Handbook of Genetic Counseling/Ehlers-Danlos Syndrome

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Ehlers-Danlos Syndrome

Contracting

- Introductions, acknowledge any prior contact
- Assess main concerns of patient
  - Why are they visiting Genetics today?
  - What do they hope to gain from the session?
  - Assess knowledge of diagnosis -- any questions?
- Overview of today's session
  - Restate patient's concerns
  - Medical history, family history, physical exam, genetics, recurrence risk, testing options and limitations

Pediatric Intake

- Pregnancy and Medical History
  - umbilical/unguinal hernia? prematurity? cervical incompetence?
- Developmental History
  - learning disabilities?
- Family History
  - heart problems? joint hypermobility? stretchy skin? fragile skin? easy to scar? scoliosis? easy bruising? congenital hip dislocations? stroke? umbilical/inguinal hernias? early loss of teeth?

Incidence and Carrier Frequency

- no well-founded figures for prevalence
- for all forms, estimates of 1/5000 have been made

Clinical Features

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  - a group of clinically diverse inherited connective tissue disorders that

have joint laxity and dermal features in common **

- Classical (Type I and Type II)
  - Major diagnostic criteria
    - Hyperextensibility of the skin
    - Widened atrophic scars
    - Joint hypermobility
      - Can lead to osteoarthritis in the 3rd or 4th decade
  - Other features
    - Poor wound healing

        - ½ of affected individuals are delivered up to 1 month premature due to premature rupture of fetal membranes
        - Some have cardiac abnormalities
            - Mitral valve prolapse
            - Aortic root dilation with occasional rupture
        - Scoliosis
        - Pes planus (flatfoot)
        - Molluscoid pseudotumors (calcified hematomas) may be associated with scars
    - Inheritance
        - Autosomal dominant single-gene disorder
    - Etiology
        - A major cause is mutations in type V collagen
        - At least 3 loci are involved
    - Biochemical Defects
        - Thickened collagen fibrils in skin as well as "cauliflower" deformities of collagen fibrils
        - Mutations in COL5A1 and COL5A2 have been seen in some families
    - Testing
        - No biochemical or molecular based testing methods have been devised to provide reliable results
- Hypermobility Type (Type III)
    - Primary characteristics
        - Hyperextensibility of large and small joints
        - Soft, velvety skin
    - Other features
        - May have normal scarring but stretchy skin
        - Dilatation and/or rupture of the ascending aorta
        - Scoliosis
        - Pes planus
    - Inheritance
        - Autosomal dominant single-gene disorder
    - Diagnosis is clinical
- Vascular Type (Type IV)
    - Major diagnostic criteria
        - Characteristic facial appearance
        - Thin, delicate, "pinched" nose
        - Thick lips
        - Hollow cheeks
        - Some have staring appearance due to decreased adipose tissue below the eyes
        - Thin, translucent skin
            - In fair-skinned individuals, subcutaneous vasculature is easily visible beneath the skin
        - Arterial/intestinal/uterine fragility or rupture which can be life threatening
        - Extensive bruising
    - Other characteristics
        - Normal scar formation
        - May be increased incidence of stroke
        - Acrogeria (aged appearance to extremities, particularly hands)
        - ¼ of affected individuals experience a significant medical problem by age 20
        - Median age of death is 48 years old
    - Inheritance
        - Autosomal dominant as demonstrated by linkage analysis
    - Etiology (COL3A1 gene)
        - Dominant mutations in the gene for the pro-alpha 1 chain of type II collagen
        - Caused by abnormal synthesis, structure, or secretion of type II collagen

        - 50% have new disease-causing mutations
        - Over 250 COL3A1 disease-causing mutations have been found
    - Testing
        - Can be reliably accomplished by analysis of type III procollagen and collagen chains harvested from cultured dermal fibroblasts
- Kyphoscoliosis type (type VI)
    - Key features
        - Neonatal onset of joint laxity
        - Kyphoscoliosis (lateral curvature of the spine accompanying an anteroposterior hump)
        - Muscle hypotonia
    - Other features
        - Ocular fragility
        - Skin fragility
        - Easy bruisability
        - Dermal hyperextensibility
        - Risk for arterial rupture
        - Most have radiologically detectable osteopenia (decreased bone density), but pathological fractures are rare
        - Intelligence is normal
        - Lifespan may be normal
    - Etiology
        - Caused by deficient activity of the enzyme procollagen lysine hydroxylase
    - Inheritance
        - Autosomal recessive
    - Testing
        - Diagnosis depends on demonstration of increased ratio of deoxypyridinoline to pyridinoline crosslinks in urine measured by HPLC
        - Mutation analysis of the PLOD gene that encodes the enzyme procollagen lysine hydroxylase is available on a research basis
        - Carrier testing is not available
- Arthrochalasia type (types VIIA, VIIB)
    - Major criteria
        - Severe generalized joint hypermobility
        - Congenital bilateral hip dislocations that are difficult to repair surgically
    - Other features
        - Tissue fragility including atrophic scars
        - Kyphoscoliosis
        - Skin hyperextensibility
    - Etiology
        - Caused by a failure to accomplish normal cleavage of the amino-terminal propeptide of type I collagen in all tissues
        - Mutations that remove exon 6 in COL1A1 and COL1A2 are seen
    - Inheritance
        - Autosomal dominant
    - Testing
        - Demonstration of exon 6 skipping in cDNAs of COL1A1 or COL1A2 followed by mutational analysis
- Dermatosporaxis type (type VIIC)
    - Very rare form of EDS
    - Diagnostic Features
        - Dermal fragility: the skin is lax but not stretchy
    - Other features
        - Joint dislocation is usually not a feature
        - Infants have been reported with premature rupture of membranes and

umbilical/inguinal hernias
    - Etiology
        - Caused by failure to cleave off the amino-terminal propeptide of type I collagen due to deficiency of the procolagen I N-peptidase gene
    - Inheritance
        - Autosomal recessive
- Other variants (VIII, V X-linked, X)
    - Type VIII
        - Rare autosomal dominant condition
        - Characterized by soft, hyperextensible skin, abnormal scarring, easy bruising, hyperextensible joints and generalized periodontitis
        - Resembles type I, but is distinguished by early loss of teeth and characteristic purplish discoloration of scars on the shins
        - Molecular basis is unknown
        - Not clear if it is truly distinct from classical form
    - Type V X-linked
        - Similar to mild classical type
        - X-linked recessive inheritance
        - Unknown molecular defect
    - Type X
        - Joint hyperextensibility, mitral valve prolapse, easy bruising, poor wound healing, clotting disorder
        - Clotting studies showed a defect in the platelet adhesion that is normally observed in response to exposure of platelets to collagen
        - May be caused by a defect in fibronectin

Management and Treatment

- Pregnancy
    - All cases should be referred to high-risk obstetric practice
    - Prematurity is a concern
    - Cervical incompetence can be treated with bed rest and the Trendelenburg position
- Musculoskeletal
    - P/T can improve strength of muscles surrounding lax joints
    - Surgical procedures can correct dislocation
    - Intervention for pain management is necessary
    - An exercise program can strengthen muscles and stabilize joints
- Cardiovascular
    - Enlarged aortic root can be treated with beta blockers but the efficacy or length of treatment is currently unknown
    - Exercise limitation may be necessary, especially competitive sports
    - Surgical complications and intraoperative problems are common
- Dermatologic
    - Plastic surgery can be done to close facial wounds or other aesthetically significant areas
    - Retention sutures tied at a distance from the incision may help support the skin during scar formation

Psychosocial Issues

- Self esteem
    - scars, bruising, scoliosis
- Financial concerns?
- Guilt at passing on mutation

- Pain management issues
- support network?
    - family? friends? church?

Support Groups and Resources

- Ehlers-Danlos National Foundation

  800-956-2902
  http//:www.ednf.org

- Ehlers-Danlos Support Group

  http//:www.ehlers-danlos.org

- Family Village

  http//:www.familyvillage.wisc.edu/lib_e-ds.htm

References

- www.geneclinics.org
- Management of Genetic Syndromes (Allanson and Cassidy)
- OMIM #130000, #130010, #130020, #130050, #305200, #225400, #130060, #130080

Notes

The information in this outline was last updated in 2002.