Myotonic dystrophy type 1 as a major risk factor for severe COVID-19?

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Abstract
The coronavirus disease 2019 (COVID-19) pandemic is challenging health care systems worldwide. People with myotonic dystrophy type 1 (DM1) represent a high-risk population during infectious disease outbreaks, little is known about the potential impact of COVID-19 on patients with DM1. We studied the clinical course of COVID-19 in three hospitalized patients with myotonic dystrophy type 1 or Steinert’s disease, between April 1, 2020-April 30-2020. All three had advanced Steinert’s disease receiving non-invasive nocturnal home ventilatory support. Two of them lived in a residential care centre. Two patients had a limited respiratory capacity, whereas one patient had a rather preserved functional capacity but more comorbidities. Two out of three patients were obese, none of them had diabetes mellitus. Two patients received hydroxychloroquine. Despite maximal supportive care with oxygen therapy, antibiotics, intensive respiratory physiotherapy and non-invasive positive pressure ventilation, all three patients eventually died due to COVID-19. Our case series of three patients with DM1 admitted for COVID-19 confirms that they are at high risk for severe disease and poor outcome. Clinical trials are needed to define best practices and determinants of outcomes in this unique population.

Keywords Steinert’s disease · Myotonic dystrophy · Neuromuscular disorders · COVID-19 · SARS-CoV-2

Abbreviations
- **COVID-19**: Coronavirus disease 2019
- **DM1**: Myotonic dystrophy type 1
- **PCR**: Polymerase chain reaction
- **SARS-CoV-2**: Severe acute respiratory syndrome coronavirus 2
- **NIPPV**: Non-invasive positive pressure ventilation
- **ARDS**: Acute respiratory distress syndrome

Introduction
Myotonic dystrophy type 1 (DM1) or Steinert’s disease is an inherited neuromuscular disorder that primarily affects muscle function, characterized by progressive weakness and sustained muscle contraction [1, 2]. Despite variable penetrance, DM is the most common type of adult muscular dystrophy, affecting at least one in 8000 people worldwide [1, 2]. The genetic background is a variable expansion of an unstable nucleotide repeat located in the non-coding region of the respective gene (DMPK for DM1), causing mis-splicing of mRNAs which affects almost all cells and organs of the human body [2]. Nocturnal non-invasive positive pressure ventilatory support is often used to ensure breathing function. The development of an acute respiratory infection is associated with a temporary reduction in muscle strength and function [3]. Unlike in normal individuals, however, these decrements in respiratory muscle function may result in more severe illness and acute on chronic respiratory failure in patients with DM1 [4, 5]. Furthermore, DM1 is often accompanied by obesity, increased insulin resistance and cardiovascular disease; three major risk factors for severe COVID-19 [2, 6–8]. Avoidant personality disorder is common in DM1 which may lead to less strict adherence...
to medical advice such as social distancing. Herein, we describe the clinical course and outcomes of COVID-19 in three patients with DM1.

**Methods**

This observational study was approved by the institutional review boards of Ghent University Hospital (including the Neuromuscular Reference Centre) in Belgium. Diagnosis of COVID-19 was made on clinical history, epidemiological data, chest imaging and nasopharyngeal swab polymerase chain reaction (PCR) testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Based on the CT findings, the level of suspicion of COVID-19 infection is graded from very low or CO-RADS 1 up to very high or CO-RADS 5 [9]. All cases were admitted to the emergency department of Ghent University Hospital after referral of the general practitioner between April 1, 2020 and April 30, 2020.

**Results**

We describe three patients with DM1 admitted to the emergency department because of COVID-19. All three were patients of the multidisciplinary Neuromuscular Reference Centre of Ghent University Hospital and had genetically proven serious DM1 with advanced disease receiving non-invasive nocturnal home ventilatory support. Table 1 shows complete clinical and genetical information regarding each patient. Figures 1, 2 and 3 show the radiologic findings on admission of each patient. Despite maximal supportive care with oxygen therapy, antibiotics, intensive respiratory physiotherapy and non-invasive positive pressure ventilation, all three patients eventually died on, respectively, day 6, 5 and 8 of admission. We should remark that patient 1 had two negative nasopharyngeal swabs for SARS-CoV-2, a presumptive diagnosis of COVID-19 was made based on epidemiological, biochemical and radiographical grounds taking into account that the sensitivity for the nasopharyngeal swab

**Table 1 Patient’s characteristics**

| Patient 1 | Patient 2 | Patient 3 |
|-----------|-----------|-----------|
| Gender    | F         | F         | M         |
| Age       | 44        | 47        | 64        |
| BMI       | 37        | 33        | 23        |
| NIPPV     | Y, for 3 years | Y, for 1 year | Y, for 18 years |
| Wheelchair-bound | Y | N | N |
| Residential care | N | Y | Y |
| Diabetes mellitus | N | N | N |
| Cardiovascular diseases | N | N | Y |
| Number of CTG-repeats | 700 | 300 | 150 |
| FVC (L)   | 0.60      | 0.86      | 2.99      |
| % predicted | 16 | 24 | 68 |
| FEV1 (L)  | 0.52      | 0.63      | 2.27      |
| % predicted | 17 | 22 | 68 |
| FEV1/FVC (%) | 86 | 73 | 76 |
| White blood cells | 11.30 | 2.76 | 4.39 |
| Lymphocytes | 680 | 740 | 131 |
| Platelets | 162 | 129 | 120 |
| CRP       | 54.3      | 37.0      | 217.2     |
| Ferritin  | 72        | 175       | 516       |
| LDH       | 496       | 335       | 514       |
| D-dimers | <270      | 810       | 1950      |
| Goals-of-care | No reanimation, no intubation | Best supportive care | No reanimation, no intubation |
| Therapy   | Hydroxychloroquine, non-invasive ventilation, empiric antimicrobial therapy and intensive respiratory physiotherapy | Hydroxychloroquine, non-invasive ventilation, empiric antimicrobial therapy and intensive respiratory physiotherapy | Non-invasive ventilation, empiric antimicrobial therapy and intensive respiratory physiotherapy |
| Outcome   | Died, 6th day | Died, 5th day | Died, 8th day |

F female; M male; Y yes; N no; NIPPV non-invasive positive pressure ventilation; NF nasopharyngeal swab; N negative; Y positive

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is around 70% [9]. Considering her precarious respiratory state, no bronchoalveolar lavage or repeat testing was performed. The CO-RADS score of 5 has a very high positive predictive value, especially in combination with the typical biochemical markers, given the high a priori-chance in this epidemic. In a high-prevalence emergency department setting, chest CT showed high probability of COVID-19 (CO-RADS 4–5) in 29.9% of patients with a negative or indeterminate initial RT-PCR result [9].

**Fig. 1** Chest CT of patient 1 showing bilateral patchy infiltrates, CO-RADS 4

**Fig. 2** Chest X-ray of patient 2 revealing bilateral infiltrates

**Discussion**

Beside the risk factors highlighted in the introduction, such as respiratory muscle weakness, obesity and cardiovascular disorders, patients with DM1 could also be more prone to the hyperinflammation which is so typical for the acute respiratory distress syndrome (ARDS) in COVID-19. On a molecular basis, DM1 is characterized by trinucleotide repeat expansion in the 3′-untranslated region of the *DMPK* gene.
The mutant RNA-transcript with expanded CUG repeats, is assumed to serve as a trigger for interferon response, and elevated levels of the pro-inflammatory cytokines TNF-α, IL-6, and IL-1β cytokines were demonstrated in DM1 patients [10, 11]. Many of these cytokines are known to be elevated during the hyperinflammatory syndrome and fulminant hypercytokinaemia (so-called cytokine storm) of severe COVID-19 [12]. It remains to be investigated whether this association does indeed lead to a more severe disease course in patients with DM1. Although inflammation is not an initiating factor in DM1, growing evidence indicates that inflammatory responses involving astrocytes, microglia, and the peripheral immune system may contribute to disease progression [3].

In Steinert’s disease, progressive muscles weakness ultimately leads to respiratory failure, which is often managed using nocturnal home ventilatory support. There is a widespread concern that the use of non-invasive ventilation could increase the risk of viral transmission in COVID-19. This statement is based on theoretical concepts rather than clinical data. We believe that a coughing patient, with effective peak cough flows exceeding 460–400 L/min, is probably more contagious than a patient on non-invasive ventilation with a well-fitted mask interface covering nose and mouth [13–15]. An analysis of 75,465 COVID-19 cases in China did not report airborne transmission [16]. This is why, in our hospital, we have the policy to continue NIPPV in patients with DM1 with their home ventilator with a well-fitted interface. The patients were admitted into individual negative-pressure rooms with airborne and contact precautions.

Several candidate therapies have been tested in DM1 models, but none have reached clinical practice yet. Bargiela et al. suggested chloroquine as a possible strategy based on the finding that chloroquine treatment is able to upregulate musclebind levels in in vitro and in vivo models [17]. At the beginning of the COVID-19 pandemic, (hydroxy)chloroquine was proposed as one of the most promising drugs due to its anti-viral and immunosuppressive properties. However, this hypothesis has become highly controversial with an overall weak evidentiary basis [18]. As mentioned, hydroxychloroquine was initiated in two out of three cases without apparent improvement, although randomized trials are needed to confirm our findings. Moreover, hydroxychloroquine can trigger a flare-up in several neuromuscular disorders and can cause chloroquine myopathy [19–21].

Lastly, COVID-19 is overwhelming health care systems worldwide, putting pressure on infrastructure and staff and thereby provoking ethical issues [6]. Patients with DM1 who have a great burden of chronic illness often have limited prognosis in the ICU and may find their quality of life after prolonged life support unacceptable [22]. Therefore, advanced care planning and discussions of goals-of-care prior to the occurrence of serious acute illness should be given priority. This may prevent emotional distress in unprepared patients or their families upon admission since the psychological impact of COVID-19 on hospitalized patients and their relatives cannot be overestimated. Baseline lung function values of patients with neuromuscular disorders may be used as important prognostic values. As our third patient still had an FEV1 of 2.3 L without a more favourable

Fig. 3 Chest CT of patient 3 revealing bilateral opacities, CO-RADS 5
disease course, the respiratory function alone may not be sufficient for risk stratification. Beside the severity of DM1, comorbidities such as obesity, cardiovascular and renal involvement may be of particular significance, although the relative importance remains unclear [23].

Conclusion

Based upon the severe disease course of these three cases, the primary advice for all patients with DM1 and their caregivers is to maximally reduce the risk of contracting the SARS-CoV-2 through e.g. social distancing, handwashing, and stricter isolation. Once infected, patients with DM1 should be closely monitored, as they seem to be at higher risk for severe COVID-19.

Author contributions SD and RC wrote the manuscript. DS, FB, JDB, ED and EVB read and corrected were needed. All authors took part in the discussion leading up to the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing financial interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. The Ethic Committee of University of Ghent has approved our manuscript to ensure that they agree with local and international ethical guidelines.

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