ORIGINAL ARTICLE

Clinical Features of Ehlers-Danlos Syndrome

Jui-Lung Yen,[1,2,3] Shuan-Pei Lin,[1,2,4,5] Ming-Ren Chen,[1,4] Dau-Ming Niu[6]*

Background/Purpose: Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous connective tissue disorder characterized by hyperextensibility of the skin, hypermobility of joints, and tissue fragility. This retrospective study analyzed the characteristics of patients with EDS.

Methods: Review of medical records identified 16 cases of EDS during the study period from November 1997 to October 2002. Data on these patients, including clinical presentation, physical examinations, Beighton score, echocardiogram, bone mineral density findings and clinical classification, were analyzed.

Results: The age of the patients ranged from 13 months to 36 years. All patients had skin hyperextensibility, joint hypermobility (Beighton score > 5 points), and tissue fragility. Complete bone mineral density study was performed in 11 patients and revealed that all had osteoporosis. Echocardiographic study was performed in 14 patients and showed aortic root dilatation/valve prolapse in 6/14 (43%). Other common features of EDS had the following prevalence: premature rupture of membranes in 3/16 (19%); prematurity in 3/16 (19%); neonatal hypotonia in 5/16 (31%); congenital hip dislocation in 3/16 (19%); unstable gait in 7/16 (44%); bone fracture(s) in 3/16 (19%); motor delay in 3/16 (19%); scoliosis in 3/16 (19%); short stature in 7/16 (44%); and positive family history in 8/16 (50%). All patients had a Beighton score of more than 5 points.

Conclusion: The results of this study emphasize the importance of echocardiographic monitoring of aortic size and valvular condition, and assessment of bone mineral density in patients with EDS. Clinical evaluation and counseling should be undertaken prior to pregnancy in patients with EDS because of the risk from labor and vaginal delivery in patients with type IV and the inability to distinguish EDS subtypes in Taiwan due to the unavailability of biochemical assay or molecular mutation analysis as part of standard care. [*J Formos Med Assoc* 2006;105(6):475–480]

Key Words: aortic dilatation, Ehlers-Danlos syndrome, joint hypermobility, skin fragility, skin hyperextensibility

The first comprehensive description of a syndrome comprising laxity and fragility of the skin associated with hypermobility of the large joints was published in 1892 by Tschernogobow in Moscow.[1] The eponym of Ehlers-Danlos syndrome (EDS) was first suggested by Poumeau-Delille and Soulie.[2] It currently describes a group of connective tissue disorders distinguished not only by the triad of skin hyperextensibility, joint hypermobility and tissue fragility, but also by its heterogeneity on clinical, genetic, and biochemical grounds.[3]

In 1988, Beighton et al published an international nosology of connective tissue disease where nine subcategories of EDS were defined.[4] Subsequently, they correlated the subtypes with various biochemical and molecular abnormalities and also published an equivalent molecular nosology,[5] both of which were revised in 1998.[6] Most cases are types

Departments of [1]Pediatrics and [2]Medical Research, Mackay Memorial Hospital, [3]Department of Pediatrics, Taipei City Hospital, Branch for Women and Children, [4]Mackay Medicine, Nursing, and Management College, [5]Department of Infant and Child Care, National Taipei College of Nursing, and [6]Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan.

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***Correspondence to:** Dr. Shuan-Pei Lin, Department of Pediatrics, Mackay Memorial Hospital, 92, Section 2, Chungshan North Road, Taipei 10449, Taiwan.
E-mail: zsplin@ms2.mmh.org.tw

I (gravis type), II (mitis type) or III (hypermobile type), which consist of approximately 30% each; approximately 10% of cases are type IV (ecchymotic type), and the remaining subtypes are rare.[7] EDS is currently classified into 10 clinical forms.[8] Heterogeneity among these clinical forms both complicates the diagnosis of EDS and makes accurate diagnosis imperative. Identification of the syndrome is paramount because of its potentially life-threatening associations and unique requirements for management.

The prevalence of all forms of EDS was previously estimated at 1:150,000, but recent reports suggest a higher prevalence of 1:5000.[6,7] This increase in prevalence may be because the disorder has become easier to diagnose, and more subtypes are being identified. EDS affects all races and ethnic groups without sex predominance.[6] A thorough knowledge of the pregnancy, musculoskeletal, cardiovascular, gastrointestinal and dermatologic manifestations of EDS and their management is mandatory to prevent unnecessary morbidity and mortality. Although EDS has been widely reported in the medical literature, there is a relative lack of reports in the Taiwanese literature. This retrospective study analyzed the characteristics of patients with the clinical presentation of EDS in two medical centers in Taiwan.

Methods

This retrospective study analyzed the clinical characteristics of patients with EDS treated between November 1997 and October 2002 at the Department of Pediatrics of both Mackay Memorial Hospital and Taipei Veterans General Hospital. Sixteen patients with clinical features of EDS treated during this period were included. Most of the patients were seen in genetics clinics, some were referred by orthopedists and neurologists, or from local hospitals.

The data analyzed included family history, birth history, clinical presentation, findings of physical examinations with Beighton score evaluation, results of echocardiography and follow-up data. Bone mineral density of total body (BMD_{TB}, g/cm^2) was determined by dual energy X-ray absorptiometry (DXA). Due to the lack of available reference data for BMD with DXA in Taiwanese children, normative reference data obtained from the literature[9–11] were used in this study. These BMD results were converted to age-specific T-scores. According to the classification used by our radiologists, osteopenia was defined as a T-score less than one standard deviation below the mean (< –1 SD) and osteoporosis as a T-score < –2 SD.

Hypermobility was assessed using the scale derived by Beighton as follows: (1) passive dorsiflexion of the little fingers beyond 90°, one point for each hand; (2) passive apposition of the thumbs to the flexor aspect of the forearm, one point for each hand; (3) hyperextension of the elbows beyond 10°, one point for each elbow; (4) hyperextension of the knees beyond 10°, one point for each knee; and (5) forward flexion of the trunk with knees fully extended and the palms of the hands being able to rest flat on the floor, one point.[12] Joint hypermobility was defined as a score of 5/9 or greater.

Results

Table 1 lists the findings of physical examination, Beighton score evaluation, BMD_{TB} data, echocardiogram and clinical classification of the patients. The clinical characteristics, complications and imaging findings are summarized in Table 2. There were nine male and seven female patients with age ranging from 1 year 6 months to 36 years (mean, 11.3 years). All patients presented with skin hyperextensibility and joint hypermobility (Figures 1 and 2), all with Beighton score above 5 points (range, 6–9), and tissue fragility with ecchymosis or easy bruising. Features associated with EDS had the following prevalence: premature rupture of membranes (PROM) in three (19%) patients, prematurity in three (19%), neonatal hypotonia in five (31%), congenital hip dislocation in three (19%), unstable gait in seven (44%), bone fracture(s) in three (19%), motor developmental de-

lay in three (19%), scoliosis in three (19%), short stature (body height, < –2 SD) in seven (44%), and positive family history in eight (50%). Complete BMD_{TB} study was performed in 11 patients and all had underlying osteoporotic problems (T-score, < –2 SD). There were also 14 patients who received echocardiogram examination, of whom six (43%) had mild aortic root dilatation/valve prolapse. The 36-year-old female patient died of uterine rupture in the 37th gestational week of her second pregnancy in spite of her physician's strong suggestion of earlier cesarean section.

Discussion

The diagnosis of EDS is mainly based on clinical presentation, family pedigree analysis, and, if possible, is confirmed by demonstration of specific biochemical or genetic defects. Recognition of the disease on clinical grounds can be difficult because skin elasticity and joint mobility are graded and subjective traits. Physical examination, however, remains the initial step in the diagnosis of EDS. All of the 16 patients included in this study had clinical characteristics of EDS. Joint mobility may be quantified by the Beighton score. Pedigree analysis may be helpful to classify patients who are thought to have EDS because inheritance patterns differ among subtypes.[13] Half of the patients in this study had a positive family history, although the phenotypes were highly variable individually. Growth or feeding problems in EDS are rare and none was detected in this series. Developmental and behavioral problems, however, are more frequently observed and motor delay can sometimes be seen in patients with inability to stabilize the joints due to EDS. Motor delay problems requiring early intervention with rehabilitation were found in nearly one fifth (19%) of our patients. Standard pediatric developmental assessment is required for evaluation of motor delay in patients with EDS.

Complications of pregnancy and delivery are related to the subtype of EDS involved, and it is recommended that all pregnant patients with

Table 1. Clinical data, Beighton score, total BMD data, findings of echocardiogram and clinical classification in patients with EDS

Case	Gender	Age	BMD_{TB} (g/cm^2) / T-score / Examined age	Echocardiogram / Examined age	Others	Clinical classification*
1	Male	9 yr 9 mo	0.615 / < –2 SD / 9 yr 4 mo	Aortic dilatation / 8 yr 3 mo	Neonatal hypotonia, FH	Type I
2	Female	5 yr 5 mo	0.532 / < –2 SD / 5 yr	Negative / 4 yr 7 mo	Myopia, prematurity, PROM, FH	Type I
3	Male	19 yr 3 mo	0.768 / < –2 SD / 18 yr	Not evaluated	Neonatal hypotonia, pes planus, PROM, scoliosis	Type I
4	Male	5 yr 6 mo	Not evaluated	Negative / 5 yr	FH, unstable gait	Type III
5	Male	9 yr	0.733 / < –2 SD / 9 yr 1 mo	Negative / 9 yr		Type III
6	Female	3 yr	Not evaluated	Negative / 2 yr 2 mo	Neonatal hypotonia	Type I
7	Male	9 yr 5 mo	0.650 / < –2 SD / 9 yr 1 mo	Aortic dilatation / 6 yr 7 mo	Ptosis, easy epistaxis, FH	Type I
8	Male	8 yr	0.701 / < –2 SD / 7 yr 4 mo	Negative / 7 yr 4 mo	FH	Type II
9	Male	23 yr 7 mo	0.699 / < –2 SD / 23 yr	Aortic dilatation, MVP / 21 yr	Pes planus, scoliosis	Type I
10	Male	10 yr 4 mo	0.496 / < –2 SD / 10 yr	Aortic dilatation / 10 yr	Easy UGI bleeding, scoliosis	Type IV
11	Male	2 yr 5 mo	0.344 / < –2 SD / 1 yr 3 mo	PPS / 1 yr 3 mo	Neonatal hypotonia, FH	Type I
12	Female	1 yr 6 mo	Not evaluated	PPS / 1 yr	Neonatal hypotonia, PROM	Type I
13	Female	3 yr 9 mo	0.631 / < –2 SD / 3 yr 2 mo	Aortic dilatation, MVP, MR / 3 yr 2 mo	Ptosis, lens subluxation, FH	Type I
14	Female	25 yr	0.525 / < –2 SD / 25 yr	Not evaluated	Blue sclera, FH	Type II
15	Female	6 yr 10 mo	Not evaluated	Negative / 6 yr	Ptosis	Type II
16	Female	36 yr	Not evaluated	Right aortic arch	One live child, 2nd pregnancy ended in uterine rupture	Type IV

**Type I = gravis type; Type II = mitis type; Type III = hypermobile type; Type IV = ecchymotic type. BMD_{TB} = bone mineral density of total body; FH = positive family history; MR = mitral valve regurgitation; MVP = mitral valve prolapse; PPS = peripheral pulmonary stenosis; PROM = premature rupture of membranes; SD = standard deviation; UGI = upper gastrointestinal.*

Table 2. Clinical presentations, imaging study findings and features in 16 patients with Ehlers-Danlos syndrome

	n (%)
Clinical presentations of triad	
Skin hyperextensibility	16 (100)
Joint hypermobility (Beighton score > 5 points)	16 (100)
Tissue fragility with ecchymosis or easy bruising	16 (100)
Imaging study	
Osteopenia/osteoporosis	11/11 (100)
Aortic dilatation/valve prolapse	6/14 (43)
Features	
Positive family history	8 (50)
Unstable gait	7 (44)
Short stature (body height < –2 SD)	7 (44)
Neonatal hypotonia	5 (31)
Premature rupture of membranes	3 (19)
Premature birth	3 (19)
Congenital hip dislocation	3 (19)
Frequent bone fracture(s)	3 (19)
Motor developmental delay	3 (19)
Scoliosis	3 (19)

EDS be referred to a high-risk obstetric practice, neonatologist and geneticist in a medical center. The risk of severe uterine hemorrhage and/or rupture is a hallmark of type IV EDS, and the risk of severe hemorrhagic complications from labor and vaginal delivery, including death or shock, remain unacceptably high, in the range of 10% per pregnancy.[14,15] No published standards of care exist for delivery in affected women; however, pregnant individuals with EDS type IV should be delivered by cesarean section with special anesthetic considerations[16,17] and not allowed to enter into labor. For other EDS subtypes, vaginal delivery is possible. Counseling with regard to the risks involved, and clinical evaluation, should be undertaken prior to pregnancy in all patients with EDS, since the subtypes are not distinguished in Taiwan due to the lack of availability of biochemical assay or molecular mutation analysis as part of standard care. High rates of miscarriage and premature deliveries due to cervical incompetence may compromise the fetus in women with EDS.[18,19] The amniotic membranes are of fetal origin, and if EDS affects the fetus, PROM commonly occurs. Affected infants might exhibit changes in vascular resistance and subsequently reduced blood flow. This might explain the higher rates of fetal growth retardation in pregnancies with EDS. These features were observed in this series with prematurity in 19%, PROM in 19%, and short stature in 44%.

There have been numerous reports of cardiac and aortic abnormalities in EDS, including mitral valve prolapse, aortic dilatation, and aortic dissection/rupture.[20–22] Cardiovascular abnormalities were found in 43% of our patients who received echocardiographic examination. This finding suggests that echocardiographic evaluation of aortic size should be included in the initial evaluation of new patients with EDS, as in patients with Marfan syndrome.[23] For patients with normal echocardiograms at the initial exam, repeated echocardiograms at 3-year intervals may be sufficient. Patients with normal initial echocardiograms who are involved in competitive athletics (junior high school and beyond) should be evaluated more frequently. Patients with aortic diameters greater than +2 SD for body surface area[24] should be followed yearly, or occasionally at 6-month intervals, depending on the apparent rate of increase.

Hypermobility of the joints is a cardinal feature of EDS and joint dislocations are a relatively frequent complication of any form. Congenital dislocation of the hip is present in about 5% of affected neonates,[25] and its prevalence in this series of patients was 19%. Some reports indicated that most patients have radiologically detectable osteopenia/osteoporosis, but pathologic frac-

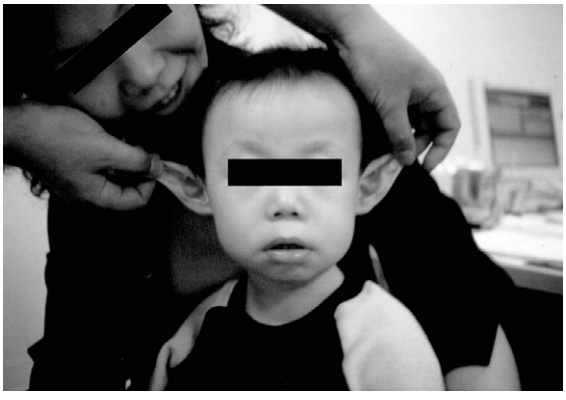

Figure 1. Stretchability of ears in a boy with Ehlers-Danlos syndrome.

tures are rare. Similar findings were also made in this study, including osteoporosis among all examined patients, and a relatively high prevalence of bone fracture episodes of 19%. Muscular hypotonicity may be an initial feature in early childhood; thus, EDS should be included in the differential diagnosis of the "floppy infant".[26] In this series, 44% of patients had an initial diagnosis of neonatal hypotonia.

In conclusion, the results of this study highlight the importance of echocardiographic evaluation of aortic size and valvular condition, and bone mineral density in patients with EDS, and regular follow-up monitoring for this condition. Clinical presentation provides insufficient information for the definite diagnosis of EDS, and EDS type IV is associated with an increased risk of death. Unfortunately, there are other diseases, especially collagen fiber disorders, which share many of the clinical features of EDS. A thorough knowledge of the systemic manifestations of EDS, its involvement in multiple organ systems, and its management are mandatory to prevent morbidity and mortality. The availability of biochemical assay or molecular mutation analysis as part of standard practice to help clinicians in Taiwan to make a more accurate diagnosis of EDS, other than clinical phenotype, is needed.

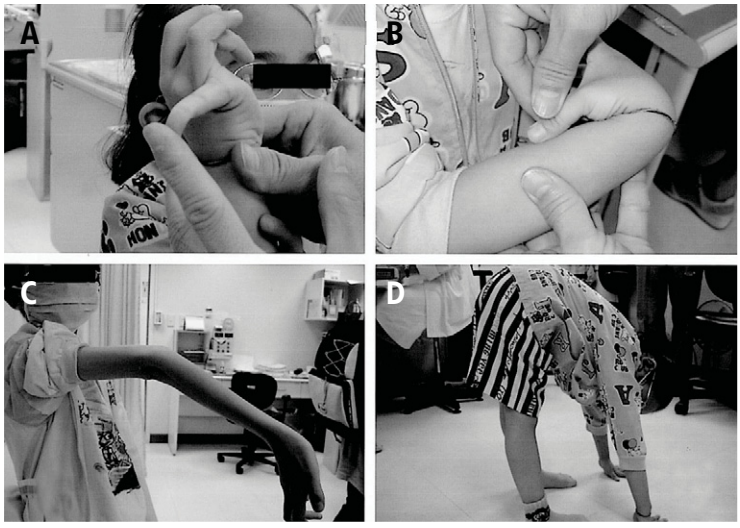

Figure 2. Clinical test for joint hypermobility: (A) passive dorsiflexion of the fifth digit beyond 90° from the horizontal plane; (B) passive apposition of the thumb to the flexor aspect of the forearm; (C) hyperextension of the elbow beyond 10°; (D) forward flexion of the trunk with knees fully extended and the palms of the hands resting flat on the floor.

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