Polish Registry of SMA Patients

Anna Łusakowska[1], Anna Kaminska[1], Piotr Działa[2], Katarzyna Janiszewska[3], Przemysław Grochowski[4], Anna Kostera-Pruszczyk[1]

1. Department of Neurology, Medical University of Warsaw, Poland; 2. IT service, Medical University of Warsaw, Poland; 3. Clinical Center of Medical University of Warsaw, Poland; 4. Student Research Group of Department of Neurology, Medical University of Warsaw, Poland
Corresponding author: anna.lusakowska@wum.edu.pl

Introduction

Rare disorders, such as neuromuscular diseases, require a specific approach due to a small number of patients, difficulty in diagnosis and lack of effective treatment in most cases. During the last two decades, many European initiatives have been set up to improve the quality of care and to accelerate an efficient treatment of patients with rare disorders. In 2007, the TREAT - NMD project (http://www.treat-nmd.eu) was initiated as a European Committee (EC) funded "Network of excellence" with the purpose of supporting translational research in the field of neuromuscular diseases. One of the important tools to achieve the aim of TREAT-NMD was creation of the Global Database based on national patient registries. A limited but uniform data of a high-quality permits studies on epidemiology, natural history and phenotype - genotype correlation on an unprecedented scale in rare diseases. When the therapies become available, the registries will play a crucial role in post-marketing surveillance ("real-world" data). The rationale to focus on the SMA Registry is the poor prognosis for untreated SMA patients as well as a need to evaluate the real world perspective of effective therapies. Spinal muscular atrophy (SMA) is an autosomal recessive disease characterized by a progressive muscle weakness and atrophy due to the degeneration of motor neurons. SMA is the most common genetic cause of death during childhood. The phenotype of SMA is variable and extends from severely affected children with hypotonia and generalized weakness at birth, to adult patients with mild proximal muscle weakness of lower legs. Based on the age of the onset and the best motor function achievement, five types of SMA are distinguished (0-IV). In most cases, SMA is caused by a homozygous deletion of survival motor neuron gene1 (SMN1). A nearly identical SMN2 gene acts as the main phenotype modifier. The number of SMN2 copies correlates with the clinical course of SMA. Currently, two breakthrough therapies are approved for SMA: Spinraza (nusinersen) in USA and Europe and Zolgensma (onasemnogene abeparvovec) in USA.

Aim

The aim of this study is to present the Polish Registry of SMA patients and its role in their care and treatment.

Material and Methods

The Polish Registry of SMA Patients

The Polish Registry of SMA Patients was created at the Department of Neurology, Medical University of Warsaw (MUW), within the project "Clinical and genetic characteristic of neuromuscular diseases for future application of gene therapy". The Registry covered the patients from all of Poland.

Data collection and entry method

The data was collected by using paper or electronic version of questionnaires. The questionnaires were completed by doctors or patients and transmitted to the Department of Neurology. The informed consent (approved by Ethic Committee - KB/180/2008) signed by the patient or a legal representative was required before the registration. The genetic test result confirming diagnosis SMA was required to be attached to the questionnaire. The data was verified and next introduced to the Registry by curators who are neurologists. The questionnaire includes the mandatory and highly recommended items covering these proposed by TREAT–NMD in 2007. In 2018, the dataset was expanded according to recommendations established in May 2017 by TREAT-NMD Global Database Oversight Committee (TGDOC).

Results

Number of patients and their distribution by type of SMA, age and gender.

The number of patients registered from 2010 to February 2019 is presented in Fig.1. The total number of enrolled patients was 675. Overall, male patients slightly outnumbered female patients (319F vs. 356M). The distribution of number of patients by sex and type of SMA is presented in Fig.2.
Age distribution of all patients by sex is shown in Fig. 3. Adult patients (age 18 y. or more) were slightly in a higher proportion than pediatric patients (355 vs.320; 53% vs.47%). The largest number of registered patients were young adults between 18 y. to 29 y. (159; 24%). Proportion of female to male patients was similar in all groups of age except the group of patients between 40-49 y.
18 patients (11 with SMA1 and 7 with SMA2) were treated with Spinraza.

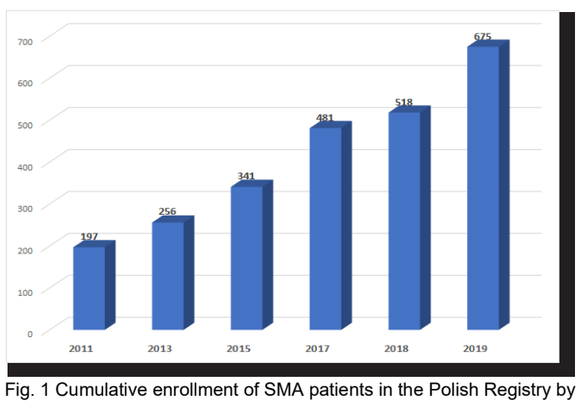


Fig. 1 Cumulative enrollment of SMA patients in the Polish Registry by year

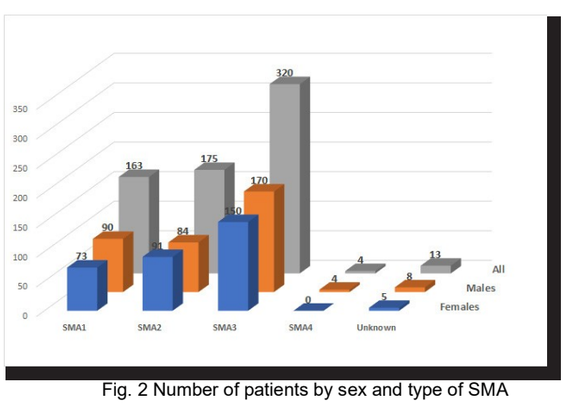


Fig. 2 Number of patients by sex and type of SMA

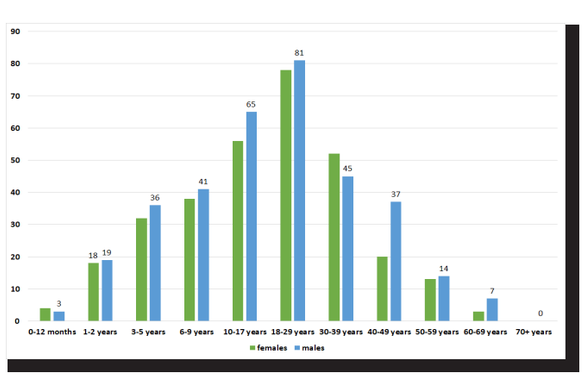


Fig. 3. Number of SMA patients by sex and current age

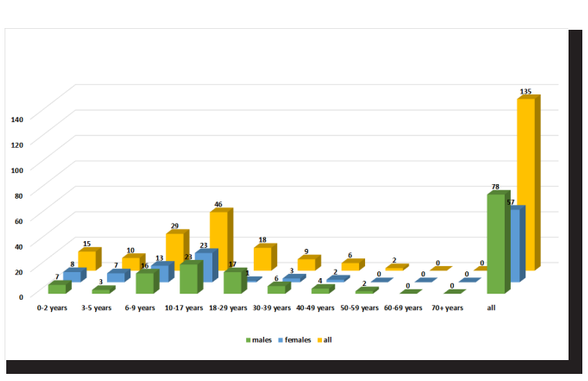


Fig. 4. Distribution of age of immobilization in SMA3 data for 135 of 164 patients

Motor functions

In all SMA3 patients, 51% of them (164 of 320) lost the ability to walk (Fig.4). Most of them were immobilized between 10 y. -17 y. of age. A mean age of immobilization in SMA3 patients was 14.3 y., with 12 y. (±22 m.) for females and 15.9 y.(± 20 m.) for males. The mean age of onset in these group was 22m (±9m.) and 30m (± 22m.) for females and males, respectively. For 80 patients only of 164 who were immobilized the age of onset and age of immobilization were known. Within this group of 80 patients, the percentage of patients who preserved the ability to walk as a function of duration of the disease is presented in Fig. 5. The rate of immobilization was found to be faster in females than in males. None of SMA3 patients was treated with Spinraza.

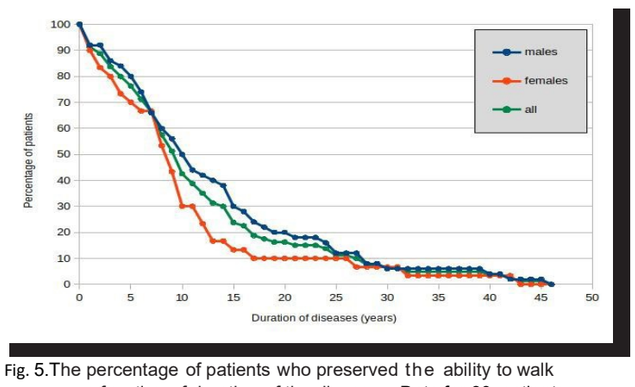


Fig. 5.The percentage of patients who preserved the ability to walk as a function of duration of the disease. Data for 80 patients who lost ambulation

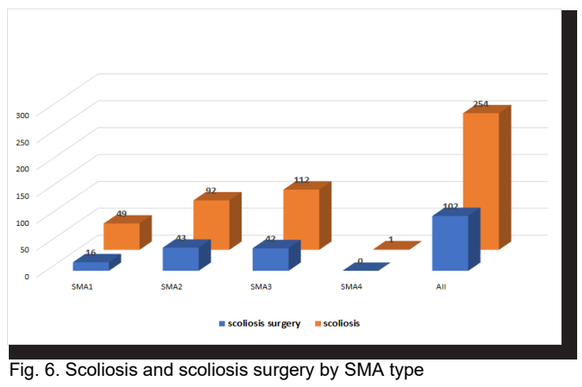


Fig. 6. Scoliosis and scoliosis surgery by SMA type

Feeding, pulmonary function and scoliosis

Only about 10% of all patients in the Registry (60 patients) needed feeding assistance – 10 patients used a nasal tube and 50 patients – a gastric tube (PEG); 80% of them were SMA1 patients. A ventilation support was used by 20% (128) of all patients. Invasive ventilation was used by 8% of patients, 80% of them were SMA1 patients. Scoliosis was diagnosed in 254 (38%) patients, and surgery intervention was done in 102 (40%) of them. Scoliosis was more frequent in SMA2 than in other groups of patients: 30%, 53% and 35% in SMA1, SMA2 and SMA3 respectively (Fig.6).

Total global impression

The total global impression, assessing the changes in health condition in the last six months, was carried out by patients themselves or by their caregivers. The data was available for 405 patients. The vast majority of patients (77%) declared no change or minimally worse health, regardless of the type of SMA. Essential improvement was experienced in 9 of 18 patients treated with nusinersen An overall worsening in health in the respondent's opinion occurred in about 10% of patients. This group of patients comprised individuals with SMA1, SMA2 and SMA3 in similar percentage.

Genetic data

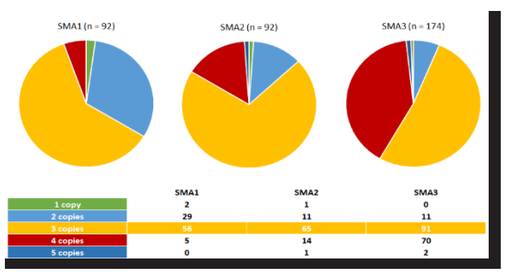
In all patients, the diagnosis of SMA 5q was confirmed by genetic test. A distribution of the number of copies of SMN2 for all SMA types (data was available for 358 patients, 53%) is presented in Fig.7.

Geographical distribution of SMA patients in Poland

The residency data allowed analysis of the distribution of SMA patients according to SMA types in 16 administrative units (voivodeships) of Poland which correspond to the National System of Health Divisions. The 2 largest areas – Mazowsze and Wielkopolska and the province with the largest density of population in Poland - Śląsk - comprise 40% of all registered SMA patients in Poland, Fig.8.

Registry impact on care and treatment of SMA patients.

Department of Neurology MUW was recognized as a clinical trial site by TREAT-NMD. Up to date, five feasibility studies for clinical trials have been carried out using the Registry and resulted in inclusion of 36 patients into clinical trials. All feasibility studies were carried out according to procedures defined by TREAT-NMD. Actually the Registry has been used for recruitment of patients within national program of treatment with nusinersen.



	SMA1	SMA2	SMA3
1 copy	2	1	0
2 copies	29	11	11
3 copies	56	65	91
4 copies	5	14	70
5 copies	0	1	2

Fig.7. Genetic data: number of *SMN2* copies in SMA types

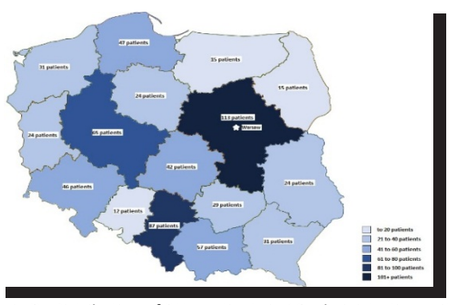


Fig.8. Distribution of SMA patients in 16 administrative units in Poland

.

Conclusions

In rare disorders such as SMA, the Registry plays a crucial role in the studyof the natural history of the disease. This knowledge is very important in times when new therapies become available and will change the natural history of SMA, producing new phenotypes of the disease. As new therapies have been continuously developed, the Registry plays a vital role in conducting the feasibility study and in recruitment process, shortening the path from the biopharmaceutical company to the suitable patients in clinical trials. Currently, a new challenge for the Registry is that it can play a pivotal role in post marketing surveillance to assess the new drugs efficacy and safety in "real world" in response to the emergence of new therapies. An international collaboration is necessary for a better understanding of the nature of the diseases, consequences of the new treatment as well as for improvement in the standards of care for SMA patients.

Acknowledgment: grant 641/N-TREAT/09/2010/0 and partially supported with Biogen grant 1WC/5BIOGEN/17