The rheumatological heritable disorders of connective tissue

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Abstract

The genetically determined rheumatological connective tissue disorders constitute a group of phenotypically related inherited conditions caused by aberrations in genes encoding for the fibrous connective tissue matrix proteins (collagens, elastins, fibrillins, tenascins). In most (but not all) of these conditions, the precise genetic cause has been identified. A common clinical feature is joint hypermobility. The frequently encountered, yet largely neglected, hypermobile type of Ehlers–Danlos syndrome and hypermobility spectrum disorder are both sources of much unrecognized morbidity and unnecessary suffering in the community.

Keywords Chronic pain; dysautonomia; Ehlers–Danlos syndrome; heritable connective tissue disorders; hypermobility spectrum disorder; intestinal dysmotility; joint hypermobility syndrome; lower urinary tract symptoms; Marfan syndrome; MRCP

Key points

- For all heritable disorders of connective tissue, except hypermobile Ehlers–Danlos syndrome (hEDS), the definitive diagnosis relies on molecular confirmation with identification of a causative variant(s) in the respective gene
- Since the publication of the 2017 classification criteria, a diagnosis of hEDS should be assigned only in those who meet all of the relevant 2017 criteria; this should help reduce heterogeneity and might facilitate efforts to discover the underlying genetic cause(s) of the syndrome
- The range of clinical expression in these disorders is broad and multisystemic
- Physiotherapy is the mainstay for the musculoskeletal problems. It is essential that techniques are modified to meet the needs of lax and fragile tissues or injury can ensue

Classification

Within rheumatology, the important heritable diseases comprise:

- Marfan syndrome
- Ehlers–Danlos syndrome (EDS: classical, hypermobile and vascular types)
- osteogenesis imperfecta
- hypermobility spectrum disorders (HSDs).

Marfan syndrome, EDS and osteogenesis imperfecta, although rare, are well described in the literature. All three have potentially life-threatening complications.[1] HSDs are very common, although under-recognized. They carry a normal life expectancy.

The definitive diagnosis for all heritable connective tissue disorders (HCTDs) (except for hypermobile EDS (hEDS) and HSDs) relies on molecular confirmation with identification of a causative variant(s) in the respective gene. A molecular diagnosis is extremely important for counselling purposes, as it allows confirmation of the precise diagnosis and gives information on inheritance pattern, risk of recurrence and prognosis, and it can guide management. Moreover, it allows for the formation of homogeneous cohorts for research purposes.[2]

'Joint hypermobility' is the term universally accepted to define the capability for a joint (or a group of joints) to move, passively and/or actively, beyond normal limits for that joint along physiological axes, taking into account age, gender and ethnic origin. Hence, joint hypermobility is a descriptor rather than a diagnosis. Joint hypermobility can exist as an isolated diagnostic finding, but is often a feature of a larger syndromic diagnosis.[3]

It is important to be aware that many individuals within the population have hypermobile joints without suffering any ill effects or with only mild musculoskeletal pain. This must be distinguished from HSD, in which hypermobility is accompanied by a range of symptoms that can extend to unremitting chronic pain and disability. It is also important to recognize that clinical overlap is frequently encountered and can cause diagnostic confusion (e.g. marfanoid habitus features in hEDS, increased skin stretchiness in Marfan syndrome and HSD, bone fragility in classical EDS). Joint laxity and joint hypermobility feature in all four conditions.

The most common diagnosis of a hypermobility-related disorder was previously called 'joint hypermobility syndrome' (JHS). The revised 1998 Brighton criteria for JHS, published in 2000, were very helpful as they recognized the association with pain and dislocations, and included extra-articular manifestations; not surprisingly, they overlapped to a certain extent with the 1997 Villefranche criteria for 'Ehlers–Danlos syndrome hypermobility type' (EDS-HT). In 2017, a new international classification for EDS was published and this subtype was renamed hypermobile EDS (hEDS) with new criteria combining the physical signs and symptoms. A diagnosis of hypermobile EDS should now be assigned only in those who meet all of the 2017 criteria; this should help to reduce heterogeneity and facilitate efforts to discover underlying genetic cause(s) of the syndrome, which, in turn, may help clinical management.[2]

'HSDs' are mostly intended as alternative labels for patients with symptomatic joint hypermobility who do not have any rare

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type of EDS and do not fully meet the criteria for hEDS in terms of high Beighton score, severity/pattern of musculoskeletal involvement and/or presence/absence of the other necessary criteria (as reported in the new EDS nosology). In many circumstances, the HSDs will become the updated diagnosis for all those individuals who met the previous criteria for EDS-HT or JHS but do not match the new hEDS criteria.[3] The new criteria are due to be reviewed and revised at the forthcoming meeting of the International Consortium to be held in Ghent in 2018.

Pathogenesis

Tissue laxity and fragility are the hallmarks of these disorders. Ligamentous laxity allows increased flexibility, a valued asset for would-be dancers, gymnasts and musicians. Tissue fragility results in impaired tensile strength, leading to mechanical failure and rupture of tissues, manifesting as a predisposition to injury and overuse, and a vulnerability to their effects. Tissue healing is also impaired.

Sequelae depend on which protein is affected and the severity of the mutation. In Marfan syndrome, a fibrillin 1 (FBN 1) deficiency disorder is responsible for aortic root dilatation (with aneurysm formation) and dislocation of the ocular lens (ectopia lentis). In EDS (vascular type), deficiency of collagen type III (COL3A1) can result in rupture of arteries, abdominal viscera or the uterus. In the classical type of EDS where the emphasis is on gross joint laxity and extreme skin hyperextensibility, the disease is principally caused by mutations in genes encoding for collagen type V (COL5A1, COL5A2). By contrast, in osteogenesis imperfecta, where bone fragility with fractures predominates, collagen 1 mutations (COL1A1, COL1A2) are present.

Clinical presentation

All forms of HCTD share to a varying degree common features, including joint hypermobility, skin hyperextensibility and tissue fragility. Joint dislocations can occur, especially in patients with EDS.

From the musculoskeletal point of view, we can recognize three tiers of clinical presentation (Table 1; BOX 1). In infancy and early childhood, hypermobility can be marked by motor delay (omitting crawling, delayed walking), unsteadiness with falling (genu valgum/recurvatum, ankle sprains, flat feet), clumsiness and dyspraxia (e.g. difficulty with ball-catching and using scissors) and pains in the leg muscles after exercise. In adolescence, the daily physical demands of school work and sport exceed the capacity of lax joints and muscles poorly adapted to their needs, leading to frequent and recurrent self-limited traumatic (acute, overuse) soft tissue lesions (Table 2).

The first prospective study evaluating the relationship between joint hypermobility, using a cut-off of ≥6 on the Beighton score, and musculoskeletal pain in adolescence was published in 2013 and involved 2901 participants. The study reported that joint hypermobility was associated with an approximately 2-fold increased risk of musculoskeletal pain within a specific distribution – the shoulder, knee and ankle/foot. The risk of knee pain was particularly high in hypermobile participants who were obese.[4]

If the musculoskeletal symptoms are not treated effectively, the individual with an HCTD descends into the second tier of presentation, which comprises widespread chronic pain (due to pain amplification), often like that of fibromyalgia. This is unresponsive to normally potent analgesics and is associated with fatigue. It leads to pain avoidance by movement avoidance (kinesiophobia) and severe muscle deconditioning, often with significant autonomic dysfunction.

The three tiers of clinical presentation

Musculoskeletal tissue laxity
- Non-inflammatory joint/spinal pain
- Dislocations/subluxations
- Ligament, muscle, tendon, enthesis injury/overuse, flat feet
- Pelvic floor, hernias, varicose veins

Non-articular
- Pain amplification, 'kinesiophobia', deconditioning
- Widespread chronic pain ('fibromyalgia')
- Fatigue
- Orthostatic intolerance, postural tachycardia
- Intestinal pan-dysmotility

Psychosocial sequelae
- Anxiety/depression, low self-esteem and negative body image, work incapacity, isolation, resentment, anger

Table 1

Unless adequate management is provided a further descent into the third tier of presentation is almost inevitable. Increasingly isolated from a previously active and productive life, immobile through muscle disuse (compounded in some cases by obesity), seemingly abandoned by sceptical health professionals and carers, depressed and angry, patients are left to their own resources and help from patient self-help groups. Fortunately, only a small proportion of patients, estimated at 5–10%, enter tier 3.

Over the past 10 years, many studies have been conducted into the association between JHS/EDS-HT, as defined by the Brighton criteria, and extra-articular disorders.[5] Autonomic dysfunction has been found to be common in JHS. The most common type of dysautonomia seen in JHS is postural tachycardia syndrome. This can be easily identified by a rise in heart rate (>30 beats per minute) on change of posture from the lying to the standing position. When more formal testing is done, including 'head-up' tilt, exercise testing, meal and thermal stimulation tests, and 24-hour heart rate and blood pressure monitoring, over two-thirds of patients have significant and clearly identifiable autonomic abnormalities. Such autonomic disturbances add to the burden of anxiety and fatigue, limit exercise tolerance and can cause syncope. It is important to identify these abnormalities as they can be treated.

There is also evidence linking functional gastrointestinal disorders (including irritable bowel syndrome) with hypermobility and JHS.[5] Approximately one-half (49%) of 129 new unselected referrals to a tertiary neuro-gastroenterology clinic were identified, using a validated five-point questionnaire, as having hypermobility. Patients with JHS and gastrointestinal symptoms experienced bloating (57%), nausea (57%), reflux symptoms (47%), constipation (38%) and diarrhoea (14%). Symptoms and functional tests revealed gastrointestinal dysmotility, which could be caused by lax gut connective tissue. Individuals with HCTDs attending hypermobility clinics often admit to similar symptoms if questioned.

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