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REVIEW

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Joint hypermobility as a distinctive feature in the differential diagnosis of myopathies

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Abstract Congenital and adult-onset inherited myopathies represent a wide spectrum of syndromes. Classification is based upon clinical features and biochemical and genetic defects. Joint hypermobility is one of the distinctive clinical features that has often been underrecognized so far. We therefore present an overview of myopathies associated with joint hypermobility: Ullrich congenital muscular dystrophy, Bethlem myopathy, congenital muscular dystrophy with joint hyperlaxity, multi-minicore disease, central core disease, and limb girdle muscular dystrophy 2E with joint hyperlaxity and contractures. We shortly discuss a second group of disorders characterised by both muscular features and joint hypermobility: the inherited disorders of connective tissue Ehlers-Danlos syndrome and Marfan syndrome. Furthermore, we will briefly discuss the extent and pattern of joint hypermobility in these myopathies and connective tissue disorders and propose two grading scales commonly used to score the severity of joint hypermobility. We will conclude focusing on the various molecules involved in these disorders and on their role and interactions in muscle and tendon, with a view to further elucidate the pathophysiology of combined hypermobility and myopathy. Hopefully, this review will contribute to enhanced recognition of joint hypermobility and thus be of aid in differential diagnosis.

Key words myopathy · joint hypermobility · Ullrich congenital muscular dystrophy · Bethlem myopathy · Multiminicore Disease (MmD) · Central Core Disease (CCD)

Introduction

Congenital and adult-onset inherited myopathies represent a wide spectrum of syndromes, ranging from severe and sometimes early fatal disorders to relatively mild conditions compatible with nearly normal life. Recent advances concerning the genetic clarification of inherited myopathies have significantly improved our understanding of their pathogenesis. It has also enabled classifications of these conditions based on both the clinical features and the primary biochemical and genetic defects. In addition to the pattern of muscle weakness, other clinical features such as cardiac involvement, myo-

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Table 1 Overview of myopathies associated with joint hypermobility and inherited connective tissue disorders associated with muscular involvement

	Protein involved	Gene	Muscle involvement	Hypermobility/dislocation/ contractures	Associated symptoms	Reference
Ulrich congenital myopathy	Collagen VI	*COL6A1/A2* 21q22.3 *COL6A3* 2q37	Hypotonia, delayed motor milestones, profound muscle weakness. Onset in 1st decade; wheelchair bound.	Distal joint hypermobility (MCP joints, PIP and DIP joints) Contractures (proximal joints)	Early respiratory failure Dermal features (hyperkeratosis, soft velvety skin, abnormal scar formation.)	[56] [40] [36]
Bethlem myopathy	Collagen VI	*COL6A1/A2* 21q22.3 *COL6A3* 2q37	Hypotonia, delayed motor milestones, reduced fetal movements, mild muscle weakness (proximal > distal, extensors > flexors) Onset in 1st or 2nd decade	Distal joint hypermobility (DIP joints) Flexion contractures (fingers, wrists, elbows, and ankles)	Respiratory failure	[8] [44] [36] [57]
Congenital muscular dystrophy with joint hyperlaxity (CMDH)	Unknown	Unknown	Hypotonia, delayed motor milestones, reduced fetal movements, generalized muscle weakness (proximal > distal)	Distal joint hypermobility Proximal contractures	Early respiratory failure Mild to moderate mental retardation	[40]
	Candidate proteins: Integrin alfa 9 Activin A IIB receptor Laminin receptor 1	Candidate regions: *ITGA9* *ACVR2B* *LAMR1* 3p23-p21	Presence of congenital hypotonia, weakness, and frequent delayed motor milestones	Distal joint hypermobility (fingers, wrists, toes, cervical spine) Contractures (ankle, knee, shoulder)	Decreased pulmonary vital capacity Scoliosis	[54]
Multi-minicore disease	Selenoproteine N "classic MmD"	*SEPN1* 1p35-36	Hypotonia, reduced fetal movements, delayed motor milestones, muscle weakness (axial > proximal > distal)	Distal joint hypermobility (MCP); to a lesser degree in all other limb joints	Respiratory failure>> muscle weakness, spinal rigidity, scoliosis, secondary cardiac (right ventricular) involvement	[19] [30] [31]
	Ryanodine receptor "MmD subgroups"	*RYR1* 19q13.1	Hypotonia, reduced fetal movements, delayed motor milestones, muscle weakness (axial > proximal > distal) Subgroup with predominant hip girdle weakness Subgroup with marked distal weakness and wasting, predominantly the hands	Distal joint hypermobility (MCP); to a lesser degree in all other limb joints	Ophthalmoplegia, milder respiratory involvement. Mild facial muscle weakness	[19] [33] [31]
Central core disease	Ryanodine receptor	*RYR1* 19q13.1	Muscle weakness with prominent involvement of hip girdle and axial muscles Mild facial involvement Rare bulbar involvement	Generalized hypermobility	Mitral valve prolapse Malignant hyperthermia	[30] [21]
Limb girdle muscular dystrophy 2E with joint hyperlaxity and contractures	Beta-sarcoglycan	*SCGB: SPATA18* 4q11-q12	Progressive limb girdle muscle weakness, onset 0–5 years, delayed motor milestones, facial weakness	Distal joint hypermobility (MCP and PIP joints) Contractures (DIP joints)	Tachycardia, arrhythmia, chest pain, scoliosis, nocturnal dyspnea	[34]
Marfan syndrome	Fibrillin	*FBN1* 15q21.1	Muscle hypoplasia, muscle cramps, easy fatigability, generalized muscle weakness	Distal joint hypermobility (DIP/PIP/ MCP joints, wrists) Contractures (elbows)	Ascending aorta dilatation and rupture, arachnodactyly, scoliosis or spondylolisthesis, pectus excavatum, highly arched palate, typical facial appearance	[16] [49] [66] [4]

Table 1 Overview of myopathies associated with joint hypermobility and inherited connective tissue disorders associated with muscular involvement

	Protein involved	Gene	Muscle involvement	Hypermobility/dislocation/ contractures	Associated symptoms	Reference
Ehlers-Danlos syndrome						
Classic type	Collagen V Collagen I Unknown	*COL5A1/A2* 9q34.2-q34.3 /2q31 COL1A1 17q21.31–q22	Muscle hypotonia, delayed gross motor development Fatigue	Generalized joint hypermobility with recurring joint dislocations (shoulder, patella, temporomandibular joints)	Skin hyperextensibility, easy bruising, velvety skin, widening of scars	[5]
Vascular type	Collagen III	*COL3A1* 2q31-q32	Tendon and muscle rupture	Distal joint hypermobility (hands/ fingers) Tendon and muscle rupture	Thin, translucent skin, extensive bruising. arterial/intestinal/uterine fragility or rupture, characteristic facial appearance, acrogeria, talipes equinovarus (clubfoot), early-onset varicose veins, arteriovenous, carotid-cavernous sinus fistula, pneumothorax/ pneumohemothorax, gingival recession.	[5]
Kyphoscoliotic type	Lysyl hydroxylase	*PLOD* 1p36.3-p36.2	Severe muscle hypotonia at birth; delayed gross motor development	Distal joint hypermobility	Scoliosis, scleral fragility and rupture of the ocular globe, arterial rupture, osteopenia, marfanoid habitus, microcornea	[5] [23] [65]
Tenascin-X deficient type	Tenascin-X	*TNXB* 6p21.3	Muscle weakness	Generalized joint hypermobility	Skin hyperextensibility, easy bruising, velvety skin	[50] [58] [60]
Hypermobility type	Tenascin-X Unknown	*TNXB* 6p21.3	Musculoskeletal pain	Generalized joint hypermobility with recurring joint dislocations (shoulder, patella, temporomandibular joints)	Easy bruising, velvety skin	[5]

tonia, cataract, cognitive impairment, and muscle rippling and mounding may assist in defining specific phenotypes. Significant joint hypermobility (or hyperlaxity) can also be a distinctive clinical feature in its own right.

Whereas contractures are quite common in the course of inherited muscle disorders, hypermobile joints occurs less often and may therefore be more discriminative. Joint hypermobility (or joint hyperlaxity) can be defined as abnormally increased active and/or passive range of motion in a joint [7]. Although "joint hyperlaxity" is used more frequently in the neuromuscular literature, we prefer the term "joint hypermobility" as it directly refers to the increased range of movement in the joints. Presence of multiple hypermobile joints can be referred to as generalized joint hypermobility (we refer to the discussion for definitions and rating scales). Great physiological variability of joint mobility occurs in the general population based on differences in sex and genetic and ethnic background. Furthermore, joint hypermobility normally decreases with ageing. In fact, generalized joint hypermobility is the end of a spectrum of physiological joint mobility. This has to be taken into account in the interpretation of severity of joint hypermobility.

In this review we will present an overview of myopathies associated with hypermobile joints. Hopefully, this will contribute to enhanced recognition of joint hypermobility and thus assist in diagnosis (Table 1). We will shortly discuss a second group of conditions characterised by both muscular features and joint hypermobility. This includes Ehlers-Danlos syndrome and Marfan syndrome, both congenital inherited disorders of connective tissue. They may be considered in the differential diagnosis of patients with muscle weakness with hypermobile joints. Furthermore, we will briefly discuss the distribution pattern of joint hypermobility in these myopathies and connective tissue disorders and present two grading scales commonly used to score the severity of joint hypermobility. We will conclude focusing on the various molecules involved in these disorders and on their role and interactions in muscle and tendon, with a view to further elucidate the pathophysiology of combined hypermobility and myopathy.

Myopathies accompanied by joint hypermobility

Collagen VI myopathies

Ullrich congenital muscular dystrophy

Ullrich congenital muscular dystrophy (UCMD) was first described by Ullrich in 1930, and subsequent publications confirmed a recognisable pattern of disease caused by autosomal recessive as well as de novo dominant mutations in the three genes coding for collagen type VI [40, 43, 55, 56]. The hallmarks of UCMD are muscle weakness of early onset with proximal joint contractures and striking hypermobility of distal joints (toes, ankles, fingers, and wrists) (Fig. 1) [36]. Posteriorly protruding calcanei are commonly seen (Fig. 1). Weakness is profound and children typically either never achieve the ability to walk independently or walk independently for a limited period of time only. Intelligence is normal. With progression of the disease, spinal rigidity, scoliosis, and variable proximal contractures develop. The distal hypermobility can gradually give way to marked long finger flexion contractures and tight Achilles tendons. Respiratory failure in the first or second decade is a common cause of death unless treated with nocturnal respiratory support. Other distinctive features observed in UCMD patients are failure to thrive, congenital hip dislocations, and transient kyphotic deformity at birth. Dermal features include follicular hyperkeratosis over the extensor surfaces of upper and lower limbs, soft velvety skin on the palms and soles, and a tendency to keloid or "cigarette paper" scar formation. Cardiac involvement has not been documented to date [36].

Serum creatine kinase activity in UCMD patients is usually normal or mildly increased and electromyography reveals myopathic changes [36]. Muscle MRI shows a characteristic pattern with diffuse involvement of the thigh muscles with relative sparing of sartorius, gracilis, adductor longus, and rectus muscles. In addition, affected muscles may show a peculiar pattern of abnormal signal intensity changes with the rim of the muscle being predominantly affected and the centre relatively spared [38]. Muscle biopsy in UCMD patients demonstrates variable pathology, ranging from non-specific mild myopathic changes to a more dystrophic-like appearance [51]. Early findings emphasise atrophic rather than dystrophic changes. Additionally, variation in fibre size, type 1 fibre predominance, an increase in endomysial connective tissue, increased numbers of internal nuclei, and focal areas of necrosis, along with other evidence of muscle fibre regeneration such as the presence of fibres containing fetal myosin can be found [40, 43].

Bethlem myopathy

Bethlem myopathy (BM) was first described in 1976 by Bethlem and van Wijngaarden as an autosomal dominantly inherited mild proximal myopathy with long finger flexion contractures occurring in 28 individuals of three Dutch pedigrees [8]. It is now known to be caused by mutations in the three genes coding for collagen VI [29]. Although Bethlem myopathy typically presents within the first or second decade in adult life, there often is a history of neonatal hypotonia or torticollis, delayed motor milestones, or even decreased fetal movements [29]. On the other end of the clinical spectrum, some

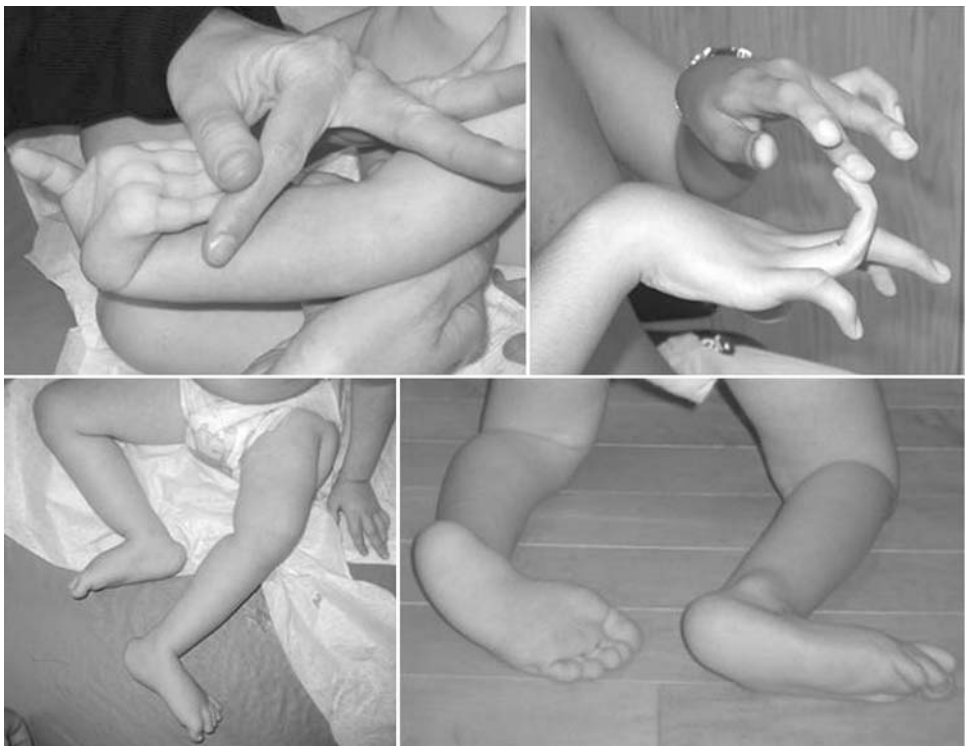

Fig. 1 Severely affected 16-month old male UCMD patient with joint hypermobility in hands (left upper image), prominent calcaneus, and soft skin (left lower image); 21-year old male UCMD patient with significant proximal contractures showing preserved hypermobility of fingers (right upper image); prominent calcaneus with ankle contractures in 2-year old male UCMD patient (right lower image)

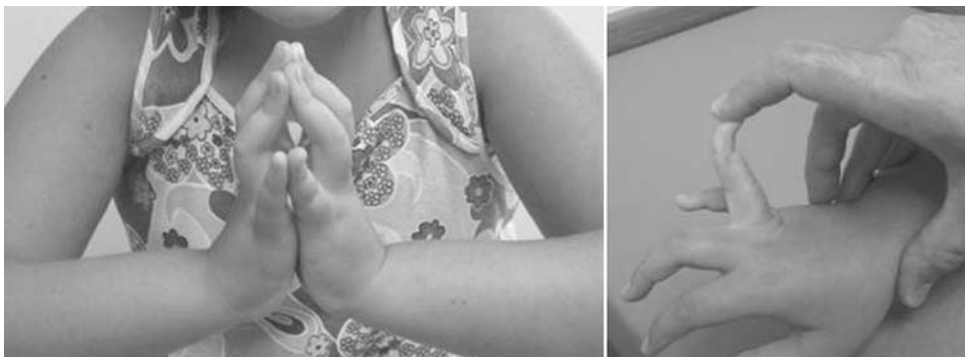

Fig. 2 Bethlem myopathy in 12-year old female patient with contractures of proximal interphalangeal joints and hypermobility of distal interphalangeal joints

adult patients are only very mildly affected and remain unaware of weakness [36]. The progressive development of contractures is a hallmark of this condition. In childhood, the contractures may be preceded by hypermobility in the same joint and be of a strikingly dynamic nature, appearing and disappearing in various joints [29]. However, nearly all patients eventually show flexion contractures of the fingers, wrists, elbows, and ankles, and those may contribute to the degree of overall disability as much as the associated weakness. Strikingly, hypermobility of distal interphalangeal joints can remain present together with long finger flexion contractures, similar what is seen in more pronounced fashion in UCMD (Fig. 2). Progression is slow and occasionally results in the patient being wheelchair-bound after 25 to 40 years [36]. Respiratory failure can be part of the clinical spectrum and may even occur in ambulatory patients [57]. To date there has been no evidence of cardiac involvement in Bethlem myopathy [57].

Serum creatine kinase activity in Bethlem myopathy patients is usually normal or only mildly increased and electromyography reveals a myopathic pattern. MRI reveals most abnormalities in the vasti muscles, with a rim of abnormal signal at the periphery of each muscle and relative sparing of the central part. Another frequent finding was the presence of a peculiar involvement of the rectus femoris with a central area of abnormal signal within the muscle [10, 38]. Muscle biopsy demonstrates a non-specific myopathy with fibre-size variation, few necrotic and regenerative fibres, and a mild increase in connective tissue [8, 42].

Mutations in all three collagen VI genes have now

been identified in both Bethlem myopathy and Ullrich congenital muscular dystrophy [36]. Collagen VI is a ubiquitous extracellular matrix protein that is present in the extracellular matrix and forms a microfibrillar network in close association with the basement membrane of most tissues. In muscle it is produced predominantly by the interstitial fibroblast population [52, 69]. Dominant mutations in the genes encoding collagen VI affect collagen VI microfibril formation, resulting in a disengagement of collagen VI with the basal lamina, whereas recessive null mutations lead to a complete absence of collagen VI in the matrix [28, 35]. The exact mechanism and the downstream effects of collagen VI deficiency on muscle cells may involve the engagement of myofibre apoptosis, but are still subject of research [1, 69]. In tendon, collagen VI is presumably synthesised by the resident tendon fibroblast population, it assumes a distinctly pericellular orientation around these cells, and as such it may represent a survival factor for these cells [14, 48].

Congenital muscular dystrophy with joint hyperlaxity

Recently, a number of cases of congenital muscular dystrophy with joint hypermobility with preservation of collagen VI in muscle and absence of COL6A1, A2 or A3 mutations have been described [39, 54]. Mercuri reported five cases with CMD associated with short stature, proximal contractures, rigidity of the spine, and distal joint hypermobility as well as early respiratory failure and mild to moderate mental retardation (Congenital muscular dystrophy with joint hyperlaxity (CMDJH)). Hypermobility was present in distal fingers, toes, and ankles but the expression of collagen VI was confirmed to be normal on muscle biopsies of all five patients; in addition, in one informative family linkage to any of the three COL6 gene loci could be excluded [39]. The differential diagnosis included a previously reported atypical variant of Ehlers-Danlos syndrome (EDS); however, muscle weakness had not been noted in these EDS cases [26, 27].

In addition, Tétreault et al. reported 14 cases affected by autosomal recessive CMD with distal joint hypermobility. All patients presented muscle hypotonia at birth, generalized slowly progressive muscle weakness, and proximal contractures predominantly affecting ankle, knees and shoulders coexisting with distal hypermobility, mainly observed in the fingers, wrists, toes, elbows, and cervical spine. No rigidity of the spine was observed, but mild to severe scoliosis was a frequent finding. Pulmonary vital capacity was usually diminished. Serum creatine kinase activity was normal or only mildly increased with muscle biopsy showing only non-specific myopathic features. Genetic studies excluded mutations in the three genes coding for collagen VI subunits and suggested linkage to a region on chromosome 3p23-21 [54]. This linkage was not found in cases with a similar phenotype in other centres, indicating genetic heterogeneity [61].

Multi-minicore disease

Multi-minicore disease (MmD) is an inherited myopathy characterised by multiple cores on muscle biopsy and clinical features of a congenital myopathy. Its prevalence is unknown. Marked clinical variability corresponds to genetic heterogeneity [19]. The classic phenotype of this condition is associated with recessive mutations in the selenoprotein N *(SEPN1)* gene and is characterised by predominantly axial muscle weakness, spinal rigidity, early scoliosis, and respiratory impairment. In contrast, recessive mutations in the skeletal muscle ryanodine receptor *(RYR1)* gene have been associated with a wider range of clinical features comprising external ophthalmoplegia, distal weakness, and wasting or predominant hip girdle involvement resembling central core disease (CCD) [19, 33, 68]. In the latter forms, there may also be a histopathologic continuum with CCD due to dominant *RYR1* mutations, reflecting the common genetic background [68].

All phenotypes may be associated with contractures (either arthrogryposis in early-onset forms or predominant Achilles tendon tightness in milder cases) and/or ligamentous laxity and joint hypermobility [19], mostly pronounced in the hands (Fig. 3). Distal hypermobility is generally more severe in patients with a *RYR1* mutation than in those with a *SEPN1* mutation, but may be present in both [32]. This is generally accompanied by atrophy of intrinsic hand muscles, hand hypotonia, and moderate weakness. Patellar and knee dislocations may be present [19]. In the majority of patients, weakness is static or only slowly progressive, with the degree of respiratory impairment being the most important prognostic factor [30, 68].

The diagnosis of MmD is based on the presence of suggestive clinical features and the finding of multiple cores on histochemical stains of the muscle biopsy highlighting mitochondria. Muscle MRI may aid genetic testing as patterns of selective muscle involvement are distinct depending on whether the mutations are in the *SEPN1* or the *RYR1* gene. Mutational analysis of the *RYR1* or the *SEPN1* gene needs to be performed for genetic confirmation of the diagnosis. Management is mainly supportive and in particular has to address the risk of marked respiratory impairment in *SEPN1*-related MmD and the possibility of malignant hyperthermia susceptibility in *RYR1*-related forms [30, 68].

SEPN1 is a glycoprotein-localised within the endoplasmic reticulum, and is present at a high level in several human fetal tissues and at a lower level in adult tissues, including skeletal muscle. This may suggest a role for SEPN1 in early development and in cell proliferation or regeneration within muscle [46]. The ryanodine re-

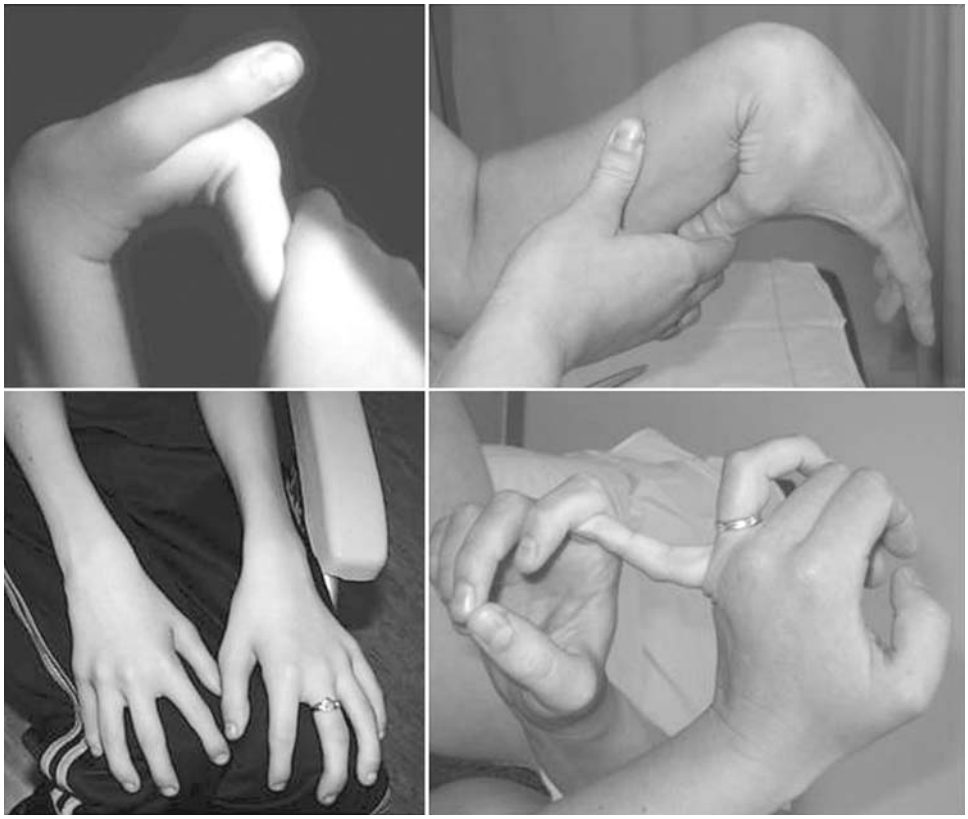

Fig. 3 MmD patient with distal hypermobility (metacarpophalangeal joints) and atrophy of intrinsic hand and forearm muscles, suggestive of RYR1 involvement, although this has not been genetically confirmed (left images); wrist and finger (metacarpophalangeal joints) hypermobility in a 22-year old female MmD patient with a RYR1 mutation (right images)

ceptor serves as a calcium release channel of the sarcoplasmic reticulum as well as a bridging structure connecting the sarcoplasmic reticulum and transverse tubule [67].

Central core disease

This relatively common congenital myopathy was originally reported in a family with congenital hypotonia, non-progressive weakness, and central areas of amorphous appearance within muscle fibres stained with the Gomori Trichome technique [37]. The term CCD was introduced later to refer to the characteristic absence of oxidative enzyme activity or of other histochemical stains highlighting mitochondria in the core area due to the absence of mitochondria from the central area of the fibres [18, 24]. CCD typically presents in infancy with hypotonia or developmental delay and a pattern of muscle weakness that is most pronounced in hip girdle and axial muscles with typically only mild or absent facial, bulbar and respiratory involvement. Progression is slow and almost all patients achieve the ability to walk independently, except the most severe neonatal cases and those having very severe orthopaedic complications; however, marked clinical variability, even within the same family, has been reported. Orthopaedic complications are common in CCD and comprise congenital dislocation of hips, scoliosis, and foot deformities including talipes equinovarus and pes planus [21, 41]. Many patients have striking ligamentous laxity and joint hypermobility, occasionally associated with patellar instability, whereas contractures other than tendon Achilles tightness are rare [21]. Interestingly, whilst the latter study was published in the orthopaedic literature, orthopaedic features other than scoliosis or hip dislocation have been rarely documented in studies with a neuromuscular emphasis, likely reflecting an ascertainment bias.

Serum CK is usually normal in CCD but may occasionally be mildly elevated. Muscle ultrasound shows a striking increase in echo intensity but relative sparing of the rectus femoris, corresponding to a similarly consistent pattern of selective muscle involvement on muscle MRI which may assist in differentiating *RYR1*-related CCD from other myopathies with cores and rods on muscle biopsy [30].

Limb girdle muscular dystrophy 2E with joint hyperlaxity and contractures (LGMD2E+)

Kaindl et al. reported a family with a severe and progressive limb-girdle muscular dystrophy with joint hypermobility, contractures, and cardiorespiratory symptoms comprising chest pain, tachycardia, arrhythmias, and

dyspnoea [34]. Muscle weakness presented in the first decade, with delayed motor milestones and a progressive Duchenne-like muscular dystrophy including facial weakness, resulting in loss of ambulation around the age of 10. Hypermobility was most pronounced in proximal interphalangeal joints and in metacarpophalangeal joints, contrasting with contractures in the distal interphalangeal joints and, to a lesser extent, in knees and elbows.[34] Genetic analysis revealed a homozygous microdeletion of approximately 400 kb on chromosome 4q11-q12 , a region containing the beta-sarcoglycan gene *(SGCB)*, which pathogenetic role in this condition was further supported by myopathic changes on muscle biopsy and immunohistochemical studies showing complete absence of SGCA and SGCB immunoreactivity [34]. Some degree of joint hypermobility in these patients may be related to the muscle weakness and hypotonia. However, since beta-sarcoglycan is not expressed in tendons or connective tissue, and hypermobility is not a common feature in other patients with beta-sarcoglycan mutations, joint hypermobility and contractures may also result from a contiguous gene syndrome [34].

Differential diagnosis

Inherited connective tissue disorders are typically characterised by joint hypermobility and tissue fragility of skin, vessels, and internal organs. They may also be associated with muscle weakness, and should be considered in the differential diagnosis of patients presenting with both muscle weakness and joint hypermobility. We will therefore briefly discuss the main clinical features of the two most important inherited connective tissue disorders that can present in this way.

Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous group of inherited connective tissue disorders characterised by generalized joint hypermobility, skin hyperextensibility, and tissue fragility [6]. In 1997, six main types were defined: hypermobility type, classical type, vascular type, kyphoscoliotic type, arthrochalasis type, and dermatosparaxis type EDS. A clinically distinct, recessive form results from tenascin X (TNX) deficiency on the basis of *TNXB* gene mutations. Hypermobility is present in all types but most pronounced in the hypermobility, classical, and TNX-deficient type. In the vascular type, joint hypermobility is usually limited to the digits, whereas in the kyphoscoliotic type both fingers and hands are involved (Fig. 4). This latter type may present with proximal contractures in the course of the disease [53]. Furthermore, muscle hypotonia, delayed motor milestones, fatigue, musculoskeletal pain, and muscle rupture are implied in the diagnostic criteria and reported in several case reports [2, 5, 6, 47, 58, 60]. Muscle involvement is probably most pronounced in the kyphoscolitic type and evident in the neonatal period already; therefore, this condition should be considered in the initial differential diagnosis of the floppy infant syndrome [5, 23, 63, 65].

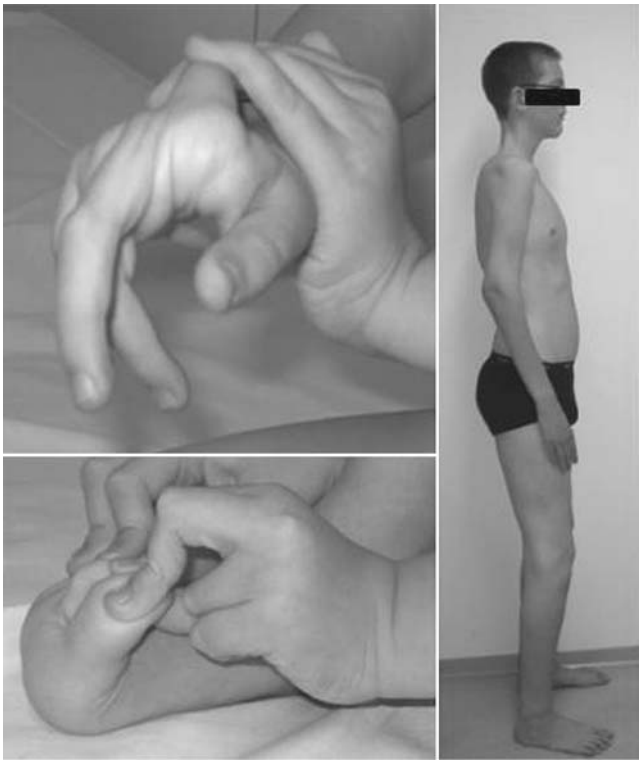

Fig. 4 Remarkable distal joint hypermobility (metacarpophalangeal and metatarsophalangeal joints) in a 4-year old male patient with the kyphoscoliotic type of Ehlers-Danlos syndrome (left images); elbow contractures and mild knee contractures in a 16-year old male patient with the kyphoscoliotic type of Ehlers-Danlos syndrome (right image)

Various extracellular matrix molecules are involved in the pathophysiology of the various EDS types, although the major genetic causation of the hypermobile type in particular awaits clarification: type I and type V collagen (classical type); collagen III (vascular type); TNX (TNX-deficient type), and lysyl hydroxylase 1, the latter of which is involved in collagen cross linking (kyphoscoliotic type) [13, 50, 64]. These collagen types occur both in muscle and tendon extracellular matrix.

Marfan syndrome is a dominantly inherited connective tissue disorder characterised by ocular, skeletal, and cardiovascular manifestations [16]. Mutations in the fibrillin-1 *(FBN1)* gene located at 15q21.1 account for most of the cases [9]; *FBN1* encodes fibrillin-1, a widely distributed major component of microfibrils in the extracellular matrix with an important role for elastin deposition in elastic fibres. Joint hypermobility is usually most pronounced in distal joints and often accompanied by arachnodactyly (Fig. 5). (Congenital) joint contractures,

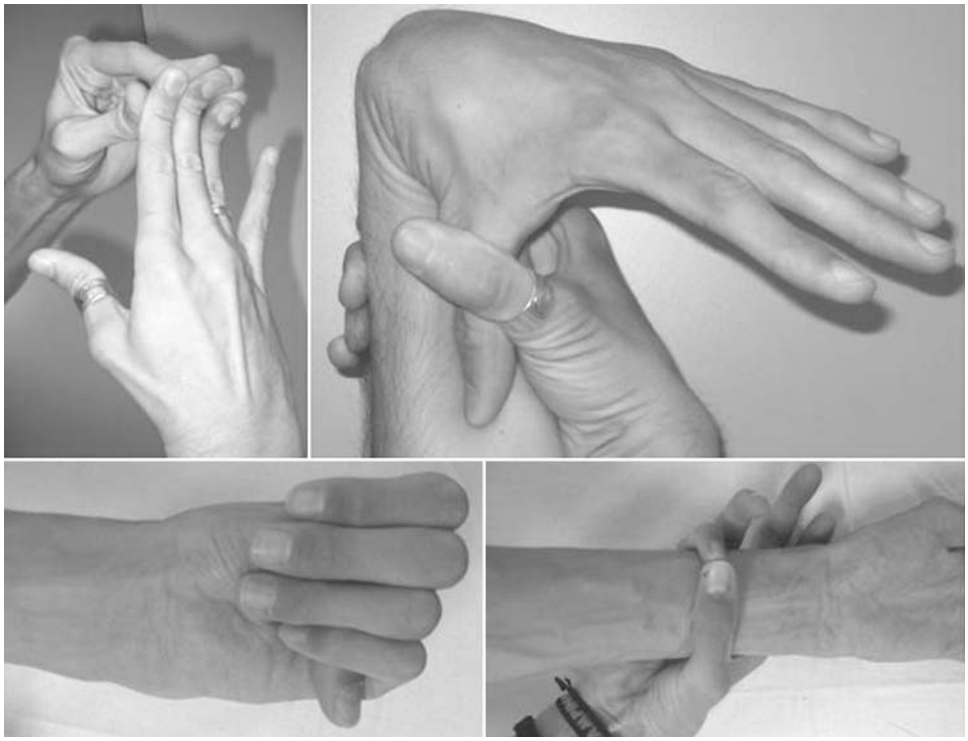

Fig. 5 Hypermobility of distal interphalangeal joints and wrist in a 28-year old male Marfan patient (upper images); arachnodactyly with positive thumb sign and wrist sign in a 27-year old male Marfan patient (lower images)

particularly of the elbow, occur with moderate frequency [16]. Marfan patients frequently report muscle fatigue, and to a lesser extent muscle weakness, muscle hypoplasia, myalgia, and cramps [4, 15, 22, 25, 45, 49, 66]. Fibrillin-1 is relatively abundantly expressed in the skeletal muscle endomysium and perimysium, suggesting a causal link between muscle symptoms and the *FBN1* abnormality [49, 66]. Recent findings also suggest that *FBN1*, in addition to its structural role, may also participate in TGF β-related signalling and thus influence muscle function [3, 15].

Discussion

In this overview we discuss clinical features of myopathies in which excessive joint hypermobility can be a significant part of the clinical picture. Hypermobility in myopathies generally occurs in distal joints, while proximal joints may show predominant contractures. Recognition of this rather unusual clinical feature can assist in diagnosis. In addition, we briefly described two inherited connective tissue disorders that may present with both mild muscle weakness and hypermobility. These disorders may have to be considered in the differential diagnosis of unclassified myopathies with hypermobility. The pattern of distribution of joint hypermobility as well as the co-existence of hypermobility with dislocations and contractures can be similar in the myopathies and inherited connective tissue disorders discussed (Table 2). Furthermore, in both groups of disorders hypermobility is dynamic and usually decreases with ageing. This may suggest that some of these disorders represent a continuous spectrum of muscle ECM disorders [59].

Remarkably, hypermobility in CCD has been most extensively reported in the orthopaedic literature [21], probably reflecting the different emphasis of orthopaedic and neuromuscular assessments, with the latter mainly focusing upon muscle strength without actively screening for increased range of motion in various joints. Contractures may be noticed more easily since they occur more often, are evident immediately on inspection, and generally cause more disability. Joint hypermobility might therefore have been underestimated in the neuromuscular literature so far [31]. Vice versa, muscle involvement in inherited connective tissue disorders has long been neglected and only recently have regained attention [4, 15, 45].

Consensus on the nomenclature and classification of joint hypermobility in literature seems to be missing. Various terms are randomly used to designate that joints can be moved to a higher than normal range, either actively or passively: e.g. *"hypermobility"* in the orthopaedic report on CCD [21], in the neurological literature on Bethlem myopathy [29], and in the clinical criteria of EDS and Marfan syndrome [5, 16]; *"hyperlaxity"* in reports on MmD [19], on LGMD 2E [34], and on UCMD [36], *"joint laxity"* [29, 40, 54] and, even less specifically, *"hyperelasticity"* [36] and *"hyperextensibility"* (in MmD [20] and in UCMD [44]). The latter two terms are con-

Table 2 Distribution of joint hyperlaxity, dislocations, contractures, and rigid spine

	DIP	PIP	MCP	Wrist	Elbow	Shoulder	Knee	Hip	Toes	Ankle	Spine	Other skeletal abnormalities
Ulrich congenital myopathy	H	H → C	H → C	C	C		C		H	C		Hip dislocation Protruded calcaneus High arched parate
Bethlem myopathy	H	C	C	H → C	C			H		C		
Congenital muscular dystrophy with joint hyperlaxity (Mercuri et al.)	H (→ C)*	H (→ C)*	H (→ C)*		C		C	C	H	H	R	Small feet Tallipes Valgus Rigid spine (Kypho)scoliosis Short stature
Congenital muscular dystrophy with joint hyperlaxity (Tetrault et al.)	H	H	H	H		C	C H	C	H	C	Cervical spine: H	Scoliosis
Multi-minicore disease	H	H	H				D (patella, knee)					Arthrogryposis; dislocations
Central core disease			H	H	H		H D (patella, knee)	D		C		Talipes equinovarus/ pes planus/pes cavus Scoliosis Club foot Camptodactyly
Limb girdle muscular dystrophy 2E with joint hyperlaxity	C	H	H	H	C		C					
Marfan syndrome	H	H	H	H	H / C	H	H	H	H	H	H	Pectus carinatum/excavatum Scoliosis Arachnodactyly
Ehlers-Danlos syndrome (various types)	H	H	H	H	H / C	H	H	H	H	H	H	Frequent dislocations Scoliosis

* Contractures in the fingers developed over time in one of the five patients reported

H joint hypermobility; *D* dislocation; *C* contractures; *R* rigidity; *H → C* hypermobility may in time develop into contractures; *DIP* distal interphalangeal joints; *PIP* proximal interphalangeal joints; *MCP* metacarpophalangeal joints

ventionally used to depict skin rather than articular features [5]. Furthermore, description of how joint mobility was determined and which joints were tested is often lacking in neuromuscular articles. This may cause inaccurateness of the clinical description [34, 36] and eventually add to under-recognition and underestimation of the presence of joint hypermobility in various myopathies [31]. We think that literally, "laxity" or even "hyperlaxity" refer to general tissue characteristics rather than functional or dynamic features of the joint. We therefore prefer use of the term "hypermobility" which precisely indicates that the joint can be moved to a higher than normal range.

To increase recognition and to assist in determining the severity and distribution of joint hypermobility, we here propose two standardised passive measures of joint hypermobility: the Beighton and Bulbena scores (Table 3), both of which can easily be measured during physical examination [7, 12]. Although commonly used among clinical geneticists, neurologists seem to be unfamiliar with the use of these standardised measures of joint hypermobility. The Bulbena score includes one item on the presence or absence of ecchymoses, which are uncommon in myopathies and may therefore be a reasonable discriminator between "muscular" hypermobility and "connective tissue" hypermobility [12]. Furthermore, in younger patients the Beighton score is less reliable and the Bulbena score is more useful. Hypermobile joints occur in the population in a normal distribution as variant, and generalized joint hypermobility is therefore defined as a score ≥ 5 (Beighton score/Bulbena score for men) or ≥ 4 (Bulbena score for women). In contrast to Ehlers-Danlos syndrome, the myopathies described above are typically accompanied by distal rather than generalized hypermobility (distal and proximal interphalangeal and metacarpophalangeal joints of hands, distal interphalangeal joints of feet, wrists, and ankles). Therefore, we suggest that reports describing joint hypermobility in myopathies also specify the distribution, e. g. naming the joints rather than differentiating between distal and proximal (Table 2).

Why certain myopathies are associated with hypermobility has not fully been elucidated in all cases but may be multifactorial, comprising factors affecting both dynamic joint function and connective tissue characteristics of myotendinous junction and tendon. First, muscle weakness in both extensors and flexors of a specific joint could allow a higher range of motion, whilst, if only agonists or antagonist muscles are weak, contractures may develop [34]. In addition to altered joint dynamics, abnormalities of the myotendinous junction may be involved. Studies in zebrafish embryo have shown that loss of selenoprotein N function causes disruption of both muscle and myoseptum architecture [17], the latter being the connective tissue layer connecting tendon to muscle that is involved in force transmission. So far, no evidence for (myo)tendinous junction defects in *SEPN1*-related myopathies has been published. This may be due to sampling error: muscle biopsies samples are generally taken from muscles at a distance from a tendon [17]. Furthermore, altered tendon and joint capsule characteristics may contribute to joint hypermobility. Firstly, structural abnormalities may be involved: type VI collagen, for example, is present in bovine tendons, where it may be involved in organising the extracellular matrix of fibrocartilage and provide a survival factor for fibrochondrocytes [14]. Consequently, *COL6* mutations may alter tendon structure and function. Similarly, extracellular matrix molecules involved in the pathophysiology of inherited connective tissue disorders (fibrillin, collagen I, III, and V, and tenascin-X) are known to be expressed in both in connective tissue of muscle, tendons, and joint capsules [5, 11]. As a result, mutations in genes encoding these extracellular matrix molecules may alter structure and function of muscle and tendon connective tissue and thus contribute to both muscle weakness and hypermobility/contractures. We refer to a recent review for a description of structure and function of these extracellular matrix molecules within muscle and their role in muscle function [59]. Furthermore, functional changes in tendon physiology may be involved. Calcium signalling by ryanodine receptor-mediated calcium release plays a role in mechanotransduction pathways of fibroblasts in tendon [62]. Hypothetically, *RYR1* mutations may thus alter mechanic function of tendon. This has not been investigated as such and calls for further research.

In summary, we have presented a clinical overview of myopathies that may present with both muscle weakness and joint hypermobility. We have discussed two inherited disorders of connective tissue that may be considered in the differential diagnosis of these myopathies. Furthermore, we stressed the importance of precise reports on the severity and distribution pattern of joint hypermobility, and made an argument for consensus on nomenclature. We hope this review will contribute to increased awareness of joint hypermobility in a wide range of myopathies and the use of standardised measures. This may be of aid in the diagnostic process, and eventually lead to enhanced recognition of distal joint hypermobility in various myopathies, with important implications for diagnosis, treatment and understanding the pathophysiology of these conditions.

Conflict of interest The authors declare no conflict of interest.

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Table 3 Two standardised measures of joint hypermobility: the Beighton and Bulbena scores

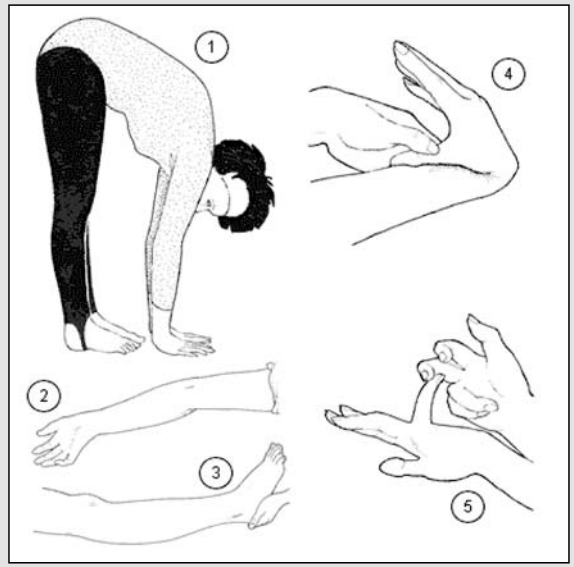
Beighton score
Degree of mobility by passive manoeuvres in 5 joints

Total score: 0–9

Hypermobility:
score ≥ 5.

- Dorsiflexion of the little fingers beyond 90°; one point for each hand;
- Apposition of the thumbs to the flexor aspect of the forearm; one point for each hand;
- Hyperextension of the elbows beyond 10°; one point for each elbow;
- Hyperextension of the knees beyond 10°; one point for each knee;
- Forward flexion of the trunk with knees fully extended so that the palms of the hand rest flat on the floor; one point.

One point for each hypermobile joint



http://www.arc.org.uk/arthinfo/patpubs/6019/6019.asp

Bulbena score
Degree of mobility by passive manoeuvres in 9 joints.

Total score: 0–10.

Hypermobility:
≥ 5 (women);
≥ 4 (men).

Upper extremity:
- Thumb: passive apposition of the thumb to the flexor aspect of the forearm < 21 mm;
- Metacarpophalangeal: with the palm of the hand resting on the table, the passive dorsiflexion of the fifth finger is ≥ 90°;
- Elbow hyperextension: passive hyperextension of the elbow ≥ 10°;
- External shoulder rotation; with the upper arm touching the body, and the elbow fixed at 90°; the forearm is taken in external rotation to > 85° of the sagittal plane (shoulder line);

Lower extremity – supine position:
- Hip abduction: passive hip abduction ≥ 85°;
- Patellar hypermobility: holding with one hand the proximal end of the tibia, the patella can be moved well to the sides with the other hand;
- Ankle and feet hypermobility: an excess range of passive dorsiflexion of the ankle eversion of the foot can be produced;
- Metatarsophalangeal: dorsal flexion of the toe over the diaphysis of the first metatarsal is ≥ 90°;

Lower extremity – prone position:
- Knee hyperflexion: knee flexion allows the heel to make contact with the buttock;

One point for each hypermobile joint.

General:
- Presence or absence of ecchymoses (1 point for the presence of ecchymoses).

Illustration of device for measurement of angles of joint mobility

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