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The natural history of Duchenne muscular dystrophy. Analysis of data from a Dutch survey and review of age related events

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Abstract - We collected data on 473 Dutch Duchenne muscular dystrophy patients born and diagnosed during 1961-1982. Life-time events were analysed for birth years 1961-1974 to avoid possible effects of downward bias of age at diagnosis resulting from inclusion of birth years 1975-1982. Mean and median in certain DMD patients were calculated for, age at onset: 2.4 and 2.0 years (range 0.5-7 years), age at first walking: 1.8 and 1.7 years (range 0.8-4.5 years), age at diagnosis: 5.3 and 5.0 years (range 0-10 years), diagnostic delay: 3.1 and 2.7 years (range 0-9.5 years), chairbound age: 9.5 and 9.0 years (range 6-12 years) and age at death: 16.7 and 16.8 years (range 3.1-21.3 years). There was a significant ($P<0.001$) downward trend in age at diagnosis and diagnostic delay during 1961-1974. Age at diagnosis is significantly ($P<0.01$) lower in boys with a retarded development (4.6 years) compared to boys presenting with locomotor problems (5.8 years). Initial locomotor problems were found in 47.6% of cases. Coincidental presymptomatic diagnosis was found in 3 cases (1.1%) by elevated creatine kinase or transaminase activities. Presymptomatic diagnosis because of family history was made in 1.5% of cases. Respiratory insufficiency (25.6%), pulmonary infections (18.6%) and cardiac complications (30.2%) were the main causes of death. Median survival was 19.4 years (95%CI 19.0-19.8 years; follow-up 1961-1985) for patients who had reached an age of 10 years or more and 23.6% of patients survived at least 23.3 years. Age of loss at ambulation was correlated positively with survival. On average deceased patients died 7.9 years after becoming chairridden (range 2.6-12.4 years). In 23 unrelated sib pairs median age at diagnosis in the second affected boy was significantly ($P=0.006$) lower (5.0 years) than in the first affected boy (6.0 years). No significant difference was found in the distributions of life-time events between 376 patients classified as certain DMD and 97 patients classified as probable or possible DMD, exept for shorter survival in possible DMD patients.
Previous reports on life-time events in DMD did not correct their results for incomplete ascertainment of cases in recent birth years and for limited follow-up of the patients. This may have lowered the estimates

of age related events. Our observation of a fall in age at diagnosis and diagnostic delay in a cohort with high ascertainment is noteworthy. Suggestions that a standing regime n, scoliosis surgery and treatment of pulmonary and cardiac complications prolong the life-span of DMD patients need further evaluation.

Key words: Duchenne muscular dystrophy, diagnostic delay, death, survival

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Introduction

Duchenne muscular dystrophy (DMD) is a progressive crippling X-linked recessive disease, with an estimated prevalence at birth of 1:3500 male live births.[1] DMD may present with delay in reaching motor milestones. Subsequently, increasing proximal muscle weakness causes progressive locomotor difficulties. About 50% of boys with DMD start walking after 18 months.[2]

DMD can be detected shortly after birth by determination of serum creatine kinase (CK) activity. But diagnosis is mostly made between 3 and 8 years. Walking becomes impossible before the age of 13 years.[3] Death usually occurs before 25 years. Respiratory infections and insufficiency and cardiac failure are the main causes of death.[4,5]

Serum CK activities are 50-100 times higher in patients than the upper normal limit in unaffected young children. The muscle biopsy shows characteristic dystrophic changes. DNA-analysis reveals gross rearrangements in the dystrophin gene in 65% of DMD patients.[6,7] Dystrophin immunocytochemistry and immunoblotting show absent dystrophin staining and dystrophin levels below 3% of normal values.[8]

Several reports give estimates of ages at life-time events in DMD.[9] However, the patients analysed in these studies, were not randomly drawn from the population, but selectively included patients refe rred to specialized clinics. Furthermore, follow-up information was often not complete on all patients. Therefore, biases may have been introduced. Before age related events can be analysed all patients from a certain birth year cohort need to be diagnosed. Patients from recent birth years represent a biased sample as they were diagnosed early. Inclusion of patients from more recent birth years also lowers estimates of age at death, because there is a selection for early deaths. In order to evaluate the possible effects of such biases, we compared estimates of age at onset, diagnosis, first walking, loss of ambulation, death and survival in all Dutch DMD patients born during 1961-1974 with those born during 1961-1982. We also compared our results with estimates from other studies.

Material and methods

Cohort definition and methods for case finding, diagnostic scoring and estimating ascertainment rate have been published previously and are briefly summarized here.[10]

Cohort definition and follow-up

Our survey aimed at the inclusion of all DMD patients born and diagnosed in the period 1961-1982 and all registered living DMD patients on January 1, 1983 in The Netherlands. Administrative follow-up data were available through the town clerk's offices of the municipalities where the patients were living until February 1985.

Case finding

DMD patients were identified through: (1) An inquiry among 698 neurologists, (2) 567 pediatricians, and (3) 168 rehabilitation physicians, together comprising more than 95% of all specialists in these fields; (4) the Dutch Muscular Dystrophy Association; (5) the National Medical Registration, which registers hospital admissions, (6) the Central Bureau of Statistics, which registers causes of death and (7) DMD patients from the department of Medical Genetics in Groningen. This survey identified 496 DMD patients.

Diagnostic scoring

Evaluation of diagnoses was based on chart review or information from the attending physician. A score was given for the: a. *Clinical picture*. A typical clinical picture with (psycho)motor retardation, progressive muscle weakness starting in the hip and shoulder girdle, pseudohypertrophy of calves and inability to walk independently before the age of 15 years gave a maximum score of 4 points. If the patient was not wheelchair bound, or if this information was lacking, 3 points were given if the other clinical information was convincing. Two points were given if the patient had progressive proximal muscular weakness and little other specific information was given. One point was given for patients with progressive proximal muscular weakness and no other clinical information. Patients who still walked independently after 15 years of age were assigned as Becker muscular dystrophy.[11] b. *Creatine kinase*. Serum CK activities gave a maximum score of 4 points with levels higher than 10 times the normal value; 3 points were given for levels between 7 and 10 times the normal value; 2 points for values between 4 and 7 the normal value or for the statement of the physician that the CK activities were very high; 1 point for values between 2 and 4 times the normal value. If the normal value of the CK could not be traced, we used an upper value of normal of 60 U/l, being 10 units above the median value of all available upper limits of normal values. The score for CK activities was weighed against the age at which the determination was done. c. *Electromyogram*. A myopathic EMG gave a maximum score of 1 point. d. *Muscle biopsy*. The score for the muscle biopsy was 4 when it was stated to be completely compatible with DMD. A score of 3 points was given when the biopsy showed severe dystrophic changes with little regeneration which was considered slightly atypical by the neurologist. Two points were given when the biopsy finding fitted DMD but also some atypical features were found. If the muscle biopsy showed only slight myopathic changes 1 point was given. e. *Electrocardiogram*. An ECG typical for DMD scored 1 point when present. This score was very rarely used. f. *Inheritance*. X-linked familial occurrence was scored between 0 and 4 points. Definite X-linked inheritance gave a maximum score. Affected sibs without other affected relatives in maternal line gave a 2 point score. Raised CK activities in the mother and sister(s) gave 3 points. Slightly raised CK activities in the mother or sisters gave 1 point. Missing data, or inconclusive test results were scored zero.

With a total score from 0 - 3 points a patient was scored as possible DMD, from 4 - 7 points a patient was scored as probable DMD and from 8 points on a patient was considered as a definite case of DMD. When the patient had scored 8 points but a muscle biopsy or CK activities were not available to us, a positive score for X-linked inheritance was needed to consider the diagnosis as definite, otherwise the patient was considered having probable DMD. Patients in whom the available information raised serious doubts about the diagnosis were assigned as not having DMD.

Our survey was done in 1983-1984 and concerned patients born during 1961-1982, therefore DNA and dystrophin analysis were not used for confirmation of diagnosis at that time. Subsequently DNA-analysis was done in 57 of these patients in our Department after 1983. The diagnostic score for the

patients in whom a dystrophin gene mutation was found was uprated when possible. The DMD birth prevalence rate in an Italian sample remained unchanged after DNA and dystrophin analysis.[12]

Five girls with DMD-like muscular dystrophy were reported during the study period. Autosomal recessive inheritance was considered likely in these patients. This means we might also have included about 5 boys with autosomal recessive DMD-like muscular dystrophy, which causes a slight over ascertainment of about 1%.[10] Application of strict clinical criteria make inclusion of Becker muscular dystrophy unlikely.[13]

Originally, maximum age at becoming chairridden was set at 15 years[11] and 496 DMD patients were identified. For this study, the upper limit for age at loss of ambulation was set at 12 years according to current diagnostic criteria.[3] Subsequently, 473 patients were classified as possible (32), probable (65) or certain (376) DMD.

Selection of cohort for analysis of main events

As shown earlier estimated ascertainment, using several methods, was more than 95% for Dutch DMD patients born in the period 1961-1974.[10] We therefore decided to restrict the analysis of life-time events to patients born in this period.

Figure 1. shows the mean age at diagnosis according to year of birth. There is a steep decline in age at diagnosis after 1974. However, also for birth years 1961-1974 the decline is significant. As the latest age at diagnosis was 12 years in this data-set, we considered to restrict the analysis to birth years 1961-1971. However, the downward trend in age at diagnosis remained significant for these birth years and a diagnosis at 12 years is very rare. We therefore decided to stick to the original choice for birth cohort 1961-1974. We compared our figures from birth years 1961-1974 with data from the biased birth year cohort 1961-1982 and with data from the literature.

It is possible that some boys die before the diagnosis of DMD is established.[14-16] To minimize effects of this selection, the survival analysis was carried out with patients born during 1961-1974, who attained minimum age of 10 years.

Statistical analysis

All results refer to patients classified as certain DMD who were born and diagnosed during 1961-1974, unless this is specified otherwise. The number of patients for the analysed parameters refers only to those patients for whom this information was available. Patients for whom information on the analysed age related event was missing were not counted.

To summarize data on age at onset, diagnosis, first walking, loss of ambulation, death and survival we calculated means, standard deviations, medians and percentiles. Linear regression analysis was done to test whether the downward trend in age at diagnosis during the birth years 1961-1982 was significant. The Wilcoxon rank sum test was used to test whether variables in the first and second born sib in a family have the same distribution. The Mann-Whitney U test was used for comparing mean age at diagnosis in boys with retarded development and boys with locomotor problems and age at life-time events in patients with certain DMD versus those with probable or possible DMD. For evaluation of survival, the standard survival analysis methods were used with the attained age as the survival time. These methods included Kaplan-Meier curves and Cox-model regression for investigation of possible relations between patient characteristics and patient survival. In order to investigate the relation of age at loss of ambulation on survival, this age was entered in the Cox regression analysis as a time dependent covariate. The statistical tests were carried out at a 5% level of significance.

Results

Table 1. summarizes data on main events in DMD in our series and in other studies. In our data-set we compared data from patients with certain DMD and all patients with DMD (certain, probable and possible DMD), born during 1961-1974, which represent the 'unbiased' samples, with the biased group born during 1961-1982. No significant difference was found in the distribution of life-time events between 376 patients classified as certain DMD and 97 patients classified as probable or possible DMD, exept for shorter survival in possible DMD patients. All mean values for the different variables in our study were slightly lower in the biased group. Mean age at first walking was 0.5 year later than in 2 other studies. Diagnostic delay (time between age at onset and age at diagnosis) in our study lies in the upper range of what other studies have reported. However, there is a significant downward trend in age at diagnosis during 1961-1974 with a concomitant fall in diagnostic delay. All other variables fell within the range of mean and median values reported in other studies. Age at diagnosis is significantly lower ($P < 0.01$) in 113 boys with a retarded development (4.6 years) compared to 120 boys presenting with locomotor problems (5.8 years).

Four boys died at or before 10 years. The causes of death in these 4 boys were: cardiac arrest during anaesthesia (2), unspecified cardiac complication (1), pneumonia (1), and respiratory insufficiency (1). On average death ensued 8 years after becoming chairridden (range 2.6-12.4 years).

Patients (n=366) born during 1961-1974 and who lived 10 years or longer had a median survival of 19.0 years (95%CI 18.4-19.7 years); the first quartile was 16.6 years, the third quartile was 21.3 years. Median survival was unaffected by inclusion of 4 patients who were younger than 10 years at the end of follow-up. Patients classified as certain DMD (n=287) had a median survival of 19.4 years (95%CI 19.0-19.8 years), for "probable DMD" patients this was 18.8 years (95%CI 17.5-19.5) and for "possible DMD" patients 16.6 years (95%CI 15.9-17.1 years), the latter median being significantly ($P<0.01$) lower than that for "certain DMD" patients. Further analysis was restricted to the group of "certain DMD" patients. 23.6% of patients survived until 23.3 years (Figure 2). The age at becoming chairbound was significantly positively correlated with survival ($P<0.01$). Relative risk of death associated with becoming one year earlier chairbound was estimated as 1.22 (95%CI 1.09-1.36). Patients who lost the ability to walk before 10 years had a

Table 1. Estimates of mean age at life-time events in our study and in other studies with at least 30 informative DMD patients.

Reference	number of cases	mean (years)	sd (years)	median (years)	range (years)
Age at onset					
all DMD					
this study 1961-1974 [1, 2]	203	2.5	1.4	2.0	0.5-7.0
this study 1961-1982 [1, 3]	378	2.4	1.4	2.0	0.2-7.0
certain DMD					
this study 1961-1974 [2, 4]	175	2.4	1.4	2.0	0.5-7.0
this study 1961-1982 [3, 4]	225	2.3	1.4	2.0	0.5-7.0
52	31	1.4			0.9-2.0

Reference	number of cases	mean (years)	sd (years)	median (years)	range (years)
22	46	2.3			0.7-5.5
77	483	2.3	1.5		
78	144	2.6			
79	70	2.9	1.5		
80	88	2.9	1.3		
81	41	3.1	2.2		
27	64	3.1	1.8		
82	100	3.2	1.7		
83	58	3.3	1.8		
9	144	3.3	1.7		
58	675	3.6	1.7		1-10
84	105	3.7	1.9		
85	46	3.8	2.2		
Age at first walking					
all DMD					
this study 1961-1974 [2]	244	1.9	0.6	1.7	0.8-4.5
this study 1961-1982 [3]	306	1.8	0.6	1.7	0.8-4.5
certain DMD					
this study 1961-1974 [2]	215	1.8	0.6	1.7	0.8-4.5
this study 1961-1982 [3]	276	1.8	0.6	1.7	0.8-4.5
52	31	1.4			0.9-2
22	57	1.4			
Age at diagnosis					
all DMD					
this study 1961-1974 [2]	305	5.3	2.2	5.0	0-12
this study 1961-1982 [3]	378	4.9	2.4	5.0	0-12
certain DMD					
this study 1961-1974 [2]	270	5.3	2.2	5.0	1-10
this study 1961-1982 [3]	342	4.8	2.3	5.0	0-10
Age at diagnosis					
22	55			4.3	1.8-9.3
20	51	4.5			0.3-8.5
54	33	4.6	2.4		
52	31	4.7			2.0-8.0
24	36	4.9			
42	93	5.2			1.5-9
2	130	5.8			
Diagnostic delay					
all DMD					
this study 1961-1974 [2, 5]	195	3.2	2.2	3.0	0-9.5
this study 1961-1982 [3, 5]	266	2.8	2.2	2.5	0-9.5
Certain DMD					

Reference	number of cases	mean (years)	sd (years)	median (years)	range (years)
this study 1961-1974 [2, 5]	191	3.1	2.2	3.0	0-9.5
this study 1961-1982 [3, 5]	216	2.7	2.2	2.5	0-9.5
53	152	1.9			
42	93	2.0			0-6
22	44	2.2			0.3-5.7
18	69	2.5			
52	31	3.0			1.5-5.5
Age at loss of ambulation					
all DMD					
this study 1961-1974 [2]	272	9.5	1.5	9.0	6-12
this study 1961-1982 [3]	286	9.4	1.5	9.0	6-12
certain DMD					
this study 1961-1974 [2]	232	9.5	1.4	9.0	6-12
this study 1961-1982 [3]	245	9.4	1.4	9.0	6-12
27	56	9.1	2.0		
79	47	9.3	1.9		
81	42	9.4	2.6		
9	120	9.4	1.7	8.5	
78	86	9.5			
83	55	9.6	1.8		
80	83	9.8	1.5		
58	96	9.8	2.1		5-16
86	49	9.9	1.6		
77	234	10.1	1.9		
54	31	10.3	2.3		
84	128	10.8	1.9		

Reference	number of cases	mean (years)	sd (years)	median (years)	range (years)
Age at death					
all DMD					
this study 1961-1974 [6]	139	16.4	3.1	16.7	3.1-23.1
certain DMD					
this study 1961-1974 [6]	91	16.7	2.9	16.8	3.1-21.3
81	40	14.7	3.8		8-23
9	129	16.3	3.1		8-25
86	59	16.6	2.3		12-21
80	47	17.8	3.2		11-29
84	65	18.0	2.9		
77	58	18.1	3.3		
58	88	19.5	3.6		11-27
4 1970-1974	63	17.8	3.7		10-29

1970-1984	176	18.3	3.6		10-29
1980-1984	48	20.0	3.9		14-28
66 1966-1970	33	15.8	2.5		
1971-1974	92	18.7	3.8		
1975-1979	126	19.4	3.5		
1980-1983	134	19.9	3.8		
Survival					
all DMD					
this study 1961-1974 (≥10 years)[7]	366	19.1		19.0	10-24
this study 1961-1974 (no age limit)[8]	370	18.9		19.0	3.1-24
certain DMD					
this study 1961-1974 (≥10 years)[7]	287	19.2		19.4	10-23.3
this study 1961-1974 (no age limit)[8]	289	19.1		19.4	3.1-23.3
54	33			22.5	0-25
58	675			22.5	7.0-27.0

[1] Excluding 34 boys with an age at onset before 1 year for whom no precise age at onset was given. When these boys are included with an age at onset of 6 months 237 cases give: mean 2.2 years (sd 1.5), median 2.0

[2] Patients born during 1961-1974

[3] Patients born during 1961-1982

[4] Excluding 30 boys with an age at onset before 1 year for whom no precise age at onset was given. When these boys are included with an age at onset of 6 months 205 cases give: mean 2.1 years (sd 1.4), median 2.0

[5] Excluding negative values caused by presymptomatic diagnosis

[6] Patients born during 1961-1974 with follow-up until 01-02-1985. Values remain unchanged in the 1961-1982 birth years interval as no additional deaths occurred in patients born after 1974.

[7] Patients born during 1961-1974 with follow-up until 01-02-1985 and an attained age of 10 years or more.

[8] Patients born during 1961-1974 with follow-up until 01-02-1985 and no minimum age for inclusion.

median survival of 17.3 years (95%CI 16.7-18.0 years) and those who became chairridden at or after 10 years had a median survival of 20.1 years (95%CI 19.4-20.9 years). Cox regression analysis, adjusting for age at loss of ambulation, showed no effect of the variables age at first walking, familial or non-familial DMD on survival ($P>0.1$). Age at diagnosis has a significant effect on survival ($P<0.01$). When adjusted for age at becoming chairbound this effect disappears. It was not possible to analyse whether life-expectancy has improved during 1961-1983 because the follow-up of patients born after 1974 was too short.

Table 2. shows the presenting symptoms in 265 informative patients born and diagnosed during 1961-1974. Mental retardation was noted in the medical file of 64 patients (16.4%). Complications during anaesthesia were found in 3 patients (malignant hyperthermia 2, cardiac arrest 1).

Table 2. Presenting symptoms in 265 DMD patients born and diagnosed during 1961-1974

symptom	**number of cases**	**percentage**
Abnormal gait	94	35.5

symptom	number of cases	percentage
Delayed motor milestones	84	31.7
Psychomotor retardation	15	5.7
Frequent falls	23	8.7
Late walking	18	6.8
Stairclimbing difficulties	9	3.4
Determination of serum creatine kinase activity because of DMD in family	4	1.5
Muscle weakness	7	2.6
Hypotonia	6	2.3
Raised liver enzymes found accidentally during hospital admission [1]	2	0.8
High serum creatine kinase activity found accidentally during hospital admission [2]	1	0.4
Other [3]	2	0.8
Total	265	100.0

[1] hospitalized for: speech delay (no further information), lymfadenitis colli.

[2] hospitalized for: intoxication and dyspepsia (liver enzymes also raised).

[3] enlarged calves, pain in calves

Table 3. shows age at onset, age at diagnosis and diagnostic delay in 23 unrelated pairs of affected brothers. Each column represents the first and second affected sib in one family. Data of the third affected sib in 2 families and the third and fourth affected sib in 1 family were not included. Median age at diagnosis in the second affected boy was significantly (P=0.006) lower (5.0 years) than in the first affected boy (6.0 years).

Table 4. shows the available causes of death in 43 patients as noted on their death certificates.

DNA-analysis in 57 patients yielded dystrophin gene deletions for 32 (56.1%) and duplications for 2 (3.5%).

Table 3. Birth year, age at onset, age at diagnosis and diagnostic delay in years for 23 pairs of sibs with DMD.

first born sib					second born sib			
birth year	age at onset	age at diagnosis	diagnostic delay (years)		birth year	age at onset	age at diagnosis	diagnostic delay (years)
1962	0.8	5	4.2		1964		7	
1962		2			1966			
1962	0.5 [1]				1969			
1963		8			1964	3.0		
1963					1965	1.3	1	-0.3

first born sib					second born sib			
1963	0.5	9	8.5		1965			
1963	2.0	7	5.0		1969	1.2	1	-0.2
1964		9			1966		7	
1965	5.0	5	0.0		1966	1.5	5	3.5
1965	2.0	6	4.0		1967			
1965		6			1968		7	
1965	1.2	3	1.8		1969	1.5	2	0.5
1966	2.0				1968			
1966		9			1969		5	
1966		7			1968		5	
1966	3.0	6	3.0		1970	0.5	2	1.5
1967	0.5[1]	9	8.9		1969	7.0	7	0.0
1967		8			1970		5	
1969		12			1971	6.5	10	3.5
1969	2.0	5	3.0		1973		1	
1969	2.0	6	4.0		1974		1	
1970		5			1974	2.0	5	3.0
1972	2.5	3	0.5		1974	1.3	1	-0.3

[1] These 2 first born sibs were diagnosed before 12 months but the exact time was unknown. Onset was set at 6 months in these cases .

Table 4. Causes of death in 43 DMD patients as noted on their death certificates.

cause of death	number of cases	percentage
Respiratory insufficiency	11	25.6
Pneumonia	8	18.6
Cardiomyopathy	8	18.6
Cardiac insufficiency	5	11.6
Combination of problems	4	9.3
Other [1]	7	16.3
Total	43	100.0

[1] fever of unknown cause, contusio cerebri, hepatitis A,infection of urinary tract, fracture of femur with fat embolism, viral infection, vetricular tachycardia.

Discussion

Duchenne muscular dystrophy (DMD) is a severe progressive crippling X-linked recessive disease. We estimated the prevalence at birth at 23.7/100,000 (1:4,215) male live births yearly and the point prevalence is 5.4/100,000 (1:18,496) males in The Netherlands.[10]

For various reasons, the diagnosis should be established as early as possible. Among them are: reducing stress for the parents due to long diagnostic delays[17,18] and genetic counselling of the family as soon as possible.[19,20] If an effective therapy emerges in the future, early diagnosis is also important to achieve the best possible results.[21]

Estimation of mean and median age at life-time events in DMD patients is important to evaluate whether diagnosis is made at an earlier age and diagnostic delays have become shorter nowadays and whether prognosis has improved in recent years. There are, however, some problems in trying to estimate such effects. We want to address some of these problems and review the literature on life-time events in DMD.

Bias

Inclusion of patients from recent birth years may give the false impression that age at diagnosis has decreased. Limited follow-up of patients reduces the estimated mean age at death, as the proportion of early deaths is higher. On the other hand, inclusion of late onset cases and cases becoming chairridden after 12 years will increase the estimates of age at main events, meaning that strict diagnostic criteria should be applied. To avoid inclusion of patients with possible other diagnosis we restricted analyses to patients with certain DMD, although we found no significant difference in the distribution of life-time events between 376 patients classified as certain DMD and 97 patients classified as probable or possible DMD, which suggests that most of these 97 patients also had DMD.

We compared analyses of life-time events in the birth years 1961-1974, with the whole group concerning birth years 1961-1982. The restriction of the analyses to birth years 1961-1974 minimizes the bias, which is most clearly illustrated for mean age at diagnosis, which is reduced from 5.3 years for

the unbiased group to 4.8 years for the biased group. However, it did not affect median age at diagnosis, which remained 5.0 years. There is a significant downward trend in age at diagnosis and diagnostic delay during 1961-1974. Thus there seems to be a real trend to diagnose DMD at an earlier age with a concomitant shorter diagnostic delay.

As there were no deaths among patients born after 1974 and followed until 1985, age at death was unaffected by inclusion of recent birth years. Mean age at first walking was 0.5 year later in our study compared to two other studies. The mean age of the other age related events were lowered about 0.1 year in the biased group. The slight reduction of the mean values for life-time events for the biased period can be explained by the fact that the 1961-1974 interval is longer and contains more cases than the bias prone interval 1974-1983. There is, however, a difference of 2.6 years between median age at death of those deceased (16.8 years) and median survival (19.4 years).

Several papers which give estimates for life-time events concern only small groups of selected patients that were followed for a short period of time. This complicates comparisons between these studies especially when it concerns mean age at diagnosis and mean age at death.

Onset and symptoms

Common signs that give the first hint that something is wrong with a boy with DMD are late walking, waddling gait, never being able to run properly, walking unsteadily with a tendency to fall easily, toe walking, difficulty in climbing stairs, muscle weakness, enlarged calves and inability to rise from the floor without using the arms.[9] These signs are usually noted by the parents between 3 to 5 years of age and are reason to consult a doctor. Initial locomotor problems were found in 47.6% in our series, which is comparable to other but smaller studies.[22,23] Although developmental delay is often noted, it is not always recognized as a presenting sign in DMD by the attending physician.

The precise age at onset is difficult to assess. In our series 10% of patients presented before 1 year, 90% presented before 4.2 years and 99% presented before 7 years. Elevated CK or transaminase activities were coincidentally found in 1.1% of our patients, whereas this percentage was 10.5% in another study.[22] Presymptomatic diagnosis because of family history was made in 1.5% in our series and may be as high as 33% in a small series which may have preferentially included familial cases.[24]

Normally on average, children start walking at 13 months and 97% walk at 1.5 years.[25] A delay in starting to walk may be the earliest sign in DMD. We found a mean and median age at first walking of 1.8 and 1.7 years (range 0.8-4.5 years). Previous studies have shown that more than 50% of boys with DMD start walking after 1.5 years.[2,9,22] However, late walking (>18 months) was reported as the presenting symptom in only 6.8% of our patients, but might partly be included in the group with delayed motor milestones (31.7%). The oldest age at first walking in our series was 4.5 years versus 6 years in the series of Gardner-Medwin.[2] One boy in our series had never been able to walk. His brother and two deceased brothers of his mother also had DMD. Dubowitz[26,27] reported a patient who never walked and died at 12 years. He was considered to have a congenital myopathy. However, as described below, DMD may rarely present as a congenital myopathy.[28,29] In the same series, Dubowitz also mentioned two half brothers of whom one lost ambulation at 3.5 years, but his brother walked until 14 years.[26,27] Topaloglu *et al*[30] reported a patient who began walking at 6 years, but already became chairridden 9 months later, without a precipitating event. Muscle power deteriorates rapidly in DMD, even after a short period of immobilisation and quickens inability to walk, even at a very young age.[26,27,31,32]

Pseudohypertrophy of the calf muscles might be found in 97% of patients, when looked for.[9] It was noted in 77.8% of the boys in our study, meaning that this sign was probably underreported. However, determination of its presence or absence is very subjective.

Psychomotor retardation was the presenting sign in the file of 5.7% of the patients in our series. Speech development is often delayed in DMD.[2,24,33] Despite low verbal intelligence quotient (IQ) performance IQ is usually normal.[9,34] The mean IQ in DMD patients is 82 and 19% have an IQ under 70.[9] Cognitive impairment is not progressive.[35,36] Mental retardation was mentioned in the file of 16.4% of our patients, but not validated by formal psychometric testing. The cause of intellectual impairment in DMD is still unknown. There is no apparent relation between intellectual impairment and site or size of the mutation,[37,38] or findings on cranial magnetic resonance imaging.[39]

DMD may present with general muscular hypotonia. In an amyotonia congenita follow-up study 3 of 109 (2.8%) patients had DMD.[40] Dubowitz[26] found hypotonia in 2 of 65 patients (3.1%) and hypotonia was the initial symptom in 6 patients (2.3%) in our study. Diminished fetal movements were noticed by the mother in 7%-12% of cases.[26,41] In the study of Read and Galasko[42] most mothers described their baby as being floppy. Thus, this sign may be a helpful symptom to alert the physician. Rarely, DMD presents as congenital muscular dystrophy[28,29,43] and some patients diagnosed as Fukuyama congenital muscular had dystrophin gene mutations.[44,45]

A less well appreciated early presentation, not reported in our series, is failure to thrive.[46-48] Weight and length may be normal at birth. Slowing of growth is noted before 1.5 years. Normal growth resumes after 3 years. Bone maturation and head circumference are unaffected.

DMD may be associated with anaesthesia-induced complications. These include hyperkalemia, systemic acidosis, rhabdomyolysis, renal failure, malignant hyperthermia and cardiac arrest leading to death[49,50] and may be the first hint to the diagnosis.[51] Anaesthesia related complications were found in 3 patients in our series and preceded other symptoms of DMD in one boy. One boy born in 1981 developed malignant hyperthermia during anaesthesia at 8 months for correction of bilateral cleft lip and palate. The second boy was suspected of having DMD. He died at the age of 3 years during a muscle biopsy under general anaesthesia because of malignant hyperthermia. In the third boy, an uncorrectable cardiac arrest occurred during anaesthesia for correction of equinus deformity of his feet.

Diagnosis

Diagnostic delay in DMD is distressing for parents.[17,18] Moreover, further affected boys may be born when the parents are unaware of the disease in their son.[19,20] Crisp *et al*[52] noted that parents often had difficulties convincing the physicians that something was wrong with their sons. Mean age at diagnosis in their study did not differ whether or not the parents had sought early medical attention. Results from a small study suggested that diagnosis was made earlier in boys with a retarded development than in patients with locomotor problems.[23] We confirmed this finding in our data-set and found a significantly lower mean age at diagnosis in boys with retarded development.

A positive family history does not always reduce age at diagnosis.[9,24] Smith *et al*[24] found a mean age at diagnosis of 5.2 years for first cases and 4.3 years for familial cases. We found a mean age at diagnosis of 6.5 years and 4.2 years in our series of 23 unrelated pairs of first and second born sibs, which is a significant difference (P=0.006).

Reported mean diagnostic delay usually varies between 2 and 3 years (range 0-6 years).[22,42,53] In a survey of 83 families with 93 affected boys, the diagnosis was missed in all 37 cases referred to an orthopaedic surgeon.[42] A positive family history was found in 60 boys from that study,[42] but only 27 mothers of 30 boys were aware of this at the time of conception. Marshall and Galasko[53] observed no improvement in diagnostic delay over the last 20 years for 152 children under the care of the Royal Manchester Children's Hospital. However, as in our study, it was found that diagnosis was established at a younger age during 1953-1983 in a small study of 33 patients followed at the Mayo clinic.[54]

Death

Respiratory insufficiency and chest infections are the most frequent causes of death in DMD.[4,5] In our series 44.2% of patients died from respiratory insufficiency or chest infections and 30.2% from cardiac complications. Boys with stronger muscles are more likely to die from cardiomyopathy, while most weaker boys die from respiratory failure.[55] Severe cardiac disease and lower mean age at death were more frequent in patients with dystrophin gene deletions including exons 48-49 than in other deletions.[56]

For deceased patients born during 1961-1974 we observed a median age at death of 16.8 years. Survival analysis may be more appropriate for estimating the mean and median life-span of DMD patients than age at death of those deceased, as it permits inclusion of follow-up information on all patients, dead or alive. Even patients who have been followed for a short period can contribute information. Thus, there is no bias toward early deaths.[57] Median survival for patients that were born during 1961-1974 and attained a minimum age of 10 years was 19.4 years. We found that age at loss of ambulation and survival were positively correlated. In our series and in other studies it was found that on average death ensues about 8 years after becoming chairridden.[9,58] However, these figures are underestimates as they only refer to deceased patients.

The mean age at loss of mobility in DMD patients with absent dystrophin labelling is significantly lower than in patients who have some labelling.[59,60] This positive relationship was also found for dystrophin abundance and age at becoming chairbound. However, even in patients with no muscle dystrophin, age at loss of ambulation varies from 6-12 years.[61]

Very early death is not a known feature of DMD, however, two studies reported a 3 to 5 times increased rate of male stillbirths and neonatal deaths in DMD families.[14,15] Vosatka *et al*[16] reported pleural effusion in a fetus with DMD. Ultrasound at 28 weeks gestation revealed pleural effusion and polyhydramnios which both resolved at 36 weeks. There was no evidence of lung hypoplasia. Most pleural effusions persist and have a poor outcome, especially when associated with hydrops fetalis. The authors speculate that effusion could be attributable to early cardiac dysfunction, which may eventually lead to pulmonary hypoplasia and early death. Four patients in our series died at or before 10 years, the youngest being 3 years.

There are conflicting opinions on better survival in DMD over the years. Several authors found no significant changes in mortality during different periods of time encompassing 1934-1983,[9] 1953-1983,[54] and 1969-1989.[62] On the other hand, a possible better recent life expectancy of DMD patients has been suggested by several authors as a result of better treatment of infections,[4,63] scoliosis,[55,64,65] special care programs[66,67] or use of respirators in terminal care.[68] However, other studies suggest no beneficial effect of scoliosis surgery on declining respiratory function,[69-72] and no increased life expectancy.[69,71,73]

Conclusions

We found a significant tendency towards a reduction in age at diagnosis and diagnostic delay in children born in the period 1961-1974. Although this is a positive sign, further improvement is still needed. General physicians, pediatricians and orthopaedic surgeons should be trained to recognize possible early symptoms of DMD, like floppiness, delayed motor development and failure to thrive and should determine serum CK activity in these children. Several authors recommend that all boys with developmental delay should be screened for DMD by measuring their serum CK activity.[24,52] Neonatal CK-screening is of course the most effective way to diagnose all cases early and has the highest chance of preventing the birth of further affected children. However, screening should be done on an informed consent basis and with availability of adequate facilities for support of the parents.[74,75] Estimates of the

theoretically avoidable proportion of cases by neonatal screening vary between 8.3%-13%.[2,76]

To evaluate possible changes in age at certain life-time events in DMD in the future, an unbiased sample of patients should be taken in whom strict diagnostic criteria have been applied, and who have been followed long enough.

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Mean age at diagnosis in years
0
1
2
3
4
5
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7
8
61
63
65
67
69
71
73
75
77
79
81
Year of birth


Cum Survival
1,0
,8
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,4
,2
10
12
14
16
18
20
22
24
survival years from birth till death or 1/2/85