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HYPERMOBILITY EHLER DANLOS SYNDROME: A CASE REPORT SHOWING UNDERDIAGNOSES OF A COMMON CONDITION

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Case Report:

A 31 year old female presented with central hypothyroidism, hypermobility Ehlers Danlos syndrome (hEDS) and Stargardt disease.

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INTRODUCTION:

Ehlers Danlos syndrome-hypermobility type (EDS-HT) is a hereditary connective tissue disorder (HCTD) defined by the association of generalized joint hypermobility, joint instability complications, widespread musculoskeletal pain, and (minor) skin features. [1] Over the decades, EDS emerged as a clinically and genetically heterogeneous group of disorders, including an increasing number of variants (**Table 1**) which share the variable combination of dermal fragility, internal organ and vessel ruptures, and joint hypermobility (JHM). [2] Pain is common in Ehlers Danlos syndrome (EDS) and may correlate with hypermobility, frequency of subluxations and dislocations, soft tissue injury, history of previous surgery, myalgias, and may become chronic. Pain may be musculoskeletal or widespread. (3). Stargardt's disease (STGD) is a bilateral, symmetrical and progressive macular dystrophy that usually starts between the ages of 6 and 20 years and rapidly leads to loss of central vision. (4) Genetically, STGD is a heterogeneous disorder that is usually inherited as an autosomal recessive disorder but rarely can present as an autosomal dominant trait with a later onset of clinical symptoms. (4, 6).

CASE PRESENTATION:

A 31 year old female presented to our endocrinology clinic for treatment of hypothyroidism diagnosed at the age of 19. The patient had presented with complains of weight gain, fatigue, muscle pain, hair loss and puffy face. Her primary care physician conducted a thyroid profile test and diagnosed her with central hypothyroidism. She treated her with Levothyroxine and it significantly improved her symptoms.

The patients past medical history included a diagnosis of Ehler Danlos Syndrome at the age of 28 and Stargardt's disease at the age of 15. Upon taking a detailed history she told us that she was physically active as a child and was able to perform various unusual movements which included forward flexion with hands flat on floor and knees extended, hypermobility of her trachea and thumb apposition to the flexor aspect of forearm. Her symptoms went unnoticed at home because her mother and some other members from her maternal side were able to perform these kind of movements and they were never been diagnosed with any kind of hypermobility disorder. She was very active in school sports especially gymnastics and soft ball and none of her doctors took into account any of her unusual movements until she was unable to continue her sports due to the pain and hip instability associated with joint hypermobility. She was under chiropractic treatment for her symptoms during these years. She was referred to orthopedic and rheumatology for detailed evaluation due to complains of pain and numbness bilaterally in her feet. On thorough investigations she was diagnosed with Tarsal tunnel syndrome and had surgical management with titanium screws. They ruled out all other diseases involving joints and made a clinical diagnosis of EDS with joint hypermobility type as she fulfilled the criteria of Brighton's score. Now she manages her joint and muscular pains with CBD oil massage and regular exercise.

On further inquiry she informed us that since early childhood she had difficulty in reading from the blackboard at school as she used to copy notes from her friend. This was not paid due attention until she failed her math test in grade eight and on being questioned by her teacher she informed her that she had difficulty in copying her lessons from the board. They advised her see an ophthalmologist and on detailed examination including visual acuity, OCT and genetic testing a final diagnosis of Stargardt's disease was made. She stopped playing soft ball at the age of 15 because of her vision abnormality and is legally blind with no central vision. The patient is taking multivitamin however there is no proven treatment for Stargardt's disease and several options are under clinical trials. **Figure 1** shows some pictures of patient showing different joint movements including dislocation of temporomandibular joint and displacement of her trachea. Before taking pictures, we explained to her the nature of case report and took consent.

DISCUSSION:

Ehlers Danlos syndrome hypermobility type is considered an underdiagnosed heritable connective tissue disorder (HCTD), explaining the delay in diagnosis for our patient. Symptoms of EDS-HT can be vague and present a challenging picture to unite into one diagnosis. (8) Chronic pain is one of the major symptoms presented by patients with hEDS. It often presents as diffuse body pain affecting almost every part of the body. It is common and, may be severe. In one study the prevalence of chronic pain was 90% in patients with various types of EDS, with the highest scores on severity of pain found in hEDS.(3)In view of the vast genetic heterogeneity and phenotypic variability of the EDS subtypes, and the clinical overlap between many of these subtypes, but also with other CTDs, the definite diagnosis relies for all subtypes, except hEDS, on molecular confirmation with identification of (a) causative gene.(5) According to the original definition of the Beighton score and its

subsequent incorporation into the Villefranche nosology for the hEDS, the cut-off for the definition of GJH is 5 points out of 9. However, joint range of motion decreases with age and there is an inverse relationship between age at ascertainment and the Beighton score **(Figure 2)**, so the cut-off of five may prompt an over-diagnosis in children and an under-diagnosis among adults and elders. (5) Thus its becoming very important for physician to be aware of multiple presentations of this disease because failure/delay in diagnosis affects quality of life of patients suffering from hEDS.

A proposed questionnaire for investigating JHM by history. (7)

1	Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2	Can you now (or could you ever) bend your thumb to touch your forearm?
3	As a child did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4	As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
5	Do you consider yourself double jointed?

Along with hEDS our patient also has Stargardt disease which is an autosomal recessive disorder and causes macular degeneration with loss of central vision bilaterally. According to literature review Stargardt disease (STGD1; MIM 248200) is the most common inherited macular dystrophy in both adults and children with a prevalence of 1 in 8000–10 000. STGD1 has an autosomal recessive mode of inheritance associated with disease-causing mutations in the *ABCA4* gene. It is both clinically and genetically highly heterogeneous.

Patients present with bilateral central visual loss, including dyschromatopsia and central scotomata, with characteristic macular atrophy and yellow–white flecks at the level of the retinal pigment epithelium (RPE) at the posterior pole. Onset is most commonly in childhood, with the next peak being early adulthood, and least frequently in later adulthood, with a better prognosis generally associated with a later onset. There is slow progressive loss of retinal function and structure over time; however, there is marked variability both within and between families, suggesting that other important factors influence phenotype, including genetic modifiers and the environment. Although there are currently no proven treatments, there are three main avenues of intervention being explored, with human clinical trials of stem cell therapy, gene replacement therapy and pharmacological approaches. (9) Once diagnosed patients should be advised to avoid any blunt trauma to the eyes as ocular trauma occurring in patients of Stargardt's disease can precipitate a sequence of events leading to the development of sub retinal fibrosis and significant visual loss. (10)

CONCLUSION:

Hypermobility type Ehler danlos syndrome is one of the most underdiagnosed condition and can present with variety of vague symptoms from joint hypermobility to only chronic pain conditions thus leaving a great challenge for physicians to make a clinical diagnosis. Every physician should be aware of these symptoms and also should give importance to family that can draw our attention to think about this condition. Our patient also has Stargardt disease that is an autosomal recessive inherited condition and early diagnosis of which can help patients to avoid any kind of trauma and can prevent early changes in their vision. Also she has central hypothyroidism, we don't know either it's because of pure TSH deficiency or there is a deficiency of TRH as her insurance didn't cover for TRH testing but all her other pituitary hormones came out to be normal. We reviewed much literature to see any association between these conditions but didn't find any such reports/studies. We suggest physicians to report such cases in future to see any association between these if exists.

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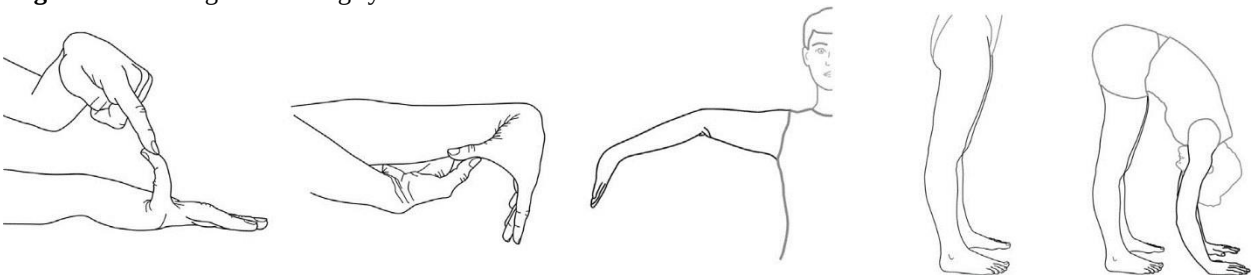
Tables and Figures:
Figure 1: Pictures from patient with different joint movements.

Figure 2: The Beighton scoring system.



Each joint is measured using a goniometer and each side is scored independently as outlined [Juul-Kristensen et al., 2007]. (A) With the palm of the hand and forearm resting on a flat surface with the elbow flexed at 90°, if the

metacarpal-phalangeal joint of the fifth finger can be hyperextended more than 90° with respect to the dorsum of the hand, it is considered positive, scoring 1 point. (B) With arms outstretched forward but hand pronated, if the thumb can be passively moved to touch the ipsilateral forearm it is considered positive scoring 1 point. (C) With the arms outstretched to the side and hand supine, if the elbow extends more than 10°, it is considered positive scoring 1 point. (D) While standing, with knees locked in genu recurvatum, if the knee extends more than 10°, it is considered positive scoring 1 point. (E) With knees locked straight and feet together, if the patient can bend forward to place the total palm of both hands flat on the floor just in front of the feet, it is considered positive scoring 1 point. The total possible score is 9. Figure courtesy of Dr. Juul-Kirstensen.

Table 1: Variants of Ehler Danlos syndrome.

Classification of Ehler Danlos	**Syndrome**	
Subtype	Inheritance	Genes
Major forms:		
Classic	AD	COL5A1, COL5A2
Hypermobility(JHS)	AD?	Mostly Unknown
Vascular	AD	COL3A1
Kyphoscoliotic	AR	PLOD1
Arthrochalasia	AD	COL1A1, COL1A2
Dermatosparaxis	AR	ADAMTS2
Rare/Emerging forms		
Tenascin X-deficient	AR, AD?	TNXB
Classic with vascular rupture	AD	COL1A1
Cardiac-valvular	AR	COL1A2
EDS/OI overlap With periventricular heterotopia	AD XLD	COL1A1, COL1A2 FMNA
Musculocontactural	AR	CHST14
Spondylocheirodysplastic	AR	SLC39A13
Progeroid	AR	B4GALT7
Kyposcoliotic with deafness	AR	FKBP14
Parodontitis	AD	Unknown
Fibronectin deficient	AR	Unknown

AD: autosomal dominant, AR: autosomal recessive, EDS/OI: Ehlers Danlos syndrome/osteogenesis imperfecta, JHS: joint hypermobility syndrome, XLD: X-linked dominant.