Miyoshi-type distal muscular dystrophy
Clinical spectrum in 24 Dutch patients

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Summary
Miyoshi-type distal muscular dystrophy has now been found to be more frequent outside Japan than was previously thought. We studied 24 Dutch patients with Miyoshi-type distal muscular dystrophy and focused on its clinical expression and natural history, muscle CT-scans and muscle biopsy findings. Our study shows that Miyoshi myopathy is a heterogeneous, slowly progressive disorder. The disease starts with weakness and atrophy of the calves and progressively involves the proximal leg and hip muscles and, in a later stage the shoulder and upper arm muscles. After 10 years disease duration, one-third of the patients are dependent on wheelchairs for out-of-door transportation. Disease progression is related to disease duration and not to early age of onset of symptoms. Onset may be at any age and is asymmetrical in roughly half of the cases. Four cases had been initially diagnosed as idiopathic hyper-CK-aemia.

Keywords: Miyoshi myopathy; clinical heterogeneity; muscle biopsy; muscle CT scan; idiopathic hyper-CK-aemia

Abbreviation: CK = creatine kinase

Introduction

Early adult onset distal myopathy (Miyoshi myopathy) was first described in 1967. Thereafter most cases have been reported from Japan (Miyoshi *et al.*, 1967, 1986). In western countries Miyoshi myopathy has been described only in anecdotal cases (Kuhn and Schroder, 1981; De Visser, 1983; Barohn *et al.*, 1991; Crespo and Codina, 1994).

Onset of Miyoshi myopathy is said to occur between 15 and 25 years (Miyoshi *et al.*, 1986, Barohn *et al.*, 1991). One of the first characteristics is weakness and atrophy of the calf muscles, preventing the patients from standing on tip-toe. The serum creatine kinase (CK) activity is always markedly elevated, to as much as 10–150 times the upper limit of normal (Barohn *et al.*, 1991). Inheritance is autosomal recessive, but in Western countries cases are usually considered sporadic. Recently, the locus for early adult onset distal myopathy has been linked to chromosome 2p12–14 (Bejaoui *et al.*, 1995), but as yet the mutation itself has not been pinpointed. Therefore, the diagnosis of Miyoshi myopathy is still based on specific clinical features, elevated CK, and histological characteristics. Follow-up data are often lacking and, if present, usually deal with neurological impairment over a short period of time.

We have collected data from 24 Dutch patients with Miyoshi myopathy. The objectives of this study were (i) to determine whether clinical and laboratory features in our patients are identical with those previously described and (ii) to provide follow-up data in functional terms.

Patients and methods

After a survey among the neuromuscular centres of the University hospitals in the Netherlands, 24 patients in which a diagnosis of Miyoshi myopathy had been made were recruited for this study. Patients were included on the following criteria: (i) initial weakness and atrophy of calf muscles; (ii) no sensory abnormalities; (iii) no fasciculations;

Table 1 *Functional grading scales**

Functional grade of arms and shoulders
(1)   Starting with arms at the sides, the patient can abduct the arms in a full circle untill they touch above the head.
(2)   Can raise arms above the head only by flexing the elbow (i.e. shortening the circumference of the movement) or using accessory muscles.
(3)   Cannot raise hands above head but can raise an 8-oz glass of water to mouth (using both hands if necessary).
(4)   Can raise hands to mouth but cannot raise an 8-oz glass of water to mouth.
(5)   Cannot raise hand to mouth but can use hands to hold pen or pick up pennies from the table.
(6)   Cannot raise hands to mouth and has no useful function.

Functional grade of hips and legs
(1)   Walks and climbs stairs without assistance.
(2)   Walks and climbs stairs with aid of railing.
(3)   Walks and climbs stairs slowly with aid of railing (over 12 s for four standard stairs).
(4)   Walks unassisted and rises from chair but cannot climb stairs.
(5)   Walks unassisted but cannot rise from chair or climb stairs.
(6)   Walks only with assistance or walks independently with long leg braces.
(7)   Walks in long leg braces but requires assistance for balance.
(8)   Stand in long leg braces but unable to walk even with assistance.
(9)   Is in wheelchair.
(10) Is confined to bed.

*From Brooke MH *et al.* (1981)

(iv) CK levels >10 times the upper limit of normal; (v) normal motor and sensory nerve conduction studies; (vi) no myotonic discharges on routine electromyography; and (vii) predominantly myopathic features without rimmed vacuoles in the muscle biopsy specimen (Barohn *et al.*, 1991, Griggs and Markesbery, 1994). All patients gave their informed consent to participate in the study.

Clinical examination

The neurological review and examination of all patients were carried out in a standardized fashion by the same neurologist (W.L.). After taking the patient's history to determine the onset, nature and distribution of symptoms, and course of the disease, an update physical examination was carried out. Muscle involvement was evaluated clinically using the Medical Research Council (MRC) grading scale and CT scans of skeletal muscle. Inability to hop or to stand on tip-toe and a waddling gait were considered MRC grade 4 for the gastrocnemius and the gluteus medius and minimus muscles, respectively.

Functional impairment was assessed by assignment of scores for the proximal limb muscles as proposed by Brooke *et al.* (1981) (*see* Table 1). CK was determined in all patients and in most of their siblings.

Laboratory investigations

The CT scans were carried out according to a standardized protocol (De Visser and Reimers, 1994), and comprised sections through the fourth lumbar vertebra, upper edge of the acetabulum, thigh and lower leg. The CT scans were quantified following three-point scales for muscle density (0 = normal; 1 = areas of decreased attenuation; 2 = total fatty replacement) and for muscle size (0 = normal; 1 = atrophy; 2 = hypertrophy).

Conventional needle electromyography had been performed as part of the initial work-up in all patients. The electromyographic data were re-assessed and classified as predominantly myopathic (low-voltage, small motor-unit potentials), and predominantly neurogenic (positive waves and fibrillations) or mixed.

Muscle biopsy

Twenty of the 24 patients had undergone a muscle biopsy, at least one case in every family. Four patients had not been biopsied because the diagnosis had been established in an affected sibling. Three patients had two muscle biopsies at different sites. Twenty-three biopsy specimens were taken from various muscles [quadriceps femoris ($n = 15$), gastrocnemius ($n = 5$), peroneus ($n = 1$), hamstrings ($n = 1$) and deltoid ($n = 1$)] and were available for re-evaluation (by M.D.V.). Processing and staining of the tissue had been performed according to routine methods. Assessment was by simple inspection with routine light microscopy. Abnormalities were divided into three categories, i.e. slight, moderate and severe.

Statistics

Wilcoxon rank sums and Kruskal–Wallis tests (χ^2 approximation) were used for statistical evaluations. The significance of differences from normal subjects are expressed in terms of P values, unless otherwise stated. Results are given as means, standard deviations and/or ranges.

Table 2 *Initial and current complaints of the 24 patients*

Initial complaints	No.	%	Current complaints	No.	%
Pain and tenderness	4	17	Pain and tenderness	0	0
Fatigue	9	37	Fatigue	24	100
Asymmetry	11	46	Asymmetry	4	17
Wasting of calves	3	12	Wasting of calves	24	100
Weakness	8	33	Weakness	24	100
Difficulty climbing stairs	8	33	Difficulty climbing stairs*	23	96
Unable to stand on tip-toe	6	25	Unable to stand on tip-toe*	24	100
Waddling gait	4	17	Waddling gait*	24	100
Difficulty running	4	17	Difficulty running*	24	100
Difficulty rising from chair	0	0	Difficulty rising from chair*	18	75

*Wheelchair-dependent patients are included.

Results

Clinical findings

Nineteen men and five women were included in the study. The mean age at the present evaluation was 38 ± 11 years (range 20–61 years). Data on clinical follow-up were available for 23 patients. One patient who also suffered from epilepsy, had died suddenly. Four patients were already known to have idiopathic hyper-CK-aemia, and two patients were diagnosed following investigation of affected family members. These six patients were asymptomatic at that time and subsequently developed the clinical signs and symptoms of Miyoshi myopathy. In our series twelve of the 24 patients were non-familial cases. In six families two family members were affected. None of the parents or asymptomatic siblings were clinically affected. Consanguinity was never mentioned.

The mean age at the onset of the muscle complaints was 27 ± 10 years (range 13–52 years). In 15 patients (63%) onset was between 16 and 30 years, in two patients (8%) onset was before 16 years, and seven patients (29%) had their first symptoms when they were over 30 years old. The disease started asymmetrically with calf weakness and atrophy in one leg in 46% (11 patients).

The complaints at the onset of the disease and at the time of this study are presented in Table 2.

In 20 of the patients (83%) the signs and symptoms became symmetrically distributed during the course of the disease. In the other four patients (17%) signs and symptoms remained asymmetrical; in three of them weakness and atrophy were even strictly confined to one leg. These three patients had a late onset of symptoms (at 43, 45 and 51 years of age). At the time of the investigation the mean disease duration was 10 ± 6 years (range 1–26 years). Two illustrative case histories are presented (Cases 1 and 2).

Case 1. A 13-year-old girl complained of excessive fatigue after exertion and frequent falls. Within 2 years her complaints progressed and she lost the ability to jump, run and stand on tip-toe. By the age of 16 years she could only climb a staircase by using both hands for pulling herself up. The family history was negative for muscle disorders.

At the age of 16 years her legs showed severe wasting of the calf muscles and pronounced weakness of the foot flexors and extensors. She could neither walk on tip-toe nor on her heels. The Achilles tendon reflexes were absent. There were no sensory abnormalities and no joint contractures.

Serum CK activity exceeded 3000 U/l (normal values <100 U/l). Electromyography revealed normal sensory and motor nerve conduction velocities. Needle examination of muscle showed polyphasic and high frequency pseudomyotonic discharges. A biopsy from the quadriceps femoris muscle revealed marked variation of muscle fibre diameter, fibre necrosis and phagocytosis, some basophilic fibres and fibre splitting. There was an increase of peri- and endomysial connective tissue and fatty replacement. An occasional perivascular infiltrate consisting of lymphocytes and macrophages was seen.

A tentative diagnosis of polymyositis had been made. Thereupon, treatment was started with high dose steroids. Due to lack of clinical improvement azathioprine was added. Despite this treatment regime no improvement was noticed and medication was tapered after a few months.

During the next years weakness progressed to the hip and thigh muscles, necessitating her to use a wheelchair for most of her daily activities by the age of 21 years. Subsequently, shoulder and upper arm muscles also became affected.

Currently, at the age of 32 years, she is totally confined to a wheelchair, unable to move her legs voluntarily or to sit without support. She can hold her arms stretched in a horizontal plane for 5 s. There is only slight weakness (MRC grade 4+) of the hand flexors and extensors.

In the meantime, diagnosis had been changed to distal myopathy with very early onset.

Case 2. This 57-year-old man had experienced difficulty standing on tip-toe on the right for 2 years. His brother, who was 5 years younger, was known to have had idiopathic hyper-CK-aemia for 7 years, with bilateral wasting of his calf muscles without weakness, slight myopathic features on electromyographic examination and single fibre necrosis on muscle biopsy. Examination of our patient revealed pronounced unilateral wasting of the medial head of the right
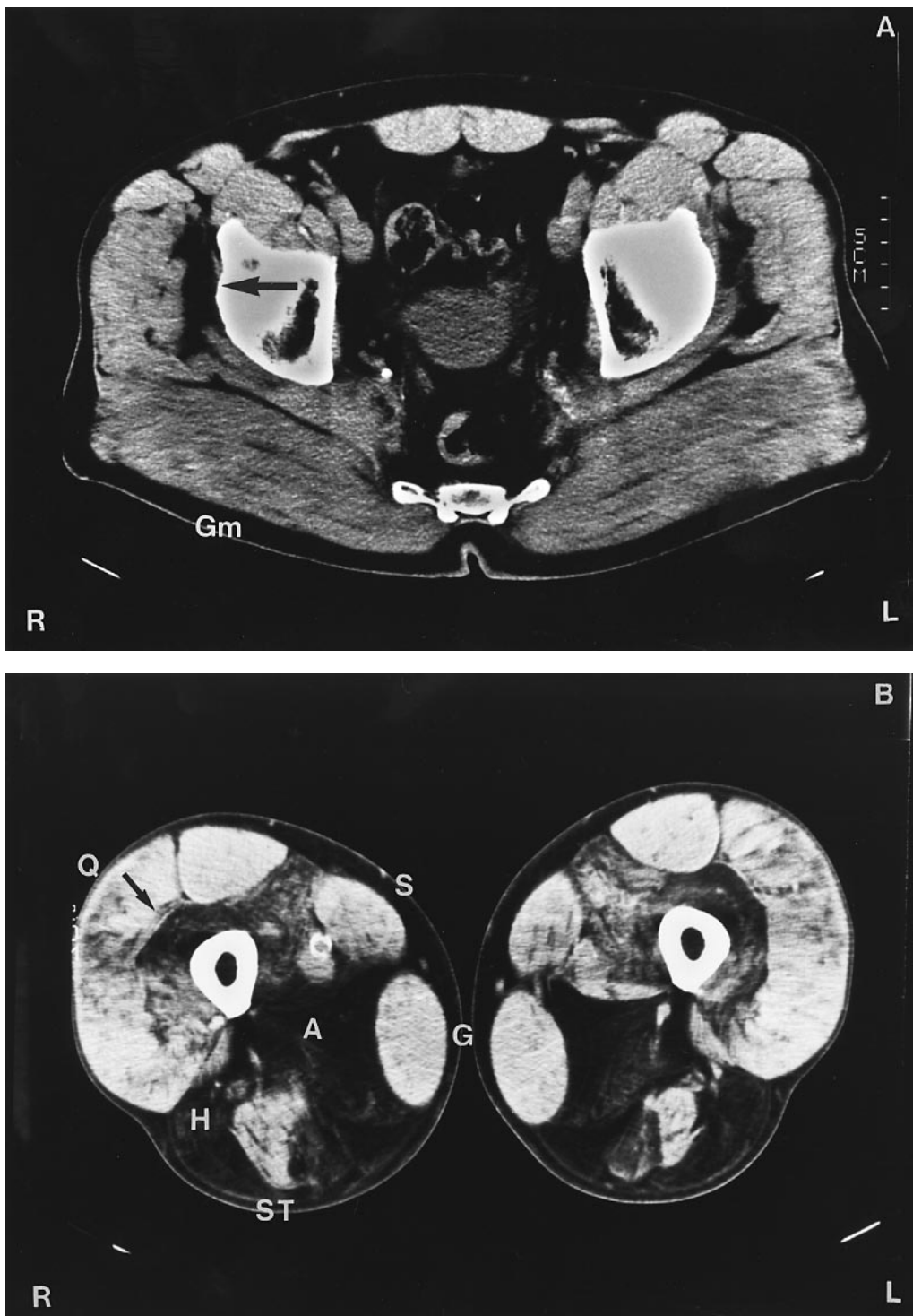
gastrocnemius muscle, and weakness of his right triceps surae muscle. The tendon reflexes were normal except for the right achilles tendon reflex which was absent.

Despite the lack of pain, a lumbar radiculopathy was considered to be the most probable diagnosis, but imaging studies of the lumbar roots were negative. However, ancillary investigations revealed a serum CK activity exceeding 5000 U/l. CT-scan examination of his muscles showed areas of lower attenuation in the gastrocnemius muscles and also in the adductor magnus, hamstrings and gluteus minimus muscles (Fig. 1). The muscle biopsy was consistent with a necrotizing myopathy.

The disorder of both brothers was diagnosed as distal Miyoshi myopathy with very late onset. During the next 2 years our patient showed no clinical disease progression. (His brother, whose CK activity exceeded 6000 U/l, gradually developed unilateral atrophy and weakness of his left calf muscle by the age of 53 years.)
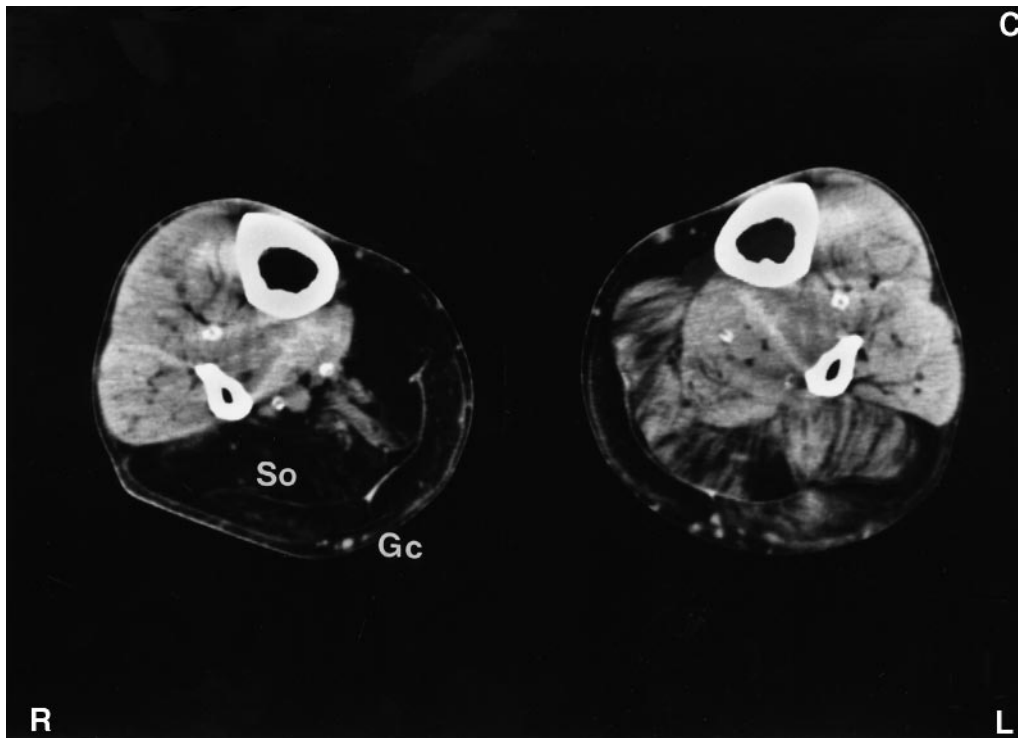
Fig. 1 (**A**) CT scan of the pelvic girdle region. The gluteus minimus muscles (arrow) have been completely replaced by fat. The gluteus maximus (Gm) muscles show some streaks of lower attenuation. (**B**) CT scan of the thighs. The hamstrings (H), adductors (A) and vastus intermedius muscles (arrow) have been replaced by fat. Areas of lower attenuation are seen in the remaining quadriceps femoris (Q) muscles and in the semitendinosus (ST) muscles. The gracilis (G) and sartorius (S) muscles are hypertrophic and pseudohypertrophic, respectively. (**C**) CT scan of the lower legs. The gastrocnemius (Gc) and soleus (So) muscles have been replaced by fat, right more than left.

The mean disease duration was significantly longer ($P = 0.002$) for patients with difficulty rising from a chair (12 ± 5.3 years) versus those with no difficulty (4.5 ± 2.4 years). Patients with difficulty rising from a chair also had a significantly earlier onset of disease (24 ± 6.6 years) versus patients without difficulty (38 ± 12.5 years, $P = 0.02$).

Eight patients experienced weakness of the upper arm and shoulder muscles. When patients with and those without complaints of arm weakness were compared, no significant differences were found for mean disease duration (with, 12 ± 4.5 years; without, 10 ± 6 years) nor for age of onset (with, 25 ± 8 years; without, 28 ± 11 years).

Clinical examination revealed that muscle atrophy of the calves, present in all patients, was most pronounced in the medial head of the gastrocnemius muscle. In more than half of the patients the quadriceps femoris muscle had decreased in volume. Examination of the shoulder girdle revealed that in up to 54% of the patients the deltoid and biceps brachii muscles were preferentially atrophied. One patient had had enlarged calves during the early phase of the disease and subsequently developed calf atrophy.

Weakness was most pronounced in the gastrocnemius, gluteus medius and minimus, hamstrings, quadriceps femoris and iliopsoas muscles (Fig. 2).

In the upper extremities weakness was found in the biceps brachii in 50% of the patients. In 10% of the patients slight weakness was found in the lower arm muscles. Weakness was never found in the intrinsic hand, neck and facial muscles.

Ankle jerks were absent in all patients while other tendon reflexes could normally be elicited. About 50% of the patients had an increased lumbar lordosis and 8% had thoracic kyphosis.

Handicaps and duration of the disease

Eight patients (33%) used a wheelchair for out-of-doors transportation. According to the Functional Disability scales (Brooke *et al.*, 1981) for the arms, 83% of the patients scored grade 1, three patients were graded 2 or 3, and one patient was graded 5. For the legs only one patient had grade 1, ten scored grade 2 or 3, another 10 patients were graded between 4 and 6, and three patients were graded between 7 and 9.

Ambulatory patients had a shorter mean duration of disease (9 ± 6 years) compared with those who were dependent on wheelchairs (14 ± 4 years, $P = 0.02$). The mean age of onset was not significantly different for wheelchair dependency (22 ± 7 years) and ambulation (30 ± 11 years, $P = 0.15$).

Patients with a high functional disability of the leg (above grade 3) had significantly longer disease duration (13 years
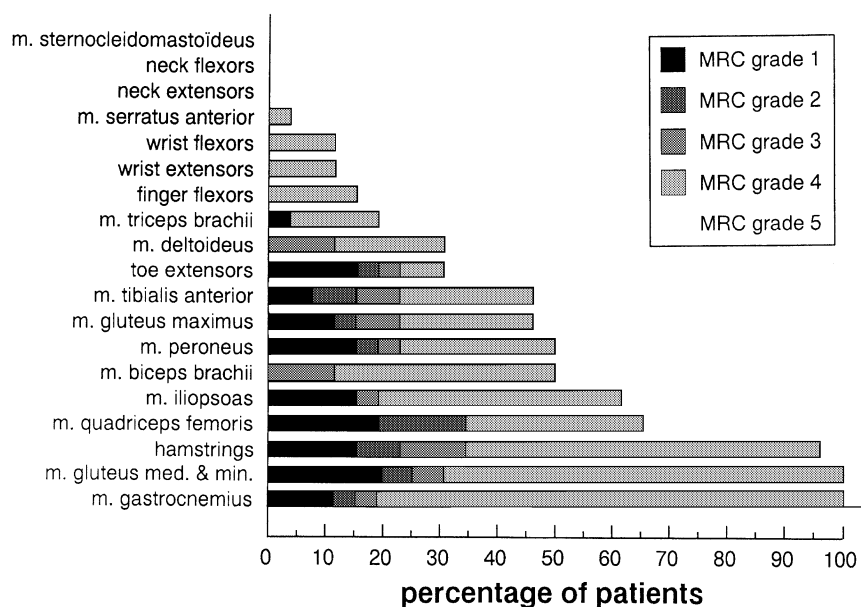
Fig. 2 The distribution of muscle weakness is presented as percentages of patients with weakness (MRC graded) in identified muscles. m. = musculus; med. = medius; min. = minimus.

versus 6 years, *P* = 0.008) compared with those with low functional disability.

Laboratory findings

At follow-up, all patients had markedly elevated CK activities ranging from 25 to 100 times the upper limit of normal CK, with the exception of one patient who had a CK of 751 U/l. Initially, the CK of this patient had been 2800 U/l (normal < 100 U/l).

Twenty CT scans were re-evaluated and results are presented in Fig. 3. Muscle hypertrophy was found in the gracilis (32%) and sartorius (23%) muscles. All patients had bilateral areas of lower attenuation and atrophy of distally and proximally located muscles even when symptoms were strictly confined to one leg (Fig. 1).

EMG had been performed in 20 patients and showed diverse findings including normal data (15%), positive waves and fibrillations (25%), low-voltage, small motor-unit potentials (15%), and a combination of both (45%). Nerve conduction was always within normal limits.

Muscle pathology

Of the 23 muscle biopsies, one gastrocnemius biopsy specimen contained only fat and connective tissue and was therefore excluded from the study. In two patients a quadriceps femoris biopsy showed an occasional necrotic and regenerating fibre. At that stage, the clinical diagnosis could not be established and therefore these muscle biopsy specimens were also excluded from the analysis.

The results of the histopathological re-evaluation of the 20 muscle biopsies that are included in the study, are

summarized in Fig. 4. In more detail, six biopsies showed occasionally necrotic fibres that were surrounded by mononuclear inflammatory cells, and in one muscle biopsy a large perivascular cell infiltrate was present. Small groups of atrophic fibres were observed in two-thirds of the muscle biopsies; in two biopsies a group of moderate size (up to 30 atrophic muscle fibres) was present. There was no relationship between any of the observed abnormalities and age of onset, duration of the disease at the time of biopsy or site of the muscle biopsy. Dystrophin was analysed in seven patients and showed a normal staining pattern.

Discussion

This study of 24 Dutch Miyoshi-type distal muscular dystrophy patients is larger than the original series of 17 patients reported by Miyoshi *et al.* (1986) and indicates that Miyoshi myopathy is not as rare in Western countries as previously thought.

In the series of Miyoshi *et al.* (1986), all the patients showed an onset of the disease at or before the age of 30 years. In 14 of their 17 patients disease onset was even before the age of 20 years, justifying the classification as early adult onset distal myopathy. However, our study revealed a considerable variation in the time of disease onset; it may be as early as 13 years of age or as late as the sixth decade.

A conspicious observation concerns the asymmetrical presentation of muscle weakness in 50% of our patients. This has been described only once before (Galassi *et al.*, 1987). Weakness remained asymmetrical in four patients (17%) and even strictly unilateral in three of them. These cases all started over the age of 40 years. The atypical presentation
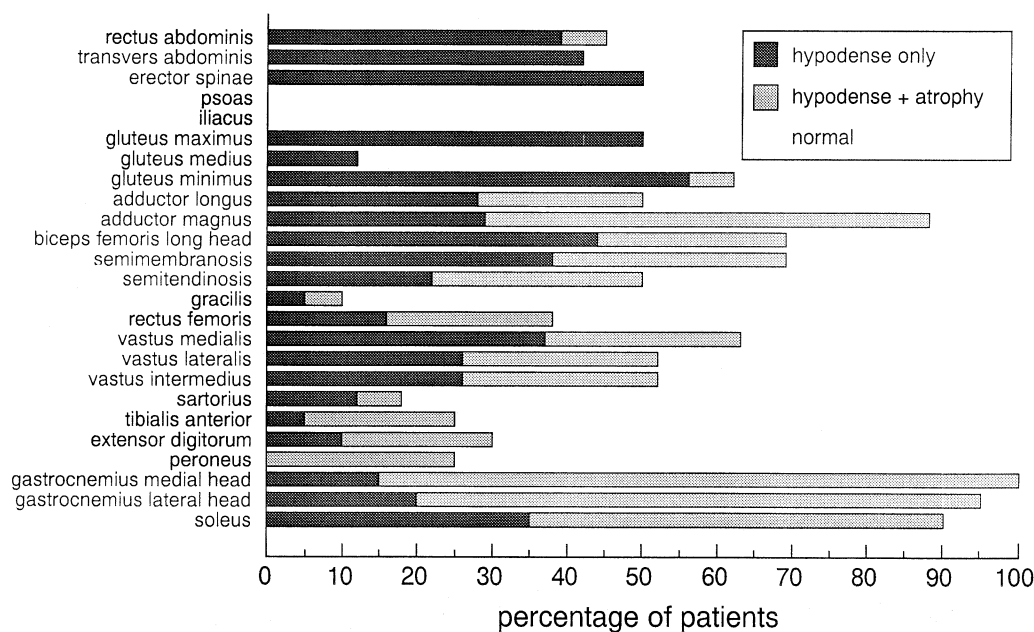
Fig. 3 The muscle CT-scan evaluation is presented as percentages of patients with abnormalities in identified muscles. The findings are classified as hypodense only, hypodense and atrophy, or normal.
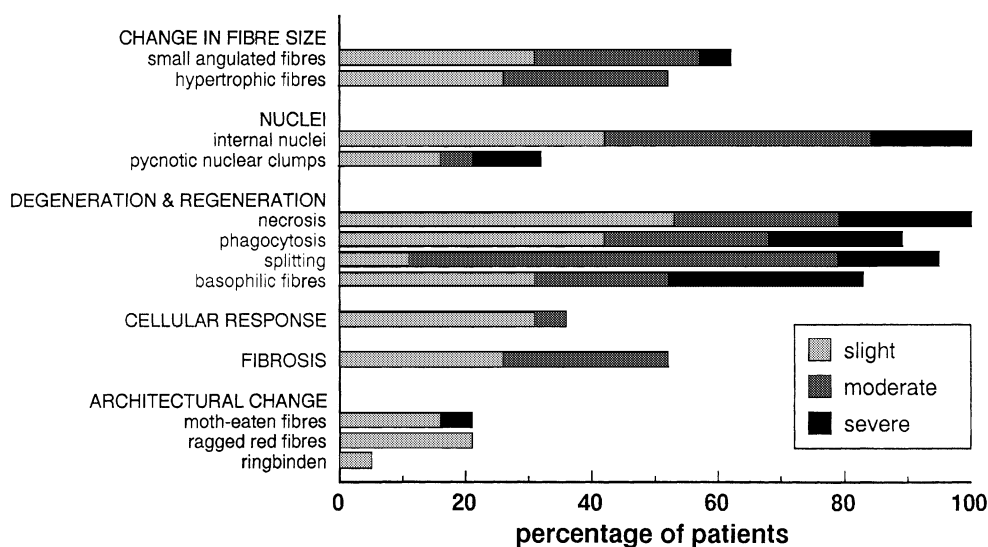

Fig. 4 The muscle biopsy findings are presented as percentages of patients that show abnormalities, classified as slight, moderate or severe.

caused diagnostic delay since other diagnoses including radiculopathy had been considered first.

Another difference between our patients and those described by Miyoshi *et al.* (1986) concerns the presence of weakness and atrophy of the deltoid, biceps and triceps brachii muscles in 50% of the patients at a relatively early stage of the disease (after only 12 years duration). Miyoshi *et al.* (1986) reported weakness of the arm and shoulder girdle only in an advanced stage of the disease. About 10% of our patients had weakness of distal arm muscles; none had weakness of intrinsic hand, neck and facial muscles.

Our study focuses on the clinical course of the disease. As in the description of Miyoshi *et al.* (1986), we show that weakness starts in the calf muscles and that shoulder girdle muscles are less affected than upper arms. Recently, co-segregation of limb-girdle muscular dystrophy and Miyoshi myopathy has been demonstrated in two large consanguineous families and it seems to link Miyoshi myopathy to the LGMD2B gene on chromosome 2p13 (Illarioshkin *et al.*, 1996; Weiler *et al.*, 1996). Further molecular genetic analysis will eventually elucidate whether the clinical heterogeneity is caused by different mutations.

Given the fact that 33% of our patients are wheelchair dependent for out-of-doors transportation after 10 years one may conclude that Miyoshi-type distal muscular dystrophy runs an unfavourable progressive course. We found that disease progression, difficulty in climbing stairs and rising from a chair, and disability (i.e. wheelchair dependency) is significantly linked to disease duration but not with early onset of the disease.

An elevation of serum CK of at least 10 times the upper limit of normal is one of the hallmarks of Miyoshi-type muscular dystrophy and this was also found in all of our patients. One patient had a CK of 751 U/l at follow-up. This patient had a very early onset at the age of 13 years and was most severely handicapped (Case 1). Four patients had been initially diagnosed as idiopathic hyper-CK-aemia illustrating that the differential diagnosis of idiopathic hyper-CK-aemia should also include Miyoshi myopathy (Galassi *et al.*, 1987).

The results of our CT evaluations confirm the findings of De Visser (1983), who showed that muscle CT may offer an important contribution to the clinical examination. Muscle CT scan can identify affected muscles that are clinically difficult to evaluate separately from other muscles or that appear normal on clinical examination. It should be performed in all cases with idiopathic hyper-CK-aemia.

The muscle biopsy changes are essentially in line with the previously described findings by Barohn *et al.* (1991). Most of the biopsies showed a dystrophic process, although in more than half of the biopsy specimens signs of active denervation were observed as well. In a few patients, these so-called neurogenic changes were even more prominent than the dystrophic changes. Likewise, electromyographic signs of active denervation were found in a considerable number of patients.

Occasionally necrotic fibres were surrounded by sparse mononuclear inflammatory cells. In one patient, in whom onset of the disease had been at the age of 13 years, these changes had initially been interpreted as inflammatory myopathy whereupon she had been unsuccessfully treated with prednisone for a period of time (Case 1).

From the muscle biopsy analysis two quadriceps femoris biopsies, showing single fibre necrosis, have been excluded because they were not diagnostic at that stage of the disease. In retrospect this finding might be considered as an early diagnostic feature of Miyoshi-type distal muscular dystrophy.

We conclude that 'early adult onset' distal myopathy is a rather heterogeneous and progressive type of muscular dystrophy. Onset is not restricted to early adulthood and weakness may be confined to one leg. Miyoshi myopathy should be considered in cases of idiopathic hyper-CK-aemia.

Acknowledgements

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