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Coronavirus Pandemic

COVID-19 and myotonic dystrophy: Case reports and systematic review

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Abstract

Introduction: Steinert's disease is a rare genetic disorder characterized by progressive myotonia and multi-organ damage. It is associated with respiratory and cardiological complications often leading patients to *exitus.* These conditions are also traditional risk factors for severe COVID-19. SARS-CoV-2 has affected people with chronic diseases, but the impact on people with Steinert's disease is poorly defined, with only a few reported and described. More data are needed to understand whether this genetic disease is a risk factor for more serious evolution or death in patients with COVID-19.

Methodology: The study describes two cases of patients with SD and COVID-19 and summarizes available evidence of the clinical outcome of COVID-19 in patients with Steinert's disease, by performing a systematic review of the literature (following PRISMA statements and performing PROSPERO registration).

Results: Overall, 5 cases were retrieved from the literature review, with a median age of 47 years, of whom 4 had advanced SD and unfortunately died. By contrast, the 2 patients from our clinical practice and 1 from literature had a good clinical outcomes. Mortality ranged from 57% (all cases) to 80% (only literature review).

Conclusions: There is a high mortality rate in patients with both Steinert's disease and COVID-19. It highlights the importance of strengthening prevention strategies, especially vaccination. All SD with SARS-CoV-2 infection/COVID-19 patients should be identified early and treated to avoid complications. It is still unknown which treatment regimen is best to use in those patients. Studies on a greater number of patients are necessary to provide clinicians with further evidence.

Key words: COVID-19; SARS-CoV-2; Steinert's disease; myotonic dystrophy; neurologic disorders.

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Introduction

Since December 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) started to spread worldwide, rapidly causing a pandemic [1]. SARS-CoV-2 can produce not only pneumonia with respiratory and flu-like symptoms, but can also involve all the systems, with cardiological, dermatological, autoimmune, psychiatric, alterations of smell and taste, and neurological manifestations, and [2-6]. As for neurological complications, cerebrovascular diseases, encephalitis, myelitis, disorders of consciousness, myopathies, and hemorrhages have been reported in patients with COVID-19, especially if severe [7].

Steinert's disease (SD), also known as myotonic dystrophy type 1 (MD1), is a rare genetic disorder involving muscles characterized by progressive myotonia and multi-organ damage. It is associated with different grades of muscle weakness and other systemic disorders such as cardiac conduction disorders, ocular disorders, endocrinopathies, sleep disturbances, and hair loss [1]. Its prevalence is about 1 out of 8,000 subjects and the genetic background of this autosomal dominant disease is linked to abnormal expansion of a CTG triplet repeat on the long arm of chromosome 19 [8]. Anticipation phenomena may occur in the following generations [8].

The clinical course of SD implies a progressive and slow worsening, even if rapid progression can also be observed in some cases, and both progressive myopathies and the other clinical features seen in the classical form of DM1 can be developed, although this does not start until early adulthood [8]. Death in subjects with SD usually occurs for cardiac or respiratory complications [8]. Respiratory complications, beyond the effects of SARS-CoV-2, can be also observed in patients with COVID-19 for other overlapping respiratory infections [9].

Certainly, the SARS-CoV-2 pandemic had a huge impact on both healthcare systems and people suffering from chronic conditions around the world [1], including neuromuscular disorders, but the impact on people with rare diseases, such as DS, has not yet been fully defined.

SD is associated with the onset of both acute/chronic respiratory and cardiological disorders, which are major risk factors for developing severe Coronavirus disease 19 (COVID-19) [10-11]. Moreover, these patients are more likely to experience behavioral disorders such as avoidant personality disorder that can lead to poor adherence to medical advice on prevention strategies [12], such as social distancing. This can be enhanced in patients with COVID-19, who are likely to experience depression during hospitalization [6].

To date, only a few cases of SD and COVID-19 have been described and more data are needed to understand whether SD is a risk factor for more serious evolution or death in patients with COVID-19.

The aim of this work was to describe two cases of patients with SD and COVID-19 from our clinical practice and to summarize available evidence of the clinical outcome of COVID-19 in patients with SD.

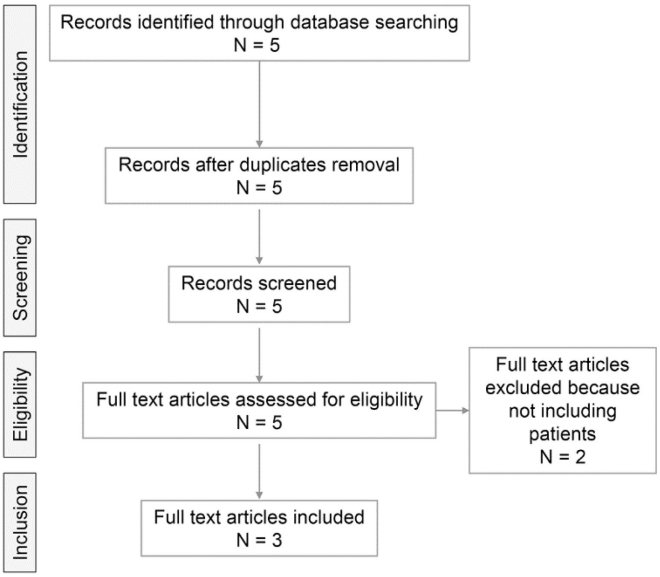
Methodology

This study was conducted at the Infectious and Tropical Diseases Unit of Padua University Hospital (Padua, Italy). Due to the nature of the study, this retrospective analysis did not require ethical approval and was in part conducted as part of clinical practice.

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statements [13]. The study protocol was registered in the PROSPERO system with the registration number (CRD42021253518).

Since the first cases of SARS-CoV-2 infection were reported (December 2019) until April 30th, 2021, both EMBASE and MEDLINE databases were screened by using the following keywords "Steinert disease", "Steinert's disease", "Myotonic Dystrophy type 1", "Myotonic Dystrophy", and both "COVID-19" and "SARS-CoV-2". All the forms of SD were included: congenital, childhood, and classic (adult-onset). Case reports, case series, retrospective studies, cross-sectional evaluations, and reviews were considered. Duplicated and redundant records were excluded. Papers were considered eligible if containing case descriptions of patients with SD and COVID-19. PRISMA flow diagram is depicted in Figure 1.

Figure 1. PRISMA flow diagram.



Case reports

Patient A

On April 15th, 2021, an 87-year-old male started experiencing asthenia and anorexia. The day after, due to the onset of shortness of breath and desaturation (SpO_2 88%), he was referred by his general practitioner to the Emergency Department where he was diagnosed with COVID-19 pneumonia, and thus admitted on April 17th, 2021 to the Infectious and Tropical Diseases Unit. He was not vaccinated against SARS-CoV-2 yet. In his past medical history: SD, Alzheimer's disease, mild dysphagia, hypothyroidism, hypertension, and behavior disturbances with reported aggressive episodes. It was not possible to know the precise year of SD diagnosis.

The patient was on chronic treatment with pantoprazole 40 mg/daily, aspirin 100 mg/daily, dutasteride 0.5 mg/daily, levothyroxine 25 mcg/daily, memantine 10 mg/daily, quetiapine 25 mg/daily, silodosin 8 mg/daily, sertraline 50 mg/daily. At admission, he was prescribed oxygen support with a nasal cannula at 4 liters per minute, enoxaparin 4000 UI/daily, dexamethasone 6 mg/daily, remdesivir 200 mg as a loading dose, and then 100 mg/daily for 4 days. Main laboratory/clinical parameters and radiological findings at admission are reported in Table 1 and Figure 2A, respectively.

During hospitalization, the patient did not experience clinical worsening from the respiratory point of view, and weaning from oxygen nasal cannula was soon after possible on April 27th, 2021. During hospitalization, on May 2nd, the patient developed a fever (39 °C) and mild hematuria. Blood and urine cultures were performed, coming back positive for

Citrobacter koseri. Urosepsis was treated empirically with meropenem (2 days) and then de-escalate to piperacillin/tazobactam (5 days). The length of stay was particularly long because the patient underwent an appropriate course of physiotherapy and rehabilitation. Due to the stability of clinical conditions, the patient was discharged to a long-term care facility on May 17th, 2021.

Patient B

A 58-year-old male who from April 12th started experiencing diarrhea, cough, fever (up to 38.5 °C), asthenia, and anorexia. On April 17th, due to the onset of shortness of breath and desaturation (SpO_2 88%), he was referred by his general practitioner to the Emergency Department where he was diagnosed with COVID-19 pneumonia, and therefore admitted to the Infectious and Tropical Diseases Unit. In his past medical history: SD was diagnosed when he was 28 years old, dyslipidemia, diabetes, hypertension, and baldness. For an atrioventricular block (2:1) with a right bundle branch block and left anterior hemiblock, the patient received a cardiac device implant in 2010. He also underwent phacoemulsification for bilateral cataract and colon polypectomy in 2014. Bilateral ptosis was present as well as diffuse muscular hypotonia and severe weakness in lower limbs. He was on chronic treatment with atorvastatin 10 mg/daily, perindopril, bisoprolol 1.25 mg/daily, and metformin 500 mg thrice daily. He did not receive yet the SARS-CoV-2 vaccination. At admission, metformin was stopped and replaced by on-demand insulin, and the patient started treatment with enoxaparin 4000 UI/daily, dexamethasone 6 mg/daily, and ceftriaxone 2 grams/daily.

Main laboratory/clinical parameters and radiological findings at admission are reported in Table 1 and Figure 2B, respectively.

During hospitalization, the patient never required oxygen support; however, cough became importantly productive and bronchial aspiration procedures were repeatedly necessary. N-acetylcysteine both intravenously and per aerosol was prescribed. The patient's clinical conditions progressively improved, and he was discharged to a long-term care facility on May 17th, 2021. Also, for this patient, physiotherapy and rehabilitation were performed during hospitalization.

Results

The literature screening detected 5 studies, all case report-based, two of which were excluded because they were not eligible (see PRISMA flow diagram, Figure 1). Therefore, three studies were included, describing five cases of patients with SD and COVID-19 [11,14,15]. A full description of the five cases from the literature review is provided in Table 2. Four out of these five subjects (80%) unfortunately died. Patient #1 was reported as post-mortem analysis. Three patients were male and two female, the median age was 47 years

Table 1. Parameters at admission of patient A and patient B (case reports).

Parameters (normal range)	Patient A	Patient B
Full blood count		
White blood cells (4.4-11.00 × 10^9/L)	3.74	4.15
Haemoglobin (140-175 g/L)	155	130
Lymphocytes (1.1-4.8 × 10^9/L)	1.73	0.28
Platelets (150-450 × 10^9/L)	162	124
Chemistry		
CRP (0-6 mg/L)	3	34
Procalcitonin (0.00-0.50 µg/L)	< 0.04	0.26
CPK (20-180 U/L)	201	328
Ferritin (31-409 µg/L)	424	1133
LDH (135-225 U/L)	286	318
D-dimers (0-400 µg/L)	< 150	163
Fibrinogen (1.5-4.5 g/L)	2.6	Not Available
Creatinine (59-104 µmol/L)	108	51
AST (10-45 U/L)	45	59
ALT (10-50 U/L)	23	41
Clinical parameters		
Blood pressure (mmHg)	130/60	100/80
Heart rate (ppm)	62	70
Temperature (°C)	36	36.5
Weight (Kg)	80	75
SpO_2 (%)	88	88
Respiratory rate (acts/minute)	14	20

(interquartile range, IQR: 43-63.5). All patients, but one (patient #2), had severe SD, required admission to the intensive care unit and, unfortunately, died. Three patients out of five were obese and two had known cardiovascular disease. As for COVID-19 presentation, only for patient #1 and #2 symptom onset is well detailed. For patient #2, COVID-19 showed up as acute pulmonary embolism with loss of consciousness, without any other prodromal signs or symptoms [15]. In this case, interestingly, no signs of pneumonia were detected. It is known that patients with SD have a greater risk of developing pulmonary thromboembolism when compared to the general population [16]. For this case, the coexistence of SD and SARS-CoV-2 infection presumably increased the risk further, as discussed by the authors [15]. However, it is impossible to conclude which disease (SD or COVID-19) contributed most to the embolic event for this patient.

The three patients described by Dhont *et al.* [11] were receiving non-invasive nocturnal home ventilatory support due to pre-existing chronic lung failure. For patient #3 diagnosis of COVID-19 was made accordingly to computerized tomography scan and laboratory results, PCR on the nasopharyngeal swab came back as negative. However, the authors

Figure 2. Chest X-rays imaging at admission.

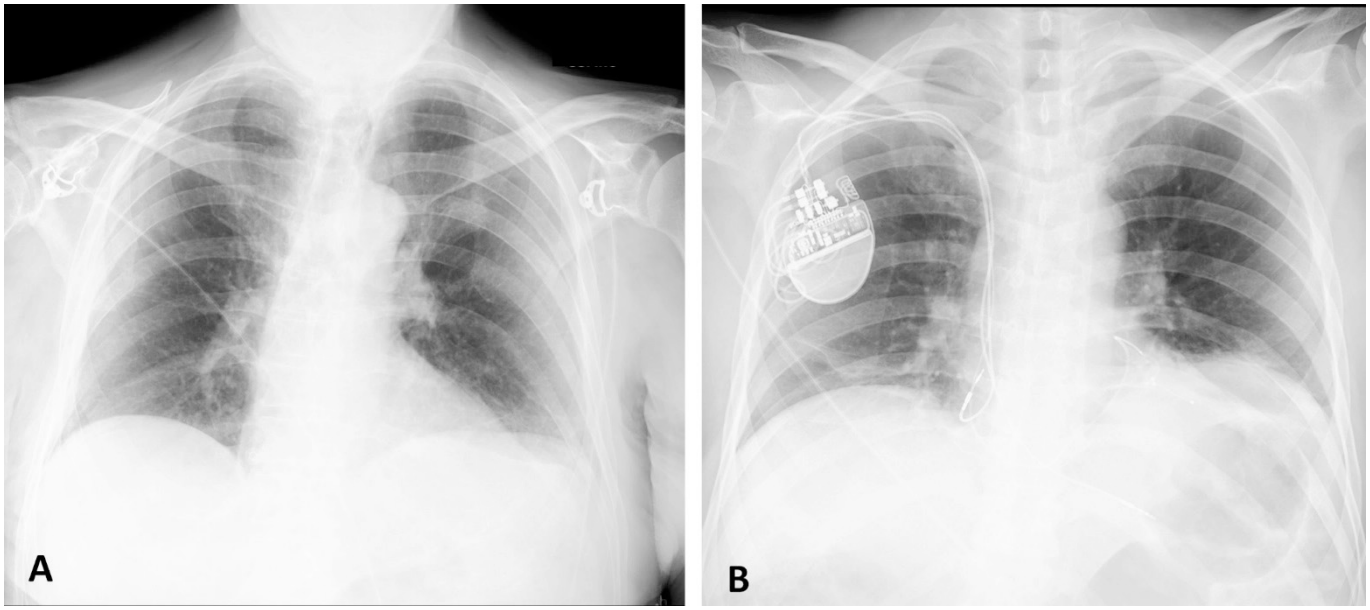


Table 2. Patient data from literature review.

Author	Year	Patient number	Age	Gender	Comorbidities	Stage of SD	COVID-19 symptoms at presentation	Treatment	Admission to ICU	Clinical outcome	Time to outcome
Barton *et al.*	2020	1	42	M	Obesity, cirrhosis, mild coronary atherosclerosis	Advanced	Abdominal pain, fever, cough, shortness of breath	Not available	Yes	Death	2 days
Chalela *et al.*	2020	2	63	M	Hiatal hernia, Smoker	Mild	Syncope	Enoxaparin 12 mg/kg twice daily	No	Recovery	7 days
Dhont *et al.*	2020	3	44	F	Obesity	Advanced	Severe respiratory failure	HCQ, NIV, empiric antimicrobials	Yes	Death	6 days
		4	47	F	Obesity	Advanced	Severe respiratory failure	HCQ, NIV, empiric antimicrobials	Yes	Death	5 days
		5	64	M	Cardiovascular disease	Advanced	Severe respiratory failure	HCQ, NIV, empiric antimicrobials	Yes	Death	8 days

stated that it was not possible to perform PCR on bronchoalveolar lavage.

Discussion

To the best of our knowledge, this is the first study assessing the clinical outcome of COVID-19 in patients with SD. A recent study described how these patients faced important stress and challenges during the pandemic era and how important is to encourage a better understanding of the impact of the pandemic both on SD and other neurological genetic disorders [17].

As for the treatment that patients from the literature received, unfortunately, it was possible to retrieve very little information. It is well known that some drugs such as azithromycin, steroids, and chloroquine, used to treat COVID-19, can be considered myotoxic and may worsen the clinical outcome in patients with SD [18]. We report the first case of SD with COVID-19 who was treated with remdesivir, without reporting any side effects. Therefore, a note of caution should be applied when using such drugs in patients with SD.

Our patients experienced a good clinical outcome probably because hospitalization and supportive care have been carried out timely after symptoms onset and COVID-19 diagnosis. The onset of symptoms was characterized by respiratory problems rather than fever, which was present in only one patient in our literature review. Fever, which is a very common primary symptom in the general population, may be absent in immunocompromised patients, such as SD patients. Moreover, our experience demonstrated how such patients required attention for the high risk of developing further infections (both bacterial and fungal).

The high mortality rate (4/7, 57% overall and 4/5, 80% in the literature review) reported by this analysis may lead to several conclusions. It mainly suggests and highlights the importance of strengthening prevention strategies in this population (social distancing, wearing masks, but most importantly performing vaccination). Indeed, all SD patients with SARS-CoV-2 infection/COVID-19 should be identified and pro-actively offered vaccination, especially those who have a more severe SD. Moreover, in the case of asymptomatic/mild form of infection, also early treatment with monoclonal antibodies could play a role in preventing the progression to severe form of COVID-19 disease. Population with SD should also be carefully monitored for early hospitalization in case of COVID-19 and unusual presentation of COVID-19 itself [14]. Moreover, it is still unknown which treatment regimen is best to be given to those patients.

From our experience, it can be stated that patients with severe SD are more likely to die due to COVID-19, and that the mortality rate is quite high.

However, this study is limited by its retrospective nature and by the small number of patients included. Therefore, further studies will provide clinicians with more evidence and information both about the clinical outcome of these patients and management of complications.

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