The Collagen VI-Related Myopathies: Muscle Meets Its Matrix: The Clinical Spectrum of Disease

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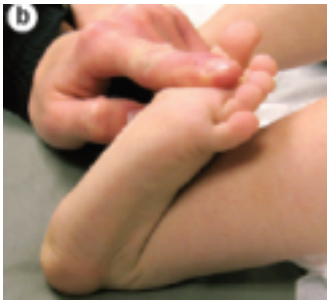
THE CLINICAL SPECTRUM OF DISEASE

On the basis of clinical as well as genetic findings, Ullrich CMD and Bethlem myopathy can justifiably be regarded as being positioned at the flanking ends of a continuous spectrum of disease, rather than as distinct clinical entities.

Ullrich Congenital Muscular Dystrophy

Presentation. Prenatal movements might be reduced in fetuses with Ullrich CMD;[4-10] however, the classic phenotype described by Ullrich[4,5] (Box 1) is usually evident at birth. Symptoms such as hypotonia and weakness are present, with striking hyperlaxity in particular of the distal joints (Figure 1a,b). The hands and fingers are extremely flexible and can bend backwards against the forearm, while the feet are often bent backwards against the shin, a finding that parents often remember as one of the first signs noticed. Coexisting joint contractures might also be evident at birth, affecting the elbows, knees, spine (kyphoscoliosis) and neck (torticollis). Clubfoot can also be seen, instead of the retroflexed foot mentioned above.

Figure 1.



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Joint Laxity and Progressive Joint Contractures in Patients with Ullrich CMD and Bethlem Myopathy. **a,b |** Typical pronounced distal hyperlaxity seen in children with Ullrich CMD. particularly...

Course of Disease. Some transient feeding difficulties might occur in the neonatal period, leading to moderate to severe dysphagia in patients with severe forms of Ullrich CMD.[11] Even some children without overt dysphagia may need a temporary or permanent gastric feeding tube support to maintain an adequate nutritional and fluid intake.

In the most severe presentation of Ullrich CMD, the ability to walk is never achieved. Patients with this presentation were referred to as having 'early severe' disease in a large French series of early-onset collagen VI-related myopathies.[12] However, even these severely affected infants can usually learn to roll, crawl and maintain a sitting position. Some severely affected children who are not able to ambulate owing to knee contractures that prevent an upright posture might walk on their knees for a period of time. The majority of patients with typical Ullrich CMD will, however, achieve the ability to ambulate after a delay of up to about 2 years. This group was referred to as having 'moderately progressive' disease in the French series (Box 2).

[12] These children will, however, eventually lose the ability to walk, often by the early teenage years, but sometimes at a considerably younger age or as late as young adulthood (Figure 1c).[11,12]

The muscle weakness itself is slowly progressive, but the resulting disability is aggravated by progressive contractures of the large joints, in particular affecting external rotation in the shoulder, elbows, hips, knees and ankles. Some early contractures can improve during the first year of life, but will recur at a later point and then continue to worsen over time. The presence of multiple lower extremity contractures, in particular, interferes with the ability to ambulate. After the loss of ambulation, patients tend to be quite stable in terms of their muscular strength, although the contractures might still show ongoing progression, particularly in the ankles, knees, hips and elbows. Of particular concern is the development of substantial scoliosis, which might have developed as early as the preschool years, but is frequently evident by the end of the first decade of life and requires spinal instrumentation in many patients.[11,12]

Although respiratory insufficiency is not common at birth, it becomes an important aspect of the disease as the

condition progresses. Respiratory insufficiency usually manifests following the loss of ambulation, but some patients can develop impending respiratory insufficiency while they still have the ability to walk.[11] A progressive decline in the percentage of predicted forced vital capacity is observed, on average, from the age of 5 years to the early teens.[11] Respiratory insufficiency typically manifests initially at night, as nocturnal hypoxemia, and sleep studies may be necessary to identify its first signs. The introduction of noninvasive bilevel positive airway pressure ventilation is usually sufficient to treat this situation effectively for many years. In most patients respiratory support is only needed at night; however, it should not be overlooked. Failure to institute adequate respiratory support has led to the death of teenagers with Ullrich CMD.

Careful studies are now required to establish the long-term course of the disease under the current standards of medical care. Early data on the long-term outcomes of patients with Ullrich CMD are difficult to evaluate, as much of that experience was gathered from patients who had not received active respiratory intervention, with the result that many of these individuals succumbed to respiratory failure in their late teenage years.[7] With the availability of effective respiratory interventions, other aspects of the disease could potentially surface now that patients with Ullrich CMD routinely survive into adulthood.

Intermediate Collagen VI-related Myopathies

Presentation. Patients with collagen VI-related myopathies of intermediate severity cannot be easily classified as having either Ullrich CMD or Bethlem myopathy. No exact definitions exist yet as to where the Ullrich CMD phenotype stops and the intermediate-severity phenotype begins. Similarly, at the other end of the range, a transition from intermediate-severity disease to the classic Bethlem phenotype occurs. To define this disease spectrum, and to determine whether discrimination between the various phenotypes is possible, an international study capturing the range of phenotypic expression in patients with collagen VI-related myopathies is currently underway.

Patients with intermediate phenotypes of collagen VI-related myopathies were referred to as having 'mild' early-onset collagen VI myopathy in the French series.[12] Similarly to children with Ullrich CMD, these patients also typically present in the neonatal period but achieve the ability to walk, usually ambulating into young adulthood and sometimes beyond. They are, therefore, considered to have a milder form of disease than patients with the typical Ullrich CMD phenotype. However, most of the clinical features outlined for Ullrich CMD will still be clearly recognizable in these patients.

Course of Disease. Although contractures are not necessarily prominent early on in intermediate-severity disease, they start to develop during childhood and are progressive, particularly in the ankles and the elbows, but also in the knees. Scoliosis and/or spinal rigidity can be marked. Patients might be able to walk for limited distances, particularly on flat surfaces and indoors, but they may require assistance such as a mobility scooter for prolonged ambulation. However, spending increased amounts of time in the sitting position will aggravate contractures of the knee flexors and the hips, and further interfere with the patient's ability to walk. Upright mobility should, therefore, be maximized for as long as possible.

Progressive respiratory insufficiency is also of concern in patients with intermediate phenotypes of collagen VI-related myopathy, and a consistent decline in the percentage of predicted forced vital capacity is observed in the early teenage years.[11] This group of patients is again particularly susceptible to nocturnal respiratory insufficiency, which can develop even in individuals who are still able to walk and, therefore, careful monitoring of these patients is required.[11]

Bethlem Myopathy

Presentation. Considerable variability exists within the Bethlem myopathy phenotype. Many of the same clinical problems described for the other forms of collagen VI-related myopathy can be encountered in principle, but the symptoms are altogether milder. Although often understood to be a myopathy of adulthood, the clinical symptoms experienced by patients with Bethlem myopathy can frequently be traced back to early infancy;[13] affected babies might exhibit hypotonia, foot deformities and torticollis (which has been noted in up to 50% of patients).[13] However, the congenital contractures largely tend to resolve in the first 2 years. Young children might exhibit evidence of mild weakness only, and at this early age display distal joint hyperlaxity rather than contractures. Some patients present with weakness in a proximal distribution without notable contractures and have been reported as limb-girdle muscular dystrophy.[14] By contrast, others have contracture-predominant disease without much weakness, a phenotype referred

to as myosclerosis.[15,16] In such individuals, the muscles are said to have a 'woody' feel. A specific recessive mutation has been associated with this phenotype, as discussed later in this article.

Course of Disease. In Bethlem myopathy, typical contractures of the Achilles tendons (Figure 1d) and elbows tend to develop late in the first decade of life and during teenage years. These contractures progress to involve the long finger flexors and the shoulders; they can also affect the spine and cause a degree of spinal rigidity in some patients. On dorsiflexion of the wrist, contractures of the long finger flexors prevent complete finger extension—the typical 'Bethlem sign' (Figure 1e).[13] Even in patients whose muscle weakness progresses only very slowly, progression of the contractures can be the cause of serious disability in their own right (as they are for patients with severe forms of collagen VI-related myopathy). Eventually, the combination of weakness and contractures can lead to walking difficulties—about two-thirds of patients over the age of 50 years require help with ambulation, usually using a mobility scooter or wheelchair.[13] Patients with Bethlem myopathy who had been stable for many years often report a noticeable decline in muscle strength in their 4^{th} and 5^{th} decades of life (Figure 1f).

Patients with Bethlem myopathy have an increased risk of restrictive lung disease, with the possibility of resulting respiratory insufficiency, particularly if this impairment occurs in combination with other causes of obstructive sleep apnea. Sleep studies are, therefore, useful to diagnose nocturnal hypoventilation proactively.

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References

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