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ORIGINAL ARTICLE

Quality of life in children and adolescents with Spinal Muscular Atrophy

Calidad de vida en niños y adolescentes con Atrofia Muscular Espinal

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What do we know about the subject matter of this study?

The quality of life in children and adolescents with Spinal Muscular Atrophy (SMA) depends on several factors such as the level of disability and available therapies. In general, there are few studies worldwide and no information is available in Chile.

What does this study contribute to what is already known?

In a group of children and adolescents with SMA in Chile, the quality of life reported by parents was between regular and good in most cases, influenced mostly by their level of motor function and ability to communicate.

Abstract

Introduction: Quality of life (QoL) is a key aspect in the treatment of patients with Spinal Muscular Atrophy (SMA). International information regarding QoL in SMA is scarce, and is not available in our country. **Objective:** To characterize QoL in a sample of Chilean children and adolescents with SMA. **Subjects and Method:** Observational, cross-sectional study. A general questionnaire and the PedsQL™ 3.0 Neuromuscular Module Inventory were applied to parents of children with SMA aged 2 to 18 years. It has three areas: Disease, Communication, and Family. A score > 60 was considered as good QoL, 30-60 as regular, and < 30 as low. MINITAB-17® software was used, considering significant a $p < 0.05$ value. **Results**: We recruited 38 patients, with median age 8 years (2-18), 52.63% were male, and 17 (44.7%) with SMA I. All had genetic confirmation. The total score of QoL was 51.92

Keywords:
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± 17, representing 31% good, 55% regular, and 14% low. Regarding SMA I, it was 46.5 ± 15.2 and SMA II-III, 56.3 ± 17.4 (p = 0.071). Concerning the area of Disease, it was 53.83 ± 18.1, Family 48.6 ± 23.14, and Communication 33.3 (IQR: 0.0; 83.33). In this last area, children with SMA II-III, older than 6 years., with non-invasive ventilatory support, or living out of the metropolitan area had higher scores, however, in multivariate analysis, only SMA type was significant, which explained 40,9% of the variation in the communication area score. **Conclusions:** In this sample of SMA pediatric patients, the QoL was regular or good in most of them. The lowest area was communication, with a higher score in those children with higher motor function.

Introduction

Spinal muscular atrophy (SMA) represents a group of neuromuscular disorders characterized by alpha motor neurons degeneration of the anterior horn of the spinal cord, secondary to a homozygous deletion in the *SMN1* gene in 95% of patients. A smaller percentage of patients are compound heterozygous due to an intragenic deletion and point mutation in *SMN1*. This gene is located on the long arm of chromosome 5 in the 5q13 region[1].

The principal clinical manifestations are muscle weakness and progressive muscular atrophy, which may cause paralysis of the muscles involved. Patients can present a variable phenotype, classified into four types, according to the maximum motor function achieved. Patients with the most severe type (I) never achieve sitting position and die before the age of two years in the absence of ventilatory support; type II have a later onset and reach sitting position; type III can walk independently, and type IV refers to patients that begin symptoms in adulthood[2].

SMA is an autosomal recessive inherited disease, with an incidence of 1:6,000 to 1:10,000 live births, and a carrier frequency of 1:35 to 1:50[3]. In Chile, there is no data on its incidence[4]. In the last decades, life expectancy in SMA patients has improved considerably due to technical support and medical advances, therefore to optimize their quality of life (QoL) is a central issue in the treatment, which has been highlighted in the international standards of care for SMA[5,6].

The World Health Organization defines QoL as the individual's perception of her/his position in life, in the context of the culture and value system in which she/he lives and regarding their goals, expectations, standards, and interests[7]. It is a complex concept of multidimensional nature with several definitions in different disciplines[8]. The domains covered by QoL in children are heterogeneous, especially in those with disabilities[9,10]. Although motor function influences QoL, recent studies have shown low correlation between them[11], suggesting that children can have good QoL despite their physical limitations.

Health-related quality of life (HRQoL) is defined as the impact that the disease and its treatment have on the patient's perception of her/his well-being[12]. This concept is central to guide treatment of children with chronic diseases, evaluate new therapies, generate new research, and develop public policy.

Due to advances in technology, ventilatory support, and international consensus guidelines on SMA health care standards, the QoL of people with SMA has improved, however, the application of these recommendations by health teams differs in different countries and socio-economic realities[13,14].

Although no definitive cure exists, new specific therapies have recently been approved[15,16] that have improved functional prognosis, respiratory capacity and life expectancy. However, due to their low availability and high cost, ethical decisions need to be considered, especially in patients with SMA I. In this decision-making, the concept of quality of life is a key[17].

Worldwide, there is few knowledge of QoL in SMA patients and no information is available in our country. The objective of this study was to describe QoL in a sample of Chilean children and adolescents with SMA.

Subjects and Method

A descriptive and cross-sectional study was conducted in a convenience sample of patients diagnosed with SMA, aged between 2 and 18 years. Families were verbally invited to participate at the international symposiums organized by the Corporation of Families with Spinal Muscular Atrophy (FAME), in November 2016 and 2017. Information leaflets were also sent through their website, the Hospital Josefina Martinez, and the treatment teams. Families interested in participating provided their contact details (telephone and e-mail).

The study was approved by the Scientific Ethics Committee of the Faculty of Medicine of the Pontificia Universidad Católica de Chile (Nº 161213009) and the Scientific Ethics Committee of the South East Metropolitan Health Service (23-03-17). The parents signed

an informed consent and the children older than 12 years old gave their informed assent.

Two surveys were applied to parents or caregivers; a general questionnaire for the patient´s data, such as current age, sex, age at diagnosis, genetic confirmation, treatment, and ventilatory support, among others. The second one was specific for parents and caregivers, the neuromuscular module pf the PedsQL™ quality of life inventory, validated for children with SMA aged from 2 to 18 years in its original version[18], in Spanish version[19], and translated to Chilean Spanish in 2010. Appropriate authorization was obtained for this purpose (Varni JW et al., Pediatric Quality of Life Inventory™ _User Agreement _ March2017_22.0).

This questionnaire consisted of 25 questions divided into 3 areas, 17 regarding the disease, 3 to communication, and 5 to the family, with scores ranging from "never" (0) to "almost always" (4) that are analyzed on an inverse scale from 0 to 100 (0 = 100; 4 = 0), therefore the higher the score the better the QoL (Appendix 1). Considering that the PedsQL™ survey has reported a score of 81.34 ± 15.2 in healthy children[18], we arbitrarily defined a good QoL as a score higher than 60 (comparable with children without disease), regular QoL between 31 and 60, and poor QoL equal or less than 30.

The surveys were applied by 2 interviewers in 2 modalities: by e-mail, through the *Surveymonkey* platform, or face-to-face in a home visit, and then completed by telephone.

The data were analyzed with the MINITAB-17® software. The nominal variables were expressed as number and percentage. The distribution of the numerical variables was analyzed (Ryan-Joiner test), expressing them as a mean ± standard deviation (SD) if it was normal, if not, as a median and interquartile range (IQR). For comparison, ANOVA or Kruskal-Wallis tests were used, respectively. Dichotomous variables were compared with the Chi-square test or Fisher's exact test. A p-value ≤ 0.05 was considered significant.

Results

The surveys were sent to 54 families who sent us their contact details. Finally, 38 (70.4%) families of children and adolescents with SMA, over 2 years old, were included. More than 90% of the surveys were answered by their parents or caregivers and all signed the informed consent and assent documents. Four surveys answered by parents of children younger than 2 years of age were excluded, due to the lack of validation of PedsQL™ in that age range. 15 families were surveyed at home and 23 by e-mail, complemented by a telephone call. There was no difference in the QoL scores between the 2 interviewers, nor according to the modality (face-to-face or remotely).

The 38 patients had a median age of 8 years (range: 2 to 18). Table 1 describes their characteristics. No patients were on specific drug therapy when the data were collected. Six families did not register their residence and one did not answer the family area in the QoL questionnaire, as the patient was hospitalized. Out of the patients with SMA I, 11/18 (65%) lived in the Metropolitan Region, 4/18 (24%) in other regions, and 2/18 did not report it.

Table 2 details the total and partial scores of the QoL survey; in the whole group the Communication area presented a non-significant lower score (ANOVA p = 0.342).

From all the answered surveys, 5 (13.2%) reported a poor QoL, 21 (55.3%) a regular QoL, and 12 (31.6%) a good QoL (Figure 1).

Table 3 shows the univariate comparison between the total and per area QoL scores according to: age, gender, clinical type of SMA, place of residence, and ventilation support. We did not find a significant association for the Disease or Family areas (which are not shown), but for the Communication area, QoL scores were lower in patients with SMA I (vs. SMA II and III), in patients under 6 years old (vs. the elderly), or in those living in the Metropolitan area (vs. Other regions).

Figure 2 shows the QoL score comparison according to ventilation support: those with invasive assistance (IVA) had a lower score for the communication area than those with non-invasive or without ventilation. The QoL score for communication was similar between the last two groups. All children with invasive ventilation had SMA I (n = 17).

Subsequently, a multiple regression analysis was performed to explain the score for the Communication area, including as categorical explanatory variables: age, type of SMA, place of residence, and ventilatory support. The best model only indicated the type of SMA (p = 0.012) as the significant variable (S: 30.8, R^2: 40.9%, and adjusted R^2: 34.5%). The variable "type of ventilatory support" could not be included due to its close association with the type of SMA, without improving the model by replacing it.

Discussion

This study describes QoL in SMA patients older than two-years-old from a Chilean cohort of children and adolescents, reported by their parents or caregivers. Most of them considered their daughter or son's QoL as regular to good and a minority as poor. The group with less motor disability showed slightly better overall scores reaching significance only for the Com-

munication area. This study is the first in our country that explores QoL in patients with SMA, a neurodegenerative disease that is dramatically changing its natural history and prognosis with the development of new therapies[15,16,21].

The overall score (51.92 ± 17 points) in our cohort was comparable with the study conducted in 2014 in the Czech Republic (5), which was 52.08 ± 16.37. Nonetheless, it was lower than the reported in another study from the United States of 59.74 ± 16.75[17]. Otherwise, the score obtained in the Communication area was considerably lower than both studies mentioned above (44.30 ± 39.0 vs. 62.38 ± 29.94 and 67.01 ± 31.09, respectively). These differences could be due to better availability of technical support devices or more representation of patients with SMA II and III, whose performance in Communication is significantly higher. This aspect is well-illustrated in our study because the type of SMA explained 40% of the variation in the Communication score.

When comparing with other degenerative neuromuscular disorders such as Duchenne Muscular Dys-

Table 1. General characteristics of 38 children and adolescents with Spinal Muscular Atrophy (SMA)

Characteristic		
Male, n (%)		20 (52.63)
Female, n (%)		18 (47.37)
Clinical type of SMA, n (%)	Type I	17 (44.74)
	Type II	17 (44.74)
	Type III	4 (10.53)
Genetic confirmation, n (%)	Yes	38 (100)
Ventilator support, n (%)	IVA	17 (44.74)
	NIVA, permanent	2 (5.26)
	NIVA, partial	12 (31.58)
	NVS	7 (18.42)
Demographic data, n (%)	Metropolitan Region	18 (47.36)
	Other regions	14 (36.84)
	No data	6 (15.78)

SMA: Spinal Muscular Atrophy. IVA: Invasive ventilatory assistance. NIVA = Non-invasive ventilatory assistance. NVS: Non-ventilatory support.

Table 2. Quality of Life Survey (PedsQL™) scores in 38 children and adolescents with SMA (parent proxy-report)

Scale	n°	Mean ± SD	Median (IQR)	Range
Total score	38	51.92 ± 16.98	52.5 (38.75; 67.00)	16.00 to 89.00
Disease area	38	53.83 ± 18.11	54.41 (43.75;66.91)	14.71 to 91.18
Communication area*	38	44.30 ± 39.04	33.3 (0.00;83.33)	0.00 to 100.00
Family area	37	48.6 5± 23.14	45 (30.00;70.00)	10.00 to 90.00

*Variable with a not-normal distribution (Ryan-Joiner test).

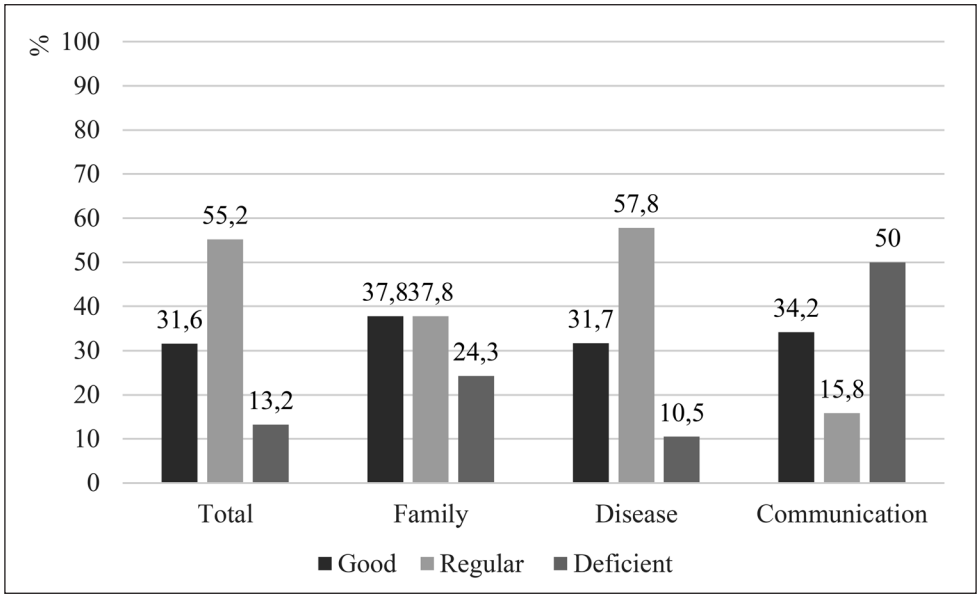

Figure 1. Quality of life measured with the Neuromuscular Module (PedsQL™): Scores for parent proxy-reports of 38 children and adolescents with SMA. Good: score > 60. Regular: score = 31 to 60. Deficient: score < 30.

Table 3. Quality of Life Survey (PedsQL™) univariate analysis of scores according to different factors. in 38 children and adolescents with SMA

Survey	Factor		n	Score	p
Total score	Age	≤ 6 years	15	49.2 ± 14.8	0.411 [a]
		> 6 years	23	53.7 ± 18.4	
	Gender	Female	18	55.6± 15.3	0.211 [a]
		Male	20	48.6± 18.1	
	Clinical type of SMA	Type I	17	46.5 ± 15.2	0.071 [a]
		Type II - III	21	56.3 ± 17.4	
	Residence	MR	18	50.2 ± 16	0.647 [a]
		Other regions	14	53.4 ± 20.9	
	Ventilatory support	NVS	7	59.3 ± 11.7	0.613 [a]
		NIVA	14	54.9 ± 19.9	
		IVA	17	46.5 ± 15.2	
Communication Area	Age	≤ 6 years	15	16.67 (0.0-25)	0.016[b]
		> 6 years	23	66.67 (16.67-100)	
	Gender	Female	18	62.5 (16.67-91.67)	0.096[b]
		Male	20	25.0 (0.0-75)	
	Clinical type of SMA	Type I	17	0.00 (0.0-25)	0.000[b]
		Type II - III	21	83.3 (45.83-95.83)	
	Residence	MR	18	16.67 (0.0-58.33)	0.012 [b]
		Other regions	14	66.67 (25-100)	
	Ventilatory support	NVS	7	83.3 (50; 91.7)	0.001[b]
		NIVA	14	75.0 (22.9; 100)	
		IVA	17	0.00 (0.0; 25.0)	

[a]ANOVA test. b: Kruskal Wallis test. SMA: spinal muscular atrophy. MR: MetropolJitan region. NVS: Non-ventilatory support. NIVA = Non-invasive ventilatory assistance. IVA: Invasive ventilatory assistance.

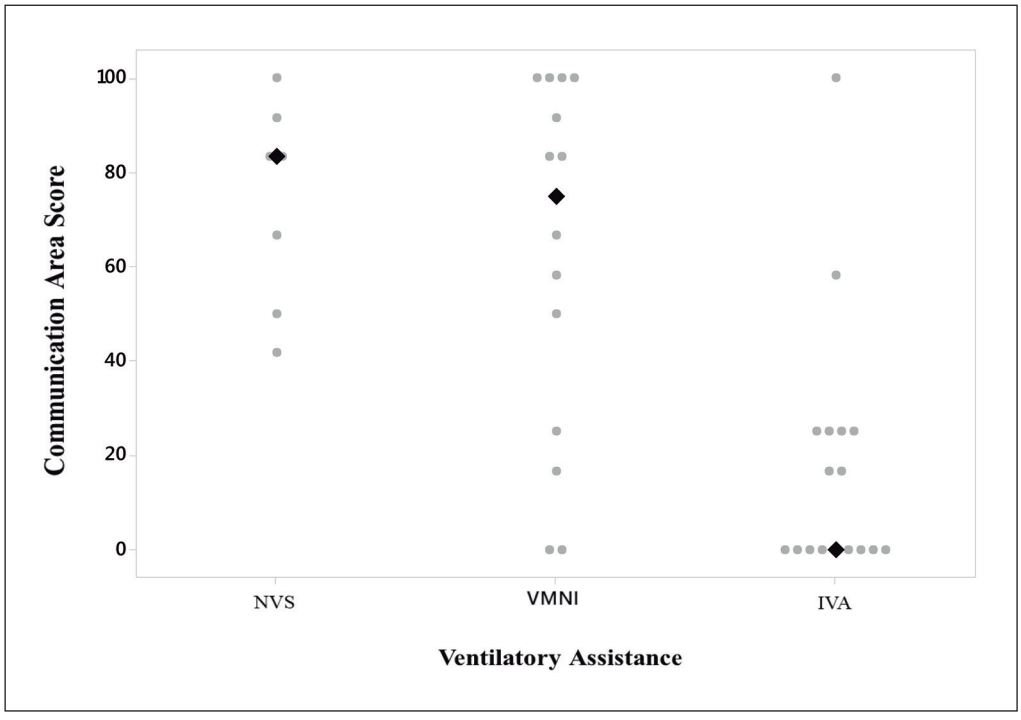

Figure 2. Quality of life in 38 children and adolescents with SMA: Communication Area of the Neuromuscular Module (PedsQL™) scores according to ventilatory support (*). Ventilatory assistance: NVS: Non-ventilatory support. NIVA = Non-invasive ventilatory assistance. IVA: Invasive ventilatory assistance. The grey spots correspond to individual values and black diamonds to Medians. *Kruskal Wallis test (p = 0.001).

trophy[22], in a study conducted in 2010 on the QoL of 44 patients using the same survey, the results were 59.6 ± 15.47 (Total Score), 60.28 ± 15.32 (Disease), 62.12 ± 27.81 (Communication), and 55.8 ± 24.92 (Family), all higher than those of our sample. Duchenne patients present greater independent mobility and verbal communication until more advanced stages of their disease, that might explain this difference.

The better overall score in SMA type II and III patients reached significance only in the Communication area, probably due to the inability of patients with SMA I to communicate verbally. In a recent systematic review on QoL in SMA[23] that included 15 studies, only 6 of them applied the same survey. The averages obtained in Disease, Communication, Family and Total Score were: 39, 4, 30 and 34 for SMA I, 54, 78, 49 and 56 for SMA II, and 68, 82, 69 and 69 for SMA III, respectively. It was found that the better the functional capacity, the better the quality of life. Our results were slightly higher in SMA I, except in Communication, and lower in SMA II-III, but the same trend remains.

However, it is also necessary to consider the suitability PedsQLTM neuromuscular module in SMA. Although it has been used to measure QoL in these patients[24], a systematic review[25], concluded that there is not yet a specific instrument that allows the evaluation of younger children with SMA I, due to the difficulty of verbal communication in this population.

Although the secondary degree of disability from the diseases affects the QoL[26], not always a linear relationship between them exist[27]. Indeed, patients with severe motor limitations can report a good QoL if they have the necessary support to develop their abilities. Our results agree with this statement, with a significant difference only in the Communication area, between the patients with a severe disability and the rest. Adequate access to comprehensive treatment and assistant technologies might be the principal factor playing a role in the final score in these patients[28]. Nevertheless, there are other factors, such as family support, social integration, and spirituality, among others, which also influence QoL[29,30].

The QoL varies according to the reality of each country and region[31]. However, there were no differences in the total scores of QoL between patients living in the capital of the country -with a better access to the health system-, and other regions. A similar approach to health care all over the country and the availability of an assisted home ventilation program in our public health system, which benefits the majority of participants, can explain this lack of differences between regions. The lower score in the Communication area in the Metropolitan Region was explained by the higher proportion of patients with SMA I.

The main strength of this study is that it addressed an unexplored area in Chile, including a significant sample representing the different types of SMA, considering its low incidence.

The study's limitations are related to the loss of few data, with incomplete records in the minority, as described in the results. Likewise, the survey was applied only to parents and caregivers and not to patients, since a significant proportion of the sample was under 5 years and the neuromuscular module is validated only for children over this age. Besides, it is challenging to confirm that a survey is answered without adults' intervention when applied by e-mail. Nevertheless, a good correlation has been described between the QoL surveys answered by parents and their children[32], and that the perception of the caregivers may be better than the one of the health team[33]. Also, the remote application is reliable and gives advantages in patients with limited mobility[34].

There was no estimate of socio-economic status, which can influence the access to health technologies and complementary care[35]. Also, four families of children under 2 years of age, all with SMA I, who may have had a lower QoL, were not included. A final important aspect to consider is that there might be a selection bias as this is a convenience sample, since the parents who decided to participate might be those with higher motivation. This work may serve as a baseline for future research in SMA, especially given the great and recent advances in its treatment.

Conclusions

The parents of most of the children and adolescents with SMA in this sample report a regular to good quality of life, communication was the most affected area, which was determined to a great extent by the motor function limitation. No differences were found in overall QoL scores when considering the type of SMA, ventilatory support, sex, age, or residence.

We hope that this study will add information to improve clinical practices and public policies, and strength the participation of civil organizations such as FAME, where families can become informed, collaborate, and improve the QoL of children and adolescents with SMA.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according 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 have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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Appendix 1: Neuromuscular module 3.0 of PedsQL™ Survey questions

Disease area
1. My child has trouble breathing
2. My child gets sick easily
3. My child is injured and / or gets a rash
4. My son's legs hurt
5. My child feels tired
6. My child feels a stiff back
7. My child wakes up tired
8. My child's hands are weak
9. My child has a hard time using the bathroom
10. My child has a hard time gaining or losing weight when he or she wants
11. My child has trouble using his hands
12. My child has a hard time swallowing food
13. My child takes a long time to bathe or shower
14. My child is accidentally hurt
15. My child takes a long time to eat
16. My child has a hard time turning over in bed at night
17. My child has a hard time traveling to different places with his equipment
Communication Area
18. My child has a hard time telling doctors and nurses how he feels
19. My child has a hard time asking the doctors and nurses
20. My child has a hard time explaining his illness to other people
Family Area
21. Our family has trouble planning activities like vacations
22. Our family has trouble for getting enough rest
23. I think money is a problem in our family
24. I think our family has a lot of problems
25. My child does not have the equipment they need

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