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Frailties and critical issues in neuromuscular diseases highlighted by SARS-CoV-2 pandemic: how many patients are still "invisible"?

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Almost 90% of neuromuscular diseases (NMDs) are classified as rare diseases, defined as conditions affecting less than 5 individuals in 10.000 (0.05%). Their rarity and diversity pose specific challenges for healthcare and research. Epidemiological data on NMDs are often lacking and incomplete. The COVID-19 pandemic has further highlighted the management difficulties of NMDs patients and the necessity to continue the program of implementation of standard of care. This article summarizes the Italian experience during pandemic.

Key words: COVID-19 pandemic, neuromuscular diseases

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Note of the Editor

This paper summarizes the speeches on *Fragility and critical issues related to the management of patients with neuromuscular disorders*, presented during the webinar organized by the Italian Association of Myology (AIM) in September 2021. They had as focus the management of the patients with neuromuscular disease in the period of the pandemic, at the National level.

Introduction

Rare diseases (RDs) are defined as conditions affecting less than 5 individuals in 10.000 (0.05%) [1]. Despite their low prevalence, RDs are collectively common conditions involving from 6 to 10% of the European population, raising critical issues for the whole community in terms of best clinical practices, diagnosis achievability, health services planning and public health programs.

RDs are often complex conditions requiring integrated, long-term care delivery settings and highly specially designed management. Although their chronic and often progressive course, long-term complications of RDs can be lessened or delayed by early diagnosis, allowing an optimal management and prompt supportive and/or targeted therapies if available. In addition,

appropriate and timely diagnosis ameliorates patient health status reducing psychological and social burden of the diseases and allows proper genetic counselling.

Almost 90% of neuromuscular diseases (NMDs) are classified as rare diseases. NMDs are a broad group of neurological disorders that represent a major cause of mortality and lifelong disability in children and adults. NMDs are caused by acquired or genetic defects of motoneurons, peripheral nerves, neuromuscular junctions or skeletal muscle. They may be difficult to recognize, result in progressive muscle weakness and wasting, often leading to difficulties in swallowing and breathing or in cardiac failure. Patients can experience long delays in diagnosis and, in some cases, may be forced to move from their own towns in order to access to the best medical care. Their rarity and diversity pose specific challenges for healthcare and research [2].

NMDs and standard of care in Europe

In order to strengthening the fight against complex and rare diseases, in 2017 the European Commission created the European References Networks (ERNs). These are virtual networks, each focused on a specific group of rare or low-prevalence diseases, that involve national Health Care Providers (HCPs) across Europe. ERNs seek in tackling rare diseases by easing diagnostic processes and equalizing therapeutic approaches, making national and European health systems more efficient, accessible and resilient. There are 24 ERNs involving 25 European countries, more than 300 hospitals with over 900 HCP units covering all major disease groups so far. Though each ERN focuses on a specific set of diseases, HCPs belonging to different ERNs can easily interface from each other. In these networks, medical specialists across different disciplines are connected in a sort of 'virtual' advisory board trough a dedicated IT platform and telemedicine tools. EURO-NMD is a European Reference Network for the thematic grouping of rare neuromuscular diseases (NMDs) [3].

The expertise for diagnosis and management available in each HCP could be enriched by data sharing, thus resulting in an increasing request for cross-border e-health technologies providing means for teleconsulting and exchanging knowledge across medical experts. The use of telemedicine is at the basis of the ERN network to diagnose and treat rare and complex diseases at a continental level, providing the critical advantage of expanding the set of knowledge available to any patient. Periodic meetings and boards are instrumental for networks maintenance, but one of the most outstanding telemedicine tools in ERN's network strengthening is the Clinical Patient Management System (CPMS) (https://ern-euro-nmd.eu). The CPMS is a digital platform where clinicians belonging to different HCPs can discuss about clinical cases in a secure way for patients' data protection. Using the CPMS, it is possible for health professionals to discuss about patients by sharing images, clinical reports and organizing video meeting where clinicians can discuss vis à vis. The CPMS is the foundation of one of the most important ERN core tasks: reducing health care inequalities within the European Union by providing access to expert specialized care to all patients with rare and complex diseases. In short, cases discussions happen through the opening of so-called "panels", where the clinician requiring a medical consultation provides a detailed description of clinical case. Data sharing (e.g. radiological images, exams reports, laboratory findings) via panels is possible, so that advices on virtual consultation can be easily provided by the specialists invited both using the chat tool and via video meetings. Moreover, patient's data are available for databases and registries. Overall, the CPMS could represent a new digital tool to improve data collection of patients with rare diseases across different ERNs and countries, also implementing national registries.

Efforts and levels of criticality in collecting epidemiological data on NMDs

It is estimated that in Italy at least 80,000-100,000 patients are affected by NMDs[4]. There are likely to be at least over 200 different forms of NMDs. However, epidemiological data on NMDs are often lacking and incomplete. The classifications of NMDs, also in the light of diagnostic advances and the best molecular characterization by the discovery of new causative genes, is constantly evolving. On the other hand, the lack of unambiguous indicators (for example, incomplete hospital discharge forms *Schede di Dimissione Ospedaliere* SDO, ICD-9 classifications, exemption codes for rare diseases that are not always diseases specific, out-patient cases which escape correct disease classification) makes data collection complicated, also from an administrative point of view. In last decade, this has led to an increasing awareness, also by the institutional entities, of the need of tracing rare patients, for example with development and implementation of disease registries.

In Italy the National Register of Rare Diseases (RNMR) has been established by the Istituto Superiore di Sanita' (ISS) (art. 3, Ministerial Decree 279/01) with aims to carry out the surveillance of RDs, to obtain epidemiological data, and finally support research and promoting the comparison between healthcare professionals. All Italian Regions, with different times and methods, have formally identified accredited clinical referring centers of

the National Rare Diseases Network and have established the regional/interregional registers. Since 2001 the RNMR has collected data from 20 regional or interregional registers. However, these data can be still incomplete and not to fully describe the clinical reality in the different regions. We can recognize several criticalities. It is conceivable that a submerged number of undiagnosed or not taken on care of cases continues to exist, especially in the peripheral areas far from NMDs referring centers. Moreover, there is the possibility that patients remain untracked as rare patients since they can benefit also from a non-specific disease exemption code. Therefore, the lack of unique indicators to track rare NMDs patients makes difficult to collect and merge data coming from different administrative sources.

In collaboration with the Agenzia Regionale di Sanità (ARS), a technical organism of the Tuscany Region with consultancy and research purposes (authors EG and PF), the clinicians of Neurology Unit- Department of Clinical and Experimental Medicine (GR, FT and GS) performed an epidemiological survey on NMDs patients residing in Tuscany. To identify the prevalence of patients affected by NMDs and overcome the possible limitations in using only data coming from the Tuscany Region Register of rare diseases (as discussed above), established *current health flows* have been used as data sources, originally thought for administrative-financial purposes but with secondary potential applications also for epidemiological purposes: a) hospitalizations in facilities affiliated with the regional health system converging in the SDO flow (hospital discharge forms, ICD9 CM encoding); b) exemptions codes from rare disease register; c) data of civil registry office. Analysis results opportunely filtered and thus extracted are summarized in Table I. This analysis showed that the prevalence of patients with NMDs x 1000 Tuscan residents as of January 1, 2019 is equal to 1.8 (about 0.2%), which corresponds to expectations based on literature [5-10]. The analysis also made it possible to stratify the patients according to the different forms of diseases, data also consistent with the expectations. This would therefore confirm that the algorithm selected on the basis of administrative data is sensitive in tracking patients with NMD diseases. Nonetheless, for some diseases, such as spinal muscular atrophy (SMA), we obtained higher rate of prevalence than expected, also based on cases known in our Center. In ruling out any founder effect on this result, we interpreted that as due to a possible bias linked to the lack of unique disease codes for SMA that also select patients with other diagnoses. In fact, if we further stratify the selected cases in the different subgroups of clinical codes/forms, as shown in Figure 1, we observe that the number of registered cases diagnosed with Werdnig-Hoffmann disease and Kugelberg-Welander disease is lower and closer to the real estimates of the clinical practice [8]. Nevertheless, it is likely, however, that there are still "invisible patients", that is cases not known to the referring centers. Notably, concerning SMA, it is considerable that in this last years the availability of new therapies and communication also through non-institutional channels such as patient associations should have led to more opportunities to contact by patients themselves with the referring centers.

COVID-19 pandemic and vaccination programs: the Italian experience and roles of patients association

NMDs patients felt the impact of SARS-CoV-2 pandemic in many ways, including concern for worsening of disease course and respiratory status with infection [11,12]. Since the vaccines against COVID-19 have being available, great hope for protection against the virus but also numerous questions and uncertainties about safety and possible side effects in NMDs emerged among patients' community.

From December 2020 - January 2021 European countries had started to develop plans to roll out their vaccine programs, and have necessarily had to adopt strategies with prioritization.

The scientific community (on behalf of World Muscle Society: www.worldmusclesociety.com, TREAT NMD, and in Italy the Italian Association of Myology and Peripheral Nervous System Association) strongly advocated that patients with NMDs should be considered as a high risk, priority group and supported statements made from organizations around the world calling for prioritization for vaccination for individuals affected with NMDS and their care givers.

In Italy the first Ministerial Decree on February 2021 regarding national vaccination program, that identified patients' priority groups, did not include the majority of NMDs forms, which then led to a subsequent rapid correction and inclusion of these diseases in the following weeks, thanks also to the prompt intervention of technical scientific committee of health ministry, scientific associations and patients' community. Moreover, in the early phases of the vaccination program, the different regions along the country had not yet equipped themselves with IT platforms which then allowed and facilitated the direct access for patients with their exception codes to booking the vaccine in the following months.

Therefore, the first recruitment of patients had been difficult with a non-standardized methodology on the national territory. For example, in Tuscany the clinical referring centers have had the task of contacting by themselves patients directly, and this had led to the identification of some cases that were not known to the centers because they were fol-

Table I. Prevalence of neuromuscular disorders in Tuscany.

ICDIX disease code	Rare disease identification code	Disease description	Hospital Discharge Form Codes Number (SDO)	Disease-specific Identification Codes Number (SEA)	SDO ∩ SEA	Total	Prevalence x 1000 Tuscany residents
35781	RF0180	**Chronic inflammatory demyelinating polyneuropathy**	**1.069**	**27**	**15**	**1.111**	**0.3**
3580	034	Miasthenia gravis	387	219	219	825	
35800		Miasthenia gravis without acute exacerbation	295	0	146	441	
35801		Miasthenia gravis with acute exacerbation	145	0	67	212	
		Miasthenia gravis	**827**	**219**	**432**	**1.478**	**0.4**
33520	RF0100	Amyotrophic lateral sclerosis	303	26	107	436	
33529		Other motor neuron diseases	87	0	26	113	
3352	RF0100	Motorn neuron disease	78	0	7	85	
33524	RF0110	Primary lateral sclerosis	39	6	15	60	
33522		Progressive bulbar palsy	16	0	6	22	
33521		Progressive muscular atrophy	39	0	6	45	
		Amyotrophic lateral sclerosis/motor neuron diseases	**562**	**32**	**167**	**761**	**0.2**
3350	RFG050	Werdnig-Hoffmann disease	30	11	6	47	
33510	RFG050	Spinal muscular atrophy, not specified	23	5	8	36	
33519	RFG050	Other spinal muscular atrophies	22	8	5	35	
3351		Spinal muscular atrophy, not specified	14	0	12	26	
33511	RFG050	Kugelberg-Welander disease	7	0	4	11	
		Spinal muscular atrophy	**96**	**24**	**35**	**155**	**0.0**
3591	RFG080	Hereditary progressive muscular dystrophy	376	116	162	654	
		Muscular dystrophy	**376**	**116**	**162**	**654**	**0.2**
3592	RFG090	**Myotonic disorders**	**134**	**78**	**106**	**318**	**0.1**
3560	RFG060	Hereditary peripheral neuopathy	152	108	28	288	
3561	RFG060	Muscular-peroneal atrophy	143	16	43	202	
		Hereditary peripheral neuropathy	**295**	**124**	**71**	**490**	**0.1**
3570	RF0183	**Infectious acute polineuritis**	**114**	**0**	**0**	**114**	**0.0**
27787		**Mitochondrial metabolism disorders**	**134**	**0**	**5**	**139**	**0.0**
2710	RCG060	**Glicogenoses**	**112**	**21**	**23**	**156**	**0.0**
7103	RM0010	Dermatomyositis	209	49	93	351	
7104	RM0020	Polimyositis	344	44	87	475	
		Inflammatory myopathies	**553**	**93**	**180**	**826**	**0.2**
			4.272	**734**	**1.196**	**6.202**	**1.ß8**

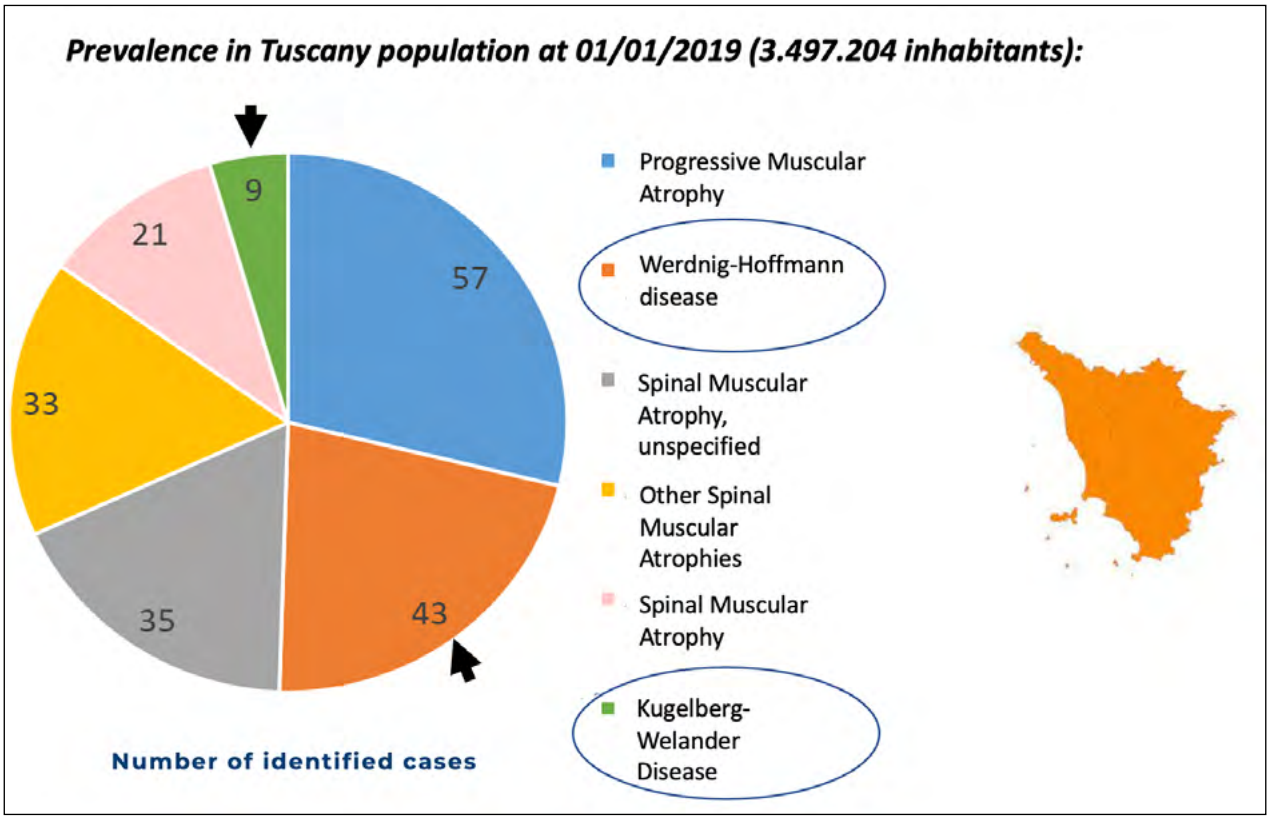

Figure 1. Prevalence of neuromuscular disorders in Tuscany population at 1st January 2019.

lowed outside the region or not taken in charge. However, although without a defined and planned methodology, the transversal and synergic actions carried out at different levels by specialists, general practioners and patients' association allowed to partially fill up these health system gaps.

How to overcome the health system frailties that the SARS-CoV-2 pandemic has brought out: future prospective and challenges towards a new standard of care NMDs

The clinical management of NMDs patients is an articulated and complex process, which makes use of numerous specialist figures alongside the central figure of the neurologist or neuro-pediatrician. The definition of complete and multidisciplinary paths for diagnosis and treatment becomes a fundamental requirement to ensure care and standards of care.

The clinical pathways named diagnostic, therapeutic and integrated care programs (Percorsi Diagnostico-Terapeutici Assistenziali, PDTA) can be multidisciplinary tools aimed at sharing decision-making processes and organizing care for a specific group of patients during a well-defined period of time, thus improving the quality of care [13]. PDTA should:

- include a clear explanation of the objectives and key elements of evidence-based care;
- facilitate communication between team members, caregivers and patients;
- coordinate the assistance process through the coordination of roles and the implementation of the activities of the multidisciplinary assistance teams. PDTA should also include documentation, monitoring and evaluation of outcomes and identify the resources necessary for the implementation of the path itself. Overall, the purpose of the PDTAs is therefore, in this view, to increase the quality of assistance perceived and effectively delivered, improving outcomes and promoting patient safety through the use of the right resources needed.

In these last years, for instance, the Tuscany Region has started the promotion and the definition of several PDTAs at regional level for various forms of NMDs, with the collaboration of a working group that involves specialists from different areas and regional territorial companies, as well as patient associations.

The COVID-19 pandemic has further highlighted the management difficulties of NMDs patients and the necessity to continue the program of implementation of standard of care yet started in Europe with the definition

of the ERNs and with different applications in the various European countries. It will be increasingly necessary to favor and further develop *smart* management care through the implementation of IT platforms, telemedicine services and other eHealth technologies [14,15].

The Europe has responded to the pandemic crisis with an unprecedented investment program having highly ambitious objectives, where Italy will be one of the first recipients.

Among the missions of the Italy's recovery plan (*Piano Nazionale di Ripresa e Resilienza*, PNRR), there will be the digitalization of health system. In the near future we are moving towards a health system that supports scientific research, strengthens prevention, and brings "medicine home". The view is that of a digital health service which integrates health and social services. The PNRR aims to renovate healthcare in Italy by upgrading its technological infrastructure, strengthening the training of operators and creating contact points with patients also through telemedicine. Overall, this will offer a proactive top-quality opportunity to network with organizations and people that value quality health information as well as effective integrated system and innovative solutions in order to improve diagnosis, treatment and care of patients with NMDs.

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Conflict of interest statement

The Authors declare no conflict of interest.

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Authors' contributions

GR, FT, FB, GS: writing the manuscript, acquisition of data, analysis and interpretation of data; EG, PF: acquisition of data, analysis data; LF, ES, DG, TM: revising the manuscript.

Ethical consideration

Not applicable.

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