distal joint deformities, visceral tissue involvement, and partial alopecia may accompany.		

The most common three types

Classical EDS (cEDS)

It is characterized by loose to velvety skin, joint hypermobility, fragile tissue, delayed wound healing, and atrophic scars. According to the committee decisions, the clinical diagnosis of cEDS requires the presence of 2 major or 1 major and 3 minor criteria (Table 2) [2,5,6].

Table 2: cEDS diagnosis criteria.

Major Criteria
1. Skin hyperextensibility- laxity* and atrophic scars 2. Generalized joint hypermobility (Beighton scoring) **
Minor Criteria
1. Easy bruising (especially in the pretibial region, which is often dark due to hemosiderin deposition from bruising caused by repetitive trauma) 2. Soft, doughy skin 3. Increased tissue fragility 4. Molluscoid pseudotumors (Herniated fatty tissue usually seen in areas subjected to pressure such as fingers and elbows) 5. Subcutaneous spheroids (round, hard, mobile nodules, often palpated under the skin on the forearm and proximal tibial process) 6. Hernias (should also be questioned in the story) 7. Presence of complications secondary to joint hypermobility such as luxation/subluxation, pain, flatfoot 8. Epicanthal folds 9. Family history

*Skin elasticity can be determined by pulling the skin on the volar aspect of the forearm. Elongation is considered pathologic if it exceeds 1.5 cm in the distal forearm and dorsum of the hand and 3 cm in the neck, elbow, and knee skin. Spheroids can also be visualized radiologically when calcified [2]. **According to the Beighton scoring, a score of 6/9 in children up to puberty (5/9 after puberty) and above is considered positive

Hypermobile EDS (hEDS)

Primarily affecting both large and small joints, characterized by marked joint hypermobility with subluxations, moderate skin involvement, and lack of fragility in tissues. They complain of easy bruising and chronic pain in muscles and bones. Degeneration of the joints often develops. The presence of the "three criteria" in table 3 clinically diagnoses hEDS [2,7].

Table 3: hEDS diagnosis criteria.

CRITERION 1
Presence of generalized joint hypermobility (GJH) (Beighton scoring)
CRITERION 2
"Criterion 2 is considered positive" when any two of the following findings are present together: **Finding a**. Presence of systemic findings suggestive of generalized connective tissue involvement * **Finding b**. Presence of positive family history ** **Finding c**. Presence of expected musculoskeletal complications ***
CRITERION 3
Exclusion criteria. The presence of at least one of the following excludes the diagnosis of hEDS; Presence of fragile skin (seen in other types of EDS) Presence of other known inherited or acquired connective tissue diseases, including autoimmune rheumatologic diseases Presence of alternative diagnoses that may cause hypotonia and/or connective tissue

*** To call finding "a" positive, at least 5 of the following findings must be present;** [1] extremely soft, velvety skin [2], increased skin elasticity, even mildly [3], striae (if there is no other cause) [4], bilateral "piezogenic" heel papules [5], recurrent/multiple hernias (umbilical, inguinal) [6], atrophic and/or hemosideric scars in at least 2 locations [7], rectum, uterine prolapse (unless there is another underlying cause) [8], crowded teeth and high or narrow palate [9], arachnodactyly [10], toe length/height ≥ 1. 05, 11MVP, 12aortic root dilatation (Z score >+2).

****** For **finding "b"** to be considered positive, at least 1 of the first-degree relatives must meet the diagnostic criteria for EDS.

***For **finding "c"** to be considered positive, the presence of at least one of the following for the musculoskeletal system [1] musculoskeletal pain (lasting at least three months involving at least two extremities) [2], chronic widespread pain (longer than three months) [3], recurrent joint dislocations or significant instability (without trauma) [4], three or more dislocations in the same joint or two or more dislocations in 2 different joints at different times [5], instability in at least two joints [2].

Vascular EDS (vEDS)

Life expectancy is remarkably shortened due to the increased risk of spontaneous rupture of internal organs such as arteries, uterus, and intestines. The skin in these patients is thin, fragile, and translucent but not hyperelastic. In addition, joint hypermobility is limited to small joints. The rate of gonadal mosaicism in families of sporadic cases diagnosed with vEDS is reported to be approximately 23%. (3/13) The rate is too high to be ignored. This rate varies between 11-20% in patients with Hemophilia A-B, DMD, and FSHD [2,8].

If a positive family history, arterial rupture occurring under the age of 40, unexplained sigmoid colon rupture, or spontaneous pneumothorax is accompanied by any finding suggestive of EDS, or if more than one vEDS minor criterion is present together, molecular examination for vEDS is recommended (Table 4) [2].

Table 4: vEDS diagnosis criteria.

Major Criteria
Presence of positive family history Arterial rupture Spontaneous rupture of sigmoid colon (if there is no diverticulum, etc. intestinal pathologies) Uterine rupture associated with pregnancy Spontaneous carotid-cavernous fistula
Minor Criteria
Observation of bruises without obvious trauma or in unusual areas Thin translucent skin (thinned so that the underlying veins can be clearly observed) Characteristic facial appearance (large eyes, a thin nose, and lobeless ears) Acrogeria (premature aging of the skin of the hands and feet) Hypermobility in small joints Varicose veins observed at an early age Congenital hip dislocation Spontaneous pneumothorax "Talipes equinovarus" Tendon, muscle ruptures Keratoconus Gingival recession, fragility

Follow-Up Treatment

There is no known specific treatment for EDS. Follow-up and treatment should be planned individually based on the patient's current findings, considering the underlying mutation. It should be kept in mind that the findings may differ even among family members. Regardless of the subgroup, follow-up, and treatment require a multidisciplinary approach. Protocols have been established to prolong life and ensure a complication-free life.

Carrying a bracelet or necklace with the patient's diagnosis on it can be life-saving in some cases. It should be hung on a place such as a refrigerator at home (it is one of the first places 911 will look when they arrive). Care should be taken when suturing skin and organ injuries and strip/wound adhesive should be preferred if possible. It should be ensured that certain precautions are taken in diagnosed patients and that the patient and family are informed in as much detail as possible about the activities to be avoided. Traumas should be avoided because the skin can be injured even with minor trauma, and wound healing is slow. It is also important that the home organization should be made accordingly.

It is important to ensure that the patient is included in national/international disease groups, that they are constantly connected so that they can attend conferences on the subject, and that they are constantly in contact with environments where up-to-date data such as social media, "webinars," "web" sites, new publications are shared.

Rest, good nutrition, plenty of fluids, and an active but careful lifestyle are important. Restricting potential irritants such as carbohydrates, caffeine, alcoholic beverages, and processed foods is recommended.

In every environment where the child is present, an adult, such as the family, class teacher, or counselor, should be informed about the subject. The child should know about his/her illness, what to pay attention to, and who to contact when he/she has a problem.

The child should also be informed in advance so that he/she can cope with the problems he/she experiences when he/she is alone. For example, when experiencing anxiety, suggestions such as taking five deep breaths or counting the alphabet backward can make the child feel better. Suggestions such as resting when in pain, massage, and using heat pads should be conveyed to the child to improve the quality of life.

The family and school should work together. If he/she has difficulty writing, he/she should be given special thick pens, a "keyboard," or a voice recording system. It would be good for him/her to keep a detailed diary about the nature and frequency of his/her complaints, the medications he/she is taking, and the problems he/she is experiencing. The child should be made to feel that he/she is very valuable, deserves everything, and should be encouraged to make new friends and experiences.

Adolescence is difficult for every child. However, these children may feel lonely and have difficult days with the addition of disease-related symptoms such as inadequacy, chronic fatigue, and excessive restlessness. It will be useful to let them know this is normal and to ensure they receive psychological support.

These patients should be monitored for the development of scoliosis, incontinence, constipation, diarrhea, blood pressure, depression, anxiety, and excessive weight gain, and necessary precautions should be taken.

The patient and/or his/her family should be informed in detail about the mode of inheritance, recurrence risks, prognosis, and complications. Other family members should also be screened.

The treatment approach should be individualized. The aim is to reduce complaints, improve functional capacity and quality of life. In addition to recommendations for the common symptoms seen in almost all patients, follow-up and treatment options for symptoms specific to certain types should be planned in detail for each patient.

Monitoring and Treatment of the Most Common Problems. Specific Solutions [2,9-13]

Pain

It is one of the most common problems the patient has to cope with. To determine the pain level, a classification is made by asking patients to give a score between 1-10. It absorbs the person's energy, restricts activity, and causes sleep disturbance and depression, ultimately leading to chronic fatigue. The child needs to recognize his/her body, change position frequently, and learn the posture that is right for him/her. Head and neck pains increase if the child stands in the wrong posture for a long time. It is also very important to provide physical therapy support for such findings that increase with age to improve quality of life. The patient should listen to their body, be aware of themselves, learn to move slowly and safely and protect their joints.

The patient's choice of shoes is very important because it affects all joints, such as ankles, knees, spine, and neck. "Flip flop" slippers should not be used. Resting the extremity in a water bath prepared with "Epsom salt" provides significant relief.

Regular but not heavy exercises should be recommended, as hypermobile joints need firm and strong muscles to ensure stability. Activities such as cycling, swimming, and games with friends should be integrated into his/her life.

Physical activity provides strength, endurance, and stability. Ensuring joint stability is very important. At least 60-90 minutes of daily work and exercise programs such as yoga for about 1 hour 3 times a week should be recommended. The most important point when applying these exercises is to emphasize that the patient should take a break when he/she feels that he/she cannot maintain joint stability and continue exercising after resting.

Different pain types require different treatment approaches for inflammatory pain, NSAIs (ibuprofen, celecoxib, etc.), steroids for mechanical pain, muscle relaxants (cyclobenzaprine, tizanidine), warm application, massage, physical therapy, dry needles should be recommended. Neuropathic pain (expressed as burning) can be prevented with gabapentin, pregabalin, duloxetine, and milnacipran. Physical therapy, home exercises, acupuncture, and devices such as TENS (Transcutaneous Electrical Nerve Stimulation) provide very useful results. In more severe cases, antidepressants (duloxetine), neuropathic analgesics (gabapentin), muscle relaxants, and local treatments such as cream gel, patches, opioids, and cannabinoids (in some countries) may be recommended.

As the condition becomes chronic, depression arises because of the behavior of trying to ignore the pain. It is important to remember that someone depressed does not necessarily look sad. Neurotransmitter deficiencies can be present even when clinical depression is not evident. Hugging family members or feeding animals may be more effective than medication.

Sleep Disturbances

It can take various forms; they sleep little, wake up often, or cannot fall into a deep sleep. Different types of sleep disorders require different treatments. Sleep monitoring and cardiac monitors can help identify this:

1. If there is difficulty falling asleep, environmental factors such as anxiety, pain, restless legs, uncomfortable bed, noise, and light (they are more sensitive to sound and light due to autonomic dysfunction) may be the cause.

2. If they wake up after a short time and have difficulty falling asleep again; pain, sleep apnea, snoring, and dreams may be factors

3. Sleep disturbance may sometimes manifest as not waking up rested despite sleeping. For reasons similar to the above, the patient cannot have quality sleep or experience all sleep phases.

It would be beneficial to ensure regular sleep periods in a comfortable, quiet environment, if possible, at the same time every night. Patients with sleep problems may be advised to create a routine beforehand, such as drinking herbal tea or reading. In this way, the body can be made to feel that it is time to sleep. Attention should be paid to hygiene, a comfortable bed, a dark and quiet environment should be provided, and problems such as sleep apnea and pain, if any, should be solved. If necessary, sleep medication may be recommended in consultation with neurologists.

Dysautonomia

Autonomic dysfunction in patients with EDS may increase the problem of stabilization of already hypermobile joints. It may present with findings such as dizziness, feeling of imbalance, and falls. It may cause minor restlessness/ stress/ excessive response to stimuli and mood fluctuations. It is important to rule out all other neurologic, metabolic, and cardiac causes.

Chronic Fatigue - Exhaustion

EDS can cause chronic fatigue, like many diseases. Pain, sleep disorders, and depression are the most important underlying causes. In addition, autonomic system dysfunction (often overlooked), anemia, metabolic factors, lack of adequate rest, emotional stresses, and daily living conditions may also play a role. Each of these can trigger the other. If any one of them is ignored, no improvement will be seen. Each individual shows different symptoms, and each patient responds differently to medication and various treatments. Diversity is almost the law.

Monitoring and Treatment of Rare Problems. Specific Solutions

In rarer types of EDS, problems related to different systems may be observed more frequently. Follow-up and treatment recommendations for these systems can be summarized in Table 5 [4,6,12,14-20].

Table 5: Monitoring and treatment for rarer problems.

CARDIOVASCULAR SYSTEM
Rare cases of Classical EDS due to COL1A1 mutations, Cardiac-valvular EDS (COL1A2), Kyphoscoliotic EDS (PLOD1, FKBP14), Spondylo-dysplastic EDS (B3GALT6, B4GALT7, SLC39A13) and Vascular EDS patients should be monitored with respect to cardiovascular problems.
In these patients, an echocardiographic examination (ECHO) should be performed at the time of diagnosis and/or at the age of 5, especially to evaluate the aortic root and heart valves. ECHO control is recommended at 1-2 years intervals depending on the findings and type of the patient. Blood pressure should be kept within normal limits
OPHTHALMIC
Detailed ophthalmic evaluation should be performed in Dermatosparaxis EDS (ADAMTS2), Kyphoscoliotic EDS (PLOD1, FKBP14), Brittle cornea syndrome (ZNF469, PRDM5), and Musculocontractural EDS (CHST14, DSE).
Routine ophthalmic examination at the time of diagnosis and repeat examinations at 1 to 2-year intervals thereafter are recommended. The use of protective polycarbonate eyeglasses to prevent corneal rupture, especially in patients with "Brittle" corneal syndrome, can be necessary.
ENT
Kyphoscoliotic EDS (FKBP14), "Brittle cornea" Syndrome (ZNF469, PRDM5), Musculocontractural EDS (CHST14, DSE) and Spondylodysplastic EDS (B3GALT6).
Hearing evaluation at the time of diagnosis and routine audiometric monitoring is recommended in patients
TEETH AND GUMS
Dermatosparaxis EDS (ADAMTS2), Spondylodysplastic EDS (B3GALT6), and Periodontal EDS (C1R, C1S9)
Regular examinations and resolution of detected problems are recommended.

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