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COVID-19

Clinical heterogeneity in patients with myoclonus associated to COVID-19

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Abstract

Objective This study aims to report the clinical heterogeneity of myoclonus in 6 patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods Patient data were obtained from medical records from the University Hospital Dr. Josep Trueta, Girona, Spain.

Results Six patients (5 men and 1 woman, aged 60–76 years) presented with different myoclonus phenotypes. All of them had a medical history of hypertension and overweight. The latency of myoclonus appearance ranged from 1 to 129 days. The phenotype most observed was generalized myoclonus. Special phenotypes such as painful legs and moving toes syndrome with jerking feet, Lazarus sign-like, action myoclonus/ataxia syndrome, and segmental myoclonus secondary to myelitis have been described too. Levetiracetam and clonazepam were medications most used successfully. Two patients died for complications not related to myoclonus.

Conclusions Our 6 cases highlight the heterogeneity of the clinical spectrum of myoclonus associated to COVID-19 (MYaCO). MYaCO pathogenesis is suspected to be due to an immune-mediated para- or post-infectious phenomenon; nevertheless, further research is needed to elucidate this hypothesis.

Keywords Myoclonus · COVID-19 · SARS-CoV2 · Ataxia · Encephalopathy

Glossary

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Introduction

From the first case of nervous system involvement associated to COVID-19 reported on February 2020, many cases have been disclosed in medical literature, among them some patients with movement disorders [1]. Myoclonus is one of the uncommon neurological symptoms related to SARS-CoV-2 infection [2]. We want to show the clinical heterogeneity of myoclonus associated to coronavirus (MYaCO).

Methods

Data were obtained from patients admitted to the University Hospital Dr. Josep Trueta, Girona, Spain.

Standard protocol approvals, registrations, and patient consents

Written informed consent was obtained from the patients (consent for research).

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Data availability

The data supporting the findings of this study are available within the article.

Case series

Patient 1 A 62-year-old woman with no relevant medical history was admitted at the emergency department because of cough, fever, and malaise for 5 days secondary to SARS-CoV-2 infection. One week after her admission, she complained of pain in both legs even when she felt light touches. On general examination, painful legs were accompanied by "jerking feet" and erratic movements of toes (video 1, patient 1). Lab tests showed an increase of polymerase chain reaction (PCR) from 0.6 mg/dL 2 days before to 2.2 mg/dL (Table 1). This finding allowed us to diagnose painful legs and moving toes (PLMT) syndrome associated to SARS-CoV-2 infection. Spinal cord, coeliac disease, and peripheral nerve disorders were discarded. During the clinical course, corticosteroids were used for treating pulmonary involvement; coincidentally, PLMT also improved after its administration, and there was a sustained improvement 3 months later after her discharge from the hospital.

Patient 2 A 60-year-old man was admitted at our center because of history of 7 days of fever and swelling of left leg secondary to deep venous thrombosis. On chest X-rays, a pneumonia due to SARS-CoV-2 infection was also observed. He had history of celiac disease and psychomotor delay secondary to Down's syndrome. Ten days after his admission, he developed a generalized myoclonic tremor accompanied by distal jerks in all limbs, predominantly in the left side (video 1, patient 2). Concomitantly dyspraxia and disorientation were observed. Electroencephalogram and brain CT scan did not reveal any abnormal findings. Lab tests showed an increasing of PCR (from 4 to 12 mg/dL) (Table 1). Myoclonus improved after using clonazepam and levetiracetam, but 2 weeks later, the patient died because of respiratory failure in spite of using methylprednisolone and tocilizumab.

Patient 3 A 76-year-old man was hospitalized at the neurosurgery department due to post-traumatic cervical spine fracture with no neurological deficit. During his stay at the hospital, he presented fever, cough, and dyspnea due to pneumonia by SARS-CoV-2. Three days later, he developed severe respiratory failure and was transferred to ICU. On 38 days at ICU, he suddenly presented stereotyped and slow movements of raising his arms, specially his left arm. At this time, the patient presented an impaired level of consciousness but spontaneous eye opening. He also did not maintain eye contact with the explorer (video 1, patient 3) On neurological examination, we observed absence of reaction to nociceptive stimuli nor voluntary movements of his limbs. At this time, he was not under the effects of sedative drugs. EEG showed slowing background with generalized theta rhythm and an intermittent delta rhythm interposed on the background rhythm in both frontal lobes (Fig. 1A). Levetiracetam 1500 mg was started with no response in the first 48 h; nevertheless, he improved at the third day after initiation of this treatment. Disappearing of abnormal movements coincided with progressive improvement of the level of consciousness. At hospital discharge, he had not neurological deficits, modified Rankin scale (mRS) 1.

Patient 4 A 60-year-old man was admitted at our center due to 1 week of shortness of breath secondary to COVID-19. He was treated with dexamethasone and tocilizumab without improvement and was transferred to ICU because of severe acute respiratory failure. He stayed 118 days at ICU. Four days after being discharged from this unit, he developed a general zed myoclonic tremor predominantly in left limbs alongside "jerks" in both legs but specially in feet induced by tactile stimuli in sole of the foot. He also presented oculogyric crisis probably secondary to using of haloperidol to control an episode of delirium (video 1, patient 4). Lab tests showed an increase of PCR compared to previous determinations (Table 1). CT scan was normal, and EEG demonstrated a diffuse slowing specially in the posterior areas. There were no epileptic paroxysms.

The myoclonus disappeared after starting treatment with levetiracetam.

Patient 5 A 62-year-old man with no past medical history was admitted to ICU after having respiratory distress and fever for 7 days. On 42 days at ICU, he developed a generalized myoclonus accompanied by spasmodic jerks in the abdominopelvic region and on the left side of the body plus hypoesthesia in the left extremities. There were no spasms induced by tactile nor sound stimuli. He had spontaneous eye opening but had no response to call (video 1, patient 5). At this time, propofol and midazolam have been stopped. Due to diagnosis of segmental myoclonus, a spinal cord MRI was requested which showed mild hyperintensity in C4–C5, C6 demonstrating the spinal cord involvement (Fig. 1B). Brain MRI was unremarkable, EEG was normal, and lab tests revealed an increase of PCR (Table 1). The patient had not a good response to valproate, clonazepam, and lacosamide nor levetiracetam. Methylprednisolone 80 mg for 5 days and tocilizumab was also used without any response. Sixty-five days after his admission at the hospital, he died because of multiorganic failure.

Table 1 Clinical characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Gender	Female	Male	Male	Male	Male	Male
Age	62	60	76	60	62	68
Comorbidities	Overweight and hypertension	Overweight and hypertension	Overweight and hypertension	Overweight and hypertension	Overweight and hypertension	Overweight and hypertension
Myoclonus appearance latency	12 days	17 days	41 days	129 days	49 days	1 day
Myoclonus description	Jerking feet and moving toes	Generalized myoclonus	Lazarus sign-like	Generalized myoclonus	Abdominal pelvic spasms plus generalized myoclonus	Generalized and action myoclonus Phenotype: myoclonus/ataxia
PCR pre myoclonus, PCR myoclonus diagnosis	**0.6 to 2.2**	4 to 12	0.4 to 1.8	1.2 to 6	0.8 to 10.1	0.9 to **8.2**
Neuroimaging	Unremarkable	Unremarkable	Unremarkable	Unremarkable	Signs of myelitis in cervical spinal cord	Unremarkable
EEG	N/A	normal	slow background rhythm with generalized theta waves and an intermittent delta rhythm interposed on the background rhythm in both frontal lobes	Diffuse slowing specially in posterior areas	Normal	Normal
Other ancillary tests	N/A	N/A	N/A	N/A	N/A	DaT scan: irregular and decreased uptake of ioflupane in both putamen
Myoclonus treatment	Methylprednisolone	Levetiracetam and clonazepam	Levetiracetam	Levetiracetam	Levetiracetam, valproate, and clonazepam	Levetiracetam and clonazepam
Functional outcomes 3 months	mRS = 0	Death	mRS = 1	mRS = 0	Death	mRS = 0

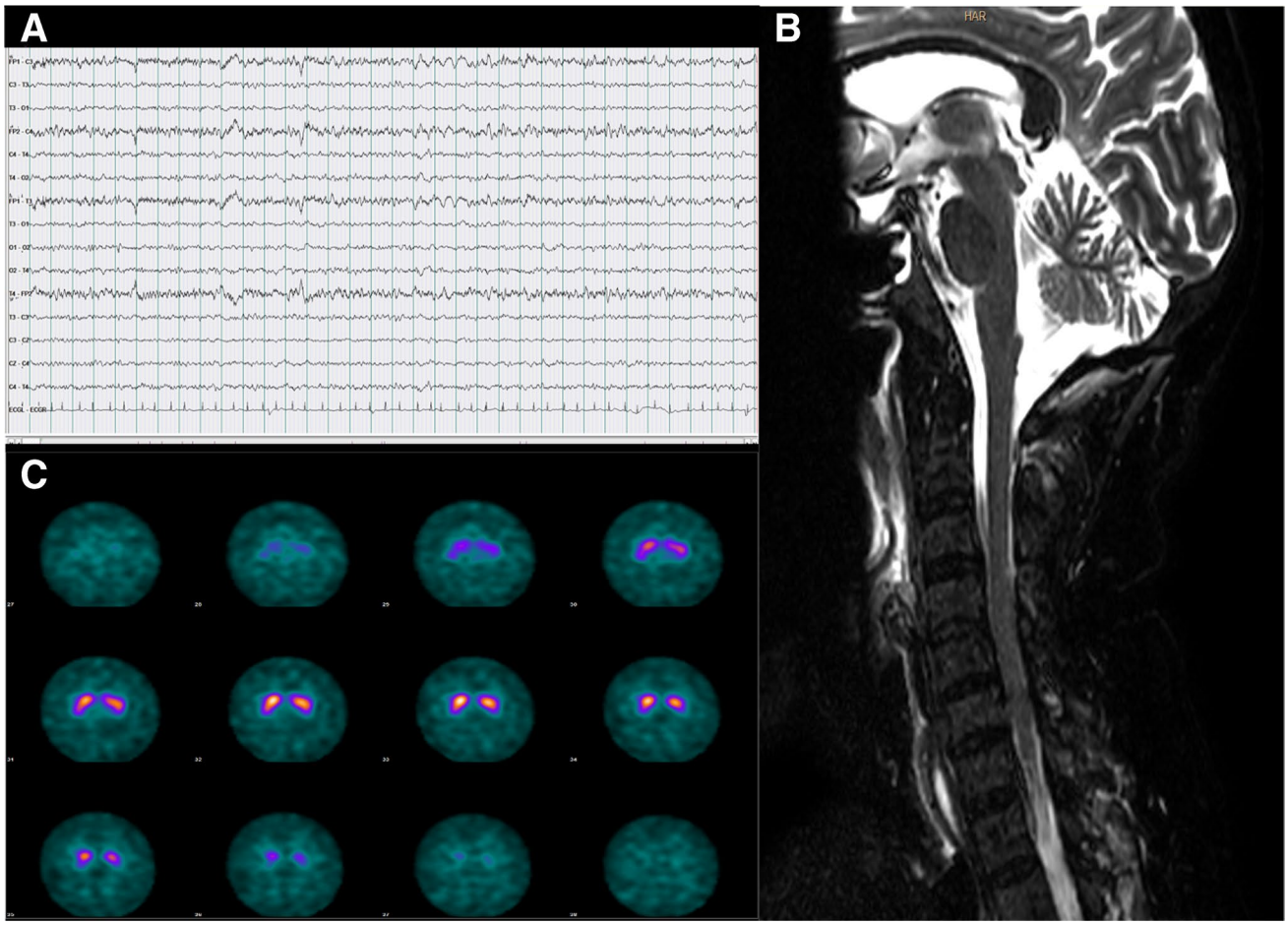

Fig. 1 **A** EEG shows slowing background with generalized theta rhythm and an intermittent delta rhythm interposed on the background rhythm in both frontal lobes. **B** Cervical spinal cord MRI showing edema in C5 to C7 levels. **C** DaT scan showing irregular and decreased uptake of ioflupane in both putamen and globus pallidus

Patient 6 A 68-year-old man with no relevant medical history was seen at the emergency room after developing unsteady gait which caused falls, upper limbs tremor, and fever in the last 10 days. PCR for admission to neurology department was positive for SARS-CoV-2. On neurological examination, he had generalized rigidity and bradykinesia in all extremities, postural and action myoclonus, orthostatic myoclonus, hyperekplexia with auditory and tactile stimuli, generalized hyperreflexia, and truncal ataxia which prevented the gait. His mental status was good (video 1, patient 6). He received treatment with methylprednisolone 80 mg for 5 days plus clonazepam and levetiracetam with good response.

DaT scan showed irregular and decreased uptake of ioflupane in both putamen and globus pallidus with a pattern different what is typically observed in most common organic parkinsonism (Fig. 1C).

EMG addressed to study orthostatic myoclonus showed a semi-rhythmical bursts of motor activity lasting less than 50 ms often firing synchronously, particularly in the bilateral tibialis anterior medial gastrocnemius.

Lab tests at admission revealed a PCR of 8.2 mg/dL which was decreasing over the next days (Table 1).

Brain MRI did not show any remarkable finding.

At time of discharge from the hospital 10 days after his admission, he had mild action myoclonus and parkinsonism with no other neurological symptom.

Discussion

Myoclonus is a sudden and brief involuntary twitching or jerking of a muscle or group of muscles [3]. In the last year, some cases of myoclonus associated to COVID-19 have

been reported [4]. Chronic conditions such as overweight and hypertension can be risk factors to develop MYaCO according our case series.

Latency of myoclonus appearance is variable depending on the series or cases [4, 5]. In our series, the time of myoclonus appearance ranged from the outset of disease until 129 days later of first symptoms. MYaCO onset was linked to increasing of PCR levels with respect to previous determinations in all cases. This finding supports a likely underlying hyper-inflammation mechanism [6]. (Other inflammatory parameters were not measured because they are not included in routine tests.) Of 6 patients, 5 were male, showing a special vulnerability to male gender. This fact is in concordance with male susceptibility to develop complicated COVID-19 [7]. The MYaCO phenomenology is wide [6]. The phenotype most observed was the generalized myoclonus (patients 2, 4, 5, 6). We also disclosed "special phenotypes" which were alone or overlapped with the generalized myoclonic tremor, so patient 1 had all characteristics required to be diagnosed as painful legs and moving toes. Patient 3 displayed an asynchronous/synchronous movement of lifting arms; we recognize these movement disorders cannot be classified as myoclonus properly, but we all authors consider it important to disclose this interesting abnormal movement because it resembled to Lazarus sign which had only been reported in encephalic death [8]. We hypothesized this stereotyped movement could be caused by disruptions of the cortical–striatal–thalamo–cortical pathways [9]. As the patient improved and recovered completely, his consciousness after being treated with levetiracetam, we coined the term "transient death of cortical–striatal pathway" to explain this unusual semiological observation. Patient 6 showed a constellation of movement disorders, such as action myoclonus, hyperekplexia, ataxia, and parkinsonism. Chan et al. and Schellekens et al. had already described cases of myoclonus ataxia related to SARS-CoV-2 [6–10]. Parkinsonism due to alteration of presynaptic dopaminergic transmission was other particularity of this case alike to previously reported by Méndez-Guerrero et al. [11].

MYaCO can originate at various levels in the central nervous system, from the cerebral cortex to the spinal cord, but its pathophysiology remains unclear. The majority of cases reported were thought to be post-infectious and immune-mediated. Some electrophysiological studies have suggested a cortical, subcortical, or cortical–subcortical mechanisms, but it could not be shown in most patients [6]. In our case series, no EEG registry revealed epileptic discharges, even though two of them showed a pattern of encephalopathy. Neuroimaging was also unremarkable in most patients, except patient 5 who developed an abdominal pelvic spasms which were secondary to cervical myelopathy. The pathogenesis of spinal cord involvement was presumably an immune-mediated post-infectious phenomenon, as an extensive workout ruled out other common causes of myelitis. To our knowledge, this is the first case of segmental myoclonus secondary to COVID-19.

Myoclonus is a condition often debilitating, and treatment is needed. Clonazepam and levetiracetam, alone or in combination, have been used to successfully alleviate myoclonus associated with COVID-19 [6–10]. Immunotherapy with methylprednisolone or IVIG may accelerate recovery. Plasma exchange may be considered in cases that are refractory to methylprednisolone and IVIG (6-4). In our case series, clonazepam and levetiracetam were used with good outcomes in most cases, except in patient 5; since the myoclonus had a spinal origin and usually this type has not good response to antiepileptic drugs [12]. Two of our patients died because of complications not related to myclonus. MYaCO tends to be a condition with good long-term functional outcomes according cases reported so far [6].

The interpretation of myoclonus was carried out by our team of neurologists who are experts in movement disorders, which could be a limitation to our report.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-021-05802-1.

Declarations

Conflict of interest The authors declare no competing interests.

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