J Neurol (1993) 240: 98–104

Unit 5
Section 2
Paper 8

The clinical, genetic and dystrophin characteristics of Becker muscular dystrophy

I. Natural history

n=77 identified → 67 examined

K.M.D. Bushby[1], D. Gardner-Medwin[2]

[1]Department of Human Genetics, 19/20 Claremont Place, Newcastle upon Tyne NE2 4AA, UK
[2]Children's Department, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne, UK

Received March 20, 1992 / Received in revised form May 22, 1992 / Accepted May 27, 1992

Abstract. We have investigated 67 patients with proven Becker muscular dystrophy (BMD) using a standard protocol including a detailed history and a functional and clinical examination. Our aim was to define the natural history of the disease in a large cohort of patients in the light of the diagnostic methods now available. In all patients with or without an X-linked family history, the diagnosis was confirmed by the identification of a deletion or other abnormality in the dystrophin gene, and abnormal dystrophin on immunoblotting and immunocytochemistry of muscle biopsy samples. In graphs of functional and muscle score against age, two groups of patients emerged. In the larger group the disease was milder and patients remained ambulant into their forties or beyond. A smaller group had more severe disease with a slightly earlier onset, much earlier loss of ambulation, more frequent abnormal electrocardiographic findings and much lower reproductive fitness. The relationship of these clinical findings to the genetic and protein abnormalities found in the patients is explored in the accompanying paper.

Key words: Becker muscular dystrophy – Natural history – Clinical assessment – Dystrophin – Diagnosis

Introduction

Becker muscular dystrophy (BMD) is most often defined in terms of comparison with Duchenne muscular dystrophy (DMD). The description by Becker and Keiner in 1955 [2] of a "new X-chromosomal muscular dystrophy" concentrated on the observation of an X-linked disease with a pattern of muscle involvement similar to that seen in DMD, but with a much slower rate of progression. For example, the ability to walk was maintained until at least 25–30 years after the onset of symptoms. Subsequent reports [1, 2, 4, 10, 12, 22, 24, 26, 30] confirmed the existence of a relatively mild X-linked dystrophy, but assessments of such salient features as age at onset, age at becoming wheelchair-bound and age at death revealed a wide range with no indication of what was the most typical pattern of disease in BMD. More precise definition required the collection of large numbers of patients with BMD, but this was hampered by the absence of any diagnostic test. The clinical, EMG and muscle biopsy findings could all be confused with such conditions as spinal muscular atrophy and the "limb-girdle" dystrophies [4, 14]. So most studies included only cases from families with proven X-linked inheritance, and inevitably an unknown number of sporadic cases were excluded.

The similarity of the pattern of muscle involvement in DMD and BMD led Becker in his original papers [2, 10] to suggest that the two diseases might be caused by problems in the same gene. This has now been established with the discovery of the gene for Duchenne and Becker dystrophy at Xp21 [21, 28] and the identification of the protein involved [19]. Precise techniques for genetic and protein analysis are now available for the investigation of the patient with Xp21 dystrophy (discussed in the accompanying paper).

Our aims in this study were to achieve full regional ascertainment of BMD, to confirm the diagnosis in all patients by means of genetic and protein analysis, to redefine the clinical course of BMD and to identify the most common patterns of the disease. Our assessment included an objective and standardised functional examination, according to the scale proposed by Cornelio et al. [8], thus avoiding the need to rely on the age at becoming wheelchair-bound as the major indicator of severity, a standard of limited value in a disease of relatively slow progression. This detailed information about natural history could then be correlated with the genetic and dystrophin abnormalities identified in the patients (see accompanying paper [7]).

Patients and methods

Patients were ascertained through the Regional Neurological Centre and Muscular Dystrophy Group Research Laboratories

Correspondence to: K.M.D. Bushby

Newcastle upon Tyne and via contact by letter with all local neurologists, paediatricians, general physicians and general practitioners. Patients were included in the initial ascertainment when the clinical history, physical signs and the results of investigations such as creatine kinase estimation, EMG and muscle biopsy were compatible with a diagnosis of BMD, and in familial cases, where the mode of inheritance was compatible with X-linkage. The distinction from DMD was based on the criterion that all of these patients were independently ambulant beyond the age of 16 years, or predicted to remain ambulant after that age by comparison of their physical and functional performance with other patients with Xp21 dystrophy at a similar age (with one exception, see later). Patients who became wheelchair-bound between the ages of 12 and 16 (the group defined by Brooke et al. as "outliers" [5]) were not included. Presymptomatic cases were included when the diagnosis was based on a grossly elevated creatine kinase (CK) level and a family history of proven BMD.

Confirmation of the diagnosis was then established in all sporadic cases and in at least one affected case in each family by the identification of a deletion or other abnormality of the dystrophin gene and/or the identification of an abnormal dystrophin pattern on immunolabelling (immunocytochemistry and immunoblotting) of muscle biopsy specimens.

Patients were investigated according to a predetermined protocol by a single examiner (K.M.D.B.). The examinations were carried out in most cases without prior knowledge of the exact genetic or protein abnormality in the family under study.

History

The following aspects of the natural history of the disease were considered: (1) early development and muscle function; (2) early symptoms of disability; (3) progression of the disease; (4) educational and employment record.

The reproductive fitness of the group was calculated by comparing the number of offspring fathered by the BMD patients aged over 20 years with those of their unaffected brothers. Details of patients with BMD who had died were collected to calculate the mean age at death in this group.

Formal IQ assessments were collected where available, performed according to the Wechsler Intelligence Scale for Children-revised [27].

Functional and clinical examination

Scores were awarded according to a modified version of the scale of Cornelio et al. [8] for performance in the following areas: gait, ability and agility and climbing stairs, rising from a chair, rising from the floor and movements of the proximal and distal upper limbs. The total score for each patient was plotted against age.

Muscle examination was performed in 31 muscle groups according to the guidelines in "Aids to the examination of the peripheral nervous system" [18] grading each muscle on a scale of 0–5, recognising the subdivisions of 4−, 4 and 4+ and converting to a wholly numerical score of 0–7 for statistical analysis. From this score values were derived for percentage of total possible muscle score (217). This score was plotted against age.

The presence of contractures, scoliosis and other orthopaedic abnormalities was noted and a general clinical examination performed. Forced vital capacity (FVC) was measured using a pocket spirometer (Micro Medical Instruments) and the results again plotted against age.

Laboratory data

Results of serum creatine kinase estimations, EMG, ECG and muscle histology were collected for each patient in whom they were available.

The methods involved in the genetic and protein investigations performed are described in the accompanying paper [7].

Results

Of 77 patients with proven BMD identified, 67 agreed to be seen, representing 43 families. The 10 unable to participate represented 7 families, in 3 of which another family member was seen. There was no previous family history in 28 patients (41.8%). Twenty-nine patients (43.3%) from 9 families had a definite X-linked family history, and 10 patients (14.9%) from 5 families had an affected brother but no other family history. All patients were male. Four were presymptomatic (aged 6 months, 10 months, 3 years and 14 years). Fifteen patients who had died were also identified.

The average age of the group was 30.3 years (range 6 months to 88.5 years). Excluding the presymptomatic cases, the average age was 32.1 years (range 3.6 years to 88.5 years).

Early muscle function

The mean age at first walking was delayed to 15.03 months (range 10–36 months, with 97% walking by the age of 2 years); 34.5% of patients had noticed problems with their early mobility, including toe-walking, problems with running and persistent falling; 68% of patients reported problems with school sport, and the reported mean age for peak physical performance was 12.7 years (range 3–25 years).

Awareness of specific disability

The mean age at which muscle problems were noticed and appreciated as such was 11.2 years (range 10 months to 38 years), excluding cases where the diagnosis was made presymptomatically, amongst whom the mean age for diagnosis was 9.2 years, range 6 months to 28 years. The cumulative frequency distribution curves for age at

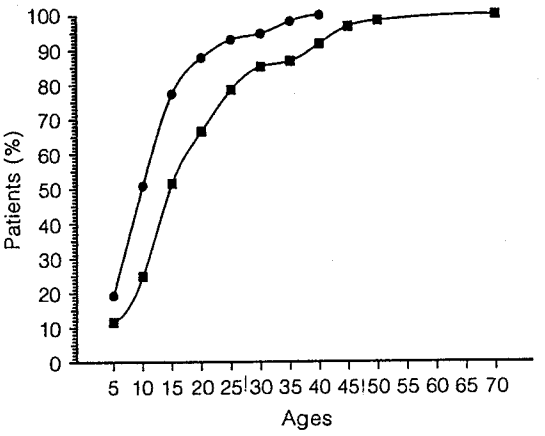

Fig. 1. The cumulative frequency distribution curve for age at first symptoms *(closed circles)* and age at diagnosis *(closed squares)* amongst symptomatic patients with Becker muscular dystrophy (BMD)

Table 1. Presenting symptoms experienced by the group of patients who are symptomatic. Some patients reported more than one symptom simultaneously

Symptom	No. of patients	%
Calf pains	22	27.5
Falling	13	16.3
Slower than peers	12	15.0
Problems on stairs	10	12.5
Waddling gait	8	10.0
Toe-walking	7	8.8
Late walking	3	3.8
Problems with heavy work	2	2.5
Myoglobinuria	2	2.5
Muscle wasting	1	1.3

first symptoms and age at diagnosis (Fig. 1) show that nearly 50% of patients were experiencing problems by the age of 10, and nearly 90% by the age of 20, whereas only 50% of patients had been diagnosed by the age of 15 and 90% by the age of 35. The mean age at diagnosis of muscle disease was 17.7 years, though in some cases the realisation that the muscle disease was BMD came much later.

Presenting symtoms

Ten different presenting symptoms were reported alone or in combination (Table 1). The commonest was calf pain, typically experienced in the early teenage years, provoked by exercise and relieved by rest. Such pains were experienced in 51 patients at some stage of their disease (80.9%). These pains often preceded any other symptoms by several years and were not brought to medical attention until other problems supervened, or were dismissed as "growing pains". In 2 patients the cramps were of an unusually severe degree and in fact the only symptom for many years. The diagnosis was made only following the dystrophin examination of their muscle biopsies. One of these patients had also experienced myoglobinuria and had been extensively investigated for a metabolic myopathy (D. Turnbull, L. Bindoff, personal communication). Myoglobinuria had also been the presenting complaint in a young boy with a strong family history of BMD, none of whose affected relatives had had a similar problem. One patient had had an episode resembling malignant hyperpyrexia under anaesthetic years before any overt muscle problems.

Patients diagnosed very young tended to present with a predominant picture of developmental delay. In terms of long-term prognosis, early presentation seemed to be correlated with reduced IQ rather than with particularly severe or rapidly progressive disease, as has been observed in DMD [15].

Progression of the problem

Progression of symptoms to the upper limb was first noticed at a mean age of 31.6 years, 20.4 years after the mean age for noticing problems in the lower limbs.

A major milestone for progression of the disease is the age at which independent mobility is lost. Twelve of the 67 patients were wheelchair-bound (18%). The mean age for loss of ability to walk in this group was 37.6 years, range 11–78 years, 26.4 years after the average onset of problems. The patient weelchair-bound at the age of 11 is the brother of a patient wheelchair-bound at the age of 30. Both patients are still alive in their early thirties. This patient was included in our data because both his parents felt that his confinement to a wheelchair had been inappropriately early, and his subsequent progression tends to support this. In many patients the loss of independent ambulation was precipitated by an incidental period of immobility, such as a fracture or surgery.

Most patients had never received any formal physiotherapy or splinting procedures. However, 6 had required Achilles tendon lengthening procedures, 3 before the diagnosis of muscle disease was made. No patients used calipers to prolong independent walking. Only 1 patient had had a Luque procedure for scoliosis, at the age of 18 years.

Amongst the 15 patients with a clinical diagnosis of BMD who had died the mean age at death was 47.3 years, range 23–89 years.

Educational and employment record

Formal IQ results were available for only 6 of the younger boys. Most of them fell into the low average range, with a tendency to a predominantly verbal-performance discrepancy, as is seen in DMD. Six patients had been classed as educationally subnormal. An informal assessment of the intelligence of the remaining patients was made from details of their school performance. Most patients (87.9%) attended or attend a normal mainstream school but 6.8% attended a school for the educationally subnormal, and 3.4% a school for the physically handicapped. One patient was taught at home.

Of the patients who had completed their education 70.5% left school as early as they could, without any qualifications, and only 1 had achieved any higher qualifications. Detailed comparison with a normal school population is difficult because of the wide range of dates at which these patients left school; however, in 1968 40.3% of the 16-year-old population were still in full-time education (the leaving age then was 15), and in 1988, 43% of 16-year-olds had enrolled for post-compulsory education. In 1988, 65.4% of all school-leavers had some basic school leaving qualifications, and 20% had passed higher examinations [11].

Of the 47 patients who had left school, only 3 (6.3%) had never been employed. Two worked in sheltered employment for the disabled following other employment, and 1 had only ever worked on this kind of scheme. One patient is in prison. Most of the older patients had continued working into their forties or fifties, often at surprisingly heavy occupations, and several had served in the armed forces in their twenties, before the diagnosis had been made.

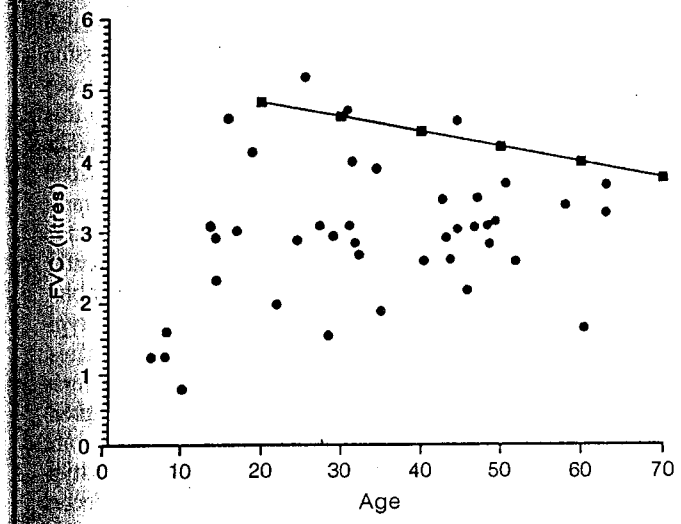

Fig. 2. Scatter plot of forced vital capacity *(FVC)* against age. *Dots* represent BMD patients and *squares* the values from a normal male population [6]

Forced vital capacity

It was possible to measure FVC in 41 patients. The mean value for the whole group was 2.91, range 0.75–5.21. The mean FVC for the patients confined to wheelchairs was 2.51, range 1.6–3.31. A scatter plot of FVC against age is given in Fig. 2, together with the change in FVC with age in a normal population of average height [9]. Comparison between the two shows a general tendency to reduction in the BMD group.

Laboratory investigations

Estimations for serum CK activity were available for 52 patients, the average age at the time of testing being 19.7 years, range 6 months to 52 years. The mean CK for the group was 5,202 IU/l, range 630–35,340 (normal up to 150). A scatter plot of serum CK activity against age illustrates a fall with age, to the extent that an elderly patient presenting late, or being reinvestigated, may have a serum CK level which is lower than usually quoted in BMD (Fig. 3). This documentation of decline of serum CK with age agrees with the data of Zatz et al. [29].

ECGs had been performed on 34 patients, at a mean age of 25.8 years (range 5–88 years). Fourteen (41.2%) were abnormal. The abnormalities seen included incomplete right bundle branch block (9 patients), Q waves in V4–6 and aVF (5 patients), voltage criteria for left ventricular hypertrophy (4 patients), tall R waves in the right chest leads (3 patients) and non-specific T-wave abnormalities (3 patients).

EMG had been performed in 30 patients at a mean age of 26.8 years. All EMGs were reported as abnormal; 20 (66.7%) had been reported a primarily myopathic and 8 (26.6%) as primarily neuropathic. The rest (6.7%) were reported as mixed.

Thirty-five muscle biopsies were reported. The most common abnormalities seen were increased variation in fibre size, a tendency to fibre type grouping, and fibre

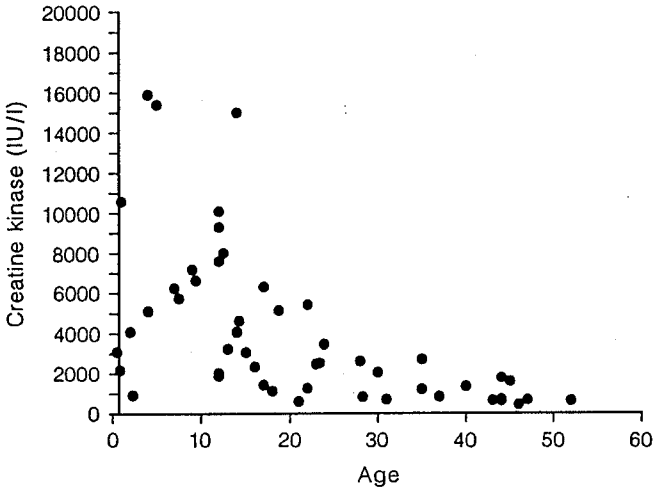

Fig. 3. Scatter plot of serum creatine kinase activity against age. One measurement (CK 35,000 at age 7) is off the scale

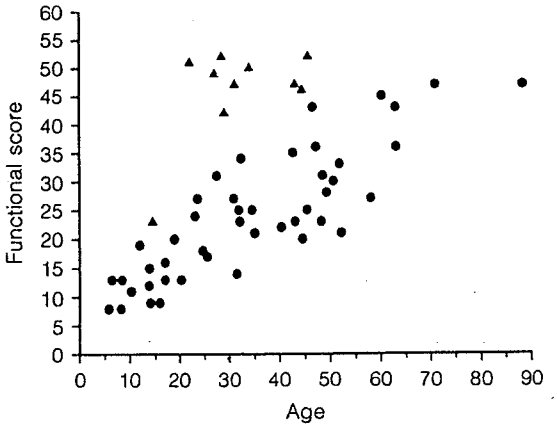

Fig. 4. Scatter plot of functional score against age. Increasing values for functional score indicate increasing disability. Patients allocated to the "severe" group are represented by *closed triangles*

splitting. Though most biopsies were reported as showing primarily myopathic features, features suggestive of a neuropathic process had been questioned in eight biopsies. These findings reflect the observations (made on some of the same patients and biopsies) of Bradley et al. [4] that the features of BMD on EMG and muscle biopsy may be difficult to distinguish from those seen in the spinal muscular atrophies.

Functional and muscle examination

Patients old enough to co-operate were graded according to the scale for functional assessment of Cornelio et al. [8]. Figure 4 shows the functional score plotted against age tested; an increasing functional score indicates increasing disability. Two distinct groups can be identified – a larger one with a relatively slow rate of decline and a smaller group with more severe disease at a younger age. The regression lines of the two groups were significantly different. A similar graph of muscle score plotted against age showed the same pattern (data not shown). Using these clinical criteria, 53 patients

Table 2. Summary of the differences in various clinical parameters between the "typical" and "severe" groups (ESN, educationally subnormal)

	"Typical" group	"Severe" group
No. of patients	53	10
Mean age of onset (years)	12.02	7.7
No. of patients wheelchair bound	4	8
Mean age of becoming wheelchair bound (years)	58.6	25.6
No. of patients with abnormal ECGs	7/26	7/8
Number formally classified as ESN	5	1
Reproductive fitness	0.82	0.06

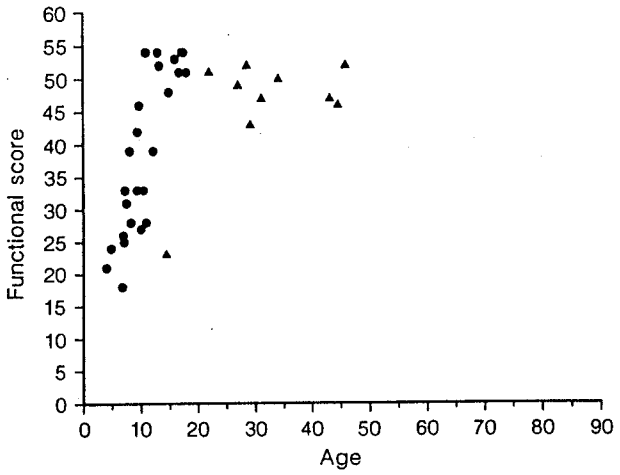

Fig. 5. Functional score of the "severe" BMD group *(closed squares)* plotted on the same scale as a random group of Duchenne muscular dystrophy patients *(closed circles)*

were allocated to the group designated "typical", and 10 to the group designated "severe" (represented by triangles in Fig. 5), including the 14-year-old nephew of three other patients clearly falling into the "severe" group who was markedly more handicapped than any other boy of his age. Four patients were excluded from this clinical categorisation because they were too young to be tested reliably, 1 of whom is the 6-month-old grandson of a patient in the "severe" group. The rest were relatives of patients in the "typical" group.

The salient clinical differences between the two groups are summarised in Table 2. Although progression was markedly swifter in the "severe" group, there was no consistent indicator in early childhood to suggest that the disease was going to be particularly severe. The mean age of onset was younger but there was a broad overlap with the cases in the "typical" group. The most striking divergence from the "typical" course seemed to occur in the early teens; for example all patients in the "severe" group had considerable difficulty in climbing stairs by the age of 20, while most patients in the "typical" group were still climbing stairs into their forties. One patient from the "severe" group, age 41 years, was in congestive cardiac failure, with an echocardiogram consistent with dilated cardiomyopathy. No symptoms or signs of cardiomyopathy were seen in any of the "typical" group. However, the maternal uncle of 3 affected boys in this group had died suddenly having developed a cardiomyopathy at the age of 35, though his muscle symptoms at that stage were relatively minor. This pattern of occasional catastrophic cardiac involvement in otherwise mild BMD has been reported by others [3, 25].

The clinical course in the patients in the "severe" group tended to be more varied than in the "typical" group. Each family in this group had an appreciably different clinical course, and one pair of brothers (mentioned previously) differed quite markedly one from the other. However, all patients in the severe group had a relatively slower initial progression of disease than that seen in DMD, and their functional performance was better than in a random group of DMD patients assessed using the same scale (Fig. 5). Similarly, survival in this group was much better than in DMD, with the mean age of the patients in the "severe" group being 32 at the time of the study (though 1 has since died at the age of 44). Patients in this group tended to develop more severe contractures, scoliosis and ECG changes than even the oldest and most disabled patients in the "typical" group, but again, later and to a less severe extent than in DMD.

Reproductive fitness

Table 3 illustrates the very low level of relative reproductive fitness in the "severe" group, but a much higher level in the "typical" group.

Table 3. Reproductive fitness in patients with Becker muscular dystrophy (BMD). Relative reproductive fitness was calculated by comparing the number of offspring born to BMD patients over the age of 20 with the offspring born to their unaffected brothers of a similar age

	No. of patients	No. of offspring	No. of unaffected brothers	No. of offspring	Fitness
Severe BMD	9	1	8	14	$\frac{1/9}{14/8} = 0.06$
Typical BMD (sporadic)	22	33	12	22	$\frac{33/22}{22/12} = 0.82$
Typical BMD (familial and brother pairs)	12	12	10	13	$\frac{12/12}{13/10} = 0.77$
Total BMD	43	46	30	49	$\frac{46/43}{49/30} = 0.66$

Discussion

Dystrophin and DNA deletion studies have made it possible to include in this study sporadic cases in whom the diagnosis of BMD could not otherwise have been confirmed. This, together with the historical and demographic advantages of the Northern Region of England for ascertaining cases of muscular dystrophy has made it possible to establish that the prevalence (2.38/100,000) and incidence (5.42/100,000) of the disease are much higher than had previously been reported [6].

The collection of data on such a large cohort of patients with proven BMD has also allowed the natural history of BMD to be more clearly established. Most patients with BMD follow a relatively mild clinical course, which is fairly predictable. The division of our group into "typical" and "severe" categories was not intended to subdivide the Xp21 dystrophies artificially yet again at a time when the discoveries in the genetic and protein fields ought to be encouraging a reapparaisal of these diseases as part of a continuous spectrum of disease severity, but the distinction between the "typical" and more severe disease does appear to be clinically valid.

While there was some variation between members of particular families, no family was seen in whom some members fell into the "typical" category and others the "severe" group. There was one family represented in this group where one brother had "severe" BMD (wheelchair-bound aged 30) while his brother had been wheelchair-bound at the age of 11, thus fulfilling the definition of DMD, though some features of his early management may have caused him to become wheelchair-bound earlier than usual, leading to his inclusion here. A clear tendency for problems to be detected earlier in the second generation of an affected family than in the original case was seen, but the subsequent progression of the younger family members suggests that this was more related to watchfullness on the part of concerned relatives than to more severe disease. Becker [1] also noted that relatives of patients were often the first to recognise the early signs of the disease in a young child.

The striking difference in reproductive fitness between the two groups probably reflects the degree of early disability in the more severely affected patients. The fitness in the "typical" group is higher than previous estimates for BMD [12, 23], but the overall figure for the two groups corresponds almost exactly to that calculated by Emery and Skinner [12]. This suggests that the very low level obtained by Passos-Bueno and Zatz [23] might have been biased towards patients at the more severe end of the spectrum. Both estimates considered familial cases only. However, we found no difference in reproductive fitness between familial and sporadic cases. The reproductive fitness together with our figures for the incidence of BMD and DMD [6, 16] can be applied to Haldane's formula, to show that the mutation rate in BMD is 0.61×10^{-5} and for the DMD/BMD gene as a whole is 2.63×10^{-5}.

Although most problems in BMD occur in adult life, a significant proportion of patients in both the "severe" and "typical" groups do experience problems during childhood in both physical and intellectual performance despite the mean age at onset being 11.2 years. Physical underachievement, as shown by poor performance at school sport and a perceived peak of physical performance at the age of 12, is paralleled by the consistently poor academic achievement in the group. Other studies have also suggested a tendency to reduced intellectual performance in association with BMD [1, 12, 20, 30]. Such problems ought to be anticipated when a diagnosis of BMD is made early, as schools are unlikely to have any idea of the potential impact of this disease on teenage boys in whom the symptoms at this stage are most often minimal. Career guidance is another area of support which is important to these patients.

The presenting symptoms reported amongst our patients were varied, but emphasised the importance of cramping muscle pains as a prominent problem in BMD (experienced by 81% of our patients at some stage of the disease). These pains were often more disabling than any actual weakness in the teenage years, and can indeed be the predominant symptom for many years, a finding also reported by others [13, 17]. The recognition of major cramps as a sometimes isolated symptom of BMD extends the range of phenotypes associated with the Xp21 dystrophies.

In conclusion, our studies on a large group of BMD patients show that, though significant problems may be encountered in childhood, the disease in the majority is relatively mild, and most patients remain ambulant into their forties and often beyond. A smaller group has more rapidly progressive disease, with more pronounced complications. The relationship of this clinical observation to the genetic and dystrophin abnormalities in our patients is explored in the accompanying report [7].

Acknowledgements. We thank all the patients who participated in this study, and their clinicians, especially Dr. P. Hudgson. J. Welch performed the psychological assessment, and D. Mantle the creatine kinase estimations, both at the Regional Neurological Centre, Newcastle upon Tyne. Pauline Battista provided expert secretarial support. This work was supported by the Medical Research Council and the Muscular Dystrophy Group of Britain. K.M.D.B. is an MRC Research Training Fellow.

References

1. Becker PE (1962) Two new families of benign sex-linked recessive muscular dystrophy. Rev Can Biol 21:551–566
2. Becker PE, Keiner F (1955) Eine neue X-chromosomale Muskeldystrophie. Arch Psychiatr Nervenkrank 193:427–448
3. Borgeat A, Goy JJ, Sigwart U (1987) Acute pulmonary oedema as the inaugural symptom of BMD in a 19 year old patient. Clin Cardiol 10:127–129
4. Bradley WG, Jones MZ, Mussini JM, Fawcett PRW (1978) Becker-type muscular dystrophy. Muscle Nerve 1:111–132
5. Brooke MH, Fenichel GM, Griggs RC, et al (1983) Clinical investigation in Duchenne Dystrophy. II. Determination of the "power" of therapeutic trials based on the natural history. Muscle Nerve 6:91–103
6. Bushby KMD, Thambyayah M, Gardner-Medwin D (1991) Prevalence and incidence of Becker muscular dystrophy. Lancet 337:1022–1024
7. Bushby KMD, Gardner-Medwin D, Nicholson LVB, Johnson MA, Haggerty ID, Cleghorn NJ, Harris JB, Bhattacharya SS

(1992) The clinical, genetic and dystrophin characteristics of Becker muscular dystrophy. II. Correlation of phenotype with genetic and protein abnormalities. J Neurol 240:105–112
8. Cornelio F, Dworzak F, Morendi L, et al (1982) Functional evaluation of Duchenne muscular dystrophy: proposal for a protocol. Ital J Neurol Sci 3:323–330
9. Crapo RO, Morris AH, Gardner RM (1981) Reference spirometric values using techniques and equipment that meets ATS recommendations. Am Rev Respir Dis 123:659–664
10. Dreifuss RE, Hogan GR (1961) Survival in X-chromosomal muscular dystrophy. Neurology 11:734–737
11. Education statistics for the United Kingdom 1969 and 1989. Government Statistical Service, HMSO
12. Emery AEH, Skinner R (1976) Clinical studies in benign (Becker type) X-linked muscular dystrophy. Clin Genet 10: 189–201
13. Fischbeck KH (1991) Mild myopathic syndromes. In: Angelini C, Danieli GA, Fontanari D (eds) Muscular dystrophy research: from molecular diagnosis toward therapy. (Excerpta medica international congress ser 934) Excerpta Medica, Amsterdam, pp 61–69
14. Gardner-Medwin D (1980) Clinical features and classification of the muscular dystrophies. Br Med Bull 36:109–115
15. Gardner-Medwin D (1982) The natural history of Duchenne muscular dystrophy. In: Wise G, Blair MRL, Procopis P (eds) Topics in child neurology, vol 2. MTP Press, Boston, pp 17–29
16. Gardner-Medwin D, Sharples P (1989) Some studies of the Duchenne and autosomal recessive types of muscular dystrophy. Brain Dev 2:91–97
17. Gospe SM, Lozaro RP, Lava NS, et al (1989) Familial X-linked myalgia and cramps: a non-progressive myopathy associated with a deletion in the dystrophin gene. Neurology 39: 1277–1280
18. Guarantors of Brain (eds) (1986) Aids to the examination of the peripheral nervous system. Baillière Tindall, Paris
19. Hoffmann EP, Brown RH Jr, Kunkel LM (1987) Dystrophin: the protein product of the Duchenne muscular dystrophy locus. Cell 51:919–928
20. Karagan NJ, Sorenson JP (1981) Intellectual functioning in non-Duchenne muscular dystrophy. Neurology 31:448–452
21. Koenig M, Hoffman EP, Bertelson CJ, et al (1987) Complete cloning of the Duchenne Muscular Dystrophy (DMD) cDNA and preliminary genomic organisation of the DMD gene in normal and affected individuals. Cell 50:509–517
22. Markland ON, North RR, D'Agostino AN, Daly DD (1969) Benign sex-linked muscular dystrophy. Neurology 19:617–632
23. Passos-Bueno MB, Zatz M (1991) Reproductive fitness and frequency of new mutations in Becker muscular dystrophy: implications for genetic risk estimates. J Med Genet 28:286–288
24. Ringel SP, Caroll JE, Schold SC (1977) The spectrum of mild X-linked muscular dystrophy. Arch Neurol 34:408–416
25. Sakata C, Yomada H, Sunohara N (1990) Cardiomyopathy in Becker muscular dystrophy. Rinsho-Shineigateu 30:952–955
26. Shaw RF, Dreifuss FE (1969) Mild and severe forms of X-linked muscular dystrophy. Arch Neurol 20:451–460
27. Wechsler D (1974) Manual for the Wechsler Intelligence Scale for children – revised. The Psychological Corporation, New York
28. Worton RG (1988) Genetics of Duchenne muscular dystrophy. Annu Rev Genet 22:601–629
29. Zatz M, Rapaport D, Vainzof M, et al (1991) Serum creatine kinase (CK) and pyruvate kinase (PK) activities in Duchenne and Becker muscular dystrophy. J Neurol Sci 102:190–196
30. Zellweger H, Hanson JW (1967) Slowly progressive X-linked recessive muscular dystrophy (type IIIB). Arch Intern Med 120:525–535