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Meeting Report

E-Health & Innovation to Overcome Barriers in Neuromuscular Diseases. Report from the 3rd eNMD Congress: Pisa, Italy, 29–30 October 2021

Remote Monitoring: New Solutions for New Avenues in Neuromuscular Disorders

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Abstract. Neuromuscular diseases (NMDs), in their phenotypic heterogeneity, share quite invariably common issues that involve several clinical and socio-economical aspects, needing a deep critical analysis to develop better management strategies. From diagnosis to treatment and follow-up, the development of technological solutions can improve the detection of several critical aspects related to the diseases, addressing both the met and unmet needs of clinicians and patients. Among several aspects of the digital transformation of health and care, this congress expands what has been learned from previous congresses editions on applicability and usefulness of technological solutions in NMDs. In particular the focus on new solutions for remote monitoring provide valuable insights to increase disease-specific knowledge and trigger prompt decision-making. In doing that, several perspectives from different areas of expertise were shared and discussed, pointing out strengths and weaknesses on the current state of the art on topic, suggesting new research lines to advance technology in this specific clinical field.

Keywords: e-Health, neuromuscular diseases, remote monitoring, telemedicine

RATIONALE OF THE CONGRESS

Neuromuscular diseases (NMDs) require integrated, highly specialized and multidisciplinary care settings to address the various long-term complications that may arise and change over time [1]. Patients and clinicians share the expectation of a care system that provides quick and easy access to services, effective research, better knowledge exchange and translatability of results in daily clinical practice [2]. Remote monitoring is a cornerstone within the broader field of telemedicine, encompassing all activities that can be carried out remotely, to learn more about patients' health status and how it evolves [3].

Telemonitoring has been the overarching theme of the III eNMD Congress with the contributions of leading researchers in this novel area.

Remote monitoring encompasses aspects in which new paradigms of efficiency and proficiency of public health policies are defined, with the aim of improving the processes of NMD diagnosis, monitoring and treatment [3]. To this end, several European Countries have launched plans for the digitization of cross-border health service, in response to the need of patients and clinicians' demand for high standards of care [4].

Despite the growing interest and increasing literature on the subject, it is difficult to determine which technologies are most effective and which IT infrastructure can provide safe, secure and interoperable access for the collection, processing, and distribution of patient data. This is a challenge to ensure a sustainable predictive, preventive, personalized and participatory healthcare system [5].

Following the face-to-face event in Nice in 2019 and a remote event in 2020 due to the pandemic, this third two-day meeting was held in a hybrid format.

A thematic track that brought together clinicians, eHealth scientists, and bio-tech experts addressed new strategies for defining appropriate outcome measures for activities of daily living in NMDs, new strategies for data acquisitions, strategies for functional motor recovery, and biotech findings for the development of innovative drugs. The meeting focused on the perspective and importance of remote monitoring solutions in tackling these issues.

NEW STRATEGIES FOR DATA ACQUISITION, MANAGEMENT, AND PROCESSING

Until the Covid-19 pandemic, telemedicine and other at-distance medical activities were little used.

A multicentre national survey led by the Italian Association of Myology (AIM) demonstrated a significant disruption in clinical and support services for NMD patients nationwide, due to the Covid-19 pandemic, and supported the extensive adoption of telemedicine (TM) to ensure the appropriate quality of care to this vulnerable class of patients which could suffer from prolonged home isolation and whose quality of life, and perceived disease burden, were significantly affected [6]. This permitted to verify that the quality of data obtained with electronic versions of existing scales for assessing the neurological and respiratory status and quality of life of NMD patients did not differ significantly in tele-visit versus face-to-face evaluations [7, 8].

Pharma and BioTech companies are increasingly engaged in drug development and synergistic digital solutions in the field of rare diseases, implementing sophisticated methodologies, such as new gene-editing therapeutic approach strategies for mitochondrial diseases, amyloid TTR-neuropathy (ATTRv), and Spino-Bulbar Muscular Atrophy (SBMA) [9], resulting in the need to be monitored for side effects, compliance and efficacy.

Moreover, TM is essential to facilitate the evolution of clinical trials. In particular, according to the rules of decentralized clinical trial models, with TM is possible to increase patient recruitment and retention, as well as the quantity and quality of data acquired in the patient environment [10, 11].

Evaluations of clinical outcomes of motor function are commonly considered primary endpoints in routine clinical care and NMD research, as they provide important information about the trajectory of the disease, response to experimental treatments and, therefore, the need for assistive devices as the disease progresses [12–14]. Several guidelines on the topic were developed and a number of Sponsors amended their study protocols introducing tele-visits as standard procedures [15]. Nevertheless efforts to compare and validate remote evaluations versus in person assessments are ongoing, the experience on the field has confirmed that some commonly used outcome measures in NMDs adapted well to be evaluated at distance and a decentralized design should be evaluated as new paradigm of clinical trial for this frail population [16].

Despite the advent of TM has been unavoidable and useful in NMDs, more than one face-to-face visit is needed from diagnosis to follow-up given the complex clinical course [17]. The combination of telematics and face-to-face visits would create a hybrid model able to meet the needs of both patient and clinicians [18–20].

In the last years, the upcoming and emerging Internet of Things (IoT) framework has pushed the fruition of a lot of original connected objects and smart services [21] capable of producing algorithms that reflect with high accuracy vital functions or motor tasks, useful to monitor natural disease progression or the effects of rehabilitation protocols. For instance, a "smart-pant" equipped with sensors provides the measure of amplitude, direction and angle of movement, distribution of the load in static and dynamic conditions. The device includes a signal processing and machine learning algorithm able to automatically recognize the type of exercise the patient is performing [22].

The conventional concept of a biosensor has evolved. Although it still refers to a device consisting of a physicochemical transducer that allows the acquisition of parameters related to a patient's health status [23, 24], a new generation of biosensors that combine nanotechnology, low-power processing devices and artificial intelligence algorithms for real-time signal processing [25, 26] is growing rapidly.

These systems can be used for a broad range of tasks: from molecular / cellular / tissue function assessment to patient functional monitoring, through minimally invasive wearable devices. Moreover, there are optical biosensors based on light interactions at the molecular level and the use of confocal microscopes to study the cell dynamics in real time [27]. More generally, most biosensors currently in use are based on biochemical markers in biofluids, such as sweat, tears, saliva and interstitial fluid [28]. Wearable molecular sensors could help to improve our understanding of the correlations between analyte concentrations in the blood and other biofluids, but there is still a long way to go for their final validation [29]. Currently none of the available biosensors holds direct promise for NMDs, but some analytes such as creatine kinase, lactate or glucose might be worth exploring in depth to assess muscle fiber integrity or the effects of pharmacological therapies. The clinical studies needed to confirm the benefits of such biosensors and systems could themselves benefit from the new possibilities offered by TM, shortening the time and reducing the costs required for their implementation [30].

Beyond biosensors and biomarkers, in the era of artificial intelligence, we should consider the possibility of selecting digital biomarkers. Indeed, increasingly accurate and flexible electronic moni-

toring devices and the rapid development of big data management methods have increased interest in the application of automated analysis approaches [31]. Few machine learning (ML) techniques are currently implemented in routine clinical care but, in several neurological diseases, ML is successfully employed to pre-screen at-risk subjects. For example, the appropriate use of smartphones and convolutional neural networks, combined with data-augmentation techniques, can achieves high predictive performance, based on tests conducted using the sensors of ordinary smartphones in home environments, even without medical supervision, to identify individuals at risk of developing Parkinson's disease [32].

Standard video assessments combined with modern computational machine learning methods can improve the robustness of data capture to quantify movement of upper and lower limbs and gait metrics [33, 34]. These technologies provide an opportunity for remote monitoring that will increase the frequency of measurement, identify key movement metrics that may be more sensitive to change, and allow for longitudinal tracking in a patient's real world environment that may be more impactful and reflective of activities of daily living.

Digital tools can facilitate assessment also of functional domains not simple to be explored, such as speech impairment [35] or respiratory muscle function [36]. The ability to monitor the progression of dysarthria in patients with amyotrophic lateral sclerosis supports clinicians in the early detection of functional changes in patients' performance. During the congress, a smartphone application (app) and data storage and analysis based on deep learning and cloud computing were presented for follow-up and rehabilitative purposes. Biometric parameters, such as the degree of lip protrusion or maximum mouth stretching, and the ability to detect fatigue during repetitive motor tasks, allow for appropriate interventional and compensatory strategies. Artificial Intelligence (AI) for speech rehabilitation in dysarthric ALS patients can improve automatic speech recognition by adapting and "translating" the speech of patients with mild to moderate dysarthria. During several reading sessions the patients pronounce predetermined selected words aloud. At the end of each session, a specific designed tool provides a measure of how much the patient's pronunciation deviates from that of the previous sessions, allowing the clinical specialists to work on phonemes that are more difficult for the patient to pronounce. The ability to monitor the quality of the patients speech over time allows tailored treatment approaches based on specific parameters (e.g. fatigue, reduced intelligibility, difficulty in producing some phonemes/clusters/specific words) [37].

All of the above mentioned sensors generate data which, especially for rare diseases, can be of paramount importance to better understand the disease evolution. In this sense, the maximization of the disease registries is fundamental to define meaningful outcome measures. Registries are standard tools in rare diseases [38], their informative values depends on doctors and patients which use them for different purposes. Clinicians reporting is useful to deeply characterize pathologies, on the other side patients reported outcome measures (PROMS) or patient reported experience measures (PREMS) reflect the needs and the expectations of patients and their carers [39] in responding to care burden [40, 41]. In addition, pharmacovigilance registries fare useful for early detection of undesirable events related to treatments [42–45].

Respect for the values, preferences and needs of the patient must include coordination and integration of care supports, patients involvement in health policies, programs of information, communication and education. Validated questionnaires, such as the Short Form Health Survey in 36-item (SF-36), or specifically designed for NMDs, as the Quality of Life in NeuroMuscular Disease questionnaire (QoL-NMD), can be integrated by technological supports to facilitate communication, medication tracking and patient monitoring and to respond to unmet patients needs [46].

From 6 to 8% of the European population – between 27 and 36 million people – are affected by one of the 5000-8000 distinct rare diseases. The RD-Connect project (www.rd-connect.eu) represents a unique global infrastructure initiative that links databases, registries, biobanks and clinical bioinformatics data into a centralised resource accessible to researchers worldwide [47, 48]. This integrated research platform facilitates the combination of complete clinical profiles with -omics data and samples for research purposes, particularly in the context of activities funded by the International Rare Diseases Research Consortium [49].

Genomic data of patients with rare diseases are stored for sharing, analysis, and long-term access at the European Genome-phenome Archive (EGA) [50], a secure, controlled-access repository, where the RD-Connect genomics analysis interface is used to process data are make it accessible for real-time analysis. The platform [47, 48] is a rich

resource containing around 20,000 whole exomes and genomes from patients with rare neuromuscular, mitochondrial, neurogenetic, immunological and other disorders contributed by large-scale discovery projects such as Solve-RD [51] and the European Reference Networks (ERNs).

In Tuscany Region is ongoing the test of a multimodal platform consisting of modules for collecting genetic data, imaging (muscular MRI), neurological examination, physiotherapy assessments, to be implemented with data collected by wearable sensors, muscular biopsy and machine learning algorithms, becoming a reference tool for genotype/phenotype association in NMDs [52].

All the above mentioned well-designed and high-performing registries are powerful data sources that help researchers to identify key points to improve clinical trial design for the development of new therapeutic pipelines [53]. It is worth noting that, due to the very nature of rare diseases, the possibility to use Machine Learning (ML) techniques and AI systems for prevention, diagnostic support, and intervention, is limited by the reduced quantity of available data. Even if in recent years there are examples of the so-called 'one shot learning' and 'few shots learnings', the most known implementations of ML algorithms require very large datasets for the training phases [54], which are generally not available for the great majority of rare diseases. In this sense, any further widening of the above mentioned repositories can increase the chances of application of ML techniques to rare diseases.

INTERVENTIONAL STRATEGIES FOR MOTOR FUNCTIONAL RESTORING

Also in the rehabilitation setting, innovative technologies attract a growing interest in preventing decline and regression, monitoring changes and promoting motor recovery.

Robotics has gone through a transformation in the last decade [55]. Traditional devices, such as exoskeletons, often had unsatisfactory performance and were uncomfortable to use due to their stiffness, bulkiness, weight and limited battery power [56]. Additionally, early generations of robotic devices did not take into account residual muscle function and activity, providing only rigid, predefined support [57]. In the early 2000 s, a conceptual revolution sparked a transition from traditional, heavy industrial robots to safe, light, and nimble co-bots that can coexist and cooperate with humans, even coming into contact with them. To achieve this, robots have become lighter, smaller, softer, and more intelligent [58]. Today, the technological revolution of soft, intelligent machines is expanding from robotics to bionics. Soft technologies are not only safer and more effective, but they can also be more natural. Their motion and interaction patterns are dictated by similar principles to those of our own human limbs [56]. In the future, users will be able to incorporate soft bionic devices into their body. These devices will send inputs and receive feedback that match our inner model of interaction with the outside world.

The design of this type of human-oriented models impose the adoption of machine learning techniques and robotic solutions able to control their actions in real time, according to the perceived feedback [59]. Augmented human-computer interaction (AHCI) can enhance human experiences by providing more natural and efficient ways for users to interact with real or virtual environments.

These capacities are applied not only in assistive or rehabilitation settings but also to enhance the user experience of specific living environments to promote social inclusion [60, 61], but several problems arise when the boundaries between care and inclusion are crossed. For instance, in NMD patients, wheelchairs are a standard of care in Italy for those who lose ambulation. However, in the same country, obtaining an assistive device from the National Health System upon loss of upper limb function is much more challenging. Various upper limb technologies can improve engagement in key social roles such as employment, self-care, sports, or community activities, but the lack of scientific evidence and the high cost of motion analysis laboratories limit their dissemination [62, 63].

Among several futuristic applications, there are:

- Brain-controlled robot which allow motor-impaired people to take virtual tours (in tele-presence) in real museums [64];
- Serious games to enhance motor ability, cognitive function and facilitate social skills [65],
- Devices to mitigate the work-related stress [64],
- Gaze-enabled devices tested in an adult SMA type 1 patient, in which an ipad, integrated with a wheelchair, is provided by sensors controlled by the hand/finger of the patient to quantify the residual movement of upper limb and by an oculometer that calculates real-time gaze orientation helping the patient to move and communicate.

DIGITAL HEALTH AND REMOTE MONITORING: ETHIC AND LEGAL ISSUES IN EU

The advantages of remote monitoring in clinical practice, research and opportunities for improving patients' quality of life are not in question. However, it is important to address the thorny ethical and legal issues that are not yet fully understood or resolved in the field of telemedicine.

Several aspects should be considered when dealing with personal data, such as informed consent, including privacy, confidentiality, data protection and security, malpractice and professional liability/integrity, equity of access and quality of care. It is important to note that the General Data Protection Regulation (GDPR), established by the European Commission, gives citizens control over their personal data. Important questions related to the medico-legal implications of storing and processing private clinical data by clinicians arise. Legal and ethical claims for remotely acquired data need to be clarified in accordance with the local regulatory framework. This is not a simple task, as current health legislation fails to keep pace with technological progress [66, 67].

DISCUSSION AND CONCLUSIONS

This report provides an overview of the 3rd eNMD congress, as discussed by various speakers with specific clinical and technical expertises. The focus is on the complexity of NMDs and the need for more specific technological tools to complement traditional medical care and address existing gaps.

In order to achieve this goal, it is essential to define a minimum common and relevant sharing of medical and technical knowledge. Furthermore, it is necessary to set the minimum conditions of interoperability between different expertises in order to enable the adequate large-scale adoption of heterogeneous and increasingly advanced technological tools.

A major bottleneck in this field is that although the mentioned solutions have been tested in research settings, they are not yet available through healthcare systems. Nevertheless the adoption of telemedicine in NMDs is slower with respect to what happens in other chronic neurological conditions, Covid-19 pandemic has acted as a driving force towards the adoption of telemedicine, revealing both its strengths and limitations. Therefore, NMDs represent an ideal model of clinical complexity and fragility to test and tailor several telemedicine tools, due to their broad phenotypic presentations and multisystemic involvement. Among several possible applications, it is suggested that a stable research network (e.g., EURO-NMD, ERN-NMD or a new, purposely-built network) should implement the concept of "distributed clinical trial" for NMDs, already successfully adopted for other diseases. The aim is to establish a stable EU-wide network that includes medical institutions, clinical research centres and research labs with advanced technical skills, as well as decision-makers, payers, patient organizations and private companies working in the field of NMDs. This network could help in translating lab experiments into clinical trials, rapidly involving more patients and clinicians, thus reducing the cost and the complexity of the procedures and permitting a quicker and more effective translational research. The involvement of patients' organizations and private companies could significantly aid in prioritizing new proposals. Evaluating patient's feedback, adopting effective business models and utilizing existing commercial networks and carer's organizations can rapidly improve and homogenize the Technological Readiness Level (TRL) of the most promising solutions across different EU countries.

To ensure better medical services that are closer to patients' demands, territorial referral facilities should be redesigned taking into account the evolution of healthcare and the need to optimize resources. In recent years, the principle of "community medicine" has been taken up. It is a way of conceiving the delivery of medicine services through territorial networks of integrated and coordinated services [68]. National governments set general regulatory plans and use various outcome indicators to monitor the quality of the services provided. Sociodemographic analysis is fundamental for mapping patients' needs and allocating fundings and resources appropriately. This is necessary to scale-up multidisciplinary primary care, create vertically-integrated hospitals and community care, promote the education and training of community-based medical and non medical professionals [68, 69].

Planning the delivery of services across national health systems in Europe needs an analysis of the determinants, taking into account the measurement of interventions and outcome measures, such as environment of action, targeted population, objectives pursued and approach adopted, including also the integration of telemedicine [70].

We envisage that ongoing successful contamination of interdisciplinary medical and technological knowledge will result in a paradigm shift in NMDs patients care. This cultural revolution is beginning to permeate scientific societies which are exchanging their specific "know-why" and "know-how" to overcome barriers in NMDs management [71].

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CONFLICT OF INTERESTS

Regarding the paper, authors do not have conflicts of interest to declare.

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