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Prevalence of Spinal Muscular Atrophy in the Era of Disease-Modifying Therapies

An Italian Nationwide Survey

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Abstract

Objective

Spinal muscular atrophy (SMA) is a neurodegenerative disorder caused by mutations in the SMN1 gene. The aim of this study 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 the number of patients with SMA subdivided according to age, type, *SMN2* copy number, and treatment were collected.

Results

One thousand two hundred fifty-five patients with SMA are currently followed in the Italian centers with an estimated prevalence of 2.12/100,000. Of the 1,255, 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 0.02/100,000, respectively. Three patients with SMA 0 and 16 presymptomatic patients were also included. Approximately 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%).

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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.

A recent review summarizing epidemiologic data on 5q spinal muscular atrophy (SMA) reported an overall incidence of 8/100,000, with a marked intercountry variability.[1] Type I SMA cases are the most frequent (60%), with type II occurring between 20% and 27% and type III between 12% and 20%.[1,2]

Because of the reduced survival (approximately 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 0.04–0.28/100,000 for type I and approximately 1.5/100,000 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.

Table 1 Epidemiologic Characteristics and *SMN2* Copies of Patients with SMA in 35 Italian Reference Centers

Characteristics	N (%)
Adults	604 (48.13%)
Pediatric	651 (51.87%)
SMA type	1,255 (100%)
Presymptomatic	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%)

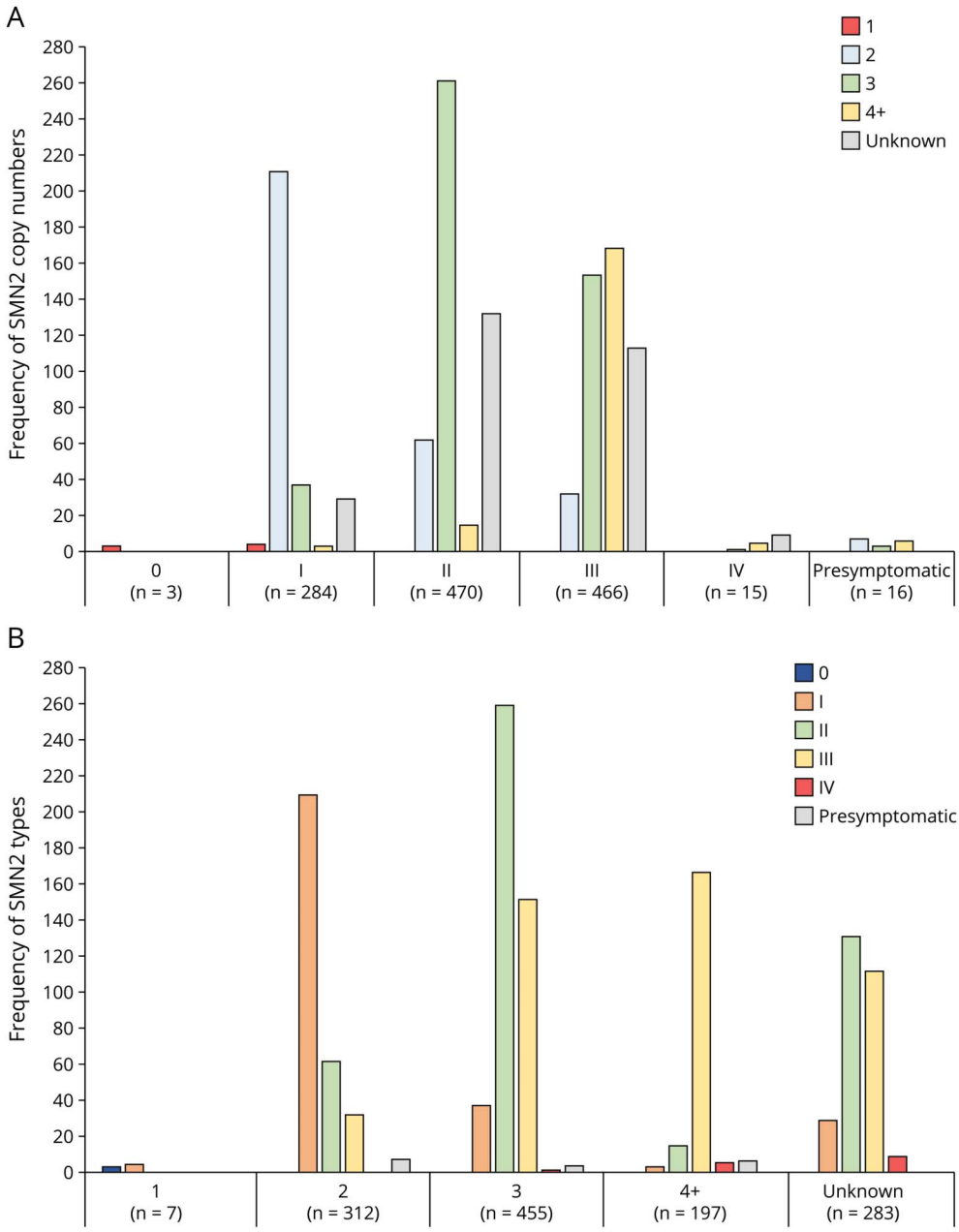
Methods

The study includes data from all the 36 centers 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 (links.lww.com/WNL/C506).

Results

There were 1,255 patients with 5qSMA (604 adults and 651 children) across the centers. The estimated prevalence for all cases of SMA, including presymptomatic patients, was 2.12/100,000 inhabitants. SMN2 copies were available in 972 of the 1,255 (77.45%) (Table 1 and Figure 1).

Figure 1 Frequency of *SMN2* Copy Numbers in Patients With SMA



Key to figure: (A) Frequency of SMN2 copy numbers according to SMA type and (B) frequency of SMA types according to SMN2 copy number. The patient with SMA III and SMN1copy = 1 + G287R was not included in the figure because of its role as positive modifier of the SMA phenotype.

Type I: this included 284 patients. The estimated prevalence is 0.48/100,000. 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 0.79/100,000.Of the 470, 400 patients were treated with the new therapies;

Type III: this included 467 patients. The estimated prevalence is 0.79/100,000. 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 patients with SMA with an estimated prevalence of 2.12/100.000 (CI 95% = 0.013–0.029). This value is higher than the one (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 because 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 0.48/100,000. This is higher than previously reported (0.04–0.28),[3] reflecting the higher survival rate beyond 2 years compared with 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 more than 3 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 2 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.

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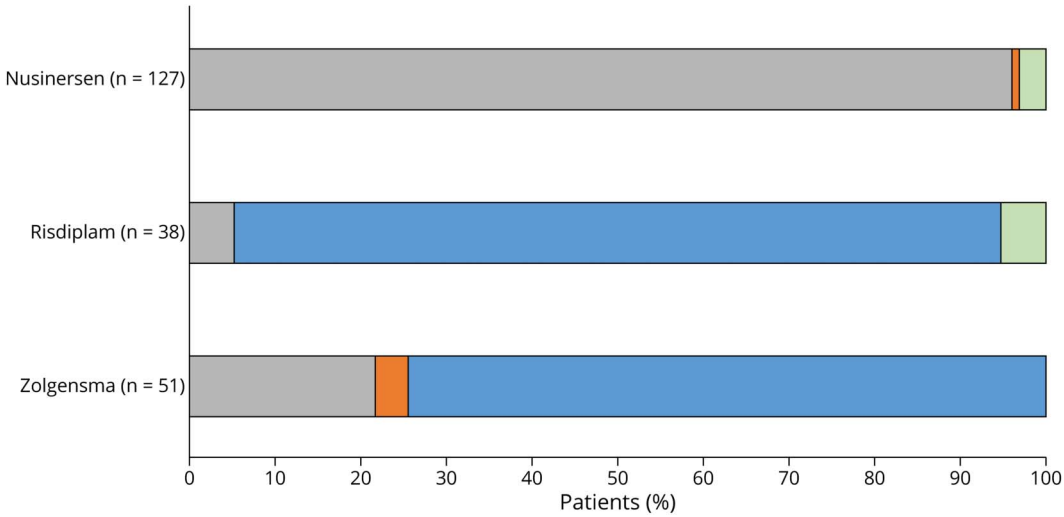
Study Funding

Doctor Pera MC is supported by GR-2018-12365706 (Italian Health Ministry). This research was partially supported by GR-2018-12365706 and Biogen that are supporting the Italian registry. Funders had no role in the study design; in the collection,

Figure 2 Distribution of Patients With SMA I Among Available Treatments



Colour key: Blue = Switched from nusinersen to risdiplam/onasemnogene abeparvovec, Orange = Switched from risdiplam to nusinersen/onasemnogene abeparvovec, Green = Switched from onasemnogene abeparvovec to risdiplam/nusinersen, Gray = Remained on the same treatment, no switch was recorded.

analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Disclosure

G. Coratti, V. Sansone, A. D'Amico, C. Bruno, S. Messina, R. Masson, A. Trabacca, L. Maggi, M.A. Donati, M.C. Pera, F. Ricci, T. Mongini, M. Pane, E. Mercuri report personal fees from BIOGEN S.R.L., Roche, AveXis, and Novartis outside the submitted work; G.P. Comi reports personal fees from Roche and Novartis Gene Therapies outside the submitted work; G. Coratti reports personal fees from Genesis Pharma and Biologix outside the submitted work; I. Bruno reports personal fees from Biogen outside the submitted work; E. Pegoraro reports from personal fees from Biogen and Roche; M. Ricci, A. Capasso, M. Coccia, V. Vacchiano, G. Siciliano, N. Carboni, M. Turri, M. Filosto, G. D'angelo, R Zuccarino, D. Gagliardi, I. Simone, L. Ruggiero, A. Varone, L. Verriello, A. Berardinelli, C. Agosto, A. Pini, M.A. Maioli, S. Siliquini, M. Garibaldi, S. Previtali, F. Brighina, L. Passamano, D. Taruscio, S. Boccia have nothing to disclose. Go to Neurology.org/N for full disclosures.

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Continued

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Coinvestigators are listed at links.lww.com/WNL/C507.

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- You can include a maximum of 5 authors (including yourself)