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ORIGINAL ARTICLES

Survival in Duchenne muscular dystrophy

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Objective: To determine the survival in a population of German patients with Duchenne muscular dystrophy.
Patients and methods: Information about 94 patients born between 1970 and 1980 was obtained by telephone interviews and questionnaires. In addition to age of death or actual age during the investigation, data concerning clinical course and medical interventions were collected.
Results: 67 patients with molecularly confirmed diagnoses had a median survival of 24.0 years. Patients without molecular confirmation (clinical diagnosis only) had a chance of 67 % to reach that age. Grouping of our patient cohort according to the year of death (before and after 2000), ventilation was recognized as main intervention affecting survival with ventilated reaching a median survival of 27.0 years. For those without ventilation it was 19.0 years.
Conclusion and clinical relevance: our study provides survival data for a cohort of DMD patients in Germany stratified by year of death. Median survival was 24.0 years in patients confirmed by molecular testing. Ventilated patients had a median survival of 27 years. We consider this piece of information helpful in the medical care of DMD patients.

Key words: duchenne muscular dystrophy, survival, ventilation

Introduction

Duchenne muscular dystrophy (DMD) affects 1 in 3500 male live births (1), showing the classical pattern of X-linked inheritance (2). Out-of-frame mutations disrupt the open reading-frame and lead to severe deficiency of the protein dystrophin (2, 3). The reading-frame rule was shown to be correct in 93 % of deletion cases and 66 % of duplication cases (4). Clinical features and an elevated serum creatine kinase level (50-100 times normal) are important in establishing the diagnosis (5). Molecular confirmation reveals 60-65 % deletions, 7 % duplications and 21 % point mutations (6, 7). As the underlying mutation is not found in at least 4 % of cases (8), and due to a possible discrepancy between mutation and phenotype, a muscle biopsy is indicated in patients without a detectable mutation (5). Biopsy material is tested via immunohistochemistry and Western blot analysis (9, 10). Clinical signs, like delay in walking and loss of it, are accompanied by progressive muscular weakness. Complete wheelchair dependence is usually reached by the age of 12 years (5). In more advanced stages, patients are affected by contractures and progressive scoliosis (9). There is no curative treatment but patients have been shown to benefit from glucocorticoid corticosteroids medication, physiotherapy, spinal surgery and noninvasive ventilatation (NIV) (11). The first sign of incipient respiratory failure is nocturnal hypoxia (9). Mean survival for patients having diurnal hypercapnoea amounts to only 9.7 months (5). NIV is the method of choice for treatment of respiratory failure and can prolong life (12). Current experimental treatment strategies aim at the production of a shorter but functional dystrophin protein by exon skipping. Respective clinical trials using antisense oligonucleotides currently have reached phases II and III (13).

Patients and methods

Patients: Of our cohort of 94 patients, a data base covering medical history, medical interventions and survival was established. At the time of data collection (summer of 2009) 56 patients had already died. Data collection involving patients born between 1970 and 1980 relied on the administrative database of the Department of Human Genetics, University of Wuerzburg. All patients with a proven out-of-frame mutation were included. Additionally, our patient cohort was extended with the help of the German family support group (Deutsche Gesellschaft für Muskelkranke e. V. (DGM)). Members of the DGM were included when "registered as a DMD patient". Patients who were not born between 1970 and 1980 were excluded. Also excluded were patients living outside of Germany. 90 families were contacted from Wuerzburg, 76 families from the DGM.

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Methods: Patient files of the Department of Human Genetics, University of Wuerzburg, were reviewed in order to collect data of birth and contact details, followed by telephone interviews with family members of DMD patients. They were asked by letter to take part in the survey. Out of the 87 families who participated in the study, 11 families preferred to fill in a questionnaire corresponding to the interview questions. Prior to beginning with the interview, the telephone partner was asked to provide informed consent. Our study design was approved by the local ethics committee.

Statistical analyses: Kaplan-Meier curves were computed to determine median survival (14). Predictive Analysis SoftWare 18 (PASW 18) was used to compare the 2 patient groups divided according to way of diagnosis. Methods used were the Mann–Whitney–Wilcoxon-test, the Fisher's exact test and the Log rank test (15-17).

Results

A total of 94 patients with DMD formed the study cohort that was divided into 2 groups. 67 patients (71 %) were in the confirmed molecular diagnosis group, 27 patients (29 %) were in the clinical diagnosis only group. This division was made to ensure that milder types of muscular dystrophy would not confound the survival statistics of the first group.

For the cohort of 67 patients, median age at diagnosis was 4.0 years (range 0-10). They achieved independent ambulation at a median age of 15.5 months (range 9-48). The median age of first wheelchair use was 10.0 years (range 6-15) for the 67 boys. Ventilation was introduced at a median age of 20.0 years (range 9-30). There was a significant correlation between age of getting the first wheelchair and age of death (p = 0.016 Pearsons r, 0.383).

The probability of surviving to at least the age of 24 years was 67 % for patients with clinical diagnosis only. Without molecular testing, we cannot rule out milder forms like Becker type of muscular dystrophy among this patient cohort. The probability of reaching 24 years was 50 % for subjects with DMD diagnosed on a molecular level. This group included 67 patients with a proven out-of-frame mutation.

Previous reports showed exceptions to the reading-frame rule concerning deletions (18-23) and duplications (24, 25). In these cases of exceptional out-of-frame mutations, there is a partly functional dystrophin protein that normally occurs in the Becker muscular dystrophy (BMD) as a consequence of an in-frame mutation. To verify 18 deletions and 10 duplications, former findings of muscle biopsy were considered. Due to the lack of information about the gene product in the findings, it was not possible to make a statement on the course of the disease. As there was no statistically significant difference between the possible exceptions and the remaining out-of-frame mutations, no possible exception mutation was excluded.

Patients diagnosed on the molecular level had a median survival of 24.0 years (95 % confidence interval 21.3-26.7 years) (Fig. 1). It is estimated to be the most important result of this study, since up to now such data have not been available in Germany. Among medical intervention, ventilation emerged as the most significant life-prolonging measure. The median survival of non-ventilated patients was 19.0 years (95 % confidence interval 17.7-20.3 years) compared to 27.0 years for those who were ventilated (95 % confidence interval 20.2-33.8

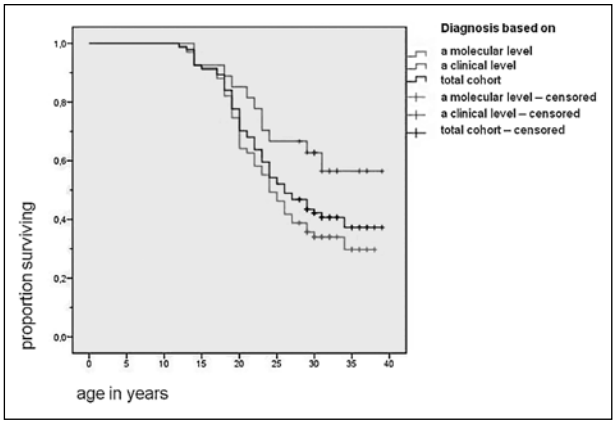

Figure 1. Survival curves (Kaplan Meier) for two patient cohorts. The green line shows percentage survival for 67 patients with molecularly proven diagnosis. The blue line reflects percentage survival for 27 patients with clinical diagnosis only (p = 0.028, log rank test). The black line represents the sum of all patients.

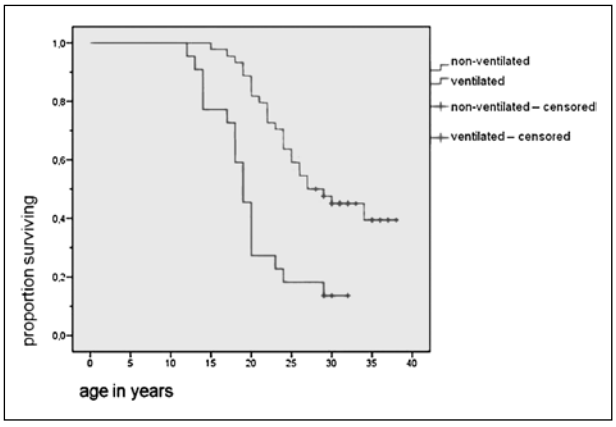

Figure 2. Survival curves (Kaplan Meier) for ventilated versus non-ventilated patients diagnosed at the molecular level. The green line denotes percentage survival for 44 ventilated patients. Information about details of ventilation is not available. The blue line shows percentage survival for 22 non-ventilated patients (p < 0.001, log rank test).

Jahre). As shown in Figure 2, there was a statistically significant difference between the respective survival curves (Log rank $p < 0{,}001$).

Discussion

Our study population consisted of patients with different diagnosis criteria. The majority of patients with an identified mutation were registered with the Department of Human Genetics, University of Wuerzburg, serving as reference center for DMD until 1985. Additional 10 patients with confirmed molecular diagnosis were recruited via the family support group DGM. Other DGM patients lacked molecular confirmation and were therefore included as a separate group. There was no statistically significant difference between the groups but for theoretical reasons the division was maintained. As illustrated in Figure 1, a tendency for a survival benefit suggests the putative presence of milder types of muscular dystrophy within the group "clinical diagnosis only". It is conceivable that this effect was caused by some boys having BMD, since the median survival of BMD patients amounts to 42 years (26).

Age at and cause of death are important clinical parameters. In 13 of our 45 deceased patients the cause of death was unknown. In literature, major reported causes of death are heart failure and respiratory insufficiency (5). Due to interviews with medical laymen, cardiac aspects like cardiomyopathy have not been considered. We understood every cause of death to be associated with the disease DMD and included patients no matter what cause of death they died of.

Reports from Newcastle (27, 28) and a prospective study of 43 patients with DMD by Kohler et al. (29) determined survival in terms of years of life, facilitating a comparison with the present study. Eagle et al. (27) divided their subjects into groups according to the decade in which they died. A later study by the same authors focused on the life-prolonging effects of ventilation and spinal surgery (28). Our data were not sufficient for survival analyses of a separate surgery group, since only 12 of our cohort of molecularly confirmed 67 patients had undergone spinal surgery. We therefore compared the 2002 study by Eagle et al. (27) to the present report. Dividing our patients up into groups "died before 2000" and "died after 2000", a difference in survival due to use of ventilation emerged (Fisher's exact test $p < 0{,}001$). As reported by a number of other authors, our study confirms that ventilation improves life expectancy. For example, Yasuma et al. (30) reported a median survival for non-ventilated patients of 20.1 years and Eagle et al. (27) reported 19.3 years. In contrast, median survival of patients using ventilation amounted to 30.4 years (30) and 25.3 years (27).

Since our study did not intent to evaluate therapies, mode of ventilation and indication to ventilation were not separately studied. We only recorded median age at introduction of ventilation. Studies considering protocols for ventilation showed the impact of home nocturnal ventilation on longevity. Recent studies on NIV revealed an improved median survival of 31 and 35 years respectively (31, 29). Compared to our study, factors like study design and other interventions influencing survival (e. g. spinal surgery, treatment of heart conditions) could explain this impressive survival advantage. However, our observed difference between non-ventilated and ventilated patients (19.0 vs. 27.0 years) clearly supports the important impact ventilation has on survival.

Conclusion

Duchenne muscular dystrophy is still not curable but can be treated to improve the quality of life and survival. Our study suggests that ventilation therapy has the most important impact on survival which is in agreement with recent international studies with long-term ventilated DMD patients. Clearly, a central feature of the management of Duchenne muscular dystrophy should be ventilation therapy. Other than confirming the beneficial effects of ventilation, the most important result of our retrospective study is a median survival of 24.0 years for a cohort of molecularly confirmed DMD patients. Up to now such data were not available for German patients. The results of our study might therefore be useful for genetic counseling and for families with affected boys in general.

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