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Concise review of end of life and palliative care in neuromuscular pathologies: still a long pathway ahead

Maria Luisa de Candia[1], Antonietta Coppola[2], Gualtiero Ermando Romano[3], Giovanna Elisiana Carpagnano[3], Paola Pierucci[3]

[1] UOC Pneumologia-UTIR, Ospedale S. Paolo, Bari, Italy; [2] UOC Fisiopatologia e Riabilitazione Respiratoria, Ospedale Monaldi, AO dei Colli, Napoli, Italy; [3] Dipartimento di Biomedicina Traslazionale e Neuroscienze, UO di Malattie dell'Apparato Respiratorio, Azienda Ospedaliera Universitaria Consorziale, Policlinico di Bari, Italy

Introduction. Neuromuscular diseases (NMD) include different types of diseases depending on the deficient component of the motor unit involved. They may all be interested by a progressive and sometimes irreversible pump respiratory failure which unfortunately for some NMD may start soon after the diagnosis. Within this vast group of patients those affected by muscle diseases are a subgroup who comprises patients with an average earlier onset of symptoms compared to other NMD. Indeed it is also important to comprehend not just the patient's burden but also the surrounding families'. Defining the end of life (EoL) phase in these patients is not simple especially in the young patient population. Consequently, the late stage of disease remains poorly defined and challenging.

Objectives. The aim of this review is to describe the EoL phase in NMD patients with attention to QoL and psycological status.

Methods. The focus would be on one hand on the management of the psychological burden, the communication barriers, and tone of humor.

Results. Those topics have been described being crucial in this group of patients as they increase tensions and burden of both patient and family, and between them and the outside world. Thus also causing their social isolation, increasing anxiety and reducing their quality of life. On the other hand the use of cough clearance devices and all the respiratory supports and their withdrawn are carefully evaluated in the view of alleviating respiratory symptoms, improving patient quality of life and above all reaching the patient's goals of care.

Conclusions. Although there is no cure, the advent of supportive interventions including multidisciplinary care (MDC) has improved all the aspects of dying for patients affected by NMD; nevertheless there still a long pathway ahead.

Key words: muscle diseases, multi-disciplinary, quality of life (QOL), burden, end-of life, palliative care, pain, depression, noninvasive ventilation (NIV), Duchenne muscular dystrophy (DMD), muscular dystrophy

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Correspondence
Maria Luisa de Candia
E-mail: marialuisadecandia@gmail.com

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Introduction

Neuromuscular diseases (NMD) are a heterogeneous group of neurological diseases whose ethio-pathogenesis differ depending on the deficient component of the motor unit involved, i.e. nerve, muscle or neuromuscular junction. The onset, clinical features, therapy and prognosis may vary a lot till a progressive deterioration of respiratory muscle function appears [1-2]. The integration of home NIV into the management of the NMD patient has improved the QoL and the survival of these patients, even if for some diseases the prognosis remains poor (i.e. Amyotrophic lateral Sclerosis (Als) [3-8]. Muscular diseases, in particular, are a heterogeneous group of genetic diseases characterised by an earlier onset compared to other NMD where other challenging psychological related difficulties

arises in the families such as the mixed presence of healthy and sick young children and the transitioning phase from paediatric to adult age [9]. The prognosis may be bleak, so a focused End of Life (EoL) care and palliative care becomes vital for patients and carers. The World Health Organization (WHO) defines palliative care as: "patient and family-centered care that optimizes quality of life by anticipating, preventing, and treating suffering. Palliative care throughout the continuum of illness involves addressing physical, intellectual, emotional, social and spiritual needs and to facilitate patient autonomy, access to information and choice" [10,11]. Thus, on one hand, palliative care aims to improving QoL, considering both the patients' and caregivers' needs, identifying the goals of care and supporting medical decision-making [12]. On the other hand, the term "End of-life care" usually corresponds to the final stage of life care and sometimes correspond to "terminal care" which focuses on supporting the dying person and their family. Specific criteria to precisely define the start for EoL care still are missing, because of the broader range in time and intensity of the varies MNDs and of the patient's personal journey [13-15]. As correctly stated by Tripodoro et al., judging prognosis in NMD patients is particularly difficult because of the difference between slow and fast diseases' progression and also for the ambivalent concept of NIV use which can improve survival without modifying the progression of the disease itself [15]. In this concise review we explore the challenges, practicalities, and technicalities of EoL care including NIV use focusing on individuals with muscle pathologies. In more details, the purpose is to analyse the management of these incurable diseases in the latter stages. Indeed, the point would be to emphasise that palliative care and pain control should not be implemented just in the terminal phase but much earlier. From the diagnosis knowing the unfavourable prognosis every available tool should be used aiming at controlling symptoms, improving quality of life and achieving the patient's goals in the management of the disease. In this big picture, the burden of care, communication, tone of humor, are aspects to be considered as early as possible at each outpatients visit when possible. Moreover, details on Non invasive ventilation (NIV) and other respiratory support options are described, but also bronchial secretion management machines for their correct use, timing and aid in avoiding unnecessary admission for severe pulmonary infections. Lastly, but non less importantly, withdrawn from NIV is an aspect often left to the experienced physician. It is instead here suggested to be discussed openly with the patient and family members with the support of the current literature. The time when the disability has not yet manifested itself, it's the right time to start talking about it, so as to give the patient and family time to formulate an informed decision with an anticipatory approach rather than postponing difficult decisions until the time of clinical emergency.

Methods

A search was performed in Pubmed and Medline database (period 2022-2024) using generic terms to refer to EoI, Palliative care, burden of care, communication, depression, and respiratory supports, noninvasive ventilation, NIV, cough machine, bronchial clearance specifically related to people with NMDs and muscle pathologies (i.e. ALS, DMD, Myopaties, muscular dystrophies etc) Only papers written in English were considered. Additional screening of the reference lists of key publications and searches using Google Scholar were performed to identify other relevant literature. A narrative non systematic approach was used to summarize the available literature as a rapid review.

Results and discussion

Communication

Communicating with patient and family is the first and most important aspect to consider during the whole course and management of NMD and their end-of-life phase. In fact, it is often reported that patients and families have no clear perception of the prognosis of these diseases until final phase becomes imminent and decisions about the patient's life have to be made in a short time. This has been shown during COVID pandemia when the scarcity of physicians available emphasized the problem and many NMD patients received emergency tracheotomies or died because of lack of specific and close follow-up [16-17]. Despite guidelines offer help recommending starting supportive therapies including NIV at early stage of the disease, this oftentimes is not what in real life happens [18].

In the big picture of muscular diseases, there are stigmas that impede communication with families. One of them is cited in a study on parents by Sadasivan et al. and it is that 'children cannot die' which is why when talking to NMD families about palliative care and the EoL they wrongly associate the topic with the risk of imminent death, thus preventing clear communication with families and long-term planning [18]. Moreover, parents often are not aware of the palliative care services and hospices offered, Chrastina et al. demonstrated that up to 85% of families with Duchenne muscular dystrophy (DMD) have no knowledge of the significance and availability of palliative care services [19]. Furthermore, Sadasivan et al. pointed out that there's a lack of clarity in communication from the parent about the child's emotional development towards his or her condition. Indeed, the parents do not completely comprehend if the child is selfaware of the own disease and whether is afraid of progressive functional deterioration or even death. Parents often are afraid to talk about the presence of the disease and so they fail to overcome the communication barrier [20]. Regarding the young patient's awareness of his illness, the literature is divided: in some studies the patient with DMD would not be aware, in others he would not be able to express himself due to his young age instead [19-20]. As mentioned by Parker et al., oftentimes, the communication about the disability remains confined to the hospital where physician are supposed to deal with the disease in a holistic approach considering every aspect including the psychological burden. Instead, the outpatients appointment are rarely a space where is possible to relax and chat about collateral experiences because the focus usually is on the urgent problems experienced between appointments. Therefore, large gaps remain unfilled in the communication within families with patient/s affected by NMD [9]. In the same study, it is remarked not less importantly that children and families front the lack of care continuity in the transitioning age between child and adulthood.Thus, the patient and the family feel abandoned, without reference points, and without the help from the usual doctor or mediator [9]. Indeed, in families with language barriers, social isolation,

different cultural contexts it becomes more difficult to understand all the details of the process of care and most of all of the EoL programme and its goals [9]. Furthermore, when urgent care is required with admission in hospital and /or in ICU oftentimes a lack of sharing goals between physicians and family is described, thus increasing the psychological burden. In a recently published review, Neukirchen et al. described the family's satisfaction about the management of EoL care and palliative care with less stress in ICU when there is a discussion and sharing of goals together with the physician [21-23] The palliative approach becomes necessary within all these topics aiding families and patients where needed but mostly the timely call for palliative care integration within the care line can reduce moral distress within the team and families [23].

Depression

Depression may involve both patients and their caregivers. With regard to NMD patients, in a review by Oliver, it usually appears within the first year after diagnosis and in patients over 65 years of age, rates in studies vary from 4.4% to 12% respectively [24-26].

The use of antidepressants was higher in adult NMD patients. Although the wish to die was common, with 25% of patients expressing it, the majority did not have depression and only 37% of this group showed evidence of clinical depression [26]

It is important to identify clinical depression because in addition to reducing quality of life, it can minimize the patient's willingness to start or continue treatment, including NIV thus, increasing the number of episodes of dyspnoea, hospitalizations and as a consequence the risk of death [27].

A recent study has evaluated the psychosocial attitude of DMD patients showing them having more obsessive-compulsive tendencies [28]. In a study on patients with type 1 myotonic dystrophy, signs of clinical depression were identified in 32% of patients, and the depressive condition was mild to moderate and comparable to ratings in other NMD [29].

Caregivers feel guilty about abandoning their loved one and leading their own lives, so they tend to isolate themselves letting their psychological tension increasing. It is important to be able to recognise the caregiver's burden in order to prevent consequences to the patient and the whole family [29-30].

The NICE guideline underlines that the supporting presence of a group of people close to the family and the carer is essential. A study using CSNAT (The Carer Support Needs Assessment Tool) showed that future planning, access to necessary tools, help when needed were the things carers and family members needed most in terms of support [31].

Recent studies show that volunteers can be also a valuable resource to include to help these families. Indeed the literature has reported that patients and caregivers may benefit from the emotional support and physical presence of volunteers like demonstrated by Cheng HW et al. during Human Avian Influenza A pandemia in 2013 [32].

The role of palliative care volunteers varies enormously from country to country: they are usually present in nursing homes, hospices, day care centres. They may look after simple but effective psychosocial aspects which in return have an enormous impact on the patient's and caregiver's burden of care (i.e. organising activities in day care centres, music therapy, bereavement care, haircutting and simple chatting and communication with the patients to understand and anticipate their needs). As Hon Wai's review underlines, in order to further decrease the burden of care of the patient and family, voluntary caregivers should have a basic knowledge of palliative care so as to better integrate themselves into care [33]. Carers instead may be hired privately or through public services or community care funding. However, some problems may be experienced by the family in terms of missing continuity of care with the same carer, there is a lack of empathy related to a non-continuous job and also the lack of adequate specialist nursing training in the territory in the event of the patient's clinical condition a worsening e.g. respiratory failure. Care agencies unfortunately did may not take responsibility in providing adequate information and high level of training regarding the different medical conditions of the individuals whom they care for [9].

There are many other important topics which need to be explored in more details and which may contribute to the onset of depression in these patients; i.e. dysphagia, sleep disturbances, pain, anxiety, insomnia and dyspnea. Dysphagia is a common condition in NMD patient, in whom a variety of swallowing difficulties are reported. They are usually related to the functional decline of the swallowing and masticatory muscles. It exposes to aspiration pneumonia and respiratory infections which can be responsible for further clinical deterioration and admission to the hospital for respiratory insufficiency related complications [34]. A periodic dysphagia evaluation is needed in the follow-up of these patients, trying to privilege oral intake as far as possible [35].

Regarding the presence of sleep disturbances in NMD recent guidelines suggest use of Noninvasive Ventilation in NM patients. The panel suggests using the AASM criteria for sleep-disordered breathing and hypoventilation for adult patients and the ERS criteria for pediatric patients [18,36-37]. However, the polysomnography is not necessary for adult patients to initiate NIV, the initial reduction of lung function tests it is a sufficient criteria and NIV may be responsible to improve the presence of sleep disturbances [18]

In patients with DMD multiple risk factors have been linked to sleep disturbances and insomnia, including medications like systemic steroids, psychological and socioeconomic stressors. Other risk factors in these patients population include the use of nocturnal video games and online gaming which can be recreational but when played late at night can contribute to sleep disturbances and insomnia [38]. Promoting good sleep hygiene is pivotal in DMD patients. Recommendation include the use of systemic steroids in the morning; melatonin may also be considered to help promoting regular sleep cycles when combined with sleep hygiene practices while other hypnotics medications should be avoided when possible, due to sedative effects which can potentially suppress respiratory drive and further deteriorate their respiratory function [38].

Moreover, the majority of boys with DMD report the presence of chronic pain, usually related to inability to independently shift body position or secondary to muscle contractures [38].

Regarding the presence of anxiety disorders, a recent meta-analyses confirmed a higher prevalence of 24.0 % in DMD boys compared to 7.2 % in non-diseased 5-19-yo, whereas it is 19.1% in young people with life-limiting conditions [38].

The 2018 DMD care guidelines recommend mental health screen-

ing at neuromuscular clinic visits and the presence of a psychologist within the NMD team in order to the earlier and better identification of anxiety disorders, which can also contribute to a good quality of sleep and as a consequence to a better quality of life in general [39].
Dyspnea is a common and distressing symptom leading to depression and poor quality of the EOL phase of disease. The use of NIV may play a substantial role in palliation of dyspnea for patients with DMD and others with advanced ventilatory failure [38].

Non invasive ventilation (NIV) and other respiratory support

As already mentioned, NIV increases survival and improves QoL and symptoms in NMD patients [18]. In patients with amyotrophic lateral sclerosis (ALS) without severe bulbar dysfunction, NIV improves survival with improvement in quality of life [40]. Duchenne muscular dystrophy (DMD) without intervention has mean survival of around 19 yrs. Through the use of NIV DMD patients may prolong their survival living till their 4th decade of life [41]. However, early discussion for NIV initiation should be a standard of care in all these patients. In 2019, the Reinvent survey conducted among members of ERS NIV group studied ventilation and ventilator prescription modalities in NMD patients. The most commonly used ventilation mode was pressure support, whether or not accompanied by a guaranteed volume. A single circuit with an intentional leak port and heated humidifier were the preferred setting together with either oronasal/mouthpiece or a rotational strategy of the ventilatory interfaces especially for those patients presenting with diurnal residual dyspnoea and/or hypercapnia [42].
In these patients' population the ventilatory support is usually initiated during the night and progressively becomes needed during the daytime hours while the alveolar hypoventilation worsens and the muscle weakness progresses [8]. Rotational strategy of different interfaces becomes important to allow more ventilation time throughout the day and the night (i.e. mouthpiece or nasal masks, nasal pillows/cushions during the day and oronasal mask at night) thus reducing the risk of interface decubitus formation. Other expedients may be to use interfaces with magnetic attachments that facilitate closure in patients with upper limb hypomobility. Mouthpiece ventilation with a very sensitive inspiratory 'kiss trigger' is also the most favourite interface for daytime ventilation, whereby simply touching the interface with the lips initiates ventilation (®Philips Respironics Murrysville, USA) [43]. The NIV adherence may be influenced by several other factors: family support, psychological factors, fear for death/intubation/tracheostomy, good communication with clinicians, close follow-up, severity of disease, perception of benefits. Intermittent abdominal pressure ventilation (IAPV) (which is not mentioned in the current guidelines and used in a few centres in combination with NIV) has been suggested for those patients who are uncomfortable with any ventilatory interface during awake time. It is a type of daytime ventilation with an inflatable belt connected to a ventilator. The IAPV provides pressure via an inflatable sac attached to a belt positioned around the abdomen; the pressure in the belt pushes inward the abdomen and elevates the diaphragm resulting in lung exhalation. After that, the sac slowly deflates and the diaphragm returns to its place promoting passive inhalation [44]. Moreover, in a case-series of patients with NMD admitted in hospital affected by an episode of severe acute respiratory insufficiency, the high flow nasal cannula (HFNC) device has been successfully evaluated. Indeed, the latter support can be an add-on combination of respiratory support which support nocturnal NIV for patients with intolerance to continuous NIV. It offers an opportunity to discontinue NIV in NMD patients as long as NIV is not interrupted during the night and the levels of PaCO2 levels remain acceptable [45].

Bronchial secretion management

Cough is an essential reflex to remove foreign bodies and secretions from airways [46].Weakness of the inspiratory muscles leads to a progressive decrease in vital capacity (VC), to add a alterations of the mechanical properties of chest wall and of the lung leading to loss of the effectiveness of cough, that is compromised both in inspiratory and espiratory phases [47] causing sputum retention with mucus plugging. These retention can cause severe and possibly life-threatening complications [48]. The cough expiratory airflow is called peak cough flow (PCF) and in individual affected by NMD it is decreased. It should be assessed in all patients with muscle weakness when forced vitality capacity is less than 2 liters [49]. Normally the effective PCF in spontaneous breathing must be greater than 270 L/; however a PCF > 160 L/min is the minimum flow to obtain an effective cough flow in people with neuromuscular impairment, it can be obtained with in-exsufflator, air stacking or other manually supporting manoeuvres. Indeed, Bach et al. suggested that in adult patients the value for PCF useful to predict successful extubation and decannulation is over 160 L/min, is the minimum flow to obtain an effective cough flow in people with neuromuscular impairment [50]. Oftentimes, cough is not assessed during outpatient visits nor a timely prescription of the cough machine is provided to these patients leading to secretions retention and frequent respiratory exacerbations and pneumonia. On the contrary correct airway clearance techniques help to prevent pneumonia, atelectasis and improve the quality of life in all NMD patients. In clinical practice there are various airway clearance techniques used [51] Manually Assisted Cough (MAC) consist of manual abdominal and costophrenic compressions, that causes a increase in abdominal pressure. Mechanical insufflator-exsufflator (MI-E) is a mechanical technique where a machine insufflate air with aims to "fill" the lungs. This is followed by a rapid exsufflation that expel air from the lungs. The rapid passage from positive to negative pressures simulate the physiologic changes during a normal cough, guarantying airway clearance [52-53]
Some therapies that are used to treat patients affected by reversible conditions are not be suitable in palliative care. Suctioning is a therapy used to remove secretion from patient's airways but is often associated with complications as uncontrollable coughing, pain, atelectasis, haemoptysis and airway injuries [54]. Being a painful procedure, palliative care guidelines suggest that the indication of suctioning procedure should be done carefully. However, therapies that aims to improve voluntary cough effectiveness are less indicated to be used in palliative care. Pharmacological therapy with mucolytics, anti-muscarinic agents and cough sedatives medications should also be considered.

Withdrawn from NIV

In the literature there is lack of information about NMD patients' choices about withdrawal from NIV during their EoL care. They have no curative treatment and the prognosis may be short, so discussion about EoL is necessary in early stage of disease [55]. The important questions are when NIV should be stopped and when it is unsuccessfull [56]. Withdrawal from NIV is when respiratory support is interrupted, favouring a natural death. Actually, there are no guidelines regarding this topic, and there is a large variability to approach. Clinical behaviour is influenced by economics, cultural, religious legal factors, and physicians experience and personal attitude [57-58].

When patients are found suitable for withdraw from NIV, there are different options whether they are competent or not [59]. A competent patient is able to understand information and prognosis about the health status and is able to express the will about own health. In competent patients who decide to withdraw from NIV, a psychiatric consult should be requested to screen for depression or psychosis. A fundamental principle that must be observed is the patient's autonomy respect, and family should be involved in the decision [60-61]. In non-competent patients, a collegial discussion is necessary and clinicians should referred to local regulations and laws [61].

Withdrawn from NIV is ethical when it is a decision taken in the full respect of patient's values and priorities. The NIV should be interrupted when it is no longer reaching the patient's goals of care [62].

The NIV interruption may be immediate or gradual and there is not consensus about the rightest approach. Usually weaning is reached in a variable time, ranging from hours to days. First step consist to gradually reduce positive expiratory pressure, while inspiratory oxygen fraction is reduced to room air. This should determinate patient distress, so a close monitoring is needed. In case of distress, an adjustment in pharmacologic sedation may be request. Most patients died when the expiratory end pressure and pressure support is zero [61]. After death, a rebriefing and psychologic support of the caring team and family should be performed.

Unmet needs of patients and caregivers

In the area of palliative care and end of life in neuromuscular patients, there are many unmet needs. Communication remains still a high barrier to overcome from both side the physician and the patient/caregiver. For instance, families of affected children still know little about the available services and tend to remain isolated, increasing the psychological burden [20]. In the Netherlands, a neurological study was conducted: The NMD patient (in that case suffering from ALS) already from the neurological outpatient clinic should be informed with frequent outpatients meeting about the evolution and progression of the pathology. With meetings at regular intervals, the patient may develop mature decisions about his life, helped by psychologists and psychotherapists, and the family itself becomes part of a pathway of self-awareness and preparation for the evolution of the disease. Thus, the patient's sense of tension and frustration is reduced by a plan that is also shared and understood by his family with the help of a multidisciplinary team: deciding in advance whether start non-invasive mechanical ventilation or undergo tracheostomy or PEG placement or withdraw mechanical ventilation [31]. Also psychological issues may be faced in this context with siblings and family. The aim should always be to reinforce the message of allowing multidisciplinary team to look after these patients (i.e. respiratory specialist, palliative care, neurologist, physiatrist, otorhinologist, gastroenterologist, psychologist, nutritionist etc). Thus, in order to detect and to adopt timely solutions to provide tailored solutions on a case-by-case basis [18]. All these measures must be part of an integrated outpatient pathway consisting of cyclic short term meetings [15]

Conclusions

In this review the importance of the multidisciplinary team in dealing with the burden of the EoL care for MD and NMD patients has been highlighted. Cyclic tailored meetings in outpatient setting to mature fundamental timely decisions should be organized in an integrated manner for these patients: investigating, NIV initiation and future potential withdrawn, use of bronchial secretion machines or technique, anxiety, depression, pain and sleep quality. It must be considered that since muscular pathologies involve younger populations of neuromuscular patients, a communication barrier may be determined by the young age of the patient himself, who is unable to express himself. The child is aware before that age but does not express anxieties directly but may doing so indirectly [20]. This difficult path to self-awareness therefore requires planning, space and time in which the child can understand, accompanied by an experienced team, the severity of his or her progressive disability and can, over time, make conscious decisions about himself or herself [20]. Moreover, parents often are not aware of the palliative care services and hospices offered as shown by Arias et al. (2011), up to 85% of families with DMD have no knowledge of the significance of palliative care services [19]. The planning and effective communication between multidisciplinary team of physicians/health care providers, patient and caregiver is crucial in the terminal phase. Isolation of the patient and caregiver must be avoided, using specific palliative care facilities or hospices where the patient can be cared of when the burden of care becomes unsustainable for the family or carer. Moreover, the presence of a dense network of caring figures including volunteers outside the hospital should be further encouraged and fostered in the complex management of these patients and their cares. Lastly, the timely start of the respiratory support in terms of NIV and secretion management is pivotal. This should lead to a meaningful multidisciplinary discussion with the palliative care team with the competent patient or the family/carer about the plan to how and when eventually withdrawn from all respiratory supports and machines for secretions clearing. The main goal whenever the time comes should always be to support as much as possible the personal and specific patients' desires in their last phase of life.

Conflict of interest statement

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Authors' contributions

MLdC, PP conceptualization; MLdC and PP, methodology, formal analysis, visualization; MLdC, software, MLdC, PP, GER, AC data cu-

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Ethical consideration

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