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Chapter 3.1

Bethlem myopathy: a slowly progressive congenital muscular dystrophy with contractures

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Abstract

Bethlem myopathy is an early-onset benign autosomal dominant myopathy with contractures caused by mutations in collagen type VI genes. It has been reported that onset occurs in early childhood. We investigated the natural course of Bethlem myopathy in five previously published kindreds and two novel pedigrees, with particular attention to the mode of onset in 23 children and progression of weakness in 36 adult patients. Our analysis shows that nearly all children exhibit weakness or contractures during the first 2 years of life. Early features include diminished fetal movements, neonatal hypotonia and congenital contractures which are of a dynamic nature during childhood. The course of Bethlem myopathy in adult patients is less benign than previously thought. Due to slow but ongoing progression, more than two-thirds of patients over 50 years of age use a wheelchair.

Introduction

Bethlem and van Wijngaarden described three families with a novel disease designated as an early-onset benign autosomal dominant myopathy with contractures.1 Nearly all patients exhibited flexion contractures of the fingers, wrists, elbows and ankles. In addition, contractures of knees, hips and shoulders were common and congenital torticollis was present in some patients. Mild weakness with some preponderance of proximal and extensor muscles gave rise to only limited functional impairment, even in old age, and involvement of cranial and cardiac musculature was absent.2 Serum creatine kinase activity was normal or slightly elevated and muscle biopsy showed non-specific myopathic changes. Subsequently several authors have described similarly affected kindreds.3-12 Mohire et al. proposed that this syndrome be called Bethlem myopathy. Despite a relatively uniform clinical picture, slight variation exists between patients.5 Onset of weakness may occur before 5 years of age with mildly delayed motor milestones3,5,8 or it may occur at a later stage, in the fourth6 or sixth decade.8 As some adult patients remain unaware of weakness, an age of onset can not always be reliably established.10 Differential findings include calf muscle hypertrophy,6,8 extensor digitorum brevis muscle hypertrophy,10 and slight facial weakness.12 In young patients creatine kinase activity may be highly elevated, up to 15 times the upper limit of the normal value.10 Some dystrophic findings, i.e. necrotic and regenerating fibres, can be present on muscle biopsy.6,9-11

Recent genetic evidence implicates collagen VI as the defective protein in Bethlem myopathy. Collagen VI consists of three peptides, α1 (encoded by COL6A1), α2 (COL6A2) and α3 (COL6A3). Bethlem myopathy families show genetic linkage to markers from either the COL6A1-COL6A2 cluster region on chromosome 21q13,14 or the COL6A3 region on chromosome 2q,15 and mutations in either COL6A1, COL6A2 or COL6A3 have
Collagen VI is a widely expressed protein with cell adhesive properties. The pathophysiology remains to be elucidated.

Investigation of two novel kindreds and re-evaluation of previously reported families, as part of a genetic linkage study, disclosed aspects that differ from previous observations shedding new light on the onset and natural course of Bethlem myopathy which often appears to present at birth. To illustrate this we provide three case histories. Furthermore, slow but ongoing progression of weakness leads to more functional impairment than apparent from previous reports.

Methods

Details of patients from seven families were studied. Families A, B and C are from the original report of Bethlem, Family D has been described by Arts and Family E has been described in a thesis. Family F (two patients) and G (five patients) were newly identified at our outpatient clinic. The diagnosis of Bethlem myopathy was made on the following criteria: generalized weakness and contractures with onset in infancy or early childhood, absence of cardiac involvement, inheritance compatible with an autosomal dominant mode and myopathic features on muscle biopsy without structural changes other than occasional necrotic or regenerating fibres.

Family B carries the COL6A1 mutation G286V while Family D and Family E share the COL6A2 mutation G250S. Both Family A and Family C show genetic linkage to the COL6A1-COL6A2 region and recombine with COL6A3 region markers. Nucleotide analysis of the COL6A1 and COL6A2 coding sequence of a patient from Family C was unrevealing whereas this analysis could not be done for Family A due to lack of mRNA. Family F was too small to contain any linkage information and Family G remains to be genotyped.

Thirteen mothers, from Families A-E, provided a detailed history of the early motor development of their 20 affected children. For three patients from Family G, this information was derived from case notes. Functional grading of impairment (modified from established scales) and information on the use of aids was assessed by telephone interview or at the last out-patient follow-up in 36 patients aged 12 years and over.
Case description

Case 1. Patient B-21 from Family B was last seen at our department at the age of 3 years 2 months. Compared with a previous pregnancy his mother had experienced less fetal movements but there had been no apparent neonatal hypotonia. The patient had difficulty raising his head while lying prone and preferred sleeping supine. Instead of crawling, he went about by sliding forward on his buttocks. He was able to sit upright at 5 months and able to walk unsupported at 20 months but he could not get up from the floor without using his hands, and being less sturdy than his peers he easily tired while playing. Otherwise there was a normal motor and mental development.

On examination there was muscular atrophy and weakness of the shoulder girdle (Figure 1), a minimal flexion contracture of the proximal and distal interphalangeal joints of the right hand and slight limitation of dorsiflexion of the ankles, which was more apparent on the right with an increase in muscle tone of the calf. While standing valgus of the ankles was apparent but there were no contractures of the other joints nor of the spine. He had a waddling gait, a positive Gowers' sign and he was barely able to run. Tendon reflexes were present.

Figure 1. Case 1 with slight weakness of the shoulder girdle.
Case 2. Patient D-05 from Family D was examined at several stages between the age of 13 and 34 years. In comparison with a later carriage his mother had felt less fetal movements and at birth bilateral dorsiflexion contractures of the ankles (Figure 2) had been apparent as well as hypotonia which persisted for some months. The club feet regressed without treatment after several months. Four weeks after birth a swelling of the neck musculature was noted. Spontaneous improvement occurred but eventually a left-sided torticollis was noticed at four months. He was never able to crawl properly but instead he slid forward on his front without support of arms and legs. He started to walk unsupported between 20 and 24 months but he still needed support for getting up. He had striking flexion contractures of the knees and fell frequently. Generalized weakness remained apparent until puberty, the Gowers' sign and flexion contractures of the knees disappeared as well.

Examination at the age of 34 years revealed slight to moderate generalized paresis with proximal preponderance and moderate weakness of the neck flexors. There were slight contractures of the right shoulder, the right elbow, fingers and ankles (plantar flexion).

Figure 2. Bilateral congenital clubfoot (Case 2).
Case 3. Patient E-07 from Family E, seen at the age of 1 year 5 months, was delivered by vacuum extraction. He had dorsiflexion contractures of the feet at birth but no apparent floppiness. Unable to lift his head he had refused to sleep pronate as a baby. At 8 months he could sit without support and at 16 months he could stand but not walk unsupported. Within 6 weeks from birth there was spontaneous regression of the right club foot and from 8 weeks onwards the left clubfoot was treated with a plaster cast with little success. At 5 months a splint was applied without regression of the clubfoot.

On examination there was slight weakness of the shoulder muscles, atrophy and weakness of the calf musculature with hyperextension of the ankles, limitation of plantar flexion of the left ankle to 90° and limitation of extension of the knees to 170°. Hypotonia, facial weakness and Gowers' sign were absent and tendon reflexes were depressed.

Because of functional impairment and absence of regression of the left-sided clubfoot with conservative treatment, operative lengthening of the peroneal tendons was performed at 2 years of age and again at 4 years.
Results

Table 1 presents the symptoms and signs in infancy of 23 patients. Diminished fetal movements were noted by two mothers in three pregnancies but six mothers could not comment as their offspring consisted only of affected children (11 patients). Five mothers with both affected and unaffected children had noticed no difference in fetal movements. Nine babies were retrospectively described as being "floppy", gradually improving in the first 2 years. Two mothers gave birth to both floppy and non-floppy babies with Bethlem myopathy. The mothers had noted a head lag phenomenon in all floppy infants and in four non-floppy babies. Two patients (A-11 and E-15) that were reported to have been floppy infants became relatively severely affected as indicated by becoming wheelchair dependent at the age of 30 and 17 years, respectively. However, the severity of weakness and contractures in adult life of the seven other patients with neonatal floppiness fell within the same range as the 15 patients without neonatal floppiness. For instance, formerly floppy D-04 with only a minimal flexion contracture of the fingers but no weakness or atrophy at the age of 36 years was definitely less affected than 30-year-old B-10 with evident weakness and widespread contractures who had not been a floppy baby.

All children from Families D and E, except one, had bilateral clubfeet with dorsiflexion contractures of the ankles at birth but clubfeet were conspicuously absent in all other kindreds. In all but one patient (Case 3, E-07), spontaneous regression occurred in several weeks to one year. Disappearance of club feet is commonly followed by slow development of tight heel cords over several years. Torticollis, truly congenital or being noted after several months, was a feature of nine patients from five families. Regression occurred in one who had undergone physical therapy after several months, the other children underwent corrective surgery. Other contractures apparent at infancy consisted of flexion contractures of the elbows, fingers and knees. These latter, observed in four children (D-04, D-05, E-10, E-11) disappeared during childhood. Hypermobility of the wrists and fingers was noted in five children (A-06, C-01, C-03, E-14, E-15), slowly evolving to flexion contractures (A-06, C-03, E-15). Several children exhibited laxity of the hip joints with an increased range of endorotation (D-04, D-05, E-02, E-07, E-10, E-11, E-14, E-15) (Figure 3).

Nearly all children fell more often than usual for their age and often on their faces. During childhood muscle weakness remained stable but deterioration of walking due to development of tight heel cords was however noted in seven patients (A-03, A-11, B-10, B-13, B-20, C-07, F-03). Achilles tenotomy in two patients resulted only in temporary improvement, in a few years the ankle contractures had returned. As the other contractures did not give rise to functional impairment, most children were unaware of any change. All patients reported improvement of muscle power in puberty resulting in disappearance of the Gowers' sign, except one (B-10) who experienced slight worsening. In early adulthood
strength remained stable except for some deterioration with pregnancy perceived by several female patients (B-03, B-10, B-13, C-07, D-02). Slow deterioration of strength is experienced from 25 to 40 years of age onwards. No objective worsening of contractures was noted on outpatient follow-up. Cramps seemed to hamper four out of five patients from Family C whereas only one patient from another family volunteered this complaint.

Table 2 summarizes the interviews on impairment and use of aids with increasing age. Of 15 patients aged 50 years and over, 11 used a wheelchair (73 %). Most patients started to use a wheelchair in their sixth or seventh decade and the mean age at onset of wheelchair use was 54 5/12 years (range 17-82 years). With an estimated maximum walking distance of 10 to 50 metres, virtually all wheelchair patients continued walking indoors with a cane or support from furniture. One patient aged 59 years, who had become completely wheelchair bound, had an extensive, powered system of ropes and railings fitted...
to the ceiling in his home for assistance with transfers. This patient also reported increasing
difficulty in keeping his head upright while sitting. Recently, respiratory insufficiency
necessitated artificial ventilation at night. The youngest Bethlem myopathy wheelchair
patient (E-15) also suffered from Klinefelter syndrome. The requirement of devices for
physical support was equally distributed among the pedigrees.

Discussion

Our systematic evaluation of the mode of onset in 23 children and review of the course in
36 patients from seven pedigrees reveals novel aspects of Bethlem myopathy. Several
authors have reported an earlier onset in some patients than originally described by
Bethlem and van Wijngaarden (1976). A previous report on a Dutch family with Polish
ancestors described a child with congenital torticollis and slightly delayed motor milestones
(our Case 2, D-05) (Arts et al., 1978). In a large French-Canadian kindred there were two
children with a congenital abnormal configuration of the shoulders and three others with
delayed early developmental milestones. In a Finnish family two children had slightly
delayed motor milestones and in a Japanese family reduced fetal movements were reported
in one patient and congenital contractures in another. In our series detailed questioning of
mothers reveals that onset in infancy appears to be the rule instead of the exception. Fifteen
out of 23 children exhibited either contractures at birth or signs of weakness within the first
year and all except two children displayed neuromuscular features in the first 2 years of
life. The dynamic nature of the contractures in infancy and childhood has previously
escaped description, neither have hypermobility of fingers, wrists and hips been reported
before in Bethlem myopathy. We feel that unless severe functional impairment has
occurred, corrective surgery for contractures in early childhood should be delayed.

With regard to the symptoms and signs in infancy there is both interfamilial and
intrafamilial variability. Congenital dorsiflexion contractures of the ankles are restricted to
two families that share the COL6A2 mutation G250S and floppiness at birth occurs more
frequently, but not exclusively, with this mutation. Neonatal hypotonia does not predict
severity later on. Except for muscle cramps, we did not observe clear interfamilial
variability in adult life. An increase in weakness precipitated by pregnancy, similar to that
observed in other muscular dystrophies and congenital myopathies, was noted by some
women from three kindreds with different genotypes.

A description of symptoms and signs in childhood was accomplished retrospectively for most of our cases, as a diagnosis of Bethlem myopathy had already been established at the time of the analysis and therefore, our data are subject to recall bias. The
neonatal and early childhood features of weakness are non-specific, including floppiness
Table 2. Self reported impairment and use of aids, patients ranked by age at ascertainment.

**Shoulder girdle:**
1) unrestrained upper arm abduction and elevation. 2) upper arm abduction and elevation only possible with bent elbow. 3) unable to raise hand above head but can bring glass of water to mouth.

**Pelvic girdle:**
1) walks and climbs stairs without railings. 2) walks and climbs stairs with aid of a railing. 3) walks and climbs stairs slowly and cumbersomely with aid of a railing. 4) walks and rises from chair unassisted but cannot climb stairs. 5) walks but cannot rise from chair unassisted. 6) able to walk 50 metres (possibly with aids) but preferential use of a wheelchair. 7) wheelchair confined, transfers without assistance. 8) wheelchair confined, transfers only with assistance.

**Aids:**
1) walking cane or orthopaedic shoes. 2) adjustments at home like raised toilet seat, staircase with lowered steps or triple chair. 3) wheelchair.

and delayed motor milestones. The diagnosis will rely heavily on the family history. The diagnostic work-up of a baby with, for example, neonatal flappiness and torticollis and an apparently negative family history should include consideration of Bethlem myopathy. Evidence for contractures of fingers, wrists, elbows and ankles should be systemically sought for in the parents, who are probably at an age where there are no sings of muscular weakness in individuals with Bethlem myopathy. The kindreds described by Taylor et al. with early onset, autosomal dominant myopathy with rigidity of the spine and a secondary deficiency of laminin β1 in adult patients, share many features with Bethlem myopathy,
thus making differentiation difficult. Differences can include cardiac conduction abnormalities (not encountered in Bethlem myopathy), spinal rigidity (rare in Bethlem myopathy) and calf hypertrophy (rare in Bethlem myopathy), but these features are not obligatory in the kindreds with secondary laminin $\beta_1$ deficiency. Laminin $\beta_1$ was normal in two patients diagnosed with Bethlem myopathy, but the criteria applied in the diagnosis of Bethlem myopathy in that study were unclear. We have not examined our patients for laminin $\beta_1$, merosin was present in normal amounts in muscle of one patient (results not shown).

From the literature on Bethlem myopathy a deceptively innocuous picture of a benign myopathy with mild weakness and little disability emerges. Progression of weakness is reported to be slight with most patients remaining ambulant with a walking cane in their seventh or eighth decade and an unaffected life expectancy. From 122 Bethlem myopathy patients only three have been reported to use a wheelchair. Our data show that with advancing age nearly all patients experience sufficient impairment to warrant alterations at home, ranging from an elevated toilet seat to a fully automated system to assist the bed-wheelchair-toilet transfer and ventilatory support at night in one patient. More than two-thirds of patients aged 50 years and over preferentially use a wheelchair for at least part of their ambulation. Typically this entails use of a wheelchair outdoors with patients remaining ambulant within their homes. As our study did not quantify muscle strength or degree of contractures, there is no evidence that the functional deterioration with time is due to worsening of either. Nevertheless, it is our experience that weakness is slowly progressive while contractures remain virtually constant in adulthood. The high frequency of the need to use wheelchairs and other aids might reflect the accessibility of such devices in the Netherlands. When informing patients about prognosis however, e.g. for career advice, one should convey the message that substantial hindrance often starts to occur in middle age. Referral to and follow-up by a rehabilitation physician should be considered.

In conclusion, Bethlem myopathy runs a characteristic course. Congenital in nature it can present with diminished fetal movements, contractures at birth including torticollis, neonatal hypotonia, or slightly delayed motor milestones. Although many children exhibit neuromuscular features in the first 2 years of life, most patients do not become fully symptomatic before 5 years of age. During childhood contractures have a dynamic nature and slight worsening of weakness often ensues to be followed by relative recovery during puberty. Except for contractures many patients are nearly asymptomatic during early adult life. From middle age onwards slow deterioration becomes established, in sufficient degree to warrant several aids, facilities and wheelchairs in most elderly patients.
Chapter 3

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References


