Brain (1998), **121,** 1557–1563

Age and causes of death in adult-onset myotonic dystrophy

C. E. M. de Die-Smulders,[1] C. J. Höweler,[2] C. Thijs,[3] J. F. Mirandolle,[4] H. B. Anten,[5] H. J. M. Smeets,[6] K. E. Chandler[1] and J. P. M. Geraedts[6]

Departments of [1]Clinical Genetics and [2]Neurology, Academic Hospital Maastricht, [3]Department of Epidemiology, Maastricht University, [4]Department of Neurology, de Wever Hospital, Heerlen, [5]Department of Neurology, Maasland Hospital, Sittard and [6]Department of Molecular Cell Biology and Genetics, Division of Genetics, Maastricht University, the Netherlands

Correspondence to: Christine de Die-Smulders, MD, Department of Clinical Genetics, PO Box 1475, 6201 BL Maastricht, the Netherlands.
E-mail: christine.dedie@gen.unimaas.nl

Summary

Myotonic dystrophy is a relatively common type of muscular dystrophy, associated with a variety of systemic complications. Long term follow-up is difficult because of the slow progression. The objective of this study was to determine survival, age at death and causes of death in patients with the adult-onset type of myotonic dystrophy. A register of myotonic dystrophy patients was set up in Southern Limburg (the Netherlands), using data longitudinally collected over a 47-year period (1950–97). Survival for 180 patients (from the register) with adult-onset type myotonic dystrophy was established by the Kaplan–Meier method. The median survival was 60 years for males and 59 years for females. Survival of the patients was also estimated from the age of 15 years to the ages of 25, 45 and 65 years and compared with the expected survival of age- and sex-matched birth cohorts from the normal Dutch population. The observed survival to the ages of 25, 45 and 65 years was 99%, 88% and 18% compared with an expected survival of 99%, 95% and 78%, respectively. Thus, survival to the age of 65 in patients with adult-onset myotonic dystrophy is markedly reduced. A weak positive correlation between the CTG repeat length and younger age at death was found in the 13 patients studied (r = 0.50, P = 0.08). The cause of death could be determined in 70 of the 83 deceased patients. Pneumonia and cardiac arrhythmias were the most frequent primary causes of death, each occurring in ~30%, which was far more than expected for the general Dutch population. In addition, we assessed mobility in the years before death in a subgroup of 18 patients, as a reflection of the long-term physical handicap in myotonic dystrophy patients. Half of the patients studied were either partially or totally wheelchair-bound shortly before their death.

Keywords: myotonic dystrophy; age at death; cause of death; mortality; mobility

Abbreviation: DMPK = myotonic dystrophy protein kinase

Introduction

Myotonic dystrophy is an autosomal dominant muscular dystrophy, with a prevalence of 1–10 per 100 000 (Emery, 1991). It is caused by an expanded CTG repeat in the myotonic dystrophy protein kinase (DMPK) gene on the long arm of chromosome 19 (Harley *et al*., 1992). The length of the repeat correlates with the age at onset and the severity of clinical symptoms. Four disease types have been recognized: late onset (mild) type; adult-onset (classical) type; childhood and congenital type (Harley *et al*., 1993). The muscular symptoms are associated with a variety of systemic complications, some of which can be life threatening, e.g. cardiac arrhythmias and aspiration pneumonias (Harper, 1989). The progression of muscle weakness in myotonic dystrophy is usually slow. Initially, only distal limb muscles are involved, but in the later stages the weakness extends more proximally. Owing to the slow progression of the disease, patients may survive for decades after the onset of symptoms. Consequently, prospective studies on the course of myotonic dystrophy are difficult to perform, and to date very little information exists on patients' overall survival and cause of death. The long-term clinical outcome and mortality have only been studied for congenital myotonic dystrophy (Reardon *et al*., 1993). The natural history of adult-onset myotonic dystrophy has not been

studied. Only data on mean age at death for all disease types combined have been reported in older studies (Bell, 1948; Thomasen, 1948; Klein, 1958; Grimm, 1975).

Our study aimed to determine the long-term prognosis of patients with adult-onset type myotonic dystrophy. We conducted a follow-up study by combining data collected by two generations of neurologists with a special interest in myotonic dystrophy. The age and causes of death were retrieved from the patients' records and a survival analysis performed. In order to get an impression of the physical handicap in the years preceding death, mobility was assessed in a subgroup of patients.

Patients and methods

The population of patients for this study was selected from the register of myotonic dystrophy families in Southern Limburg. This region is a geographically isolated part of the Netherlands, bordered by Germany and Belgium. Ascertainment of complete families and follow-up of patients is relatively straightforward because of limited population migration. Between 1950 and 1970, 85 myotonic dystrophy patients from 15 families living in this area were examined (de Jong, 1955). The collection of data was continued from 1970 by the next generation of neurologists, working in the three regional hospitals in Maastricht, Heerlen and Sittard. After 1987 the series of family records were collated by the Department of Clinical Genetics and a genetic register set up. Data on disease type, major complications, results of DNA examination and genealogical studies were documented.

The register presently contains data on 328 myotonic dystrophy patients from 56 families. For this study patients with the adult-onset type were selected from the register. This type is characterized by an age at onset between 10 and 50 years, myotonia and progressive weakness, and absence of mental retardation (Harley *et al*., 1992). Congenital and childhood-onset cases were excluded because they show a high neonatal and childhood mortality and their prognosis was recently determined (Reardon *et al*., 1993). Patients with mild disease (age at onset >50 years) were not included because their prognosis seems to be much better than that for adult-onset patients. In total, 180 patients with adult-type myotonic dystrophy were selected, of which 83 (47 males and 36 females) were deceased at the time of surveying (January 1997).

The age at death was ascertained by information from family members, medical records or from the registry office. The median and mean ages at death were determined for the whole population ($n = 83$) and for males and females separately. We calculated the mean age at death in order to compare our data with those from previous studies. Survival of the patients was estimated by the Kaplan–Meier method with the attained age as the survival time. Patients still alive at the end of follow-up were censored (in order to include follow-up information of all patients, deceased or still alive). Survival of the patients was also compared with the expected

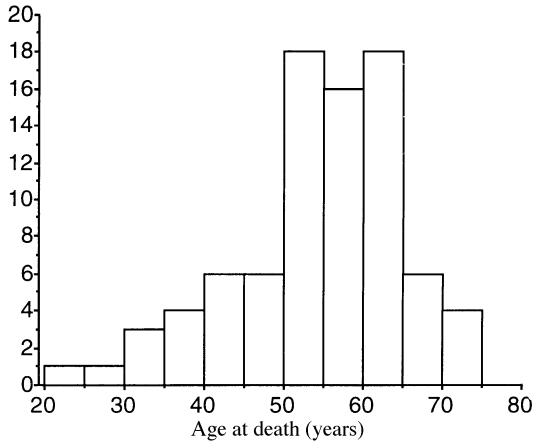

Fig. 1 Age at death ($n = 83$).

survival based on generation-survival tables from the Dutch population 1860–1989 (Tas, 1991). We calculated survival rates of the cohorts at risk from the age of 15 to 25 years (cohort born before 1972), to the age of 45 years (cohort born before 1952) and to the age of 65 years (cohort born before 1932). It was assumed that all patients survived at least to the age of 15 years. The 95% confidence intervals around the observed survival rates were calculated by the exact method using the binomial distribution. Exact *P*-values were also calculated from this distribution.

The primary cause of death was known in 70 patients. Data on cause of death were obtained either from medical records, in the case of death in hospital, or from the general practitioner, in the case of death at home. Causes of death were grouped into two main categories: disease-related causes and causes not related to myotonic dystrophy. Sudden death, arrhythmias, pneumonia and postoperative death are well-known systemic complications of myotonic dystrophy (Aldridge, 1985; Harper, 1989; Mathieu *et al*., 1997). We also considered fractures following a spontaneous fall as a myotonic dystrophy associated complication, as they probably occurred as a result of the muscle weakness. Some patients died following a series of events, e.g. a fracture after a fall, complicated by a fatal pneumonia. In these cases the initial event was recorded as the primary cause of death and the final complication leading to death as the secondary. An autopsy was performed in 22 patients. All autopsy reports were carefully reviewed.

The observed frequencies of the different causes of death were compared with expected frequencies for the general Dutch population. The expected proportion of patients dying from a certain cause was calculated using Dutch population tables of causes of death from 1970 and 1990 (to represent, respectively, patients with median year of death 1965 and patients with median year of death 1991) and was further standardized for age and sex. The analysis was confined to primary causes of death that could be classified unambiguously by ICD (International Classification of Diseases) number (ICD-8, World Health Organization,

Table 1 *Characteristics of the patients (*n = *180, including 83 deceased)*

	All patients	Males	Females
Age at death (years)			
n	83	47	36
Median age*	56	54	58
Mean age† (95% CI)	54 (52.0–56.7)	52 (48.2–55.0)	56 (55.2–60.8)
Survival time (years)			
n	180	101	79
Median time (95% CI)	59 (57.6–60.8)	59 (57.2–61.2)	60 (56.7–63.3)
Mean time‡ (95% CI)	58 (56.1–59.7)	56 (53.8–58.8)	60 (57.5–62.4)

CI = confidence interval. *Difference between males and females, χ^2 test, $P = 0.15$. †Difference between males and females, *t* test, $P = 0.006$. ‡Difference between males and females, log-rank test, $P = 0.11$.

Geneva 1967/1969 for 1970 and ICD-9, World Health Organization, Geneva 1978 for 1990). *P*-values were calculated from the binomial distribution.

The length of the CTG repeat was known for only 13 patients, as most patients died before 1992, before the myotonic dystrophy gene was identified. Genomic DNA was isolated from peripheral blood cells. The molecular analyses were performed according to methods previously described (Shelbourne *et al*., 1993). In the samples where smears were detected, the middle of the smear was sized. The expansions are expressed in kilobases of additional DNA.

In a subgroup of 18 patients, mobility within 2 years of death was assessed during their regular visit to the outpatient clinic of neurology, and scored on a four-point scale (Hoffer *et al*., 1973).

Results

The ages at death for the 83 deceased patients with adult-type myotonic dystrophy are shown in Fig. 1. The majority of patients (63%) died between the ages of 50 and 65 years. Only 12% of patients died aged 65 years or older. Further characteristics regarding the age at death are summarized in Table 1. Although mean and median ages at death were lower in male patients than in female patients, the observed differences were not statistically significant.

The median (50%) survival for male patients was 59 years and for female patients 60 years (Table 1). The Kaplan–Meier curves (Fig. 2) show that survival in both sexes declined rapidly between the ages of 50 and 70 years, from ~80% of the cohort to ~10%. In Table 2, the observed survival from the age of 15 years in the 180 patients is compared with the expected survival. Survival of the patients to the age of 45 years was slightly, but significantly, lower than expected. Survival of patients to the age of 65 years was markedly reduced, only 18% compared with an expected survival of 78%. The observed survival to the age of 65 years was lower in males (11%) than in females (29%), but this difference was not statistically significant (Fisher's exact test $P = 0.10$).

The molecular data for the 13 patients studied are given in Fig. 3. The mean CTG repeat size was 1.8 kb (600 CTG repeats) (range 0.5–4.7 kb). A weak inverse correlation between the CTG repeat length and survival was found ($r = 0.50$, $P = 0.08$).

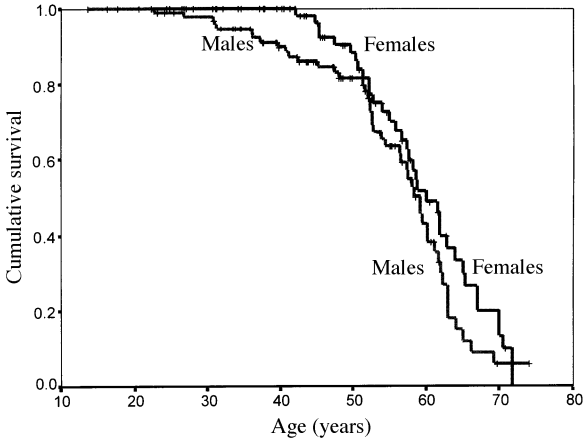

Fig. 2 Kaplan–Meier survival curves of adult-onset myotonic dystrophy patients ($n = 180$); of the 101 males, 47 had died and the other 54 were censored; of the 79 women, 36 had died and the other 43 were censored.

Table 2 *Survival (from the age of 15 years) of adult-onset myotonic dystrophy patients (*n = *180), compared with the expected survival of normal subjects*

	Survival to the age of:		
	25 years	45 years	65 years
Birth cohorts	1889–1971	1889–1951	1889–1931
Survived (*n*)/cohort (*n*)	169/170	105/120	12/66
Observed survival (95% CI)	99% (97–100%)	88% (80–93%)	18% (10–30%)
Expected survival*	99%	95%	78%
Survival ratio†	1.01	0.92	0.23
P-value‡	0.99	0.001	0.000

CI = confidence interval. *Calculated from survival tables of the general Dutch population, using the birth year of patients. †Survival ratio = observed survival/expected survival of normal subjects. ‡Probability, to three decimal places, of observed value of survival (or smaller value) given the expected survival.

Table 3 *Primary and secondary causes of death in adult-onset myotonic dystrophy patients (n = 70)*

	Primary cause			Secondary cause
	Observed no. and (%) of patients	Expected‡ (%)	*P*-value§	Observed number of patients (%)
Causes related to myotonic dystrophy				
Pneumonia	22 (31%)	1	0.000	8 (11%)¶
Arrhythmias	20 (29%)	2	0.000	3 (4%)#
Postoperative	4 (6%)			
Fractures	5 (7%)			
Causes not related to myotonic dystrophy				
Malignancy*	7 (10%)	37	0.000	
Other causes†	12 (17%)			
Total	70 (100%)			

*Two lung and two uterus carcinoma, and one breast, one brain carcinoma and one liver metastases, primary tumour not known. †Four traffic accidents, three cardiac infarctions, two with tuberculosis, one cerebrovascular accident, one diabetic gangrene and one metachromatic leucodystrophy. ‡Calculated from causes of death tables of the general Dutch population, given birth year of patients.The causes included were: pneumonia (ICD 480–486), cardiac conduction disorders (ICD 426) and cardiac dysrhythmias (ICD 427) combined with sudden death, cause unknown (ICD-9 798, data from 1990 extrapolated to 1970 because this category does not exist in ICD-8) and malignancies (ICD 140–239). §Probability, to three decimal places, of observed value (or smaller value) given the expected value. ¶Primary cause of death: fracture (three), embolic event (three) and postoperative complications (two). #Primary cause of death: fracture (two) and postoperative complications (one).

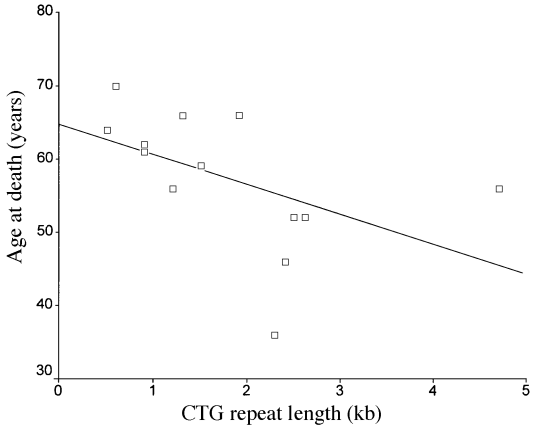

Fig. 3 Correlation of CTG repeat length and age at death ($n = 13$).

Medical documents on the cause of death were available for 70 patients; of these, 73% of the patients died from a complication related to myotonic dystrophy (Table 3). Pneumonia was the most frequent primary cause of death (31%), and it was a secondary cause of death in eight patients (11%) (three with fractures, three with embolic events and two with postoperative complications). Thus, pneumonia as the primary or secondary cause of death accounted for 42% (30 out of 70) of all deaths. Cardiac arrhythmias were the second most frequent primary cause of death (29%). For the purpose of this study we included in this group ventricular arrhythmias documented shortly before death (three), embolic events secondary to atrial fibrillation (four) and patients with sudden death at home (13), assuming that sudden death in myotonic dystrophy patients is usually caused by a cardiac rhythm disturbance. Cardiac complications were the secondary cause of death in three patients (4%) (one postoperative and two with fractures). Overall, cardiac complications as the primary or secondary cause of death were seen in 33% of patients. Pneumonias and cardiac complications were far more frequent primary causes of death than would be expected for this age group (expected 1% and 2%, respectively) (Table 3). The proportion of all deaths attributed to malignancies was 10% in the myotonic dystrophy patients. Allowing for age and sex, this frequency was strikingly lower than that found for the general Dutch population (37%).

The autopsy results confirmed the clinical diagnosis in all patients with pneumonia as the primary or secondary cause of death, as well as in the patients with carcinoma, cardiac infarction, traffic accident and postoperative embolism of the lung. Autopsy in the eight patients from the group with arrhythmia as the primary (six) or secondary (two) cause of death confirmed the cause of death in two patients as being embolism of the intestines and cerebral embolism, respectively. Non-specific myocardial changes were seen in six patients with sudden death, but no coronary artery disease, cerebral haemorrhages or other causes for their sudden death were found.

Detailed information on independence and mobility in the 2 years preceding their death was available for 18 patients (Table 4). Half of these were wheelchair-bound, either completely (22%) or only outdoors (28%). Their mean age at death was 59.7 years (which is similar to the whole group

Table 4 *Mobility in the years preceding death in a subgroup of 18 patients with adult-onset myotonic dystrophy*

Mobility	Grade*	No. and (%) of patients	Mean age at death in years (range)	Mean disease duration in years (range)
No restrictions	0	1 (6)	62	18
Community ambulator (able to walk >100 m outside without assistance, wheelchair needed for long distances)	1	8 (44)	57.8 (44–70)	26 (19–40)
Household ambulator (able to walk indoors, wheelchair needed outdoors)	2	5 (28)	59.8 (52–66)	28.4 (21–37)
Completely wheelchair-bound	3	4 (22)	63 (59–71)	33.2 (26–45)

*Hoffer *et al*. (1973).

of deceased patients) and mean disease duration was 28 years (range 18–45 years).

Discussion

This is the first longitudinal study on mortality in the adult-onset type of myotonic dystrophy. The major findings are as follows. (i) Survival of patients to the age of 65 years is markedly reduced in comparison with the expected survival for the normal population (18% versus 78%). Only half of the patients survived beyond the age of 60 years. (ii) Pneumonia and cardiac arrhythmias are the most frequent primary causes of death (31% and 29%, respectively) and they are also a common secondary cause of death.

Previous studies on age at death in myotonic dystrophy were retrospective and made no distinction between the various disease types. They showed mean ages of death in myotonic dystrophy of 43.5, 44.7, 50.6 and 53 years in Bell (1948), Thomasen (1948), Klein (1958) and Grimm (1975), respectively. We found a mean age at death of 54.3 years. A recent preliminary report of a 10-year follow-up study on mortality showed a mean age at death of 55.4 years for late adult-onset patients and 47.8 years for early adult-onset patients (Mathieu and Potvin, 1996).

Survival analysis is more appropriate for estimating the life span of patients than age at death, as it permits inclusion of follow-up information on all patients, dead or alive. Even patients who have been followed for a short time can provide valuable information. For the present population of patients, survival to the age of 45 years was slightly reduced in comparison with the normal population. However, the chance of survival to 65 years was small in comparison with expected survival in the normal population (18% and 78%, respectively). We found a median survival of 59–60 years for the adult-type myotonic dystrophy. Reardon *et al.* (1993) found a median survival of 35 years for the congenital type. Thus, patients with the adult-type of myotonic dystrophy have a considerably better prognosis than those with the congenital type.

The CTG repeat sizes in the 13 patients studied are in accordance with the adult-onset disease type (Harley *et al*., 1993). A weak positive correlation was found between increased CTG repeat size and younger age at death. Our results suggest that repeat length may have some prognostic significance for premature death, but the limited number of patients prohibits here a reliable estimation of its prognostic value.

Most patients (73%) died from systemic complications of myotonic dystrophy. Pneumonia was the most frequent primary cause of death (31%). Other studies also reported pneumonia to be the most common cause of death—48% for all disease types and 66% for congenitally affected children (Reardon *et al*., 1993; Mathieu and Potvin, 1996). Pneumonia in myotonic dystrophy results from a multiplicity of problems: aspiration owing to pharyngeal weakness in combination with delayed gastric emptying, weakness of respiratory muscles and diaphragm and impaired central respiratory drive. With longer duration of the disease the vital capacity decreases and the risk of pneumonia increases (Harper, 1989; Zifko *et al*., 1996). Several of our patients had recurrent pneumonias in the 5–10 years before their death. Early and intensive treatment, including bronchoscopy and artificial respiration, often proved successful.

In our series, arrhythmia was the second most frequent primary cause of death (29%). In congenitally affected patients cardiac arrhythmia accounted for 23% of deaths (Reardon *et al*., 1993). Cardiac arrhythmias in myotonic dystrophy are due to selective degeneration of the cardiac conducting system (Nguyen *et al*., 1988). Heart involvement was found to be progressive during the course of the disease (Fragola *et al*., 1994). However, sudden death is not confined to patients with advanced muscle disease, and serious cardiac anomalies may also be present at an early stage (Harper, 1989). To prevent the consequences of conduction defects, regular electrocardiographic monitoring and adequate treatment is important. Nevertheless, patients with a permanent pacemaker may also die suddenly and unexpectedly, as was the case in four of our patients.

Postoperative complications were the cause of death in 6% of patients in our series. This is similar to the frequency found in congenitally affected patients (Reardon *et al*., 1993). Mathieu *et al*. (1997) found that the risk of postoperative

complications was higher with ages of >37 years, as well as with severe, proximal limb weakness and after upper abdominal surgery (Mathieu *et al*., 1997). Fractures accounted for 7% of all deaths. Nearly all patients of these latter two groups ultimately died from pneumonia or cardiac problems after a long series of complications. Thus, a fracture and the postoperative period are vulnerable situations for myotonic dystrophy patients and special care is warranted. The number of patients dying from malignancies (10%) is far lower than expected (37%). So we found no evidence that myotonic dystrophy is associated with a general tendency to malignancies.

In conclusion, patients with adult-type myotonic dystrophy are particularly susceptible to pneumonia and cardiac arrhythmias when aged >45 years. These systemic complications can occur either primarily or as a fatal complication in risk-bearing situations. Therefore, it may be wise to refrain from surgical intervention in myotonic dystrophy patients aged >45 years, for conditions that are not life threatening.

The data for this study were collected between 1950 and 1997 and were analysed retrospectively. This approach offered the opportunity to gather long-term follow-up data of patients, but also entailed some disadvantages. First, not all currently desirable data, e.g. exact age at onset, were recorded in the past. Therefore we cannot give survival according to disease duration for all patients. Secondly, selective inclusion of patients who died young (in the group with complete data) may give a false impression of age at death. We think that this bias is limited, because patients were ascertained in several independent ways, e.g. by family studies and by regular follow-up. Selective follow-up was also limited: only three patients of the original cohort of 58 patients with adult-type myotonic dystrophy, examined by de Jong (1955) before 1970, were lost to follow-up. Finally, we may have under- or overestimated the frequency of fatal cardiac arrhythmias. Underestimation may arise because patients who die suddenly are usually at home (and not in hospital) and medical documents from hospital are generally more easily obtained than information from the general practitioner. However, this underestimation may be limited as the cause of death was unknown in only 16% (13 out of 83) of patients. The assumption that we made, that all sudden deaths are owing to cardiac arrhythmias, may give an overestimation of this cause of death. However, the autopsies of the eight patients who died suddenly did not uncover any other cause of their sudden death. Overall, we are fairly confident that our data represent a true picture of mortality in adult-onset myotonic dystrophy.

We have only preliminary data on mobility in the years before death. We found that nine out of 18 patients were partially or completely wheelchair-bound shortly before death (Table 4), which is far more than reported by Mathieu *et al*. (1992). In this latter cross-sectional study wheelchair dependence was found in only 4.4% of patients, although by the age of 50 years, or more, 14% of patients were wheelchair-bound. A possible explanation for the observed difference is that in the study of Mathieu *et al*. (1992) the proportion of patients with a disease duration >20 years is relatively small (21%). The mean disease duration of the 18 patients we studied was 28 years (range 19–45 years). We presume that muscle weakness tends to progress to proximal muscles in the last years of patients' lives. Further prospective studies on progression of muscular weakness in the advanced stages of the disease may serve to answer the question of impairment of mobility in the years before death.

Acknowledgements

We wish to thank Carlo Marcelis for help in data collection, Fren Smulders for statistical support, Tineke Spaans-van der Bijl for genealogical studies and Connie Schrander-Stumpel and Henk Kerkhoff for their critical comment. The work was supported by the Dutch Beatrixfonds (Grant number 93.006).

References

Aldridge LM. Anaesthetic problems in myotonic dystrophy. Br J Anaesth 1985; 57: 1119–30.

Bell J. Dystrophia myotonica and allied diseases. In: Fisher RA, editor. Treasury of human inheritance 4, part V. Cambridge: Cambridge University Press; 1948. p. 351–7.

de Jong JGY. Dystrophia myotonica, paramyotonia and myotonia congenita [Thesis]. Utrecht: University of Utrecht; 1955.

Emery AEH. Population frequencies of inherited neuromuscular diseases—a world survey. Neuromuscul Disord 1991; 1: 19–29.

Fragola PV, Luzi M, Calò L, Antonini G, Borzi M, Frongillo D, et al. Cardiac involvement in myotonic dystrophy. Am J Cardiol 1994; 74: 1070–2.

Grimm T. The ages of onset and at death in dystrophia myotonica. J Genet Hum 1975; 23 Suppl: 172.

Harley HG, Rundle SA, Reardon W, Myring J, Crow S, Brook JD, et al. Unstable DNA sequence in myotonic dystrophy. Lancet 1992; 339: 1125–8.

Harley HG, Rundle SA, MacMillan JC, Myring J, Brook JD, Crow S, et al. Size of the unstable CTG repeat sequence in relation to phenotype and parental tranmission in myotonic dystrophy. Am J Hum Genet 1993; 52: 1164–74.

Harper PS. Myotonic dystrophy. 2nd ed. London: W. B. Saunders; 1989.

Hoffer MM, Feiwell E, Perry R, Perry J, Bonnett C. Functional ambulation in patients with myelomeningocele. J Bone Joint Surg Am 1973; 55: 137–8.

Klein D. La dystrophie myotonique (Steinert) et la myotonie congénitale (Thomsen) en Suisse: étude clinique, génétique et démographique. J Genet Hum 1958; 7 Suppl: 1–328.

Mathieu J, Potvin L. Mortality in myotonic dystrophy: a cohort study from the Saguenay-Lac-Saint-Jean region (Quebec, Canada) [abstract]. Neurology 1996; 46 (2 Suppl): A170.

Mathieu J, De Braekeleer M, Prévost C, Boily C. Myotonic dystrophy: clinical assessment of muscular disability in an isolated population with presumed homogeneous mutation [published erratum appears in Neurology 1992; 42: 689]. Neurology 1992; 42: 203–8.

Mathieu J, Allard P, Gobeil G, Girard M, De Braekeleer M, Bégin P. Anesthetic and surgical complications in 219 cases of myotonic dystrophy. Neurology 1997; 49: 1646–50.

Nguyen HH, Wolfe JT 3d, Holmes DR Jr, Edwards WD. Pathology of the cardiac conduction system in myotonic dystrophy: a study of 12 cases. J Am Coll Cardiol 1988; 11: 662–71.

Reardon W, Newcombe R, Fenton I, Sibert J, Harper PS. The natural history of congenital myotonic dystrophy: mortality and long term clinical aspects. Arch Dis Child 1993; 68: 177–81.

Shelbourne P, Davies J, Buxton J, Anvret M, Blennow E, Bonduelle M, et al. Direct diagnosis of myotonic dystrophy with a disease-specific DNA marker. N Engl J Med 1993; 328: 471–5.

Tas RFJ. Generatie-overlevingstabellen naar geslacht en leeftijd afgeleid uit waarnemingen over de periode 1860–1989. In: Maandstatistiek bevolking 91/6. 's Gravenhage: Centraal Bureau voor de Statistiek; 1991. p. 15–26.

Thomasen E. Myotonia. Aarhus: Universitetsforlaget; 1948.

Zifko UA, Hahn AF, Remtulla H, George CF, Wihlidal W, Bolton CF. Central and peripheral respiratory electrophysiological studies in myotonic dystrophy. Brain 1996; 119: 1911–22.

Received October 18, 1997. Revised March 12, 1998.
Accepted April 6, 1998