

Bethlem myopathy

Author: Professor J. Andoni URTIZBEREA¹
(member of the European Editorial Committee of Orphanet Encyclopedia)

Creation date: October 2001
Updated: November 2003
February 2005

¹Service de Médecine Physique et Réadaptation de l'Enfant, Hôpital Raymond Poincaré, 92380 Garches, France.
ja.urtizberrea@wanadoo.fr

[Abstract](#)
[Key-words](#)
[Disease name and synonyms](#)
[Excluded diseases](#)
[Diagnosis criteria / definition](#)
[Differential diagnosis](#)
[Prevalence](#)
[Clinical description](#)
[Management including treatment](#)
[Etiology](#)
[Diagnostic methods](#)
[Genetic counseling](#)
[Antenatal diagnosis](#)
[Unresolved questions](#)
[References](#)

Abstract

Bethlem myopathy is a benign autosomal dominant form of slowly progressive muscular dystrophy. To date, fewer than 100 cases have been reported in the literature, thus illustrating its rarity. The clinical features do not differ markedly from those of other mild forms of progressive muscular dystrophy with the exception of finger contractures, which are sometimes suggestive of the diagnosis. Serum creatine kinase (CK) levels and histological findings are not very conclusive. Mutations in one of the three subunits of collagen VI are responsible for the disease. Molecular studies are however hampered by the size and expression pattern of these genes. Treatment remains purely supportive.

Key-words

Bethlem myopathy, limb girdle muscular dystrophy, collagene VI, finger contractures.

Disease name and synonyms

Bethlem myopathy
Benign congenital myopathy with contractures

Excluded diseases

-Emery-Dreifuss muscular dystrophy,
-Ullrich muscular dystrophy.

Diagnosis criteria / definition

Bethlem myopathy was first described in 1976 by Bethlem and van Wijngaarden. Since then, other reports have confirmed the existence of

this separate entity even though multigenerational and multiplex familial cases remain scarce. This myopathy is a benign form of autosomal dominant muscular dystrophy (MD). It generates mild clinical symptoms with proximal muscle weakness and early contractures notably in the fingers. The slow progression of the disease and the absence of pseudohypertrophic calves and cardiomyopathy are distinctive features. The diagnosis is based on clinical findings and should be confirmed at the molecular level whenever possible. The 3 genes subject to

mutations and responsible for this disorder have been cloned while routine laboratory investigations (CK levels, electrophysiological studies, muscle pathology) are not very specific.

Differential diagnosis

Sporadic and atypical cases are the most difficult to deal with.

Emery-Dreifuss muscular dystrophy (EDMD) shares some clinical features with Bethlem myopathy, such as early contractures of the elbow or ankle. Nevertheless, marked contractures of the neck and spine are rarely reported in Bethlem myopathy. Furthermore, the detection of heart conduction defects is a hallmark of EDMD and is not seen in Bethlem myopathy.

Subtypes of autosomal dominant limb girdle muscular dystrophy (LGMD 1A to 1G) have also to be considered. Some of these disorders have been mapped and their genes identified, thus making differential diagnosis much easier. Alternatively, atypical forms of sporadic congenital MD can be mistaken both ways. Interestingly, mutations in the gene encoding collagen type VI alpha-2 COL6A2 have been found in a related autosomal recessive condition called Ullrich scleroatonic MD in which hyperlaxity and severe contractures are key-features. Some degree of clinical and genetic overlap between the two disorders have recently been established.

Prevalence

Fewer than 100 cases have been reported in the literature. In France alone, there are fewer than 30 families or sporadic cases in which the diagnosis has been suggested. A European Union-funded consortium of clinicians and scientists (Myo-Cluster) carried out a census of such patients across Europe as well as a mutation database.

Clinical description

Bethlem myopathy is a benign autosomal dominant form of slowly progressive muscular dystrophy. The clinical picture is characterized by proximal weakness and wasting of the limb girdle associated with mild contractures of the fingers and other joints.

Onset is usually in early childhood, sometimes at birth (with congenital torticollis as the presenting symptom). Hypotonia and mild muscle weakness in proximal rather than distal muscles is often noted. Contractures are an almost constant feature in this condition and occur predominantly in the fingers, elbows, knees and ankles. They are highly suggestive of the diagnosis, when they involve the interphalangeal joints of the last 4 fingers.

Progression is slow and occasionally leads the patient to be wheelchair-bound after 25 to 40 years of evolution. Interestingly, neither cardiomyopathy nor pseudohypertrophic calves are seen. Respiratory involvement is not a cardinal feature and is rarely reported.

Routine laboratory findings are not very informative. Serum CK levels are often normal or slightly elevated. Electromyographic studies show a myopathic pattern. Muscle histology demonstrates a non-specific myopathy with fiber-size variation, few necrotic/regenerative fibers and a mild increase of connective tissue, all these features appearing mild to moderate.

Management including treatment

Treatment remains supportive. Routine physiotherapy may be recommended to prevent the deleterious impact of marked contractures.

Etiology

Collagen VI is a widely expressed microfibrillar protein which is likely to play a role in bridging cells with the extracellular matrix. Three COL6A genes encode 3 subunits of collagen VI : alpha-1, alpha-2 and alpha-3, respectively. The first two genes, COL6A1 and COL6A2, form a cluster on chromosome 21, whereas COL6A3 remains isolated on chromosome 2. Mutations in any of the 3 subunits may impede the assembly of collagen VI and subsequently its anchoring to other extracellular matrix components. Most mutations result in amino-acid substitution (glycine notably) in the triple-helix region.

Gene Map Locus: 21q22.3, 21q22.3, 2q37

Diagnostic methods

The diagnosis is first considered at the clinical level. Muscle imaging may contribute to assessing the selectivity of muscle involvement. Routine tests (CK, EMG) are not very specific. Mutations in one of the 3 subunits of collagen VI can be investigated only in a few specialized laboratories : direct sequencing might be preceded by linkage analysis when the pedigree is informative. The search is made easier when fibroblast cultures are available. Disorganization of the collagen network in fibroblasts is an indirect but critical clue to the diagnosis. Given the size of the 3 genes involved, however, the mutation screening remains a tedious, time-consuming process. Moreover, there are no clinical clues to target one of the three COL6 genes specifically.

Genetic counseling

Theoretically, the risk of transmitting Bethlem myopathy to the next generation is 50% irrespective of the gender of the affected parent. No anticipation has ever been reported. So far, very few families or individuals have had their diagnosis confirmed at the molecular level. The disease course, most often slow, may vary from one individual to another, even within the same family. Therefore, one can never exclude the risk of a more severe form in the offspring of an affected individual.

Antenatal diagnosis

Technically, antenatal diagnosis could be considered once the causative mutation is identified. Nonetheless, and to our knowledge, prenatal testing is rarely requested.

Unsolved questions

The relationship between collagen VI and other components of the muscle extra-cellular matrix remains to be investigated.

The clinical overlap with some subtypes of congenital MD is intriguing : distinguishing between a severe Bethlem sporadic case and a mild form of Ullrich CMD can be very subtle.

The recent discovery of *COL6A2* mutations in Ullrich scleroatonic MD suggests a possible common pathogenic pathway.

The rather selective distribution of contractures, even if suggestive of the disease, remains poorly understood.

More straightforward diagnostic procedures need to be devised at the molecular level to speed up the search for mutation(s).

References

Arts, W. F.; Bethlem, J.; Volkers, W. S. : Further investigations on benign myopathy with autosomal dominant inheritance. *J. Neurol.* 217: 201-206, 1978.

Baker N.L.; Morgelin M.; Peat R.; Goemans N.; North K.N.; Bateman J.F.; Lamande S.R. : Dominant collagen VI mutations are a common cause of Ullrich congenital muscular dystrophy. *Hum Mol Genet* 14: 279-93, 2005.

Bethlem, J.; van Wijngaarden, G. K. : Benign myopathy, with autosomal dominant inheritance-a report on three pedigrees. *Brain* 99: 91-100, 1976.

Jobsis, G. J.; Bolhuis, P. A.; Boers, J. M.; Baas, F.; Wolterman, R. A.; Hensels, G. W.; de Visser, M. Genetic localization of Bethlem myopathy. *Neurology* 46: 779-782, 1996.

Jobsis, G. J.; Keizers, H.; Vreijling, J. P.; de Visser, M.; Speer, M. C.; Wolterman, R. A.; Baas, F.; Bohlhuis, P. A. Type VI collagen mutations in Bethlem myopathy, an autosomal dominant myopathy with contractures. *Nat. Genet.* 14: 113-115, 1996.

Leyten, Q. H.; Gabreels, F. J. M.; Joosten, E. M. G.; Renier, W. O.; Ter Laak, H. J.; Ter Haar, B. G. A.; Stadhouders, A. M. An autosomal dominant type of congenital muscular dystrophy. *Brain Dev.* 8: 533-537, 1986.

Merlini, L.; Morandi, L.; Granata, C.; Ballestrazzi, A. Bethlem myopathy: early-onset benign autosomal dominant myopathy with contractures: description of two new families. *Neuromusc. Disord.* 4: 503-511, 1994.

Mohire, M. D.; Tandan, R.; Fries, T. J.; Little, B. W.; Pendlebury, W. W.; Bradley, W. G. Early-onset benign autosomal dominant limb-girdle myopathy with contractures (Bethlem myopathy). *Neurology* 38: 573-580, 1988.

Pepe, G.; Luciola, S.; Camacho Vanegas, O.; Minosse, C.; Giusti, B.; Urtizbera, J. A.; Muntoni, F.; Bushby, K.; de Visser, M.; Bönnemann, C.; Sabatelli, P.; Bertini, E.; Merlini, L.; Chu, M. L. Genotype-phenotype correlation in Bethlem myopathy. *Neuromuscul Disord* 12:720, 2002.

Speer, M. C.; Tandan, R.; Rao, P. N.; Fries, T.; Stajich, J. M.; Bolhuis, P. A.; Jobsis, G. J.; Vance, J. M.; Viles, K. D.; Sheffield, K.; James, C.; Kahler, S. G.; Pettenati, M.; Gilbert, J. R.; Denton, P. H.; Yamaoka, L. H.; Pericak-Vance, M. A. Evidence for locus heterogeneity in the Bethlem myopathy and linkage to 2q37. *Hum. Mol. Genet.* 5: 1043-1046, 1996.

Tohyama, J.; Inagaki, M.; Nonaka, I. Early onset muscular dystrophy with autosomal dominant heredity: report of a family and CT findings of skeletal muscle. *Brain Dev.* 16: 402-406, 1994.

Van der Kooi, A.J.; de Voogt, W.G.; Bertini, E.; Bushby, K.; Merlini, L.; Muntoni, F.; Talim, B.; Urtizbera, J. A.; de Visser, M. Cardiac and pulmonary investigations in Bethlem myopathy. *Neuromuscul Disord* 12:723, 2002.