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Prevalence of Spinal Muscular Atrophy in the Era of Disease-Modifying Therapies: An Italian Nationwide Survey

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Disclosures:

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Abstract

Objective: Spinal muscular atrophy (SMA) is a neurodegenerative disorder caused by mutations in the SMN1 gene. The aim was to assess the prevalence of SMA and treatment prescription in Italy.

Methods: An online survey was distributed to 36 centers identified by the Italian government as referral centers for SMA. Data on number of SMA patients subdivided according to age, type, *SMN2* copy number and treatment were collected.

Results: 1255 SMA patients are currently followed in the Italian centers with an estimated prevalence of 2.12/100000. Of the 1255, 284 were type I, 470 type II, 467 type III and 15 type IV with estimated prevalence of 0.48, 0.79, 0.79 and 0.02/100000 respectively. Three SMA 0 and 16 presymptomatic patients were also included.

Around 85% were receiving one of the available treatments. The percentage of treated patients decreased with decreasing severity (SMA I: 95.77%, SMA II: 85.11%,SMA III: 79.01%).

Discussion: The results provide for the first time an estimate of the prevalence of SMA at the national level and the current distribution of patients treated with the available therapeutical options. These data provide a baseline to assess future changes in relation to the evolving therapeutical scenario.

Introduction

A recent review summarizing epidemiological data on 5q Spinal muscular atrophy (SMA) reported an overall incidence of 8/100,000, with a marked inter-country variability [1]. Type I SMA cases are the most frequent (60%), with type II occurring between 20-27% and type III between 12-20% [1, 2]. Because of the reduced survival (around 5-8% at 2 years) there is a large difference between incidence and prevalence data in type I infants. Studies performed before the advent of the new therapies report prevalence values of 0.04-0.28/100000 for type I and around 1.5/100000 for type II and III [3]. The aim of the study was to assess the prevalence for SMA and the number of patients treated with the different therapeutic options across Italian reference centers.

Methods

The study includes data from all the 36 centres identified by the Italian government as referral centers for SMA. Approval was granted by the Ethics Committee of Fondazione Gemelli (26/05/2020 N.1894). An online survey was performed to obtain an estimate of the number of patients currently followed and treated. Data were manually collected from hospital medical records

from all patients with a diagnosis of 5qSMA attending the centers. Survey completion rate was 100%. Period prevalence was calculated as the proportion of persons affected by SMA in one year divided by the Italian population at 2021 (59.258.000 persons). A global identifier number was used to avoid patients being recorded more than once. Requests for anonymized data not published within this article should be addressed to the principal investigator (EM). Details on methodology can be found in the eMethods.

Results

There were 1255 5qSMA patients (604 adults, 651 children) across the centers. The estimated prevalence for all cases of SMA, including presymptomatic patients, was 2.12/100000 inhabitants. SMN2 copies were available in 972 of the 1255 (77.45%) (Table 1 and Figure 1).

Type I: this included 284 patients. The estimated prevalence is 0.48/100000. Of the 284, 272 were treated with the new therapies. Figure 2 shows details of the therapies distribution and patients who switched from one therapy to another.

Type II: this included 470 patients. The estimated prevalence is 0.79/100000.Of the 470, 400 patients were treated with the new therapies;

Type III: this included 467 patients. The estimated prevalence is 0.79/100000. Of the 467, 369 were treated with the new therapies. Table 1 reports details of the distribution in all SMA types (0-IV).

Discussion

Our nationwide survey includes 1255 SMA patients with an estimated prevalence of 2.12/100.000 (CI 95%= 0.013-0.029). This value is higher than that (1.81, CI 95%= 0.010-0.026) recorded in 2016 by the Institutional National Registry of Rare Diseases of the ISS. The higher number was only partially influenced by presymptomatic patients as neonatal screening was limited to 2 of the

20 Italian regions. In contrast, the large number of adults previously lost at follow up, going back to the centers to discuss the new treatments[4], may have contributed. The estimated prevalence of type I was 0.48/100000. This is higher than previously reported (0.04-0.28)[3], reflecting the higher survival rate beyond two years compared to the 5-8% reported in natural history studies[5-7]. Our results confirmed previous findings of a strong association between SMN2 copy number and severity of SMA. In our nationwide cohort copy number was available in nearly 80%, this value reflecting the ongoing effort to obtain this information in patients in whom this was not available.

The survey also allowed to establish the number of treated patients and of possible therapeutic changes over time. The high number of patients currently treated with nusinersen largely reflects the fact that this was the first drug to be approved and the only available option for over three years. At the time of the survey Risdiplam was only available for compassionate use and onasemnogene abeparvovec could only be prescribed to type I infants younger than two years and with a weight below 13.5 Kgs. The percentage of treated patients decreased with decreasing severity. Further follow up will allow to establish how these numbers will change with the recent commercial availability of Risdiplam.

Our results establish for the first time the national prevalence of SMA also subdivided according to types, in the era of disease modifying therapies. Our nationwide registry will allow to monitor changes over time and to capture the evolving scenario due to changes in the drug labels and to a wider distribution of neonatal screening.

Appendix 1: Authors

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Figures

Figure 1. Frequency of SMN2 copy numbers in patients with SMA. Key to figure: (a) Frequency of SMN2 copy numbers according to SMA type (b) frequency of SMA types according to SMN2 copy number. The SMA III patient with SMN1copy= 1+G287R was not included in the figure as this is a positive modifier of the SMA phenotype.

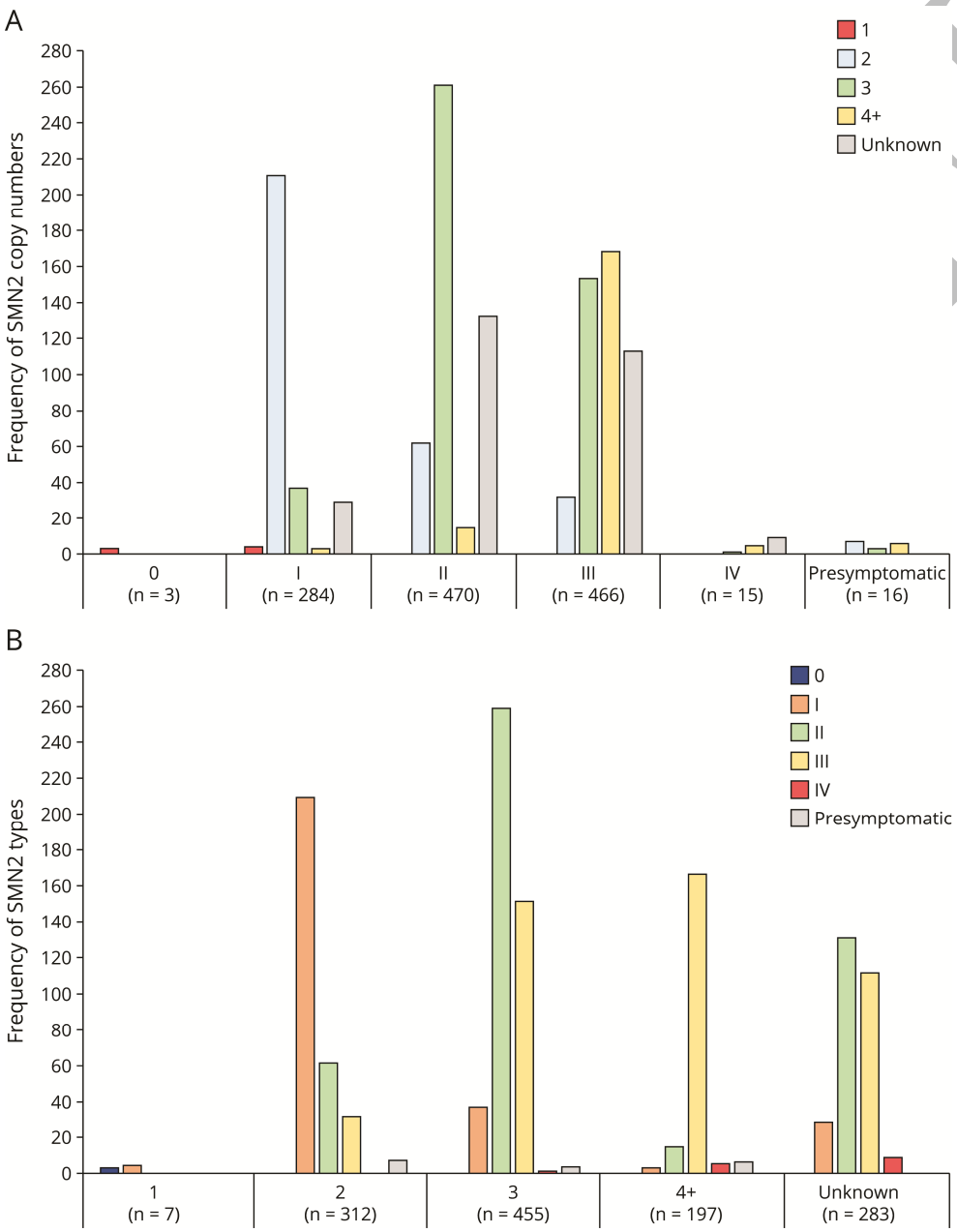
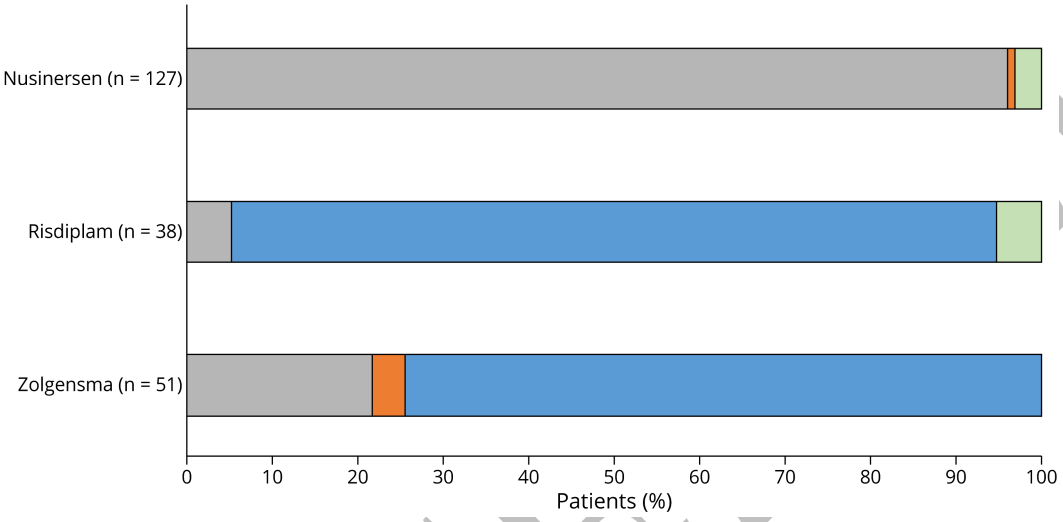


Figure 2. Distribution of SMA I patients among available treatments. Colour key: Blue= Switched from Nusinersen to Risdiplam/Zolgensma, Orange= Switched from Risdiplam to Nusinersen/Zolgensma, Green= Switched from Zolgensma to Risdiplam/Nusinersen, Dashed grey= Remained on the same treatment, no switch was recorded.



Tables

Characteristics	**N (%)**
Adults	604 (48.13%)
Pediatric	651 (51.87%)
SMA type	1255 (100%)
Pre-symptomatic	16 (1.27%)
Type 0	3 (0.24%)
Type I	284 (22.63%)
Type II	470 (37.45%)
Type III	467 (37.21%)
Type IV	15 (1.20%)
***SMN2* copy number**	
1 SMN2	8 (0.64%) SMA 0: 3 SMA I: 4 SMA III: 1 (+G287R)
2 SMN2	312 (24.86%) SMA I: 211 SMA II: 62 SMA III: 32 PRESYMPTOMATIC: 7
3 SMN2	455 (36.25%) SMA I: 37 SMA II: 261

	SMA III: 153 SMA IV: 1 PRESYMPTOMATIC: 3
≥4 SMN2	197 (15.70%) SMA I: 3 SMA II: 15 SMA III: 168 SMA IV: 5 PRESYMPTOMATIC: 6
Unknown SMN2	283 (22.55%) SMA I: 29 SMA II: 132 SMA III: 113 SMA IV: 9
Patients treated with disease modifying therapies	
Type I	272/284 (95.77%) Nusinersen: 127/272 (46.69%) Risdiplam: 38/272 (13.97%) Onasemnogene abeparvovec: 51/272 (18.75%) Clinical trials: 56/272 (20.59%)
Type II	400/470 (85.11%) Nusinersen: 163/400 (40.75%) Risdiplam: 148/400 (37.00%) Clinical trials: 89/400 (22.25%)

Type III	369/467 (79.01%) Nusinersen: 321 (68.74%) Risdiplam: 23 (4.92%) Clinical trials: 25 (5.35%)

Table 1. Epidemiological characteristics and *SMN2* copies of SMA patients in 35 Italian reference centers

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