REVIEW

Ullrich congenital muscular dystrophy: clinicopathological features, natural history and pathomechanism(s)

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ABSTRACT

Collagen VI is widely distributed throughout extracellular matrices (ECMs) in various tissues. In skeletal muscle, collagen VI is particularly concentrated in and adjacent to basement membranes of myofibers. Ullrich congenital muscular dystrophy (UCMD) is caused by mutations in either COL6A1, COL6A2 or COL6A3 gene, thereby leading to collagen VI deficiency in the ECM. It is known to occur through either recessive or dominant genetic mechanism, the latter most typically by de novo mutations. UCMD is well defined by the clinicopathological hallmarks including distal hyperlaxity, proximal joint contractures, protruding calcanei, scoliosis and respiratory insufficiency. Recent reports have depicted the robust natural history of UCMD; that is, loss of ambulation by early teenage years, rapid decline in respiratory function by 10 years of age and early-onset, rapidly progressive scoliosis. Muscle pathology is characterised by prominent interstitial fibrosis disproportionate to the relative paucity of necrotic and regenerating fibres. To date, treatment for patients is supportive for symptoms such as joint contractures, respiratory failure and scoliosis. There have been clinical trials based on the theory of mitochondrion-mediated myofiber apoptosis or impaired autophagy. Furthermore, the fact that collagen VI producing cells in skeletal muscle are interstitial mesenchymal cells can support proof of concept for stem cell-based therapy.

INTRODUCTION

Collagen VI is an important component of the ECM of skeletal muscle and is involved in maintaining tissue integrity by providing a structural link between different ECM molecules and in promoting adhesion,[1 2] proliferation,[3] migration[4] and survival[5] of various cell types. Collagen VI-related myopathies are the hereditary myopathies caused by mutations in either COL6A1, COL6A2 or COL6A3 gene, each encoding a subunit of collagen VI. Patients have the clinicopathological features of a muscle disorder as well as of a connective tissue disorder, although the link between this defect of ECM and phenotype remains to be fully elucidated.

Recent advance in molecular biology has evolved the aetiological definition of collagen VI-related myopathies; these myopathies are known to encompass a clinical continuum with Ullrich congenital muscular dystrophy (UCMD) and Bethlem myopathy (BM) at each end of the spectrum, originally described separately.[6–8] Intermediate phenotypes, named as mild UCMD or severe BM, have been known but less well defined as there is currently no clear-cut boundary between two major phenotypes. In addition, it should be noted that genotype–phenotype correlation is very difficult to establish; for example, both extremes of the clinical spectrum are seen in patients with p.Gly284Arg mutation in the COL6A1 gene, the most commonly observed mutation, while half had an intermediate phenotype.[9] In this context, several researchers have proposed the clinical stratification of patients with collagen VI-related myopathies (figure 1A).[10–12]

The hallmarks of UCMD include marked distal joint hyperlaxity associated with proximal joint contractures, a rigid spine and normal intelligence. Furthermore, children presenting UCMD phenotype have been referred to as having 'early severe' or 'moderately progressive' course of early-onset collagen VI-related myopathies according to maximal motor ability and disease progression.[10–12] Thus, UCMD is relatively well defined as compared with BM or intermediate phenotypes.

CLINICAL PICTURE

In 1930, Otto Ullrich described two boys with an unusual congenital myopathy characterised by muscle weakness and wasting, marked distal joint looseness and contracture of the proximal joints since birth or early infancy and termed this new condition "Kongenitale, atonisch-skelerotische Muskeldystrophie, ein weiterer Typus der heredodegenerativen Erkrankungen des neuromuskulären Systems".[6 7] Subsequent publications confirmed a likely autosomal-recessive inheritance and a recognisable pattern of disease.[13] The diagnostic clinical and molecular criteria for UCMD have been proposed by the European Neuromuscular Centre.[14]

Epidemiology

UCMD is the second most common congenital muscular dystrophy (CMD) after CMD with laminin α2 deficiency (also known merosin-deficient CMD; or MDC1A) in Europe,[15] after Fukuyama CMD in Japan[16] and after α-dystroglycanopathies in Australia.[17] The prevalence of UCMD is reported to be 1.3 per million in Northern England.[18]

Perinatal features and development

Prenatal movements might be reduced in fetuses with UCMD.[19] Some patients have congenital hip dislocation, torticollis and transient kyphotic deformity.[19 20] Multiple joint contractures may be evident at birth, affecting the elbows, knees, spine

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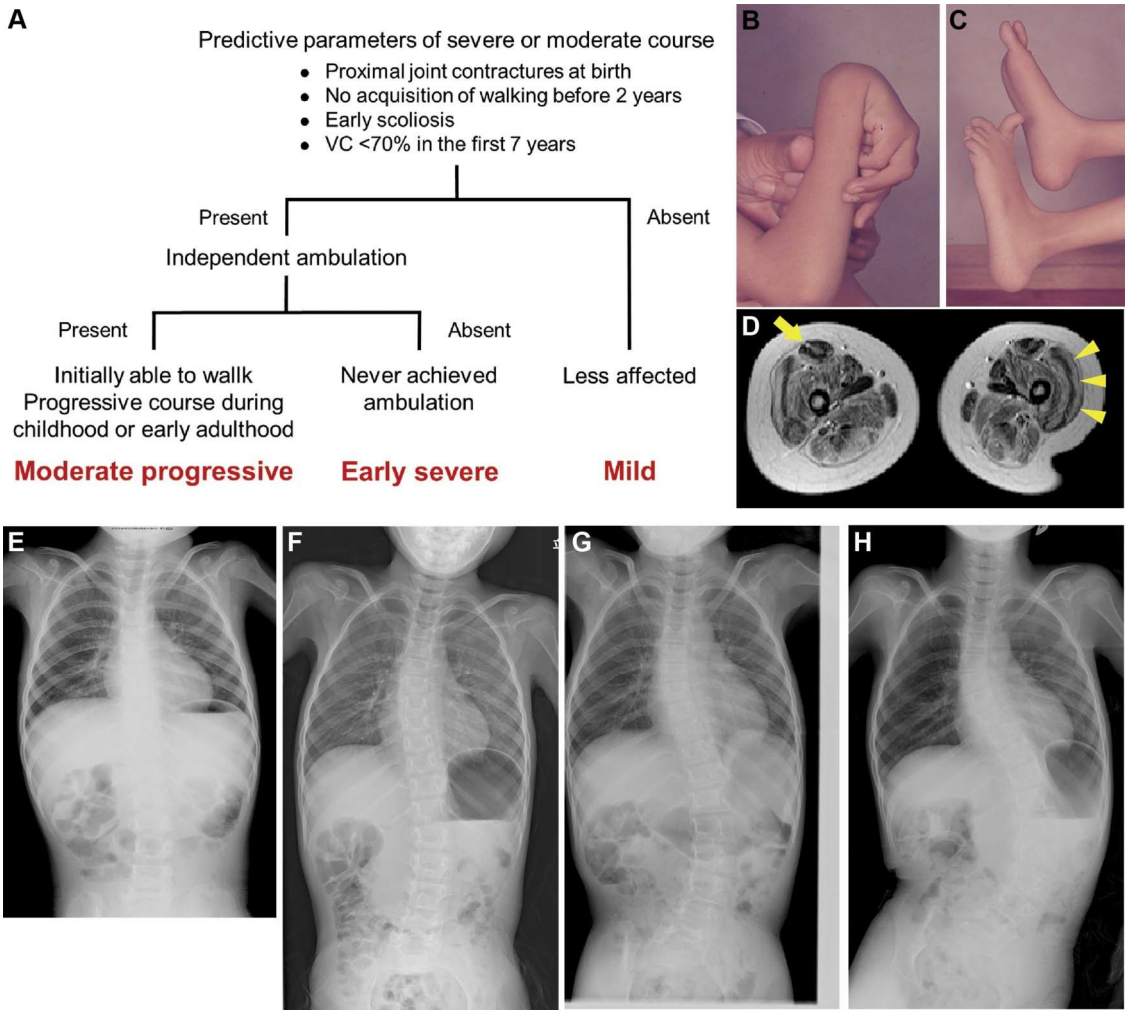

Figure 1 Phenotypic stratification of early-onset collagen VI-related myopathies; modification from Quijano-Roy et al[10] and Briñas et al[11] (A). Typical distal hyperlaxity and protruding calcanei in a patient with Ullrich congenital muscular dystrophy (UCMD) (B,C). Diagnostic muscle MRI findings of the thigh (D): fatty regeneration along the fascia in the centre of the rectus femoris (arrow) and in the periphery of the vastus lateralis with relative sparing of its central part (arrowheads). Early-onset and rapidly progressive scoliosis in UCMD (E–H). E, 3.7; F, 6.1; G, 6.9; H, 7.9 years of age at assessment. (Images courtesy of Drs Ikuya Nonaka and Akihiko Ishiyama).

(kyphoscoliosis) and ankles. Arthrogryposis multiplex are seen in 20.0% of patients.[19] Some transient feeding difficulties or poor sucking might occur in the neonatal period.[19 20]

The most common presentations are delayed motor milestone and proximal muscle weakness. Patients with UCMD usually become able to sit independently with or without delay.[19] The majority of patients with typical UCMD achieve the ability to walk by 2 years of age. The age at independent ambulation is reported to be 1.7±0.8 and 1.7±0.5 years in English and Japanese natural history studies, respectively.[19 20] This group is referred to as having 'moderate progressive' disease in the phenotypic stratification of early-onset collagen VI-related myopathy (figure 1A).[10 11] In the remaining patients, ambulation is never achieved. Those with the most severe presentation, accounting for 19.4–25.7% of UCMD patients,[11 19] are referred to as having 'early-severe' disease (figure 1A). However, even these severely affected children can usually learn to roll, crawl and maintain a sitting position. Patients who never walk due to severe contractures that prevent an upright posture may walk on their knees for a certain period of time. Achievement of speaking phrases is not delayed, ranging from 12 to 25 months of age.[19]

Clinical manifestations

Patients show generalised muscle weakness predominantly in trunk and proximal limbs. Neck flexors are weak. Facial weakness is reported respectively in 24.1% and 30.8% of patients in two different studies.[19 20] The most striking feature is hyperlaxity of the distal joints (figure 1B), although it can be absent in severely affected individuals. Spinal rigidity, scoliosis and various proximal joint contractures develop with progression of the disease. Typically, initially flexible distal joints, such as fingers, wrists and ankles, eventually become contractured with time. Interestingly, calcanei are often protruded posteriorly (figure 1C). Distal joint hyperlaxity, proximal joint contractures, scoliosis and protruding calcaneous are observed in >50% patients in a Japanese cohort.[19] Many patients have a characteristic facial appearance with round-shaped face with slight drooping of the lower lid and prominent ears.[15] Intelligence is normal. Other features include follicular hyperkeratosis over the extensor surfaces of upper and lower limbs, a softer consistency of the skin in the palms and soles and the tendency to keloid formation.[15] Respiratory insufficiency is not common at birth, although it becomes a critical complication of the disease as the condition progresses. Cardiac involvement is not documented to date.[21 22]

Serum creatine kinase (CK) activity in patients with UCMD is usually within normal range or only mildly elevated,[19–21] which is unusual in other (congenital) muscular dystrophies. Electromyography shows action potentials of low amplitude and short duration.[13] Muscle MRI shows a characteristic pattern on transverse T1-weighted images—diffuse involvement of the thigh muscles with relative sparing of the medial muscles (sartorius, gracilis and adductor longus).[23] Rectus femoris is variably involved with a typical central area of high signal, called 'central shadow'.[23] In vastus lateralis, the peripheral part is mainly involved and signal intensity is markedly increased while the central part is relatively spared (figure 1D).[23]

Muscle pathology and collagen VI immunohistochemistry

Variable degrees of histological changes can be observed in muscle biopsies from patients with UCMD. The spectrum includes fibre size variation affecting both fast and slow fibres, type 1 fibre predominance, increased endomysial connective tissue or adipose tissue, increased number of internal nuclei and mild necrotic and regenerating process along with indirect evidence of regenerating fibres such as the presence of fibres containing fetal myosin.[21 24] One report described that, early in the disease, UCMD presents as a non-dystrophic myopathy with predominant fibre atrophy, showing a bimodal size distribution of type 1 fibres or a diagnostic pattern of congenital fibre-type disproportion.[25] Unlike other muscular dystrophies, interstitial fibrosis seems disproportionately prominent considering the relative paucity of necrotic and regenerating fibres in UCMD.

Collagen VI is widely distributed throughout ECMs in various tissues. In skeletal muscle, collagen VI is found in the epimysial, perimysial and endomysial interstitium, but it is concentrated in particular in and adjacent to basement membranes of myofibers, blood vessels and intramuscular nerves. Muscle biopsies from UCMD patients can show anything from mild reduction of endomysial or basal lamina collagen VI staining to complete deficiency (CD) of collagen VI in the ECM. We previously showed that, in the majority of patients with UCMD, collagen VI is present in the interstitium but is absent from the sarcolemma by using double immunostaining for collagen IV and VI (figure 2), and named it 'sarcolemma specific collagen VI deficiency (SSCD)'.[26] Electron microscopic findings support a lack of connection between collagen VI microfibrils in the interstitium and the basal lamina, leading to SSCD.[26] Space is observed between muscle fibres and connective tissue that are normally closely attached. Basal lamina appear intact even in degenerating muscle fibres with disorganised myofibrils. These findings suggest a loose connection between the basal lamina and other ECM collagens in UCMD.[27] Collagen VI is deficient also in capillaries in muscle.[13] The absence or alteration of collagen VI can be demonstrated by immunocytochemistry of cultured skin fibroblasts, although this analysis is available only in limited laboratories. In skin, collagen VI expression is decreased in the papillary dermis and skin hair follicles, but not in vessels, peripheral nerves, smooth muscle and sweat glands.[13] One report described that collagen VI levels were greatly decreased in peripheral blood macrophages from three patients with UCMD.[28]

Natural history of disease

Muscle weakness is slowly progressive. Most affected children become able to walk independently but eventually lose ambulation often by early teenage years. Loss of ambulation is reported to occur at 10.7±4.8, 10.1±4.4 and 8.8±2.9 years of age in English, French and Japanese group of patients with UCMD, respectively.[11 19 20] However, this can be widely variable: some patients never walk while others can still walk even beyond late teens. After loss of ambulation, progression of muscle weakness becomes less prominent. In contrast, the contractures can still be progressive, particularly in the ankles, knees, hips and elbows, aggravating physical disability. These clinical features may well be in line with strikingly progressive interstitial fibrosis on muscle pathology.

Respiratory insufficiency usually occurs after the loss of ambulation. It is noteworthy, however, some patients have impending respiratory dysfunction while they are still ambulant. Progressive decline in the predicted forced vital capacity (FVC) or vital capacity (VC) is observed from the preschool age to the early teens.[19 20] Of note, restrictive respiratory dysfunction develops rapidly in the first decade of life; indeed, %predicted FVC declines by 6.6±1.9%/year from 6 to 10 years of age compared to by 0.4±3.0%/year from 11 to 15 years of age.[20] Similarly, VC declines exponentially with a sharp decrease by 10 years of age.[19] This may well be associated with proximal joint and vertebral contractures together with weakness of the diaphragm. The introduction of non-invasive ventilation (NIV) is usually sufficient to treat this situation effectively for many years. The percentage of patients with NIV increases with age; half require NIV by age 11–12 years.[12 19] Natural history study from UK reported that age at initiation of NIV was 14.3 ±4.7 years, with a mean FVC of 20%.[20] The other two studies have recently reported similar findings: an estimated predicted VC of 36% at the time of initiation of NIV at 11.2±3.6 years in a Japanese cohort[19] and an average FVC of 34% just before NIV initiation at 11.3±4.0 years in a large international cohort,[12] demonstrating a remarkable consistency of the pulmonary function declining in patients with UCMD among different cohorts, regardless of different approaches to data acquisition.

Scoliosis, which may require surgical correction, is a common complication.[15 20] Substantial scoliosis appears as early as preschool years and its onset precedes loss of ambulation.[19 20] Development of scoliosis in Duchenne muscular dystrophy (DMD) is strongly related to the loss of walking ability—scoliosis is not typically evident in ambulatory patients and develops after they become wheelchair dependent. In contrast, in UCMD, scoliosis develops even when patients are still ambulant and is progressive from early stage. In our cohort, a maximum progression rate of Cobb angle was 16.2±10.0°/year.[19] Importantly, scoliosis progresses rapidly within years, once it starts (figure 1E–H). The early-onset and rapidly progressive scoliosis in UCMD may well accelerate physical disability, such as difficulty sitting, standing and walking, and cause pain. More importantly, scoliosis can aggravate respiratory function by reducing the rib cage compliance in combination with other proximal joint contractures.

Differential diagnosis

Differential diagnosis includes wide range of neuromuscular disorders in infants and children, such as other forms of muscular dystrophy, congenital myopathies, spinal muscular atrophy (SMA), especially type 2 and 3, and other diseases of connective tissue such as Ehlers–Danlos syndrome (EDS). However, combination of normal or minimally elevated CK levels, lack of cardiac manifestation and specific pattern of thigh muscle involvement is often suggestive of UCMD. Brain MRI is usually normal unlike other CMD forms such as MDC1A, Walker–Warburg syndrome, muscle-eye-brain disease and Fukuyama CMD, which may show structural abnormalities or white matter

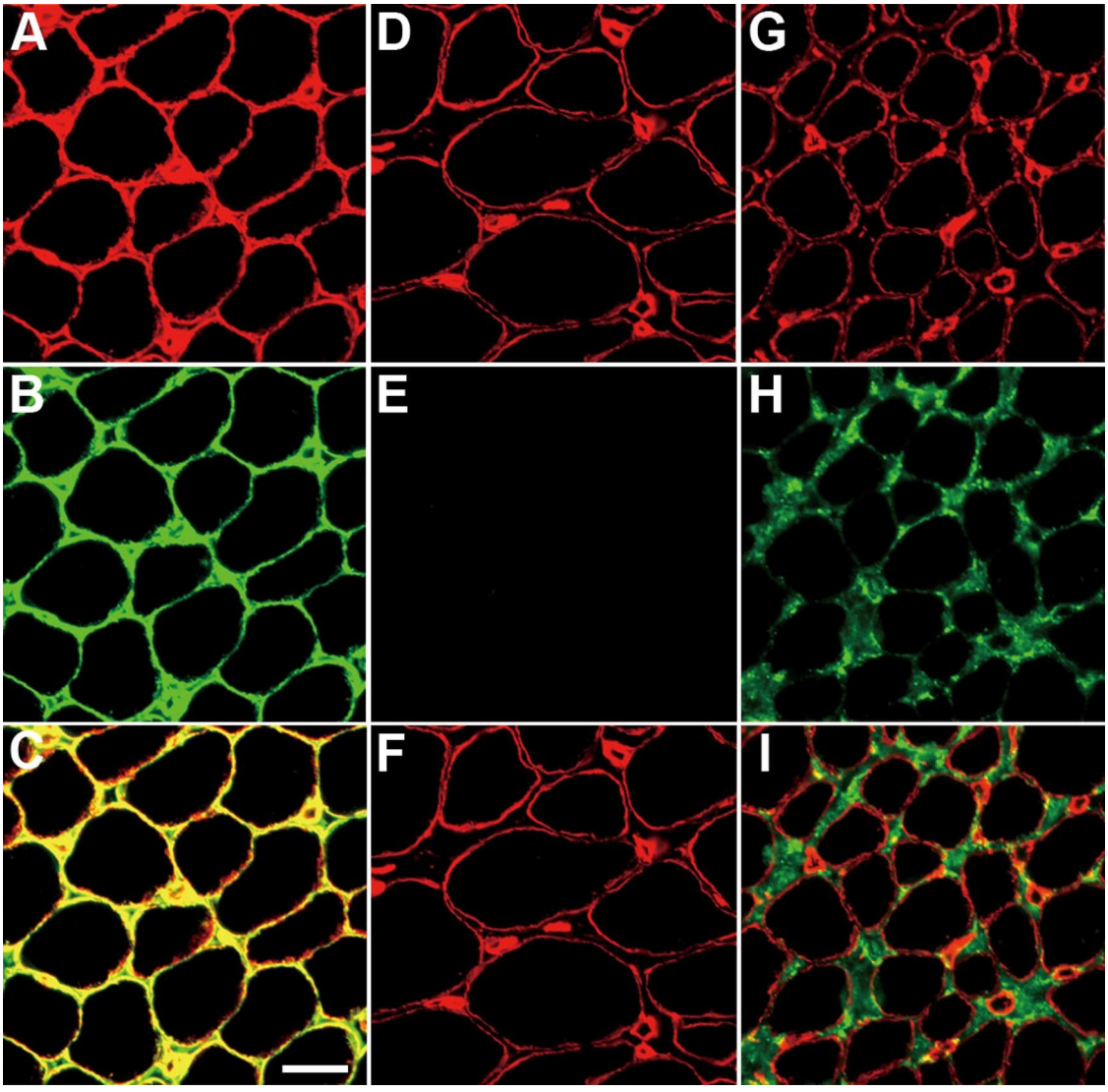

Figure 2 Double immunostaining for collagen IV and VI. (A–C) Patient with non-diagnostic muscle pathology; (D–F) UCMD patient with CD; (G–I) UCMD patient with SSCD. (A,D,G) Immunostaining for collagen IV. Collagen IV is present in the sarcolemma. (B,E,H) Immunostaining for collagen VI. Collagen VI is absent in a patient with CD, while it is present in the interstitium but markedly reduced in a patient with SSCD. (C,F,I) Merged images. Both collagen IV and VI are present in the sarcolemma in a patient with non-diagnostic pathology, as indicated by yellow; in contrast, collagen VI is absent in the sarcolemma in a patient with SSCD, as indicated by only red. UCMD, Ullrich congenital muscular dystrophy; CD, complete collagen VI deficiency; SSCD, sarcolemma-specific collagen VI deficiency, bar 20 µm.

changes. RYR1-related core myopathy, including central core disease (CCD) and multiminicore disease, may also show similar clinical features as they can multiple joint contractures and spinal deformity. Progressive respiratory muscle involvement, often disproportionate to the skeletal muscle weakness, is also seen in multiminicore disease. However, significant respiratory insufficiency is unusual in CCD. Interestingly, a recent report demonstrated that muscle pathology in a patient with a heterozygous COL6A3 gene mutation included cores, rods and lobulated fibres.[29] SMA is characterised by fasciculation and diagnosed by identifying mutations in the SMN gene. EDS may mimic UCMD in terms of joint laxity. Furthermore, various types of EDS are commonly associated with mild to moderate muscle weakness. Muscle pathology can demonstrate mild myopathic features but necrotic fibres and fibrosis are absent and collagen VI staining is normal.[30]

Of particular importance is rigid spine with muscular dystrophy type 1 (RSMD1) in forms of CMD, which results from mutations in the SEPN1 gene, because it can show a significant clinical overlap in the late stage of the disease. RSMD1 patients typically show combination of mild or moderate proximal muscle weakness, Achilles tendon tightness, spinal rigidity and scoliosis, and require ventilator assistance in the first decade of life,[15] similarly to UCMD.

Management

Treatment for patients with UCMD is supportive for symptoms such as respiratory insufficiency and scoliosis, and is dependent on age of the individual and severity of symptoms. Respiratory failure is a common complication of UCMD and careful follow-up with regular assessments of respiratory function, including spirometry and nocturnal oximetry studies, is important to detect asymptomatic decline in patients. In a recent review based on expert consensus on the standard care for CMD, cough assistance using mechanical insufflation-exsufflation is generally accepted as the method to improve cough efficiency.[22] Other methods such as

breath stacking with Ambu bag maintain thoracic compliance and reduce the risk of chronic atelectasis.[22] Respiratory support with nocturnal NIV usually becomes necessary in the first or second decade of life for patients[12 19] and might be effective in reducing symptoms and promoting quality of life. There are times when chronic ventilation can require an invasive application via tracheostomy.

For scoliosis, conservative management including standing frame, positioning and bracing is widely used, although controversial whether those approaches are preventive.[22] However, scoliosis may require active management including spinal surgery to prevent progression, although there have been no formal studies on the efficacy of scoliosis surgery. The choice of the instrumentation such as growing rods depends on the age of the individual, his/her ability to grow and the severity of scoliosis.[22] Suggested contraindications to spinal surgery includes family decision, very poor or deteriorating cardiac status and/or respiratory status, very young age, potential loss of function after spinal fixation and severe scoliosis.[22] Severe respiratory insufficiency may not be a contraindication in certain high specialised centres. In fact, one study on surgical correction of spinal deformity from Japan reported that scoliosis surgery was successfully performed in three patients with UCMD at 11, 13 and 17 years of age, respectively[31]; spinal surgery, however, did not prevent deterioration of respiratory function in these patients, suggesting that at such older ages pulmonary and chest wall compliance might be too severely compromised for patients to benefit from scoliosis surgery, and earlier surgical intervention may be more beneficial. Indeed, a single case report described that slower decline of predicted VC in a patient after scoliosis surgery performed at 5 years of age compared with another patient who had undergone surgical correction of scoliosis at 9 years of age.[19] Further studies are necessary to conclude the efficacy of early scoliosis surgery.

Equipment recommended for assistance in standing, ambulation and/or other forms includes walking frames, standing frames, swivel walker, knee-ankle-foot orthoses, ankle-foot orthoses, scooters and wheelchairs.[22] The joint contractures of patients with UCMD in particular seem to be progressive and regular stretching is recommended to maintain a certain level of mobility of the joints. In addition, feeding and swallowing difficulties can be encountered in UCMD.[20] Issues of feeding and nutrition are multifactorial and closely related to other areas of care; for example, nocturnal hypoventilation can affect appetite and growth and respiratory insufficiency can result in easy fatigue and difficulty in swallowing.[22] Consultation with a nutrition specialist is often helpful to boost energy intake. Some children may need a temporary or permanent gastric feeding tube support to maintain an adequate nutritional and fluid intake.[20 21] Survival has not been fully documented under the current standards of medical care, but failure to introduce adequate respiratory support might lead to the death of teenagers with UCMD.[11 21] With the availability of effective respiratory interventions, patients commonly survive into adulthood to date, and other potential aspects of the disease could surface.

MOLECULAR DIAGNOSIS, PATHOGENESIS AND THERAPEUTIC AVENUES

Collagen VI is a ubiquitously expressed ECM protein composed of three α-chains, α1, α2 and α3. The three chains are encoded by the genes COL6A1 and COL6A2 on chromosome 21q22.3 and COL6A3 on chromosome 2q37.[13] The basic monomer, made up of two globular domains connected by a triple helical structure, is composed of one of each of the these α-chain subunits (1:1:1 ratio). Prior to secretion into the extracellular space, the two basic monomers assemble into dimers (two antiparallel, overlapping monomers) and such dimers associate in a staggered parallel orientation to form tetramers (four monomers) in the cytoplasm.[13 32] Outside the cell, these tetramers, the secreted form of collagen VI, associate in an end-to-end fashion to form collagen VI microfibrillar structures, which interacts with collagen IV and other ECM components including proteoglycans decorin and biglycan, collagen I, hyaluronan, heparin and integrin.[13 33]

Collagen VI gene mutations in UCMD

UCMD used to be regarded as an autosomal-recessive disorder. However, soon after the initial discovery of recessive mutations in the COL6A2 gene,[34 35] a total of four patients with sporadic UCMD were found to carry de novo autosomal-dominant mutations in either COL6A1, COL6A2 or COL6A3.[36 37] UCMD is now known to be caused by either recessive or dominant genetic mechanism, the latter most typically occur as de novo mutations.[32] This is most likely because these dominant mutations are associated with too severe phenotype to allow patients to produce their offspring. In contrast, in BM, the phenotype is typically mild enough for patients to produce children, resulting in autosomal-dominant inheritance condition.[8 13]

The most common types of mutations are point mutations, exon skipping and mutations leading to premature termination codons (PTCs).[32] Among point mutations, missense changes affecting glycine residues in the Gly-Xaa-Yaa motifs of the N-terminal triple helical domains are the most common and are often dominant de novo.[32 33] Splice mutations resulting in in-frame exon skipping are generally dominant de novo mutations.[32 33] These dominant mutations can result in secretion of some mutant-containing tetramers into the extracellular space; in the multistep collagen VI intracellular assembly process, only 1/16 of the tetramers produced by patients with dominant mutations could be composed entirely of normal α-chains, thus exerting a dominant negative effect.[37] This leads to loss of normal localisation of collagen VI in the basement membrane and eventually results in a severe phenotype. Nonsense mutations and small deletions or insertions inducing PTCs with consequent nonsense-mediated mRNA decay (NMD), an mRNA quality control mechanism that degrades aberrant mRNAs containing PTCs, and loss of the mutated chain are mostly inherited as recessive mutations.[32 33] Patients with these mutations are unable to assemble or secrete functional collagen VI protein, as all three α-chains are required to form a collagen VI monomer. Thus, such functional null alleles, which underlie typical UCMD, mostly lead to CD mode of collagen VI in skeletal muscles.[16 26 33 34] On the other hand, complete deletions of one copy of these genes also act in a recessive fashion. In support of this notion, carriers of the deletion are in fact clinically asymptomatic, indicating that complete haploinsufficiency of any of the three collagen VI genes does not cause the disease. Interestingly, two reports demonstrated that autosomal-recessive inheritance can also underlie BM, in which patients carried a truncating or null COL6A2 mutation associated with missense changes in the partnering allele lying within the C2 domain of the α2 chain.[38 39] Furthermore, myosclerosis syndrome was reported to be responsible for a homozygous nonsense COL6A2 mutation.[40] Unlike nonsense mutations associated with UCMD, the mutated mRNA escaped NMD and was translated into a truncated α2 chain, but secreted collagen VI was reduced and structurally abnormal and thus did not correctly localise in the basement membrane of myofibers. These facts suggest that the

severity of collagen VI gene mutations and the resulting functional abnormality of collagen VI in the ECM dictate a phenotypic spectrum of collagen VI-related myopathies, meaning that a fundamentally different genetic and biochemical mechanism among these myopathies can no longer be assumed.

We previously showed that there are two modes of collagen VI deficiency, CD and SSCD,[26] which respectively result from recessive and de novo dominant mutations in the collagen VI genes.[16] There is no straightforward correlation between protein levels and phenotypes; CD, however, is most likely to be associated with the more severe phenotype than SSCD.[11 19] Unlike patients with CD, a great heterogeneity in the maximal motor capacity was observed in patients with SSCD, ranging from no acquisition of walking ability to retaining ambulation throughout childhood.

Properties of collagen VI and its pathological roles

Collagen VI is widely distributed throughout ECMs in various tissues, including muscle, skin, tendon, cartilage, intervertebral discs, lung, blood vessels and adipose tissue.[4] Given the clinical features seen in patients with collagen VI-related myopathies, the tissues in which collagen VI has the most important roles include muscle and tendon. In muscle, the cell source producing collagen VI is the interstitial mesenchymal cell.[41 42] In tendons, abundant collagen VI is present in immediate pericellular ECM of the resident tendon fibroblasts.[43]

Collagen VI contributes to the properties of the local ECM microenvironment by forming a discrete network of beaded microfilaments, which interact with a large number of matrix molecules and cell surface receptors. One possible molecule mediating its interaction would be collagen type IV, the most important collagenous component of basement membranes.[13] On the other hand, collagen VI might be indirectly linked to muscle cell surface receptors via biglycan and the dystrophin-associated protein complex, as collagen VI binds to biglycan,[13] which interacts with the sarcoglycan and dystroglycan complex.[33] The functions of collagen VI pertaining to various cell types also include the promotion of adhesion,[1 2] proliferation,[3] migration[4] and survival.[5 44 45] Attachment of cells to the ECM is important for preventing apoptosis,[46] which could be particularly relevant for muscle disorders that directly involve interactions between matrix and muscle, as is the case for high early implanted cell death, partially due to 'anoikis', in cell transplantation treatment of DMD.[47] Studies with cultured fibroblasts from patients with UCMD have shown that mutant cells or mutated collagen VI exhibit decreased adherence to their surroundings, emphasising that loss of cell ECM interactions is the key mechanism of collagen VI-related myopathies.[2 48] Collagen VI also has crucial roles in the regulation and differentiation of adipocytes.[49]

Studies on muscle fibres from Col6a1$^{-/-}$ mice, engineered by genetic ablation of the Col6a1 gene,[50] and human myoblast cultures has suggested that collagen VI may be involved in preventing myofiber apoptosis, which seems to be mediated by regulating the mitochondrion-mediated cell death cascade[5 51]; a key event appears to be inappropriate opening of the mitochondrial permeability transition pore. These findings therefore link a defect of the ECM to mitochondrial dysfunction followed by apoptosis that is preventable by inactivation of cyclophilin D by using cyclosporine A, its derivative Debio025 or genetic inactivation of cyclophilin D.[51–53] However, there are contradictory reports in which researchers did not find evidence of myofiber apoptosis in biopsied muscles from UCMD patients or Col6a3 mutant mice muscles,[54 55] suggesting that muscle cell death by apoptosis is not a universal phenomenon in all patients and collagen VI-deficient mice.

In addition, a study of the autophagic process in muscles of Col6a1$^{-/-}$ mice revealed that autophagy was not induced efficiently, which determines the presence of dysfunctional organelles in muscle fibres.[56] A similar alteration of autophagy was also detected in muscle biopsies derived from nine patients with UCMD or BM.[56] This defective autophagy provides the link between the previously described mitochondrial dysfunction and myofiber degeneration. These data thus provide a basis for novel therapeutic targets to reactivate of the autophagic flux by either nutritional approaches[57] or by pharmacological and genetic tools in collagen VI deficient skeletal muscle.

Therapeutic advances

The events responsible for myofiber atrophy and loss might be different in UCMD than in other forms of muscular dystrophy with prominent membrane fragility such as DMD. To date, no single hypothesis can fully explain variation in fibre size, ongoing interstitial fibrogenesis and adipogenesis even in mild necrotic and regenerating process in UCMD or provide all targets for therapies, although important clues have been discovered.

Pathological hypotheses leading to myofiber degeneration in collagen VI-deficient skeletal muscle have been proposed and therapeutic targets have been suggested. There have been pilot studies on patients with UCMD based upon the theory of mitochondrial dysfunction or impaired autophagy.[51–53 57] A recent report has shown that collagen VI is a key component of satellite cell niche and lack of collagen VI causes impaired muscle regeneration and reduced satellite cell self-renewal capability after injury in Col6a1$^{-/-}$ mice.[58] Additionally, when normal collagen VI is supplied in vivo by grafting wild-type interstitial mesenchymal cells, the biochemical properties of collagen VI-deficient muscles are ameliorated and satellite cell defects also rescued.[58] These results can open new venues for a better understanding of the pathomechanism underlying collagen VI-related myopathies. Furthermore, multipotent mesenchymal stem cell (MSC) is the most common type of adult stem cells and is isolated from several sources such as bone marrow and adipose tissue. Another report has recently shown that transplanted human adipose-derived stem cells, with phenotypic and functional features of mesenchymal progenitors, secrete collagen VI protein in Col6a1$^{-/-}$ mice.[59] Thus, MSC-based therapy can be an attractive option as transplanted cells are able to self-renew and to differentiate into collagen VI-producing cells in skeletal muscle.[41 42]

Advances in molecular genetics provide gene-based therapies; that is, antisense oligonucleotide or small interfering RNA (siRNA) inhibition of mutant transcripts exerting dominant negative effects[60–62] and upregulation of mutant transcripts by specific inhibition of NMD.[63] As 60–80% of UCMD cases are attributed to dominant negative mutations,[11 16] the allele-specific antisense approach can be applied to the majority of patients. Recent reports have shown that siRNA-mediated knockdown of SMG-1 and Upf1, essential components for NMD, or SMG-8, a subunit of SMG-1 kinase, gives rise to the upregulation of mutant triple-helical collagen VI, thus ameliorating mutant phenotypes from UCMD fibroblasts with a homozygous frameshift mutation causing a PTC in the COL6A2 gene.[64 65]

CONCLUSION

UCMD is caused by mutations in either COL6A1, COL6A2 or COL6A3 gene, thereby leading to collagen VI deficiency in the ECM. We here presented the clinicopathological features, robust

natural history and the current supportive care for symptoms. Of special interest is progressive interstitial fibrosis even in very mild necrotic and regenerating process in muscle. Patients with UCMD have unique manifestations attributable to both muscle and connective tissue disorders. Collagen VI contributes to the properties of the local ECM microenvironment by forming a discrete network of beaded microfilaments, which interact with a large number of matrix molecules and cell surface receptors. Advanced researches have provide important clues to explain how collagen VI deficiency in the ECM can cause the development of muscle weakness in Col6a1$^{-/-}$ mice or patients with UCMD, although the link between the ECM defect and phenotype remains to be fully elucidated. Further studies are necessary to elucidate exactly how collagen VI deficiency in the ECM makes muscle cells vulnerable to apoptosis or interstitial fibrogenesis and adipogenesis strikingly progressive.

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