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Clinical Analysis Supports Articulo-Autonomic Dysplasia as a Unifying Pathogenic Mechanism in Ehlers-Danlos Syndrome and Related Conditions

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Abstract

Findings in 1656 patients referred for evaluation of Ehlers-Danlos syndrome, 710 evaluated systematically using novel history and physical forms, defined a characteristic clinical pattern termed arthritis-adrenaline disorder, a genus that provides immediate therapy while delineation of particular tissue laxity/dysautonomia species is underway. Preliminary diagnoses, clinical findings, and laboratory results were entered into an MS Excel© database with IRB approval and correlations or statistical significance analyzed using Excel© functions. Frequencies of 80 findings by history and 40 on physical were similar among EDS groups, females paralleling males with more total history (35 versus 23) and physical (18 versus 15) findings. Finding frequencies in joint-skeletal (6.2 of 15) and dysautonomia (11 of 20) subcategories were substantial regardless of age, EDS diagnosis, or referral source, the latter was shown by 6.4 and 13 average findings for cardiology, 5.3 and 8.3 for orthopedic referrals. Early affliction evidenced by history findings averaging 19.5 in those under 12 increased dramatically to 25 for teens and 32 for adults with plateauing at older ages arguing against degenerative disease. Frequent neuromuscular symptoms in females emphasize surrounding muscle support and protection of joint-connective tissue as a key factor in decreased male severity. The congruent clinical profile suggests operation of an articulo-autonomic dysplasia cycle where lax vessels and lower body pooling elicit sympathetic response, autonomic imbalance in turn affecting small nerve fibers and enhancing connective tissue laxity. Recognition of this arthritis-adrenalin disorder can guide management strategies while underlying causes are pursued, among them, physical therapy, exercise, and vitamin D to build muscle/bone strength; lower gluten/dairy and antihistamine protocols for low bowel motil-

ity/mast-cell activation; hydration, salt, and exercise for postural orthostatic tachycardia syndrome.

Keywords

Ehlers-Danlos Syndrome, Arthritis-Adrenaline Disorder, Connective Tissue Dysplasia, Hypermobility, Dysautonomia, Joint Laxity, Skin Elasticity, IBS, POTS, MCAD

1. Introduction

Many opportunities for prevention and management are afforded by recognizing patients with joint and tissue laxity [1] [2] [3] [4], a group represented by the restrictive eponym Ehlers-Danlos syndrome (EDS), a term biased by patients with rare and extreme disease [5]. Increasing the gap between primary care recognition of a trait that affects 10% of the population and appropriate subspecialty referral is the "splitting" of EDS into types, major ones based on hypermobility (hEDS-[6]), skin scarring and elasticity (classical or cEDS-[7]), or susceptibility to vessel and tissue rupture (vascular or vEDS-[8]), current diagnostic criteria for these types excluding that most treatable and disabling complication of EDS: *Dysautonomia* [9]!

Here I delineate a characteristic clinical profile that transcends EDS type, a pattern of joint, skeletal, skin, and autonomic findings based on 1656 patients referred for EDS. I propose articulo-autonomic dysplasia as an underlying mechanism in EDS and related tissue laxity disorders, its consequent pattern of findings in turn described as arthritis-adrenalin disorder (AAD for both process and disease—the term "adrenaline" is shorthand for the complex mixtures of catecholamines that mediate adrenocortical/adrenergic activity). AAD can be the genus for multiple EDS and connective tissue dysplasia species, a mechanism that informs preventive and therapeutic strategies, a diagnosis that directs further clinical/DNA delineation as described in one patient [10] and will be detailed in a follow-up article.

Just as nosology begins with septic shock and proceeds to specific infectious agents, so should AAD encompass flexibility [11], fibromyalgia [12], and chronic fatigue [13] until further investigation defines specific genes and environmental triggers [14]. The AAD process involves small fiber neuropathy [15] on one side and connective tissue abnormalities [16] on the other, bringing objective diagnosis to symptoms often assumed to be subjective in nature [17]. Preliminary recognition of the AAD clinical profile can unify diseases from tryptase gene amplification [18] to EDS or Marfan syndrome [19], their anxiety-fatigue-pelvic congestion [20] [21] disproportionately affecting women and their frequent dismissal reminding of historic misnomers like hysteria. The distinctive and systematically scored clinical pattern of AAD presented here becomes the genus for myriad arthritis-adrenaline species, disorders that threaten the many who are

flexible and most of us as we age [22].

2. Methods

My experience with EDS expanded from 4 - 5 annual patients in a traditional academic setting to over 400 private practice visits per year, most of them self- or subspecialty referrals to evaluate EDS based upon joint hypermobility and concern about vascular complications [8]. Reported here are patients evaluated from January 2011 to June 2018 when ordering whole exome sequencing [23] [24] became practical via preliminary ascertainment of insurance coverage by the GeneDx Company. Standardized history and physical forms were developed based on common findings in the first 946 patients and used for 710 EDS referrals after September 2016. EDS examinations were on clothed individuals with consequent under-ascertainment of covered skin findings or subtle deformations.

I gave patients (parents for minors) forms to consent for medical genetic evaluation/treatment and de-identified sharing of DNA results during patient intake. Provisional clinical diagnoses following criteria for hypermobile hEDS [6]—more hypermobility-related subluxations and joint injuries with elastic and velvety skin; classical cEDS [7]—milder joint issues and elastic/fragile skin with typical scarring; benign joint hypermobility [11]—hypermobility with minimal joint issues; or dysautonomia [9]—autonomic imbalance out of proportion to skeletal issues. A minority of this informed and/or referred population were told that they did not meet EDS criteria and 12 patients had obvious diagnoses like Marfan or Stickler syndromes [19] and were not included in this study. Although the great majority of patients sought genetics to exclude vascular vEDS [8], no typical cases were observed after 2011 and only 2 before. Consents for testing and report of de-identified findings had IRB approval as did entry of clinical and molecular findings into a password-protected MS Excel database. Tallies of findings and statistical analyses (limited by large standard deviations among self-reported findings) used Excel© functions and formulae.

3. Results

Evaluation of 946 patients among the 1656 total defined recurring symptoms, complications, and other findings on history and physical, allowing design of forms for systematic documentation of 80 frequently reported historical (**Figure 1**) and 40 physical findings (**Figure 2**) in a subsequent 710 patients. The forms can be used by patients to consider or prepare for evaluation of EDS and related connective tissue laxity disorders, their finding scores then confirmed and refined by direct discussion and examination. The history form has 12 sections that can be combined into 8 categories (see **Figure 3**), beginning with infantile (5 finding) and childhood-teenage (10 finding) sections that can be combined into a youth category (**Figure 1** and **Figure 3**). The joint-skeletal (15 finding), skin (5 finding), and cardiovascular (3 finding) categories are traditionally relevant

Figure 1. History form for EDS and related conditions

(optional photo or clinic label)

Please check ☒ boxes below for any positive findings and circle choices where presented (e. g., ☒poor breast/bottle feeding); *leave blank if you are unsure. Those performing self-assessment should place the number of positive findings in the right column and total them at bottom to give the total history score. If filling out for a clinic visit or online evaluation, the clinician will confirm findings and complete scoring.*

Patient Name _____ **BD:** ___/___/____ **Date completed** ___/___/ **20**___ **Age** _____

Findings	Number
Infancy ☐colic ☐poor feeding-breast bottle ☐flexible, boneless baby ☐motor delays ☐clumsy-many falls	/5
Child/teen ☐slow weight gain ☐aware of being hypermobile ☐showed off joint tricks ☐early joint pain ☐clumsy as teen ☐activities—*PE gymnastics dance cheer*--limited by-*pain injury fatigue* ☐glasses age ___ years ☐orthodontics—*braces extractions* age___ years ☐gum disease ☐poor enamel/many cavities	/10
Joint issues ☐joints pop ☐come out of joint/subluxation-*shoulders hips knees ankles* ☐TMJ (jaw joint) issues ☐joint pain-*neck shoulders wrists hands fingers back hips knees ankles feet toes* ☐joint surgeries/injections ☐many sprains ☐fractures--number ___ *neck shoulders wrists hands fingers back hips knees ankles feet toes* ☐tendon/ligament tears, plica-*shoulder wrist knees ankles* ☐disc/back surgeries/bracing _____ ☐spinal disc problems-*herniation degeneration--cervical thoracic lumbar sacral* _____	/10
Skeletal issues ☐scoliosis _____ ☐pectus (chest *in out*) ☐leg bowing ☐toeing in out ☐feet-*flat high arches*	/5
Skin ☐easy bruising ☐stretchy skin ☐unusual scars/slow healing ☐stretch marks *pregnancy only* ☐dry/scaly skin	/5
Genitourinary ☐heavy-irregular periods ☐endometriosis ☐ovarian-*cysts PCOS* ☐bladder issues *infection frequency leakage*_____ ☐hernia-*umbilical inguinalpelvic floor collapse*	/5
Neuromuscular ☐migraines ☐daily headaches-*front side back* ☐headache therapy _____ ☐seizures_____ ☐Chiari (__ mm herniation) ☐neurosurgery _____ ☐numbness/tingling ☐poor balance ☐neuropathy _____ ☐reflex sympathetic dystrophy/CRPS ☐muscle aches/spasms_____ ☐muscle weakness/atrophy _____	/12
GI/bowels ☐constipation/diarrhea ☐bloating/reflux/stomach pain_____ ☐gall bladder-*failure removed* ☐difficult swallow_____ ☐frequent nausea/weight loss_____	/5
Heart ☐valve prolapse/regurgitation ☐vessel dilation/aneurysm _____ ☐arrhythmia _____	/3
POTS ☐dizzy on standing ☐faint-syncope_____ ☐chronic fatigue ☐sleep difficulties ☐brain fog (poor memory/focus) ☐heat/cold sensitivity ☐abnormal sweating ☐rapid heart rate ☐anxiety-panic attacks_____ ☐feet on standing *discoloration swelling* ☐love salty foods	/11
Immune/mast cell ☐transient rashes ☐hives/reactive skin _____ ☐asthma/shortness of breath ☐food-medication intolerances _____	/4
Lab/Imaging ☐low bone density ☐low vitamin *D/B12* ☐thyroid-*low high Hashimoto* ☐low-*ferritin iron* ☐high titers ANASjogren rheumatoid factor_____	/5
Total *add all findings to give total number out of 80→*	/80

Additional evaluations (place year of study in blank)

Gastroenterology ☐scope studies _____ **Diagnoses** ☐irritable bowel/gastroparesis ____ ☐Crohn disease ____ ☐celiac disease_____
Cardiology ☐tilt-table abnormal _____ ☐echocardiogram ____ findings_____ ☐ECG _____ findings_____
Diagnoses ☐POTS ____ ☐arrhythmia____aneurysm/vessel dilation ____-_____ ☐median arcuate ligament syndrome
Mast cell/allergy ☐allergy testing ____ **Diagnoses** ☐asthma _____ ☐mast cell activation disorder ____☐tryptase-*positive negative*
Rheumatology ☐evaluation _____ **Diagnoses** ☐fibromyalgia _____ ☐Sjogren ____ ☐Arthritis-*rheumatoid osteo psoriatic*_____
Orthopedics ☐evaluation _____ **Diagnoses** _____☐ Procedures_____
Neurology ☐head MRI ____ ☐upright head MRI____ ☐EMG____ ☐EEG ____**Diagnoses** ☐MS____ ☐neuropathy/myopathy ____
Beneficial treatments/medicines _____
Unhelpful treatments/medicines _____

Figure 1. History form for EDS and related conditions.

to EDS while the 20-finding dysautonomia category with irritable bowel syndrome (IBS, [25]), postural orthostatic tachycardia syndrome (POTS, [26]), and mast cell activation disorder (MCAD, [27]) sections is often ignored despite both being of crucial importance to EDS diagnosis as described below. Also underappreciated but of significant frequency in tissue laxity disorders are the genitourinary (5 finding), neuromuscular history (12 finding), and laboratory (5 finding) categories, aspects of pelvic congestion [20] like menorrhagia providing evidence of lower body blood pooling that triggers adrenergic stimulation. In turn, the presence of autoimmune markers like anti-nuclear antibody along with mast cell activation shows the influence of sympathetic stimulation on immunity and inflammation (**Figure 3**). Some findings like Chiari deformation or aneurysms, though less frequent or specific for EDS, were included on the history form because of their implications for management.

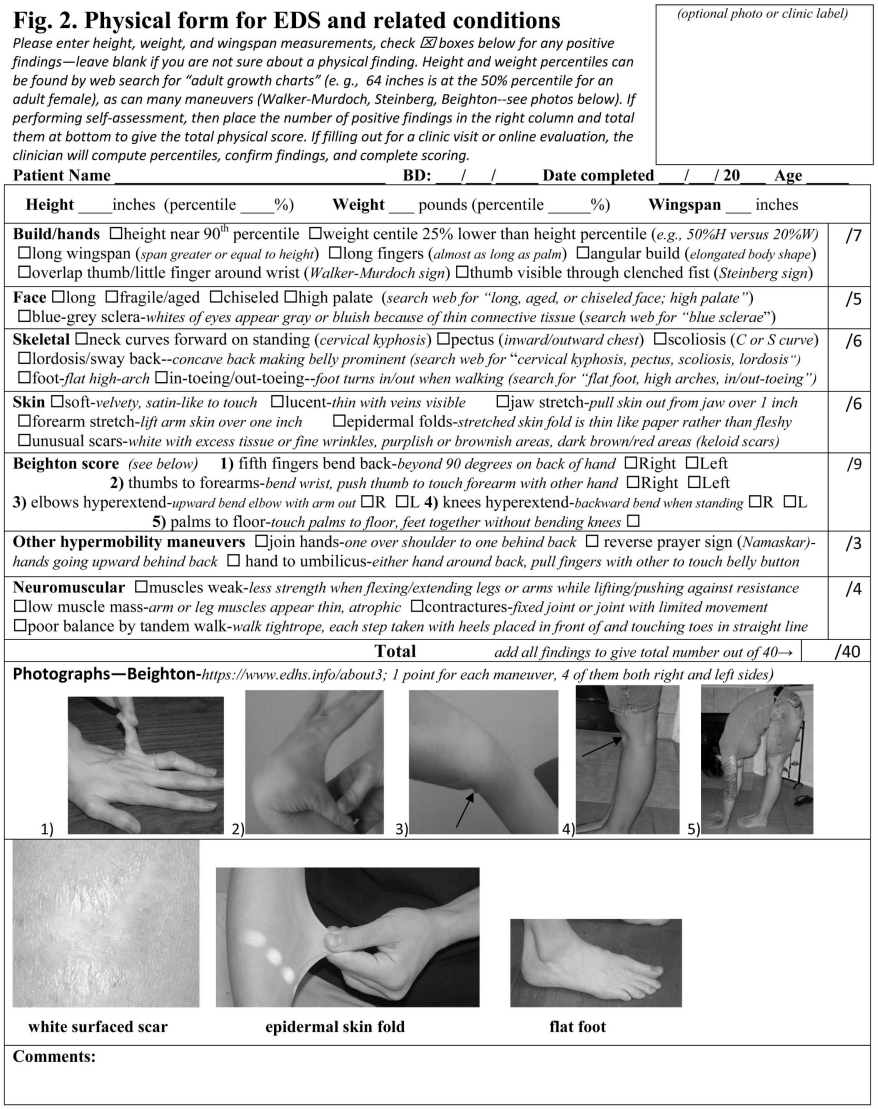


Fig. 2. Physical form for EDS and related conditions

Please enter height, weight, and wingspan measurements, check ☒ boxes below for any positive findings—leave blank if you are not sure about a physical finding. Height and weight percentiles can be found by web search for "adult growth charts" (e. g., 64 inches is at the 50% percentile for an adult female), as can many maneuvers (Walker-Murdoch, Steinberg, Beighton--see photos below). If performing self-assessment, then place the number of positive findings in the right column and total them at bottom to give the total physical score. If filling out for a clinic visit or online evaluation, the clinician will compute percentiles, confirm findings, and complete scoring.

(optional photo or clinic label)

Patient Name _____ **BD:** ___/___/_____ **Date completed** ___/___/ **20**___ **Age** _____

Height ____inches (percentile ____%) **Weight** ___ pounds (percentile _____%) **Wingspan** ___ inches

Build/hands ☐height near 90th percentile ☐weight centile 25% lower than height percentile (*e.g., 50%H versus 20%W*) /7
☐long wingspan (*span greater or equal to height*) ☐long fingers (*almost as long as palm*) ☐angular build (*elongated body shape*)
☐overlap thumb/little finger around wrist (*Walker-Murdoch sign*) ☐thumb visible through clenched fist (*Steinberg sign*)

Face ☐long ☐fragile/aged ☐chiseled ☐high palate (*search web for "long, aged, or chiseled face; high palate"*) /5
☐blue-grey sclera-*whites of eyes appear gray or bluish because of thin connective tissue* (*search web for "blue sclerae"*)

Skeletal ☐neck curves forward on standing (*cervical kyphosis*) ☐pectus (*inward/outward chest*) ☐scoliosis (*C or S curve*) /6
☐lordosis/sway back--*concave back making belly prominent (search web for "cervical kyphosis, pectus, scoliosis, lordosis")*
☐foot-*flat high-arch* ☐in-toeing/out-toeing--*foot turns in/out when walking (search for "flat foot, high arches, in/out-toeing")*

Skin ☐soft-*velvety, satin-like to touch* ☐lucent-*thin with veins visible* ☐jaw stretch-*pull skin out from jaw over 1 inch* /6
☐forearm stretch-*lift arm skin over one inch* ☐epidermal folds-*stretched skin fold is thin like paper rather than fleshy*
☐unusual scars-*white with excess tissue or fine wrinkles, purplish or brownish areas, dark brown/red areas (keloid scars)*

Beighton score *(see below)* **1)** fifth fingers bend back-*beyond 90 degrees on back of hand* ☐Right ☐Left /9
2) thumbs to forearms-*bend wrist, push thumb to touch forearm with other hand* ☐Right ☐Left
3) elbows hyperextend-*upward bend elbow with arm out* ☐R ☐L **4)** knees hyperextend-*backward bend when standing* ☐R ☐L
5) palms to floor-*touch palms to floor, feet together without bending knees* ☐

Other hypermobility maneuvers ☐join hands-*one over shoulder to one behind back* ☐ reverse prayer sign (*Namaskar)-hands going upward behind back* ☐ hand to umbilicus-*either hand around back, pull fingers with other to touch belly button* /3

Neuromuscular ☐muscles weak-*less strength when flexing/extending legs or arms while lifting/pushing against resistance* /4
☐low muscle mass-*arm or leg muscles appear thin, atrophic* ☐contractures-*fixed joint or joint with limited movement*
☐poor balance by tandem walk-*walk tightrope, each step taken with heels placed in front of and touching toes in straight line*

Total *add all findings to give total number out of 40→* /40

Photographs—Beighton-*https://www.edhs.info/about3; 1 point for each maneuver, 4 of them both right and left sides)*

1) 2) 3) 4) 5)

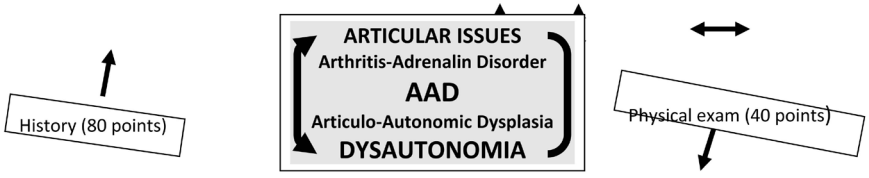
white surfaced scar **epidermal skin fold** **flat foot**

Comments:

Figure 2. Physical form for EDS and related conditions.

The physical examination form (**Figure 2**) focuses on inspection and performance of maneuvers with 8 sections and 4 categories (**Figure 3**), dominated by assessment of traditional EDS findings like the Marfanoid habitus with deformations (the 15-finding build-face-skeletal category), joint laxity (the 9-point Beighton score plus 3 additional hypermobility maneuvers), and skin texture or elasticity (6 findings). The form is preliminary to more detailed and objective assessments in medical or subspecialty clinics that will include vital signs and relevant physiologic measures like tilt-table or gastric motility measures, some of these specified for documentation on the accompanying history form (**Figure 1**). Web searches can provide examples of physical attributes (long or chiseled face, high palate, epidermal skin folds) and maneuvers (Walker-Murdoch, Steinberg signs) that facilitate patient self-assessment, the latter including the pivotal Beighton hypermobility score that is both referenced and pictured at the bottom of **Figure 2**. Utility of these forms for preliminary assessment is supported by

Area	Findings (female%;male%)	Points
Youth	**Infancy (5)** Colic 30[a];31[b] Poor feeding 23;32 Flexible 28;5.9 Motor delays 8.0;17 Clumsy-falls 22;14 **Any 63;49**	15 (6.4;5.4)
	Child-teen (10) FTT 16;24 Aware of DJ 85;65 Did DJtricks 69:45 Early joint pain 60;48 Clumsy later 52;61 Activity impaired 66;63 Glasses <age 1258;43 Braces 63;50 Gum disease 14;11 Early caries 45;25 **Any 97:78**	
JtSkt	**Joint issues (10)** Joints pop 87;68 Subluxations 72;52TMJ issues[c] 56;32 Arthralgia[d] 89:63 Frequent sprains 43:34 Joint injuries[e] 33;23 Joint procedures[f] 42;31 Fractures 46:43 Disc issues[g] 55;14 Back surgery 12;5.0 **Any 99;98**	15 (6.4;4.6)
	Skeletal (5) Scoliosis 40;29 Pectus 4.0;19 Bow-legs 2.3;8.0 Toeing-in[h] 15;14 High/flat arches 31;30 **Any 65;50**	
SkinH	**(5)** Easy bruising 65;45 Elastic 25;16 Unusual scars 43;23 Early striae 81;52 Slow healing 37;9.0 **Any 92;67**	5 (2.4;1.5)
GU	**(5)**[i] Menorrhagia 60 Endometriosis 18 Ovarian cysts/PCOS 42 Bladder issues[j] 46;13Hernia[k] 12;3.0 **Any 65;17**	5 (1.8;0.16)
NmH	**Neuromuscular (12)** Migraines 59;21 Daily headaches 66;47 Headache therapy 52;39 Seizures 5.3;11.0 Chiari 13;8.2 Neurosurgery 8.0;6.9 Numbness/tingling 65;26 Poor balance 51;25 Neuropathy 44;26 Reflex sympathetic dystrophy/CRPS 11;4.0 Muscle aches 60;25 Muscles weak 37;17 **Any 98;61**	12 (4.7;2.6)
CVS	**Cardiovascular (3)** Valve regurgitation 7.6;1.8 Vessel change/aneurysm 0.56;0 Arrhythmia 4.1;1.8 **Any 12;3**	3 (0.36;0.49)
DysA	**IBS (5)** Constipation/diarrhea 77;60 Bloating-reflux-pain 70;47 Gall bladder issues 18;5.9 Difficult swallow 29;8.9 Frequent nausea 52;27 **Any 91;60**	20 (12;8.0)
	POTS (11) Dizzy 84;75 Faint-syncope 43;22 Chronic fatigue 89;56 Sleep issues 48;38 Brain fog/poor focus 84;61 Heat/cold sensitivity 84;51 Abnormal sweating 31;33 Rapid heart rate 77;43 Anxiety-panic attacks 61;54 Foot discoloration due to blood pooling 57;38 Salt fancy 59;34 **Any 97;71**	
	MCAD(4) Rashes 42;27 Hives/reactiveskin 52;18 RAD/SOB 43;29 Food-medicine allergies 68;29 **Any 88;59**	
Lab	**Lab/imaging (5)** Low bone density 6.7;5.0 Low vitamin D 37;24 Hypothyroidism 22;2.0 Low iron/ferritin 21;7.0[l] Autoimmune markers[m] 11;2.0 **Any 43;18**	5 (1.0;0.41)
	Total points	80 (35;23)



Area	Findings (female%;male%)	Points
BMI	**Underweight≤19** 9.3;12 **Healthy20-22** 40;49 **Healthy23-25** 25;23 **Overweight27-28** 9.6;8.9 **Obese 29+**16;7.9	--
BFSkt	**Build/hands (7)**: Stature near 90[th] 34;63 Weight <25 height centile 21;25 Angular build 34;34 Long span 38;35Long fingers 41;44Walker-Murdoch sign 34;38 Steinberg sign 25;28**Any 69;52**	18 (5.6;5.3)
	Face (5): Long 41;39Fragile/aged 1.5;1.0 Thin 11;7.9 Blue sclerae 9.2;5.4 High palate 74;45**Any 73;59**	
	Skeletal (6): Unusual neck curve 51;23 Pectus 3.9;16 Scoliosis 25;16 Lordosis 43;20 Flat feet/high arches 39;34 Toe-in or -out when walking 48;34**Any 92;63**	
Flex	**Beighton (9)**: Digit5 bends back[n]18/69;13/55[o]Thumb touches forearm 6/81;11/63 Elbow hyperextension 12/77;9/62 Knee hyperextension 13/69;14/58 Palms to floor 83;32 **Scoresin females;males:0-3** 10;22**4-6** 31;49 **7-9** 59;29**incEDS:hEDS: 0-3** 30;1.0 **4-6** 60;16 **7-9** 10;83	9 (6.5;4.9)
	Other (3): Join hands[p]49;53 Reverse prayer sign[q] 56;52 Touch umbilicus[r]34;19**Any 93;58**	3 (1.9;1.0)
SkinP	**Skin (6)**: Soft 89;74Translucent[s] 31;24Stretches >1" on jaw 58;65Lifts >1"on forearm 77;58 Stretch involves epidermal fold 39;31Unusual scars[t] 43;27**Severe scars in cEDS;hEDS** 15;4.2 **Any 95;69**	6 (3.4;2.9)
NmP	**Neuromuscular (4)**: Muscle weakness 14;7.1 Muscle atrophy 12;6.9 Joint contractures 0.64;3.5 Poor balance by tandem walk 42;34 **Any 50;22**	4 (6.6;8.1)
	Total points	40 (18:15)

Figure 3. History and physical findings in patients with AAD. [a]percentage found in 596 systematically documented females with articulo-autonomic dysplasia (AAD); [b]percentage found in 114 comparable males; [c]pain on chewing, alignment problems; [d]chronic joint pain in 3 or more areas; [e]tears, etc. needing treatment; [f]surgeries (80% of patients) or injections; [g]herniation/degeneration; [h]toeing-in or out; [i]two of these findings apply to men, giving them a maximal score of 77 rather than 80 and necessitating addition of 1.2 points (sum of menorrhagia, endometriosis, ovarian cyst scores) to equate male with female history finding scores; [j]mainly urinary infections but also interstitial cystitis, urgency, frequency; [k]includes pelvic floor collapse; [l]iron 11;51% ferritin 3.0;4.0%; [m]anti-nuclear, Sjogren antibodies, rheumatoid factor; [n]bends back over 90 degrees toward back of hand; one/both sides positive; [p]over shoulder/behind back; [q]behind back (reverse Namaskar); [r]with hand around back; [s]veins easily visible; [t]white-surfaced/papyraceus (>90%), keloid, violaceous; BFSkt, build, facial, and skeletal physical findings; cEDS; hEDS, classical; hypermobile EDS—Beighton score percentages in 176 systematically evaluated patients with cEDS; 447 with hEDS; CRPS, chronic regional pain syndrome; CVS, cardiovascular; DJ, double-jointed; DysA, dysautonomia historical findings combining those of IBS, POTS, and MCAD; FTT, failure to thrive; GU, genitourinary; IBS, irritable bowel syndrome (low motility/gastroparesis); JtSkt, joint-skeletal historical findings; MCAD, mast cell activation disorder; NmH/P, neuromuscular historical/physical findings; PCOS, polycystic ovary syndrome; RAD, reactive airway disease/asthma; SkinH/P, skin findings by history/physical; SOB, shortness of breath; TMJ, temporomandibular joint.

their ongoing use for online evaluation, interaction with 100+ patients by e- and snail mail yielding scores and preliminary diagnoses that are similar to those obtained by direct clinic evaluation that will now be described (G. Wilson, unpublished data, 2018-19).

Frequencies of clinical findings in the 710 systematically evaluated patients are shown in **Figure 3**, their frequencies among 596 systematically evaluated females (among 1337 total) and 114 males (among 319) expressed as percentages separated by a semicolon. There were 147 families with 166 relatives (105 primary—parent, child, sibling) among the 1656 patients and 32 families with 44 relatives (16 primary) among those having standardized evaluations. Analyses with or without relatives yielded similar data as expected for the variable expression expected for preponderant dominant inheritance of connective tissue dysplasia. Just as the number of findings in a section can be totaled to give an individual score for that section, so can the percentage of each finding in a patient group (e. g., 0.30 points for the 30% of females with colic) be added to others in the category (e. g., 0.30 points plus 0.23 for poor feeding, 0.85 for awareness of being double-jointed, 0.63 for braces, etc.) to give an average 6.3 points for 596 females in the 15-point Youth category versus 5.4 for males (**Figure 3**). Presence of any one finding in a category can also be tallied, varying from 98% (61% for males) in the historical neuromuscular NmH category to 22% (10% for males) in the cardiovascular category (see the bold face figures to right of finding lists in **Figure 3**). Note that bladder issues and hernias are the only genitourinary findings scored for males, requiring addition of 1.2 points to male history scores to account for the average menorrhagia (0.60) plus endometriosis (0.18) plus ovarian cyst (0.42) points that will be scored in females.

Two categories are particularly demonstrative of AAD: 1) Findings like subluxations (72;52%) or arthralgia (89;63%) that contribute to 6.4;4.6 of 15 average points in the joint-skeletal category, and 2) findings like constipation/diarrhea [77;60% as part of IBS/low motility/gastroparesis-25], anxiety/panic attacks [61;54% as part of POTS-26] and food-medication intolerances [68;29% as part of MCAD-27], categories each contributing to 12;8.0 of 20 average points in the dysautonomia category. Also typical of many with EDS are findings of a Marfanoid body build (tall stature—34;63%, high palate—74;45%) and flexibility highlighted by the Beighton score [1]-[6]—observed in adults and conducted in children under 6 years, averaging 6.5 points out of 9 for females and 4.9 for males. Frequencies of physical skin findings (elasticity measured by skin stretch at mid-forearm—77;58%, unusual scars—43;27%) parallel those by history (easy bruising—65;54%, pre-pregnancy striae—81;53%), the latter (SkinH) averaging 2.4;1.5 out of 5 in that category while those by physical (SkinP) averaged 3.4;2.9 out of 5. Note that the many neuromuscular (12) and dysautonomia (20) findings assessed by history in **Figure 1** have few parallels on the superficial physical examination of **Figure 2** (the NmP category with muscle weakness/atrophy, contractures, and poor balance adding up to 6.6 average points in females and (as an exception to greater female severity) 8.1 points in males. This latter deficiency of

autonomic findings on physical will often be corrected by subspecialty measures of neuromuscular and autonomic function (electromyogram, muscle biopsy, tilt-table, gastric motility, tryptase levels, etc.), but it explains the divergence of history and physical scores in some age groups as documented below.

3.1. Patient Presentation

The characteristic arthritis-adrenaline disorder pattern can be summarized as a typical clinical presentation using the more abundant data from 596 female patients having standard evaluations (**Figure 3**). Symptoms often begin in infancy with the mentioned colic and feeding difficulties (23% but 32% in males) that are harbingers of later IBS and MCAD. Motor delays with clumsiness/frequent falls (22% early, 52% later) reflects the joint laxity that is retrospectively recognized in 85% but demonstrated by "double-jointed" maneuvers in only 69% (**Figure 3**). Complicating the transition from child to adulthood are early joint pain (60%—often written off as "growing pains" until adolescent activities like gymnastics, dance, cheer are limited), need for glasses (58%) due mostly to myopia, orthodontics (63%) due to dental crowding, frequent caries (45%) due to thin enamel, menorrhagia (60%), and painful ovarian cysts (42%) in females with rare hernias (12;3%) in both sexes.

Popping joints (87%) herald more dramatic laxity that manifests as subluxations (72%), polyarticular and symmetrical joint pain (89%—knees, shoulders, ankles with rare swelling or erythema), joint injuries (33%—mostly ankles and knees), fractures (46%—distal limbs most frequent), and disc degeneration or herniation (55%). Clumsiness from joint laxity, cumulative joint pain/injury, and skeletal deformations like scoliosis (40%), toeing-in or out (15%), flat or high arches (31%) make the typical patient uncomfortable with sports and prone to inactivity. Evidence of skin fragility fulfilled the other hallmark of EDS with easy bruising (65%), unusual scars (43%), and early striae (81%), most unnoticed unless questioned or documented as soft (89%) or elastic skin (58% pulled 1 inch folds from their jaw line, 77% from mid-forearm) on physical.

More common neuromuscular findingsinclude migraines (59%), daily headaches (66%) that when occipital may arise from Chiari deformation (13%) or cranio-cervical instability, numbness and tingling (65%), and muscle aches (60%) prompting fibromyalgia diagnoses. "Seizures" (5.3%) that may reflect syncope more than epilepsy may relate to poor balance (51% by history) that is one of the few findings verified by superficial neurologic examination (42% on physical). Although the opposite finding of joint contractures are rare (0.64%), fetal tissue laxity and membrane fragility laxity may occasionally present as arthrogryposis at birth due to fetal compression from oligohydramnios, as in a mother and daughter with a collagen type II mutation causing Stickler syndrome [10]. However, limited range of motion and injuries leading to problems like frozen shoulder (adhesive capsulitis) are common with aging and necessitate historical assessment of hypermobility in older patients [1] [2] [3] [4].

Figure 3 illustrates that bowel issues like bloating/stomach pain (70%), and

nausea (52%) begin early in life and continue with later gall bladder dysfunction [18% - 25%] accentuated by MCAD that can present as eosinophilic esophagitis [28] with frequent food intolerances (68%) or the recently appreciated median arcuate ligament syndrome [29]. Misdiagnosis as functional disease is common as might be expected when psychiatric symptoms like anxiety (61%) and tachycardia (77%) accrue from POTS [26]. Crohn [30] and celiac diseases [31] are occasionally diagnosed in EDS patients with bowel symptoms (~5% for each, data not shown) mandating additional genomic and immunologic studies to determine if their overlapping joint and autonomic symptoms have separate cause. Autoimmune factors in AAD are also indicated by the more common laboratory findings besides low vitamin D (37%), including hypothyroidism (22%) that frequently presents as Hashimoto thyroiditis [32] and the presence of markers (11%) like mildly elevated anti-nuclear or Sjogren antibodies [33].

In addition to chronic fatigue and anxiety-tachycardia, POTS symptoms [26] of brain fog/poor focus (84%) and sleep disruption (48%) are prominent regardless of referral source. They are as disabling as joint/neurologic symptoms in most, much more severe in females with the occasional extremely affected male, and together with bowel issues/weight loss, hives/reactive skin (52%), and reactive airway disease/shortness of breath (43%) were the prime reason for genetic referral in 75% of older teenage and young adult females (data not shown). Those females (13%) or males (3%) with cardiovascular disease had mild conditions, valvular regurgitation (mostly mitral prolapse—7.6;3%) most prominent with very few structural defects (<1%, not shown), the latter mostly physiologic like patent foramen ovale. Only 4 females (0.56%) and no males reported an aneurysm (2 carotid, 2 ascending aorta) and there were none among 22 patients who reported a thorough vascular survey.

Precipitous onset of dysautonomia symptoms was the rule, sometimes post-infectious, often after convalescence forced by trauma, infection, or surgery. Hormonal factors were suggested not only by female severity but also by worsening of symptoms with puberty, pregnancy, or menstruation (some cited improvement with pregnancy). Many describe life-changing benefit from institution of appropriate hydration-salt, exercise, dietary, and medication therapies for dysautonomia [26] [34], supporting explicit recognition of the latter through use of a term like AAD. A majority had seen 5 or more physicians without accurate diagnosis, adding discouragement and desperation to their pain-related depression [17].

Physical findings showed fewer patients under (9.3%) and more overweight (26%) with most of both sexes (65;72%) having a healthy BMI (**Figure 3**). Findings related to the Marfanoid habitus mentioned above including angular build (34%), arm span greater than height (38%), and long fingers (41%) with consequent maneuvers. Flexibility was assessed by maneuvers like making a prayer sign behind the back (reverse Namaskar—56%) in addition to those of Beighton, the latter more dramatic as expected in patients diagnosed as hypermobile (83%

scoring 7 to 9) as opposed to those with classical EDS (10%—Figure 3). More patients could perform bilateral than unilateral maneuvers with less flexibility on the dominant side (data not shown), indicating the importance of activity/muscle development for joint support. Deformations like neck kyphosis (51%), scoliosis on physical (25%—less than the 40% by history) or lordosis (43%) were much more frequent in females except for pectus (3.9 versus 16% in males) and toeing-in (mainly) or out (48%), a likely contributor to clumsiness.

3.2. Clinical Profile

A remarkably congruent profile is defined by comparing scores for history and physical findings among those referred for evaluation of EDS in Table 1. The preponderance of joint-skeletal and dysautonomia findings in all patient groups, further supported by the data in Figure 4 and Figure 5, justifies use of the term

Table 1. Comparison of findings in AAD patient groups.

Group	All pts (%)	Std exam (%)	Age (years)	Range (years)	History	Youth	JtSkt	SkinH	DysA	NmH	PE	BFSkt	Beighton[b]	SkinP
All AAD	1656 (100)	710 (100)	28 ± 14	0.2 - 73	33 ± 11[a]	6.2 ± 2.6	6.2 ± 2.6	2.3 ± 1.3	11 ± 4.4	4.4 ± 2.4	18 ± 5.0	5.5 ± 3.2	6.2 ± 2.3	3.3 ± 1.5
Female AAD	1337 (81)	596 (84)	36 ± 10	0.2 - 73	35 ± 11	6.3 ± 2.6	6.4 ± 2.6	2.4 ± 1.3	12 ± 4.1	4.7 ± 2.3	18 ± 4.8	5.6 ± 3.2	6.5 ± 2.1	3.4 ± 1.5
Female-child	153 (9.2)	52 (7.3)	7.7 ± 3.4	0 - 12	20 ± 10	6.2 ± 3.0	3.5 ± 2.3	1.2 ± 1.1	6.6 ± 4.1	2.0 ± 2.0	15 ± 4.3	4.3 ± 2.7	6.0 ± 2.1	1.9 ± 1.3
Female-teen	287 (17)	126 (21)	16 ± 1.8	13 - 19	31 ± 8.3	6.5 ± 2.4	5.5 ± 1.9	2.1 ± 1.2	10 ± 4.0	4.2 ± 1.9	17 ± 4.6	5.6 ± 3.4	6.1 ± 2.1	3.2 ± 1.3
Female-adult	798 (48)	372 (53)	34 ± 8.2	20 - 49	38 ± 9.7	6.3 ± 2.5	7.0 ± 2.4	2.7 ± 1.2	13 ± 3.5	5.2 ± 2.1	19 ± 4.5	5.6 ± 3.0	6.6 ± 2.1	3.6 ± 1.4
Female-older	99 (6.0)	46 (6.5)	55 ± 5.3	50 - 76	38 ± 7.1	5.6 ± 2.0	7.3 ± 2.3	2.5 ± 1.1	13 ± 2.7	5.7 ± 1.7	18 ± 5.9	5.7 ± 3.5	6.3 ± 1.9	3.6 ± 1.4
Male AAD	319 (19)	114 (16)	24 ± 12	0.1 - 63	23 ± 9.6	5.4 ± 2.7	4.6 ± 2.1	1.5 ± 1.2	8.0 ± 4.3	2.6 ± 2.1	15 ± 5.6	5.3 ± 3.3	4.9 ± 2.3	2.9 ± 1.6
Male-child	92 (5.6)	31 (4.4)	8.1 ± 3.4	0 - 12	19 ± 9.4	5.7 ± 2.6	2.9 ± 1.7	1.2 ± 1.0	6.3 ± 4.0	2.0 ± 2.0	13 ± 5.3	3.4 ± 2.2	5.5 ± 2.2	2.5 ± 1.4
Male-teen	140 (8.5)	50 (7.0)	16 ± 1.8	13 - 19	23 ± 8.7	5.3 ± 2.3	5.0 ± 1.8	1.5 ± 1.1	8.0 ± 3.8	2.4 ± 2.0	16 ± 4.5	6.2 ± 3.1	4.7 ± 2.2	3.0 ± 1.5
Male-adult	58 (3.5)	21 (3.0)	22 ± 11	20 - 39	24 ± 9.0	5.3 ± 2.5	5.1 ± 1.9	1.5 ± 1.2	8.7 ± 4.0	2.9 ± 2.1	15 ± 5.4	6.0 ± 3.2	4.7 ± 2.2	3.0 ± 1.5
Male-older	29 (1.8)	12 (1.7)	29 ± 4.3	40 - 63	29 ± 6.1	5.6 ± 2.5	5.5 ± 2.0	1.7 ± 1.3	11 ± 3.4	3.9 ± 2.0	16 ± 5.1	5.7 ± 3.4	5.4 ± 2.0	2.6 ± 1.6
Hypermobile EDS	1138 (68)	447 (47 m)	29 ± 13	0.4 - 69	37 ± 9.2	6.8 ± 2.4	6.7 ± 2.3	2.5 ± 1.3	12 ± 3.7	5.0 ± 2.2	19 ± 4.3	5.7 ± 3.1	7.3 ± 1.6	3.5 ± 1.4
Classical EDS	329 (20)	176 (33 m)	29 ± 15	5.4 - 73	33 ± 11	5.8 ± 2.6	5.7 ± 2.4	2.2 ± 1.3	12 ± 4.4	4.3 ± 2.4	16 ± 4.7	5.8 ± 3.2	4.5 ± 1.9	3.2 ± 1.7
BJH	82 (5.0)	51 (24 m)	14 ± 11	0.3 - 48	16 ± 6.9	4.4 ± 2.5	3.2 ± 1.8	1.1 ± 1.2	4.5 ± 2.8	1.8 ± 1.9	14 ± 4.4	3.8 ± 2.6	5.6 ± 2.4	2.8 ± 1.4
Dysautonomia	79 (4.8)	24 (7 m)	28 ± 12	0.9 - 49	26 ± 9.3	3.8 ± 1.8	3.8 ± 2.3	1.5 ± 1.2	11 ± 3.6	3.9 ± 2.2	12.3 ± 4.8	4.5 ± 2.9	3.5 ± 2.2	2.6 ± 1.4
Not EDS	28 (1.7)	12 (6 m)	23 ± 19	0.2 - 63	8.4 ± 0.71	2.4 ± 0.63	1.5 ± .45	0.5 ± 0.45	3.0 ± 1.3	0.50 ± 0.45	5.6 ± 1.1	1.2 ± 1.0	3.1 ± 1.1	0.75 ± 0.74
Primary referral	602 (36)	314 (58 m)	26 ± 15	0.3 - 73	33 ± 15	6.6 ± 2.6	6.2 ± 2.7	2.3 ± 1.3	11 ± 4.7	4.3 ± 2.5	17 ± 5.3	5.4 ± 3.5	6.2 ± 2.2	3.3 ± 1.4
Cardiology referral	532 (32)	233 (19 m)	32 ± 15	6.6 - 69	36 ± 9.8	5.8 ± 2.6	6.4 ± 2.3	2.3 ± 1.3	13 ± 3.6	5.0 ± 2.0	16 ± 4.8	5.8 ± 3.0	6.2 ± 2.2	3.3 ± 1.5
Orthopedic referral	158 (10)	29 (9 m))	20 ± 15	5.9 - 51	26 ± 15	5.3 ± 2.6	5.1 ± 2.6	1.6 ± 1.5	8.3 ± 5.0	3.1 ± 2.3	16 ± 2.8	4.8 ± 2.0	5.6 ± 1.9	3.0 ± 1.5

[a]All scores represent average number of findings in each category (points ± standard deviations); [b]Beighton score as described in Figure 1, average points out of 9; AAD, articulo-autonomic dysplasia; BFSkt, merged build, facial, and skeletal categories of physical findings; DysA, historical dysautonomia category merging findings in the irritable bowel syndrome, postural orthostatic tachycardia syndrome, and mast cell activation disorder categories; EDS, Ehlers-Danlos syndrome; JtSkt, merging historical findings in the joint and skeletal categories; NmH, historical findings in the neuromuscular category; SkinH or P, skin findings in the respective historical or physical categories; Std, standard.

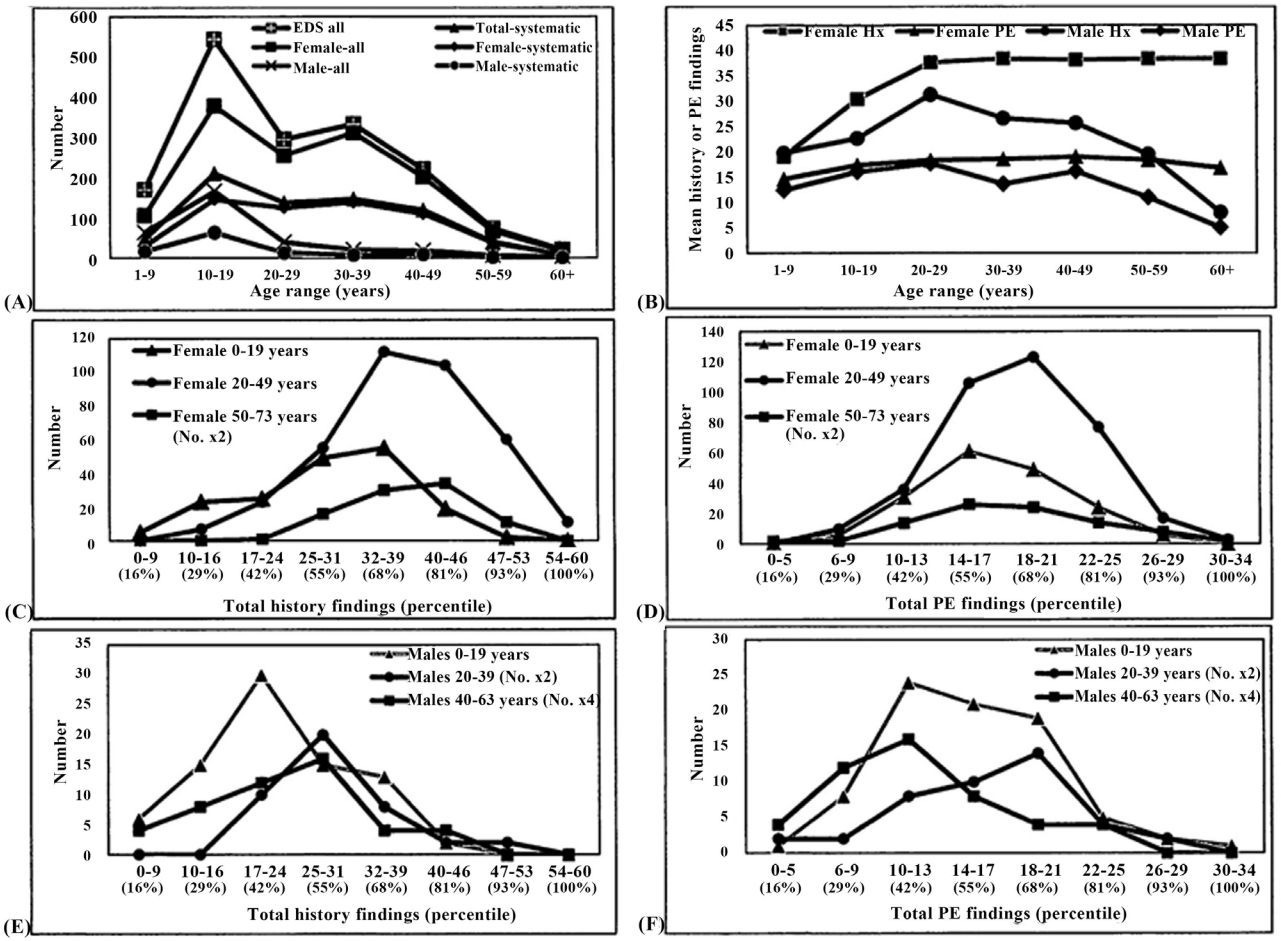


Figure 4. (A) age distribution of all (1656) patients referred for EDS including 1337 females and 319 males or 710 patients with systematic evaluations including 596 females and 119 males; (B) average number of history findings out of 80 or physical findings out of 40 for systematically evaluated males and females in different age groups; (C) numbers of females in different age groups having the indicated range of total history findings by systematic evaluation (percentiles correspond to the larger number in each range, chosen so that they correspond for history and physical findings); (D) similar to (C) but for physical findings; (E) similar to C but for males with systematic evaluations; (F) similar to D but for males with systematic evaluation. Numbers of patients in various age groups are shown in Table 1.

arthritis-adrenaline disorder (AAD) for this profile, though its qualification as AAD-EDS may be needed for familiarity. Greater female severity is again demonstrated by higher average historical (35 of 80) and physical (18 of 40) findings in the 596 females who had evaluations using standard assessment forms compared to the respective 23 and 15 for the 114 males. Lower but parallel scores across categories in males is shown by differences in the average number of joint-skeletal (6.4 of 15 for females versus 4.6 for males) and historical skin findings (2.4 versus 1.5) that are key for EDS, as well as in the dysautonomia (12 of 20 versus 8.0) and historical neuromuscular categories (4.7 versus 2.6) indicative of the accompanying autonomic dysplasia. Female hypermobility is clearly an important factor for many of these increased complications, exemplified by an average Beighton score of 6.5 versus 4.9 for males.

Differences in some finding frequencies correlated with preliminary diagnostic

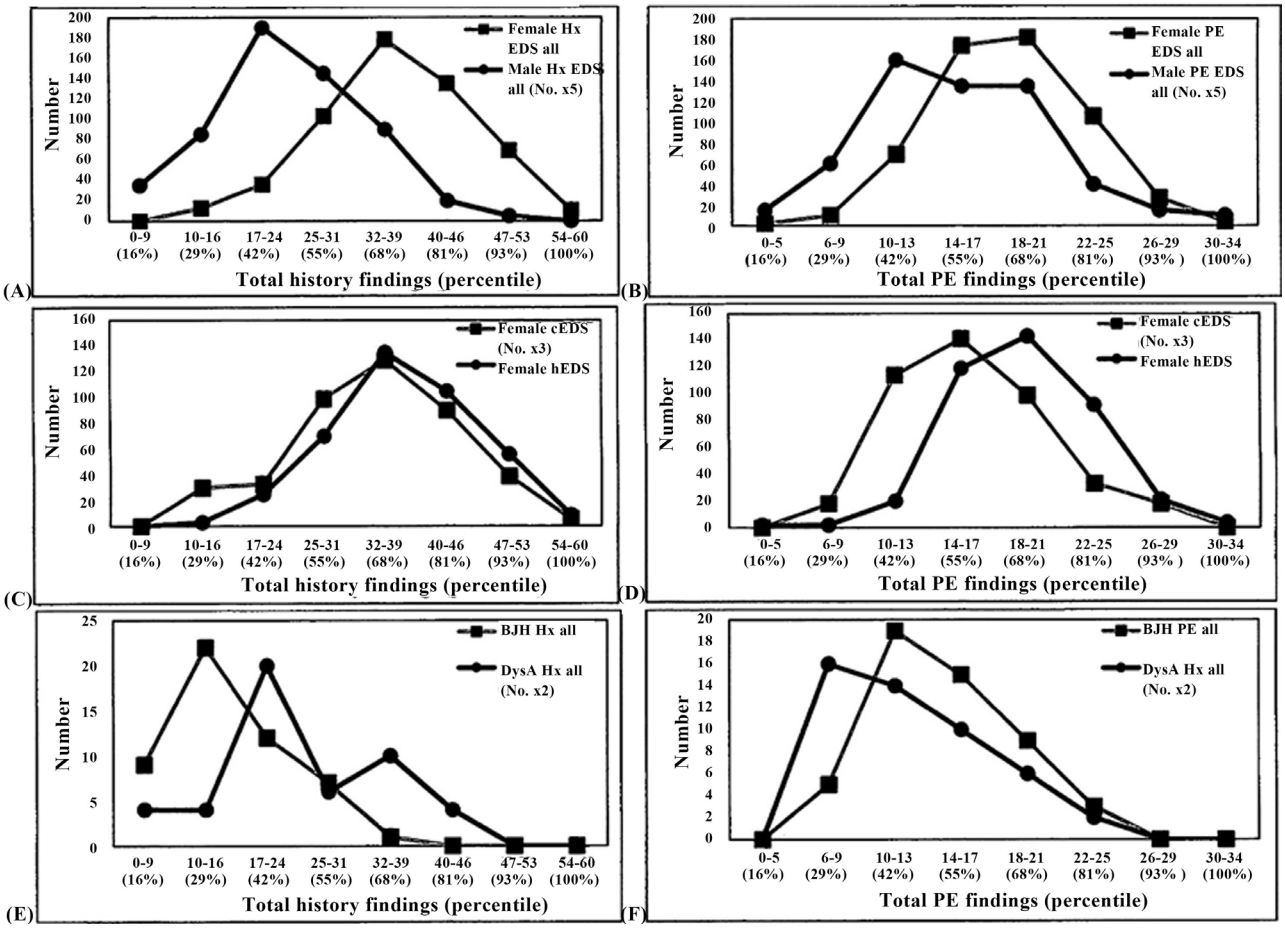


Figure 5. (A) numbers of systematically evaluated males (114 patients) and females (596 patients) having the indicated range of total history findings (percentiles correspond to the larger number in each range, chosen so that they correspond for history and physical finding numbers); (B) similar to (A) but for physical findings; (C) numbers of systematically evaluated males (47 patients) and females (400 patients) with preliminary diagnoses of hypermobile EDS having the indicated range of total history findings versus males (33) and females (143) with classical EDS; (D) similar to (C) but for physical findings; (E) numbers of systematically evaluated males (24 patients) and females (27 patients) with benign joint hypermobility (BJH) having the indicated range of total history findings versus males (7 patients) and females (17 paptients) with prominent dysautonomia (DysA); (F) same as E for physical findings; Hx, history findings; PE, physical examination findings, hEDS, hypermobile EDS, cEDS, classical EDS.

criteria with hypermobile-classical EDS patients having higher history and physical scores (37 and 33—19 and 16) than dysautonomia patients (26 and 12) and those judged as having benign joint hypermobility (16 and 14). Yet a congruent AAD profile is again suggested by lower but parallel scores in the various categories like the 3.8 - 6.8 of 15 average findings in the youth category, 3.2 - 6.7 of 15 in the joint-skeletal category, 11 - 12 of 20 (excepting 4.5 for benign joint hypermobility patients) in the dysautonomia category, 3.8 - 5.8 of 18 in the physical build-face-skeleton category, 3.1 - 4.5 of 9 on the Beighton scale, and 1.1 - 2.5 of 5 or 2.6 - 3.5 of 6 in the respective skin history or physical categories (Table 1). Only the AAD patients not deemed to have EDS had striking differences with history and physical totals averaging 8.4 of 80 and 5.6 of 40, suggesting that minimal scores of 10 and 8 on standard assessment forms might justify

further clinical and genomic testing for EDS or connective tissue dysplasia diagnoses. Even these more dramatic differences, blurred by the large standard deviations shown in Table 1, lacked statistical significance ($p > 0.01$) by pair-wise (t) comparison of individual finding frequencies between patient groups or by chi square comparison of their distributions among patient groups. Comparison within or among groups showed modest correlation coefficients of 0.35 to 0.41 for total history versus physical finding scores, again reflecting the paucity of neuromuscular or dysautonomia measures on the physical form (Figure 2).

There were expected increases of AAD severity with age in both females and males, most dramatic for the transition from children under 12 to teens as shown by history/physical scores of 20/15 to 31/17 for females and 19/13 to 23/16 in males. Severity seemed to plateau with age in females (history/physical scores of 38/19 to 38/18 in groups aged 20 - 49 to 50 - 73 years) with males showing some increase (24/15 to 29/16 from ages 20 - 39 to 40 - 63 years) that may reflect the lower age cut-off necessitated by small patient numbers. These numbers along with relative homogeneity of individual category scores emphasize that AAD is not degenerative beyond the slow deterioration of joints and circulation with age. The significant findings in youth (5.6 of 15 recalled by older women and men) and those in all categories for children under 12 emphasize the enormous opportunity for prevention and treatment occasioned by timely recognition of arthritis-adrenaline disorder. The lower rows of Table 1 again emphasize the congruent clinical profile produced by reciprocal articular and autonomic dysplasia, the 11% of patients from orthopedists averaging 5.1 of 15 findings in the joint-skeletal and a significant 8.2 of 20 in the dysautonomia category while the 36% from cardiology had even more joint skeletal-findings (6.4) together with their POTS-driven average dysautonomia score of 13.

This variation of total history and physical scores by age and sex is reinforced graphically in Figure 4. Panel 4A shows the numbers of total and systematically evaluated patients by age decile and again shows prevalent disease in the young, those presenting from ages 10 to 19 being most frequent, particularly among males. Average numbers of history findings increase sharply for males and females until age 20 - 29 (Panel 4B), then level off for older females and decrease dramatically for males. More moderate increases for physical scores again reflect the paucity of neuromuscular/autonomic findings, contributing along with less tissue laxity and genitourinary findings to the lower history and physical scores for males. The stability of scores with aging in females and their decrease in males can allay patient fears of EDS as a degenerative disease, though its exaggerated arthritis and autonomic imbalance can be viewed as a harbinger of aging that will be gradually augmented by usual geriatric progression. Average history (Panel 4C, E) and physical scores (Panel 4D, F) for young (0 - 19 years), adult (20 - 49), and older females (50+) or males (40+ because of low numbers) also reflect increasing severity with age, younger and adult females peaking at history scores from 32 - 39, young males much lower at history scores of 17 - 24. Note

that history and physical score ranges are plotted as equivalent percentiles where 60 of 80 was the maximal history score and 34 of 40 the maximal physical score registered. Physical scores by age group (Panel 4D) generally parallel history scores (Panel 4C) for females and younger males, but are quite different for adult and older males—the latter scores both peak at the 55th percentile for history (Panel 4E) but at a respective 68th and 42nd percentiles for physical (Panel 4F).

Distributions of history (Panel 5A) and physical scores (Panel 5B) for all systematically evaluated females and males are shown in **Figure 5**, their displacement to higher percentiles for females again indicating greater severity. Dramatic overlap of history score distributions for males or females preliminarily diagnosed as hypermobile or classical EDS (Panel 5C) reinforces their conformity to a typical AAD profile regardless of EDS type, though slightly higher average physical scores for the hypermobile EDS group (Panel 5D) reflects their higher Beighton scores. Those preliminarily diagnosed as benign joint hypermobility have lower history (Panel 5E) and moderate physical scores (Panel 5F) as expected, though extension of the history score curve to higher scores of 17 - 31 supports the presence of dysautonomia in these patients as previously published [9]. Although small patient numbers complicate interpretation of scores in those with dysautonomia, the several with high history and physical scores (Panels 5E, F) that reflect significant joint-skeletal findings again emphasize the ability of dysautonomia to produce joint-tissue laxity as in patients with MCAD and hypermobility from tryptase gene expansion [18].

4. Discussion

The many who have joint flexibility, anxious heart, irritable bowel, or immune reactivity are a substantial few with disabling disease, conditions best represented by a general descriptor that I suggest as arthritis-adrenaline disorder or AAD. Use of AAD as general descriptor and prelude to specific diagnosis is supported 1) by the histologic demonstration of both small fiber neuropathy [15] and connective tissue abnormalities [16] in component disorders; 2) by the characteristic pattern of history and physical findings produced by reciprocal articular-autonomic interaction [9] as presented here; and 3) by bringing attention to severe and treatable arthralgia-dysautonomia symptoms that are often dismissed as psychiatric disease [17].

AAD as a disorder is driven by an articulo-autonomic dysplasia cycle that I propose in **Figure 6** (AAD for pathogenic process and pattern). A two-cycle engine throttled by genes and environmental circumstance at each stroke (upper and lower parts of **Figure 6**), produces the easily recognized arthritis-adrenaline disorder profile that I have characterized in this article. On one side, highlighted by the genetic extremes of collagen V (classical EDS-[7]), fibrillin-1 (Marfan-[19]), and collagen III (vascular EDS-[8]) mutations, tissue laxity makes blood vessels weak and distensible, leads to blood pooling in the lower body as evidenced by pelvic congestion with extremity varicosities and discoloration, depletes cerebral

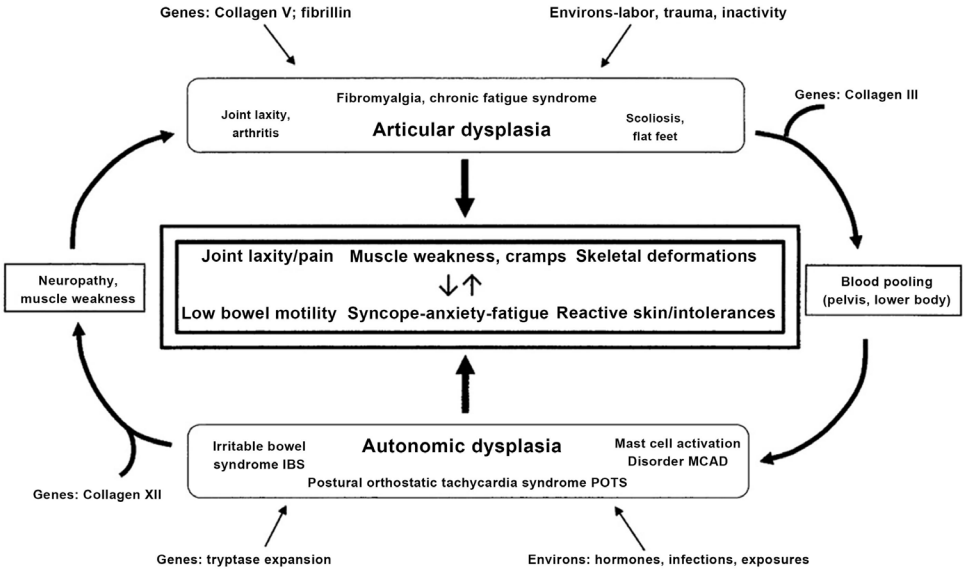


Figure 6. The articulo-automomic dysplasia cycle.

circulation as noticed by orthostatic dizziness or demonstrated by tilt-table testing [26] [34], and prompts adrenergic stimulation to restore brain blood supply (right side, **Figure 6**). The other side (left in **Figure 6**), as highlighted by the genetic extreme of tryptase gene expansion [18], has primary sympathetic (fight-or-flight) imbalance of the autonomic system, deranging small nerve [15] and muscle fibers in the connective tissue, its laxity producing cutaneous and skeletal abnormalities resembling EDS [3] [4], its vessel distensibility cycling through to reinforce dysautonomia. Collagen XII gene changes, one example among many first linked to myopathy that predicts a large myopathic EDS category [1], also will enhance the autonomic component of articulo-autonomic dysplasia.

Dysplasia, derived from the Greek (*plás*) for molding, now connotes diffuse abnormality of cells or molecules in tissue (e. g., fibromuscular dysplasia, [35]) rather than intrinsic malformation (e. g., congenital heart defect) or extrinsic deformation (e. g., valvular prolapse) of organ shape. This distinction is crucial for understanding why the consequences of connective tissue and autonomic dysplasia *syndromes*, diagrammed at the center of **Figure 6**, are mostly different from the congenital anomalies and recognizable facial appearances in disorders (like Down or Williams) that also append eponyms with the syndrome term. Although these developmental mechanisms invariably overlap to some degree, it is *dysplasia* of the ubiquitous connecting and supportive tissues that through skin elasticity causes the aged and fragile appearance in some with EDS, facial changes that are less distinctive than those in malformation syndromes like that of Down. Dysplasia leads 1) to tissue flexibility that with the action of gravity or weight-bearing produces deformities—of globe (myopia), spine (scoliosis, lordosis), feet (flat or high arches), brainstem (Chiari); 2) to tissue fragility that with the stresses of everyday living, accentuated by extreme sports

or exercise routines, produces inflammation/injury—of joints (osteoarthritis), tendons (tendonitis), muscles (myalgia, spasms), vertebrae (disc herniation/degeneration); and 3) to vessel distensibility that through lower body blood pooling produces sympathetic stimulation—the tachycardia, anxiety, distraction (brain fog), sweating, sleeplessness, hyper-reactivity, and exhaustion of POTS/MCAD [26] [27] and corresponding parasympathetic suppression—the low bowel motility/gastroparesis of IBS [25]. Once frayed and dysplastic, the connective tissue medium has many messages besides protective pain and spasm, relaying through its contained small nerve and muscle fibers commands for autonomic response. It is this underappreciated dysautonomia that is brought to attention by the preliminary AAD diagnosis, allowing objective clinical and DNA approaches to symptomatic diagnoses like fibromyalgia [12], chronic fatigue syndrome [13], or the depression that will inevitably accompany pain and activity limitation [17] **Figure 6** center.

With the weaknesses of self-reported histories, the forms in **Figure 1** and **Figure 2** allow preliminary evaluation of AAD that is easily adapted for rapid assessment and, if joint and skin laxity with some typical dysautonomia symptoms are found, easily expanded to the complete evaluation calibrated by the data in **Figures 3-5** and **Table 1**. Though preliminary to prospective studies that employ the full repertoire of adult medicine and laboratory expertise, the present study demonstrates that articular and autonomic issues occur in patients with hypermobile [6] or classical EDS [7], in those with benign [11] or life-limiting hypermobility [8], and in those brought to attention by heart [26] or joint [3] [4] issues. The data outline a spectrum best described as AAD, either as secondary to connective tissue dysplasia or other syndromes already delineated by clinical criteria, or as primary until subspecialty evaluations and genomic testing determineaspecific cause. AAD will be evaluated as a susceptibility in the former instance and used as interim guide to treatment in the latter. Sometimes the combination of AAD with symptomatic diagnoses like seronegative rheumatoid arthritis [36] will remind to check for autonomic symptoms; at other times it will foster additional exams and testing that specify environmental triggers or genetic causes of connective tissue dysplasia. A follow-up article will show that whole exome sequencing [37] [38] provides a powerful tool for delineating pathogenesis in AAD.

Most AAD findings are frequent in women but paralleled by men (**Figure 3**), most dramatic for those undergoing back surgery (12% female; 5% male), slow healing (37;9%), bladder issues (46;13%), hernias (12;3.0%), valve regurgitation (7.6;1.8%), gall bladder issues (18;5.9%), hives/reactive skin (52;18%), food-medicine intolerances (68;29%), and hypothyroidism (22;2%). These differences correlate with the greater flexibility and fragility of connective tissue in women that is conveyed by measures ranging from historical performance of hypermobility tricks (69;45%) to physical performance of Beighton maneuvers (59;29% with scores of 7 or more out of 9).

Neuromuscular and dysautonomia symptoms are also more frequent in women, the former including migraines (59;21%), muscle aches (60;25%) and weakness (37;17%) by history, muscle weakness (14;7.1%) and atrophy (12;6.9%) on physical, highlighting greater muscular development and support in men as a key factor in their reduced severity. The role of surrounding muscle for joint/connective tissue constraint and protection correlates with benefits of physical therapy and exercise for treatment of EDS [39] [40] and reminds of the benefits of exercise for healthful aging [41]. Efforts to build muscle and core strength should assume prominence among present management strategies, with mesenchymal stem cell therapy invoked for future musculoskeletal repair [42] in AAD-EDS and its more moderate parallel that we know as aging.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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