

Survival of patients with Duchenne muscular dystrophy

Sobrevida de pacientes con distrofia muscular de *Duchenne*

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Abstract

Introduction: *Duchenne* muscular dystrophy (DMD) leads to a progressive deterioration of the muscle function and premature death. There are no longitudinal studies on the course of this pathology in Chile. **Objective:** To determine survival between the years 1993-2013, divided into two periods (1993-2002 and 2003-2013), and the effect of social determinants in patients with DMD admitted in Teletón Institutes of Chile (TI). **Patients and Method:** Prospective follow-up study in a clinical series of 462 patients with DMD. The information was obtained by searching for patients with DMD in OLAP cube (Online Analytical Processing). From the clinical records of the TI of Santiago, the variables corresponding to the diagnostic method, stage of DMD described in terms of muscle deterioration and function according to Swinyard classification were recorded; existence and type of tests that conclude the diagnosis and, in the cases reported, the existence of family history. Kaplan Meier survival analysis was applied, where global survival was defined between birth and age of death. The determinant factors analyzed were estimated through the Cox-Snell's proportional risk model. **Results:** Survival at 20 years of age from TI entry was 51.7% (CI95%: 45.1-57.8), 48.5% in the period 1993-2002 and 72.8% between 2003-2013. The percentage of survival at the same age according to socioeconomic status (SES) was 82% in high SES, 67% in middle SES, and 42% in low SES, with a statistically significant difference between high and middle SES in relation to extreme poverty. According to country areas, the survival was close to 75 % at 17 years of age. **Conclusions:** The survival information from patients with DMD from childhood to adult life is valuable for predicting the clinical course of the disease with the current medical care. There is evidence of improvement in the probability of survival at the age of 20 and marked inequity according to the socioeconomic variable.

Keywords:

Duchenne muscular dystrophy;
Neuromuscular disease;
Survival

Introduction

The Duchenne muscular dystrophy (DMD), an X-linked disorder, which affects 1 in 3,600-6,000 male live births¹, as a result of the dystrophin gene mutation (DMD; locus in Xp21.2), leading to the defect or absence of the cytoskeletal protein dystrophin in both cardiac and skeletal muscle fibers² with a progressive muscular degeneration^{3,4}.

Usually, this disease is clinically diagnosed around the fifth year of age, it leads to the loss of the walking ability and wheelchair dependence around the 12 years of age and death due to cardiac or respiratory insufficiency before the 20 years of age⁵ without therapeutic intervention¹, and approximately around the 30 years of age in patients who underwent to an early intervention⁶.

The DMD diagnosis is performed based on the physical examination, family history, laboratory tests (creatine kinase levels 100 to 200 times higher than the normal value), and genetic confirmation⁷⁻¹⁰.

In 2014, a systematic review¹¹ showed a DMD prevalence rate in males of all ages in England of 8.29 [6.90-9.88] (per 100,000), and a 9.81 rate [7.52-12.58] (per 100,000) in children under 19 years in China. In Chile, the DMD rate in a male cohort under 30 years old was 11.51 [10.46-12.56] (per 100,000)¹².

The prevalence rate indicates the global extent of DMD in a determined date or in a period of time in which the natural evolution of the disease may have been intervened by the change of treatments due to the medicine and technology improvement. It has been demonstrated that patients respond positively to treatment with corticosteroids, physical therapy, spinal cord surgery, and non-invasive ventilation (NIV)¹³.

A survival analysis includes the study of the "period until an event occurs" variable and its dependence on other possible explicative variables. There are four studies of this nature in the international literature; in the United Kingdom, 2002, where a change in the death average age from 14.4 years (1960) to 25.3 years (1990) was reported in patients with ventilation⁶. In 2009, in Switzerland, the average age of patients who lost their walking ability was 9.4 ± 2.4 years, becoming dependent on a power wheelchair at 14.6 ± 4.0 years. The age of initiation of assisted ventilation was 19.8 ± 3.9 years and the survival median was 35 years¹⁴. In Germany, 2012, the chances of surviving until the age of 24 years were 0.67 (67%) in patients with only clinical diagnosis and the probability of surviving until the age of 24 years was 0.5 (50%) in patients diagnosed with DMD in a molecular level¹⁵. In Naples, 2012, in a cohort study of 835 patients with DMD, considering the age of 20 years, a survival rate of 10 years of follow-up went from 23.3% in patients born between 1961 and 1970 to 54%

in patients born between 1971 and 1980, and to 59.8% in patients born between 1981 and 1990¹⁶.

So far, there are no DMD survival studies in the Chilean literature. The Teletón Institutes of Chile had the advantage of concentrating approximately 85% of the care of children with neuromuscular and skeletal diseases in the country, becoming the main source of records¹⁷. Therefore, the objective of this study is to determine the survival rate between 1993-2013, 1993-2002, and 2003-2013; and the effect of social determinants in patients with DMD who were admitted at the Teletón Institute. The knowledge of survival curves and for specific determinants will allow redirecting the treatment, prescription, and delivery of technical aids.

Patients And Method

Prognostic study of follow-up in clinical series¹⁸. Cohort study of 462 patients with DMD admitted at the Teletón Institute between 1993 and 2013.

Data collection

The required data was obtained through a search of patients with DMD in the OLAP (*On-Line Analytical Processing*) cube, which contains the summarized data of large databases belonging to the IT area of the Teletón Chile and through the review of clinical records for the Teletón Institute of Santiago.

The collected variables from the OLAP cube were: treating Teletón Institute, birth date, socioeconomic status which was classified according to the records given by the family of the patients in an interview with the social service; functional compromise determined according to the functional performance (daily activities and the presence or absence of independent walking, observed in the first consultation), first consultation or admission date, last consultation date in 2013, last physiotherapeutic consultation date in 2013, indication date of technical assistance, delivery date of technical assistance, technical assistance type, status in the institution, causes of the status, and date of death. The latter variable was supplemented by consultation with the Chilean Office of Vital Records in all patients who reported death cause of passive status. The consultation included every active patient in the Teletón Institute in order to verify the chance of finding a higher number of deaths, which might not have been informed to the Teletón Institute. All deaths were considered until July 30, 2014.

Out of the clinical records of the Teletón Institute of Santiago, the variables corresponding to the diagnostic method, DMD stage described based on the muscular deterioration and functioning according to the *Swinyard* scale¹⁹, existence and tests type that deter-

mined the diagnosis, and in some cases, the existence of family history were recorded.

Ethical considerations

The study was approved by the Scientific Ethics Committee of the Sociedad Pro Ayuda del Niño Lisiado, considering the declaration of Helsinki and the regulations on the use of clinical records. (Certificate No 24/2014).

Statistical analysis

The database, in an Excel spreadsheet, was processed with the statistical software SPSS 17.0 and Stata 14. For the Teletón Institute admissions and deaths variables, the average age, median, standard deviation, and interquartile distance were calculated. For the survival analysis, an exploration of the probability distribution of survival time of the patients with DMD was performed and the quality of adjustments according to the Cox-Snell residuals was evaluated²¹. The overall survival was defined as the time interval between birth and death (age of death). The survival analysis was performed through the Kaplan-Meier method²².

In order to evaluate the social determinants that explain the risk of dying at a given moment, adjusted parametric estimations were made through the proportional risk model based on the Weibull distribution²¹⁻²⁴.

Results

Clinical and sociodemographic characteristics

The first consultation age at the Teletón Institute was mainly in the groups younger than five years (34.2%), and from five to nine years (51.9%), being six years the median and average age, which has been decreasing over time. For the period between 2003 and 2013, the average and median were 6.1 years [CI 95%: 5.7-6.5]. 76% of the patients belonged to the lower-middle and extreme poverty socioeconomic status. The first consultation at the Teletón Institute for the extreme poverty status was one year after the other socioeconomic status. The center area of the country had 55.2% of the patients, which corresponds to the Teletón Institutes in Valparaíso, Santiago, and Talca (Table 1).

Out of the total of patients, 29.7% had a serious or severe functional compromise; two-thirds had the indication of a wheelchair at an average age of 10.9 ± 3.3 years. 64.1% of the patients survived at the end of the study, and 50.6% of the deaths happened between 16 and 20 years of age, with an average age of 18.1 ± 3.5 years.

In the 1993-2002 period, 56.6% of the admitted pa-

tients had a mild to moderate functional compromise, and in the 2003-2013 period, it was 75.5%. According to the age of prescription of a wheelchair, 20.4% of the indications were for patients between eight and 11 years of age in the 1993-2002 period, while in the 2003-2013 period it was 36.8%. The average death age in patients admitted in the 1993-2002 period was 18.3 ± 3.5 years and 16.3 ± 1.9 years in the 2003-2013 period (table 2).

86% of the patients admitted to the Teletón Institute of Santiago had a clinical diagnosis made by an external physician, with complementary tests such as creatine kinase (87%), muscle biopsy (62%), electromyography (43%), and genetic study (19%). 32% of them report data related to family history with a similar diagnosis¹².

Global survival and periods analysis

The exposure time to the risk for the whole period was 7,373.7 days, which indicated a 15.9 ± 5.3 global survival average (range: 2.7-31.6 years). The median was 16.4 years, in other words, the time that 50% of the patients with DMD lived or died. The chances of surviving up to the 20 years of age in the whole studied period were 51.7% (figure 1).

According to the period of admission at the Teletón Institute, the time of risk exposure of the first group (1993-2002 period) was 4,661.9 days, indicating 19.1 ± 3.8 years of global survival average (range: 10.6-31.6 years). 25% of the patients survived up to 16.9

Table 1. Sociodemographic characteristics of patients admitted to IT Chile. Period 1993 - 2013

Characteristic	n	%
Total	462	100.0
No of patients admitted to IT per period (years)		
1993 - 2002	244	52.8
2003 - 2013	218	47.2
Average age (CI 95%) of income to IT per period (years)		
1993 - 2002	7.2 (6.8 - 7.7)	
2003 - 2013	6.1 (5.7 - 6.5)	
Socioeconomic level		
Extreme poverty - medium low	351	76.0
Medium - medium high	82	17.7
High	15	3.2
Uninformed	14	3.0
Geographic area		
North	96	20.8
Center	255	55.2
South	111	24.0

Table 2. Clinical characteristics of patients admitted to IT Chile. Period 1993 - 2013

Characteristic	Periods					
	1993 - 2002		2003 - 2013		1993 - 2013	
	n	%	n	%	n	%
Total	244	100.0	218	100.0	462	100.0
Functional compromise (<i>Swinyard</i>)						
Mild - moderate	138	56.6	165	75.7	303	65.6
Severe - critical	98	40.2	39	17.9	137	29.7
Unspecified	8	3.3	14	6.4	22	4.8
Age wheelchair indication (years)						
< 8	4	2.0*	13	11.4*	17	5.5**
8 - 9	20	10.2*	21	18.4*	41	13.2**
10 - 11	20	10.2*	21	18.4*	41	13.2**
12 and more	152	77.6*	59	51.8*	211	68.1**
Average age ± SD	11.6 ± 3.4		9.5 ± 2.5		10.9 ± 3.3	
Median age (RI)	11.2 (4.4)		9.1 (3.1)		10.4 (4.1)	
Age of death (years)						
10 - 15	22	14.4***	3	23.1***	25	15.1****
16 - 20	77	50.3***	7	53.8***	84	50.6****
21 and more	54	35.3***	3	23.1***	57	34.3****
Average age ± SD	18.3 ± 3.5		16.3 ± 1.9		18.1 ± 3.5	
Median age (RI)	17.7 (4.1)		16.6 (2.4)		17.6 (3.3)	

*Percentage calculated based on 196 and 114 patients respectively, who presented an indication of technical assistance, according to the period of admission. **Percentage calculated based on 310 patients who presented an indication of technical assistance. ***Percentage calculated based on the 153 and 13 patients who died as of 06/30/2014, according to the period of admission. ****Percentage calculated based on 166 patients who died as of 06/30/2014.

years. For the second group (2003-2013 period), the risk exposure time was 2,711.8 days, which indicated a 12.4±4.3 average global survival years (range; 2.7-24 years). 25% of the patients survived up to 17.9 years.

The chances of surviving up to 20 years were 48.5% for

patients admitted in the 1993-2002 period and 72.8% for patients admitted in the 2003-2013 period (figure 2).

According to the period of admission at the Teletón Institute, there were significant statistical differences in the survival age of both groups ($p < 0.05$).

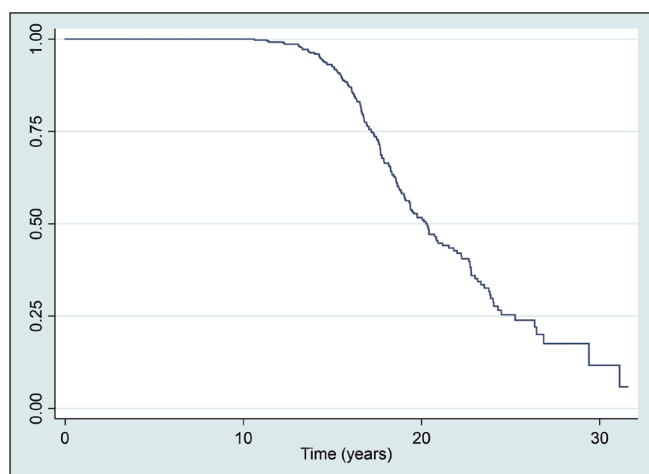


Figure 1. Survival of patients with DMD admitted to IT. Period 1993 to 2013.

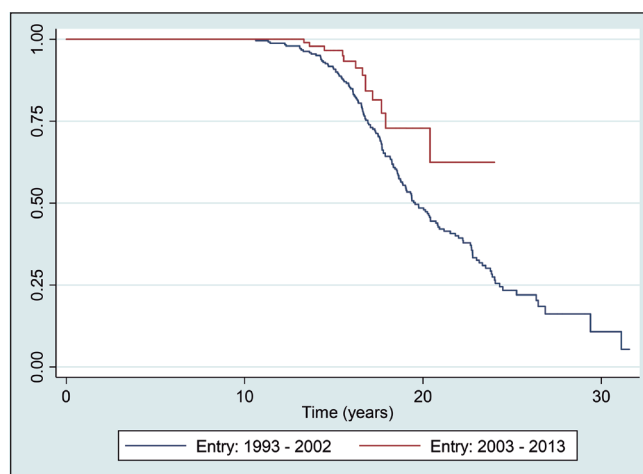


Figure 2. Survival of patients with DMD admitted to IT. Periods 1993-2002 and 2003-2013.

Survival by determinants analysis

The median global survival, according to the high, middle and extreme poverty socioeconomic status was 22.7, 23.3 and 19.0 years, respectively. At the 20 years of age, the chance of survival according to the socioeconomic status was 82%, 67%, and 42%, respectively.

Figure 3 shows that for the different socioeconomic status, the chances of surviving were similar up to 10 years, then the curves change significantly. This difference was statistically significant between the groups of high and extreme poverty socioeconomic status ($p < 0.05$) and between the middle and extreme poverty ones ($p < 0.05$), but no significant between the high and middle ones ($p > 0.05$).

The median global survival according to the geographic location of the Teletón Institute was 20.4, 20.8, and 18.6 years in the north, central, and south zones respectively. All groups showed a survival chance close to 75% for 17 years of age. According to the geographic location of the Teletón Institute, there were no significant statistical differences in survival ($p > 0.05$).

Discussion

The DMD is considered as a disease that tends to the progressive deterioration and finally to death². At the international level, very few survival studies of DMD have been published. The most recent ones focus on the effects of nocturnal ventilation, which does not allow a comparison with this study^{6,14-16}, since in Teletón the use of non-invasive ventilation variable is registered in the clinical records since 2012, due to it is a treatment given in other institutions.

There are no survival studies of DMD, being this the first one. Globally, it was determined that 50.7% of the patients admitted with DMD survived up to 20 years and 11.7% up to 3 years of follow-up. In addition, it was found a 50% improvement in the survival up to 20 years, increasing from 48.5% in the 1993-2002 period to 72.8% in the 2003-2013 period, which was a significant variation. Since deaths were supported with the verification search of deaths due to DMD in the Office of Vital Records of the country, it can be considered as a reliable increase.

The age at admission in the institution is considered as the estimator of the diagnosis age. In this study, the average admission age was 6.1 (5.7-6.5) in the second period, which indicates an increase of one year with respect to the first period. However, recent studies have indicated that the diagnosis age is approximately at four years^{15,25}. Despite the clinical suspicion of this disease may be evident, the confirmation of the clinical diagnosis takes more time in our country²⁶, which can be explained by the delay in the referral from a primary level to a hospital and then to a Teletón Institute.

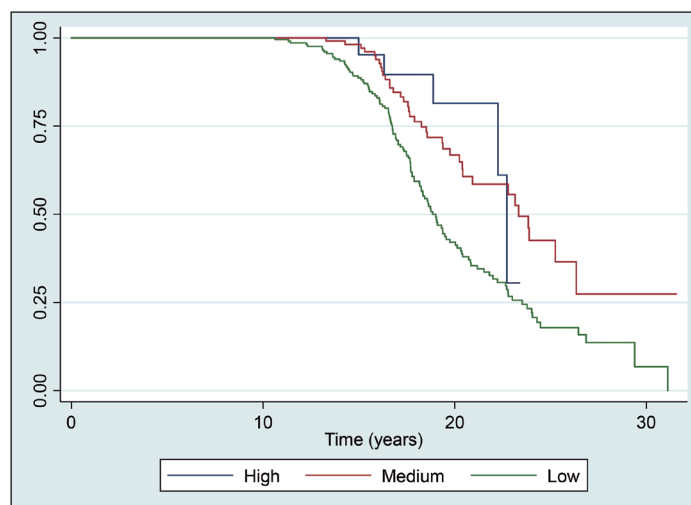


Figure 3. Survival of patients with DMD admitted to IT by socioeconomic level.

Regarding the comparison of average death age by DMD, it might seem contradictory that it was slightly lower in the second period, which can be explained by the number of deaths in the first period (153) and in the second one¹³.

The prescription age of wheelchair is considered as an indicator of the age of loss of independent walking ability. Rall and Grym¹⁵ determined that the median age of wheelchair use was ten years, similar to what was found in this study.

The health social determinants established by the WHO as 'conditions in where people are born, live, work, and age', affect the social positions of the patients and contribute to the main causes of health inequities²⁷.

The chances of surviving up to 20 years in the high and middle socioeconomic status, in comparison with extreme poverty (82% and 42%, respectively), show that this structural mechanism highly controls the health status of these patients, causing a gap of almost double in the progress of this disease. From a public health point of view, providing these figures is an incentive to increase the support interventions for patients and their families.

The geographic area does not produce significant differences in the survival age, which support that the treatments and medical indications follow a similar protocol in the Teletón Institute in cooperation with other institutions that provide support in the acute respiratory compromise.

With the advance of medicine and in line with Pasamano¹⁶, it becomes clear that DMD is not an exclusive children pathology since it has become an adult disease, which needs interventions from health authori-

ties in favor of patients and their families, especially in the phase of transition from childhood to adulthood.

Considering the genetic studies development and the new drugs that benefit patients with DMD²⁸, it is proposed to complementarily perform a genetic counseling with proper professionals, and therefore, to reduce faster the incidence of the disease.

Furthermore, it is suggested to follow an investigation line of the DMD, such as qualitative studies exploring the reasons why parents have biological children despite their family history with this pathology.

Lastly, the lack of records in the time of non-invasive ventilation assistance, the date of prescription and use of corticosteroids, have limited an effective comparison with the survival in developed countries.

In conclusion, the survival information provided by patients with DMD since childhood to adulthood is valuable to predict the clinical course of the disease with the current medical care. There is evidence of improvement in the survival age and noticeable inequity according to the socioeconomic variable.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed ac-

ording to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors state that the information was obtained retrospectively and anonymously, in which a fraction of the patients had died, hence the Research Ethics Committee, using its powers, exempted from obtaining informed consent, which is recorded in the respective minutes.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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