Title: Opsoclonus- myoclonus syndrome, a post-infectious neurologic complication of COVID-19: Case series and review of literature

Maziar Emamikhah [1], Mansoureh Babadi [2], Mehrnoush Mehrabani [3], Mehdi Jalili [2], Maryam Pouranian [4], Peyman Daraie [5], Fahimeh Mohaghegh [1],Sharmin Aghavali [1], Maryam Zaribafian [6], Mohammad Rohani [1*]

1. Department of neurology, School of Medicine, Hazrat Rasool-e Akram General Hospital, Iran University of Medical Sciences, Tehran, Iran
2. Ganjavian Hospital, Dezful University of Medical Sciences, Dezful, Khuzestan Province, Iran
3. Fajr Hospital, AJA University of Medical Sciences, Tehran, Iran
4. Amiralmomenin Hospital, Zabol University of Medical Sciences, Zabol, Iran
5. Khatamolanbia Hospital, Shoushtar University of Medical Sciences, Shoushtar, Khuzestan Province, Iran
6. Nikan Hospital, Tehran, Iran

ME: maziar.emamikhah@yahoo.com; emamikhah.m@iums.ac.ir (orcid ID: 0000-0001-8375-5262)
MB: babadi.mansoureh@gmail.com (orcid ID: 0000-0002-8907-1168)
MM: Mehrnooshmehrabani@yahoo.com
MJ: Mehdidjalili@yahoo.com
MP: Pouranian.maryam112@gmail.com (orcid ID: 0000-0003-3170-8442)
PD: Peyman.da.215@gmail.com
FM: fahmoh2013@gmail.com
SA: shaghavali@gmail.com
MZ: Zaribafian_m@yahoo.com
* Corresponding author (e-mail: mohammadroohani@gmail.com; rohani.m@iums.ac.ir orcid ID: 0000-0002-5409-1804)

Abstract

Opsoclonus-myoclonus-ataxia syndrome is a heterogeneous constellation of symptoms ranging from full combination of these three neurological findings to varying degree of isolated individual sign. Since the emergence of coronavirus disease 2019 (COVID-19), neurological symptoms, syndromes and complications associated with this multi-organ viral infection have been reported and the various aspects of neurological involvement are increasingly uncovered. As a neuro-inflammatory disorder in nature, one would expect to observe opsoclonus-myoclonus syndrome after a prevalent viral infection in a pandemic scale, as it has been the case for many other neuro-inflammatory syndromes. We report seven cases of opsoclonus-myoclonus syndrome presumably para-infectious in nature and discuss their phenomenology, their possible pathophysiological relationship to COVID-19 and diagnostic and treatment strategy in each case. Finally we review the relevant data in the literature regarding the opsoclonus-myoclonus syndrome and possible similar cases associated with COVID-19 and its diagnostic importance for clinicians in various fields of medicine encountering COVID-19 patients and its complications.

Keywords: COVID-19; SARS-CoV-2; Opsoclonus; myoclonus; parainfectious

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Introduction

Myoclonus is defined as brief, sudden, shock-like muscle contraction leading to jerky movements. It is further divided to positive and negative myoclonus based on increased activation or inhibition of muscle contraction. There are several classifications for myoclonus from different aspects; the most commonly used focusing on the generating site of myoclonus. This classifies the myoclonus as cortical, cortical-subcortical, subcortical/nonsegmental, segmental and peripheral. Etiologic classification on the other side encompasses physiologic myoclonus, essential myoclonus, epileptic myoclonus and symptomatic myoclonus (Caviness, 2019). Opsoclonus as an ocular equivalent of myoclonus is irregular, arrhythmic, and chaotic eye movements in all directions of gaze which exacerbates with pursuit (Cameron and Kilbane, 2019; Caviness, 2019). It is in fact a saccadic disorder of eye movement also known as "saccadomania" and along with ocular flutter is categorized under the umbrella disorders termed "saccadic intrusions without intersaccadic intervals". Opsoclonus is more frequently accompanied by ataxia, encephalopathy and myoclonus, accordingly the term "opsoclonus–myoclonus syndrome" (OMS) was introduced (Lemos and Eggenberger, 2013). Regarding the etiologic classification of myoclonus, OMS is placed under symptomatic myoclonus category and etiologically categorized into idiopathic, paraneoplastic, infectious and other subgroups (Caviness, 2019; Caviness and Brown, 2004).

Adult-Onset OMS, unlike the similar disorder in children (referred to as Kinsbourne syndrome) is a less well-defined entity, especially in association with infections. The majority of reported cases in adults have been paraneoplastic in nature mostly in association with antineuronal nuclear antibody type 2 [ANNA-2; anti-Ri]. However many idiopathic cases with presumed parainfectious etiology seem to occur and these patients manifest a short duration (4-6 weeks) symptomatic phase and in most cases respond to immunotherapy (Klaas *et al*, 2012). Symptoms, especially the myoclonus, alleviate with clonazepam or other drugs such as sodium valproate and levetiracetam (Kojovic *et al*, 2011).

As the new coronavirus infection disease (COVID-19) continues to be the major current health issue around the world, new symptoms regarding neurological aspect of this multi-system disease are being reported. Cerebrovascular disorders (e.g. ischemic stroke, intracerebral hemorrhage, cerebral vasculitis), altered mental status (due to encephalitis, associated encephalopathy, seizure, etc.), peripheral nervous system involvement (Guillain-Barré syndrome, myositis, etc.) and neuropsychiatric involvement (e.g. depression, personality change, catatonia, mania and psychosis) have been the major neurological manifestations of COVID-19 frequently reported (Lu *et al*, 2020; Varatharaj *et al*, 2020). Regarding movement disorder neurological symptoms in COVID-19 the semiology, pathophysiology and epidemiology of each movement disorder are still naïve. In some studies there are classifications for staging the COVID-19 disease course. These stages have been proposed as acute respiratory distress syndrome, cytokine storm, acute hyper-coagulable state, and autonomic dysfunction (Yamamoto *et al*, 2020). Although these may explain some of neurological aspects of COVID-19, we believe there are much more aspects to focus on, phenomenologically and pathophysiologically, among them to mention are para-infectious autoimmune syndromes. We have been consulted on seven cases with COVID-19 either in acute infectious phase or early after remission in whom the emergence of abnormal movements resembling OMS was noticeable.

Case report

We report here seven COVID-19 patients who developed similar symptoms i.e. myoclonus. These cases were consulted with two of authors (MR and ME) in a referral center for movement disorders. The Cases 1, 3 and 4 were reported from centers where two of the authors work and managed them (MB and MJ). Cases 2 and 5 were managed in the hospitals were two of authors are practicing (MM and MZ respectively). The 6th patient was referred for treatment to ME and MR. The 7th patient was recently managed by our colleague, FM, ME and MR were consulted on this case. All patients gave their informed consent prior to their inclusion in the study. This case series was approved by ethical committee and review board of IUMS neurology department (ID: IUMS-ND-99/08/11-01; date: 11/01/2020). Patients characteristics and their disease related information is summarized in table 1.

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Table 1. Patients characteristics and their disease related information.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (years)	51	54	52	42	44	52	39
Gender	Male	Male	Male	Female	Male	Male	Male
Presenting symptoms of COVID-19	sore throat, back pain, anorexia and mild dyspnea	malaise, fever, myalgia, coughs, two days later dyspnea	dry cough, low grade fever and headaches	fever, myalgia and coughs	fever, chills, three days later seizure	fever, myalgia and cough	Fever, cough, myalgia, nausea, vomiting, 10 days later seizure
Neurological symptoms spectrum	Myoclonus (+) Opsoclonus (+) Ataxia (+) Voice tremor (+)	Myoclonus (+) Opsoclonus (-) Ataxia (+) Voice tremor (-)	Myoclonus (+) Opsoclonus (-) Ataxia (+) Voice tremor (+)	Myoclonus (+) Opsoclonus (-) Ataxia (+) Voice tremor (+)	Myoclonus (+) Opsoclonus (+) Ataxia (+) Voice tremor (+)	Myoclonus (+) Opsoclonus (-) Ataxia (+) Voice tremor (+)	Myoclonus (+) Opsoclonus (+) Ataxia (+) Voice tremor (+)
Neurological symptom onset interval since initial COVID-19 symptoms	2 weeks	4 days	16 days	10 days	3 days	3 weeks	10 days
Laboratory finding	No abnormalities	WBC=11500/uL, lymphocyte=2300/uL, ESR=45 mm/h and CRP=2+ Normal serum electrolytes CSF analysis: normal for cell	WBC=6600/uL, Lymph=1700/uL, ESR=30 mm/h and CRP=2+ Normal serum electrolytes	No abnormalities	Normal EEG and CSF analysis	Normal CSF analysis and PCR for viral and bacterial pathogens as well as COVID-19. Negative	AST=61 U/L, ALT=69 U/L, ESR=58 mm/h, CRP=75.4 mg/L

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		count, protein and glucose				autoimmune encephalitis panel in serum and CSF. No OCBs [1].	
COVID-19 laboratory tests	Positive N-PCR [2]	Negative N-PCR, positive serum IgG and IgM	Positive N-PCR	N/A	Positive N-PCR	Positive N-PCR	Positive N-PCR
Brain imaging Findings	Normal CT scan	Normal MRI	Normal MRI	N/A	Normal MRI	Normal MRI	Normal CT
Lung imaging findings	few peripheral patchy ground-glass opacities	patchy peripheral ground glass opacities and consolidations	patchy peripheral ground glass opacities and consolidations	N/A	patchy peripheral opacities	patchy peripheral opacities	patchy predominantly peripheral ground glass opacities and consolidations
Pulmonary disease severity	Mild [3]	Moderate [3]	Moderate	Mild	Mild	Mild	Severe
Treatments	Clonazepam, Levetiracetam, IVIG	Levetiracetam, sodium valproate, IVIG	Sodium valproate, clonazepam	Sodium valproate, clonazepam	Sodium valproate, clonazepam, IVIG	Clonazepam, IVIG	Levetiracetam, sodium valproate, clonazepam, IVIG, Dexamethasone
OMS improvement status	Complete recovery after 4 weeks	Partial recovery after one week	Partial recovery after 2 months	N/A	Complete recovery after 2 months	significant improvement after 4 weeks	N/A

1. Oligoclonal bands
2. Nasopharyngeal RT-PCR test
3. Mild COVID-19 defined as no pneumonia or mild pneumonia, Moderate COVID-19 defined as pneumonia without need for supplementary oxygen, Severe is defined as dyspnea and the need for supplementary oxygen (Wu and McGoogan, 2020).

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Case 1. A 51-year-old male health-care staff (Nurse) presented with sore throat, back pain, anorexia and mild dyspnea. There was no leukocytosis, lymphopenia or increment in erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). The chest CT revealed few peripheral patchy ground-glass opacities (Fig. 1). Brain CT was normal. His nasopharyngeal swab sample RT-PCR test result for COVID-19 was positive. He was treated with Non-steroidal anti-inflammatory drugs (piroxicam IM) for myalgia, hydroxychloroquin, and azithromycin. Two weeks after initial symptoms, he noticed tremor-like jerky movements in his hands which progressively increased in severity and became worse with intentional movements. After several days his legs and voice was involved with tremors and he noticed ocillopsia. His jerky movements, diagnosed as generalized stimulus sensitive and action myoclonus was treated with clonazepam 0.5 mg qhs and levetiracetam 500 mg bid. His extra ocular movements were fragmented during pursuit movements intermixed with jerky oscillatory movements of eyes in all directions (opsoclonus) and corrective rapid head movements. There was slightly truncal ataxia (wide-based gait) more prominent during tandem walking (Online Resource 1). Based on these symptoms para-infectious OMS was presumed and IVIG was started to a total dose of 150 g (2g/kg). The improvement of abnormal movements was noticeable after one week of IVIG initiation and markedly improved three weeks after treatment (Online Resource 2-4). Clonazepam and levetiracetam 4 weeks after treatment were discontinued and there were no abnormal movements thereafter.

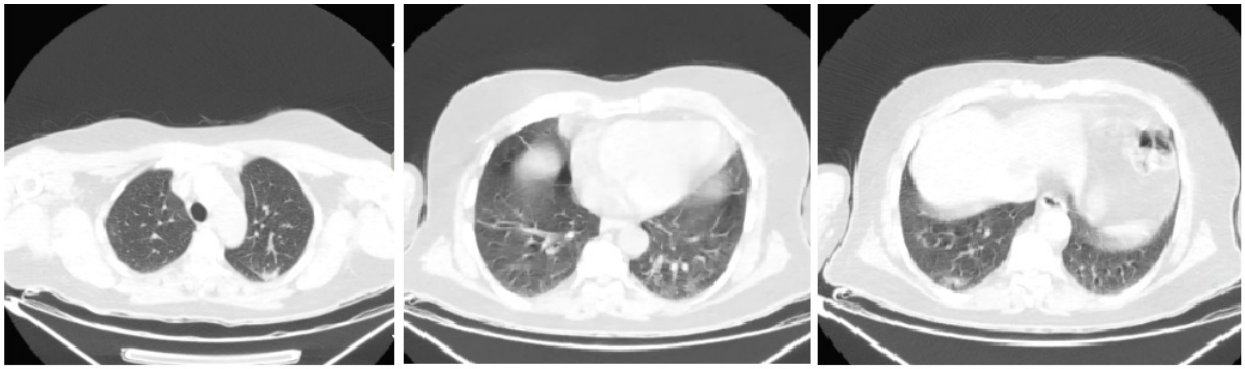

Fig. 1 chest computed tomography (CT) scan of case 1 shows few peripheral patchy ground-glass opacities in both lungs

Case 2. A 54-year-old male was admitted to the hospital with dyspnea. His symptoms started with malaise, fever, myalgia, coughs, and two days later dyspnea. After nearly four days of symptoms' onset, he developed generalized jerky movements. His voice and ocular movements were spared. Examination revealed generalized myoclonic jerks exacerbating with intentional movements and sudden noises (Online Resource 5). Chest CT showed patchy peripheral ground glass opacities and consolidations in both lungs, much more severe than case 1 (Fig. 2). Brain MRI was normal. Blood count revealed leukocytosis (WBC=11500) but lymphocyte count was 2300. ESR was 45 mm/h and CRP was highly positive (2+). Serum electrolytes were within normal limits. CSF analysis for cell count, protein and glucose were normal. Nasopharyngeal and CSF RT-PCR test for COVID-19 were negative but serologic survey for both IgG and IgM in serum were positive. Treatment with levetiracetam (2000 mg/day), sodium valproate (1000 mg/day) and IVIg (100 g total) after 5 days resulted in partial but significant resolution of myoclonic movements and he was discharged with levetiracetam and sodium valproate planned to be tapered during one month.

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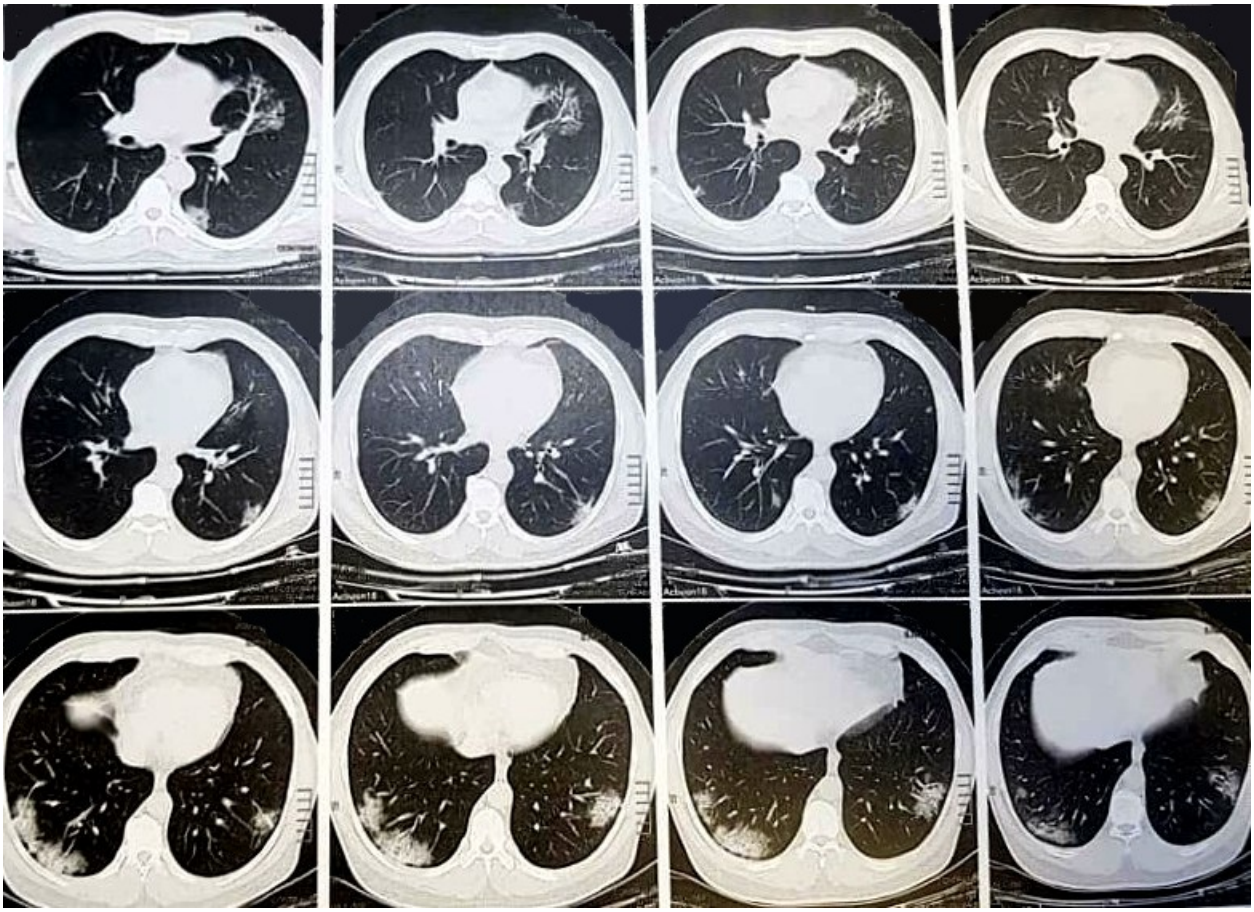

Fig. 2 Chest CT scan of case 2 showes patchy peripheral ground glass opacities and consolidations in both lungs

Case 3. This 52-year-old man with history of chronic lung disease came to hospital initially with dry cough, low grade fever and headaches started one week earlier. His laboratory tests revealed WBC=6600/uL, Lymph=1700/uL, ESR=30 mm/h and CRP=2+ and normal serum electrolytes. Chest CT showed typical COVID-19 involvements (Fig. 3). Nasopharyngeal swab RT-PCR test was positive for COVID-19. Treatment for respiratory disease started with oseltamivir, Lopinavir/ritonavir, hydroxychloroquine (hospital protocol at that time) and he was discharged after 4 days. Sixteen days after initial symptoms, he developed generalized stimulus (somatosensory and auditory) sensitive myoclonus, involving his voice as well, but not eye movements. His movements became severe and disabling after three days making him unable to walk. He was admitted again. Brain MRI was normal. Sodium valproate 1000 mg/day and clonazepam 1 mg qhs were beneficial, enabling him to walk with help. Chest CT was in favor of superimposed bacterial pneumonia and treatment with IV antibiotics started. He declined immunotherapy and was discharged with oral levofloxacin, sodium valproate and clonazepam. He did not consent for taking his video but allowed anonymous data consumption for this paper. After two month follow up his movements were still present but trivial and he was still on medications.

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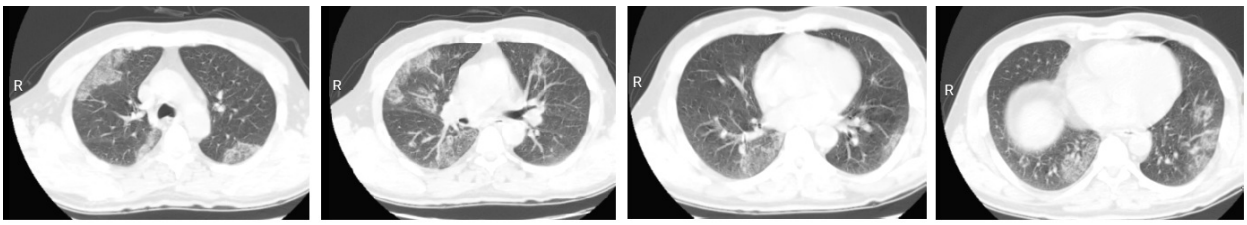

Fig. 3 Chest CT scan of case 3 shows patchy peripheral ground glass opacities and consolidations in both lungs typical for COVID-19 involvements

Case 4. A 42 year-old-female visited our clinic, 10 days after initial diagnosis of COVID-19 with initial symptoms of fever, myalgia and coughs had developed jerky movements of hands and feet (more severe on right side), voice tremor, imbalance and gait disturbance. In neurological examination she had generalized myoclonus, dysarthria and mild truncal ataxia similar to case 1 (but less severe).There was no prominent ocular movement involvement. Other neurological examinations were intact. Clonazepam and sodium valproate were started for abnormal movements. Unfortunately, we lost the follow up of this patient, but we think her symptoms got improved since her respiratory and movement disorders were mild and none of our colleagues in the local area which is a small city have visited her since then.

Case 5. The other similar patient about whom we were consulted was a 44-year-old-male, presented with fever, chills and three days later one episode of generalized tonic-clonic seizure. The same day he developed opsoclonus, generalized stimulus sensitive and action myoclonus and ataxia, which after several days made him completely disabled and unable to sit or walk. His voice was tremulous as well (Online Resource 6-9). Chest CT was in favor of COVID-19 diagnosis (Fig. 4). Brain MRI, EEG and CSF analysis were normal. Treatment with intravenous ceftriaxone, oral azithromycin and anti-viral drugs Daclatasvir/sofosbuvir (Sovodak®) were instituted. With the presumed diagnosis of OMS we started sodium valproate, clonazepam and IVIG. After one week, with partial resolution of symptoms he was discharged (see Online Resource 6-9). Follow up at 2 months showed no abnormal movements.

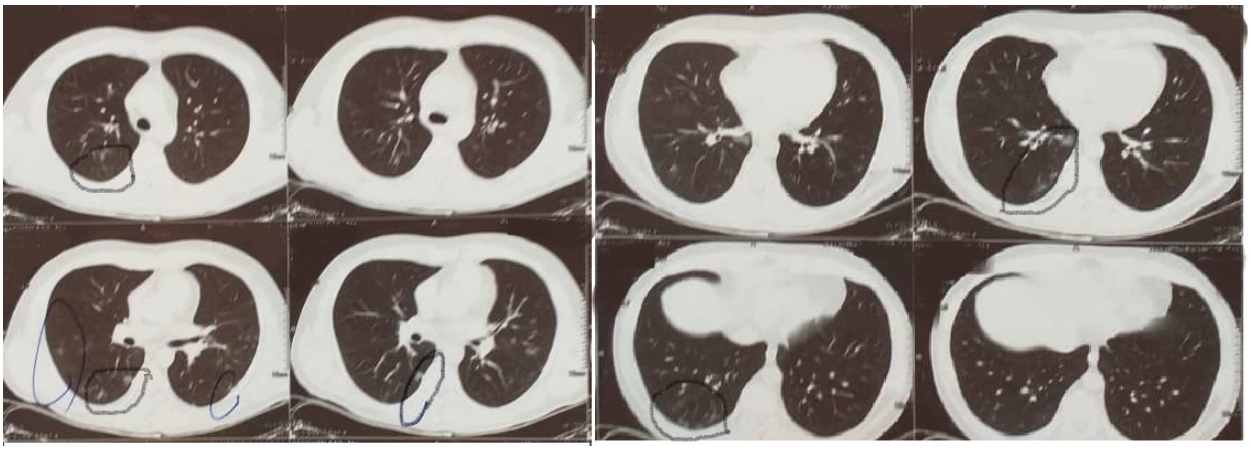

Fig. 4 Chest CT scan of case 5 shows patchy peripheral opacities (circles) in both lungs more severe in right lung in favor of COVID-19 diagnosis

Case 6. 52-year-old male nearly one month after initial symptoms of fever, myalgia and cough was referred to us for treatment of abnormal movements. Neurological examination revealed generalized myoclonus with intentional component, mild ataxia and severe shuffling gait. Voice involvement was prominent but there was no opsoclonus

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(Online Resource 10). Chest CT scan (Fig. 5) was in favor of COVID-19 diagnosis and nasopharyngeal swab RT-PCR test confirmed the diagnosis. CSF protein, Glucose and cell count were normal and PCR for common viral and bacterial pathogens as well as COVID-19 in CSF was negative. Serum and CSF panel for autoimmune encephalitis antibodies was negative. No oligoclonal bands were detected. Treatment with clonazepam and IVIG (100 g total) resulted in significant improvement after 4 weeks (Online Resource 11).

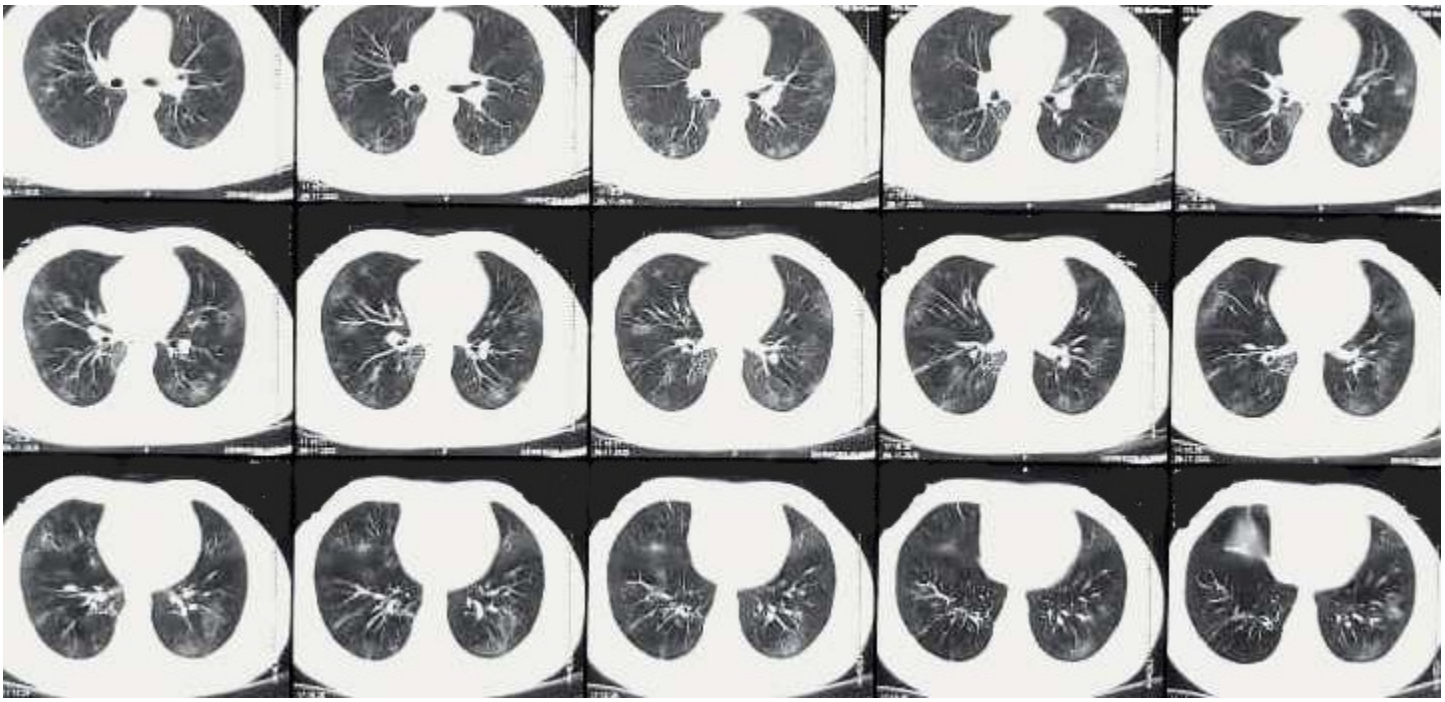

Fig. 5 Chest CT scan of case 6 shows patchy peripheral opacities in both lungs in favor of COVID-19 diagnosis

Case 7. This very recent patient of us, a 39-year-old male, presented with fever, cough, myalgia, nausea, vomiting and 10 days later one episode of generalized tonic-clonic seizure. The same day he began to suffer jerky movements. Examination revealed prominent opsoclonus, generalized myoclonus with intentional component and ataxia. His voice was severely involved (Online Resource 12). Chest CT was diagnostic for COVID-19 (Fig. 6). Brain CT was normal. Abnormal laboratory tests included AST=61 U/L, ALT=69 U/L, ESR=58 mm/h, CRP=75.4 mg/L. He was started on levetiracetam, clonazepam, IVIG and dexamethasone. After 2 days sudden increase in serum creatinine (Cr=5) made us to stop IVIG and change levetiracetam to sodium valproate. He is still under treatment for severe respiratory involvement and acute renal failure. Clonazepam and sodium valproate alleviated myoclonus but improvement in general condition and OMS merits long-term follow up.

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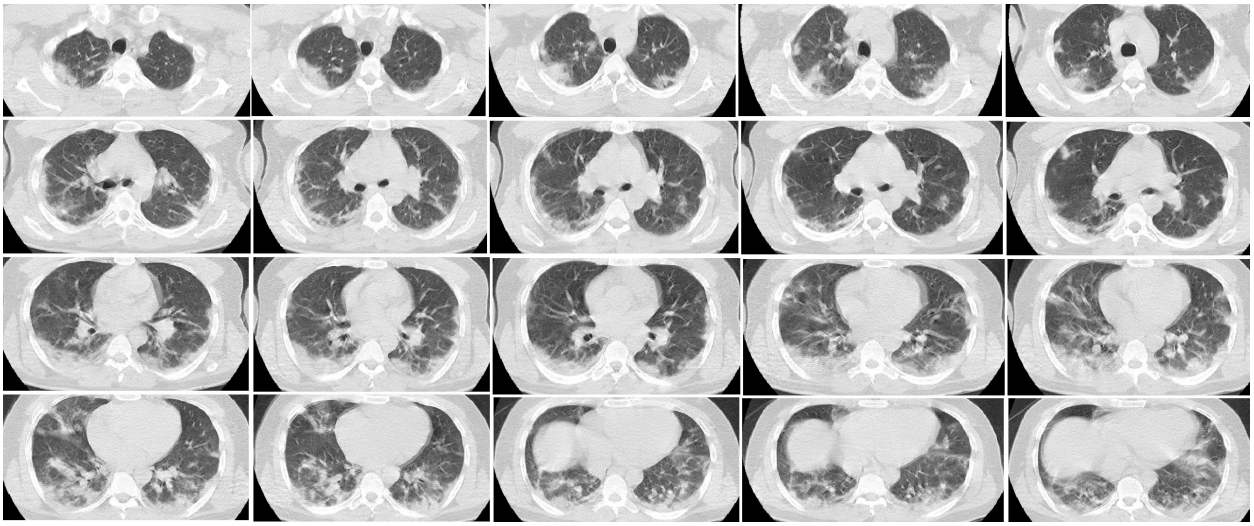

Fig. 6 Chest CT scan of case 7 shows patchy predominantly peripheral ground glass opacities and consolidations in both lungs supporting the COVID-19 diagnosis

Discussion

Opsoclonus-myoclonus-ataxia syndrome is a heterogeneous constellation of symptoms ranging from full combination of these three neurological findings to varying degrees of isolated each individual sign. In a review of patients with adult- onset OMS, one third had flu like symptoms before the emergence of abnormal movements and 40 percent revealed either elevated IgG index or oligoclonal bands, none of them being paraneoplastic cases in follow up but results for presumed infections to establish para-infectious source were negative. Eighty percent received immunotherapy (IVIG, corticosteroids, plasma exchange or a combination of them) and almost all of non-paraneoplastic cases improved. Proven infection were identified in 13 percent of OMS patients extracted from review of the literature (Klaas *et al*, 2012).

Since the emergence of COVID-19, neurological symptoms, syndromes and complications associated with this multi-organ viral infection have been reported and the various aspects of neurological involvement are increasingly uncovered. There have been a proposed staging for COVID-19 defined as acute respiratory distress syndrome, cytokine storm, acute hyper-coagulable state, and autonomic dysfunction (Yamamoto *et al*, 2020), but this may explain some aspects of neurological COVID-19. Many para-infectious autoimmune complications such as Guillain-Barré syndrome are increasingly reported (Varatharaj *et al*, 2020) and these immune mediated complications may occur with varying interval from initial COVID-19 symptoms and may overlap with each of the above mentioned stages. As a neuro-inflammatory disorder in nature, one would expect to observe OMS after a prevalent viral infection in a pandemic scale, as it has been the case for many other neuro-inflammatory syndromes (Paterson *et al*, 2020).

However, the syndrome as a specific consideration related to COVID-19 has not been discussed fully in the literature. Here we presented seven similar OMS cases after COVID-19, which we were consulted for as a movement disorder referral center.

The best similar report regarding this disorder has been in three patients, presented with generalized myoclonus following the inflammatory phase of COVID-19. None of them had opsoclonus, all three had encephalopathy and responded to immunotherapy indicating a para-infectious immune mechanism (Rábano-Suárez *et al*, 2020).

Myoclonus as a component of COVID-19 associated delirium has been reported by others and presumed to be a feature of generalized brain dysfunction in encephalopathic patients (Beach *et al*, 2020). Others also have reported COVID-19 associated encephalopathy to have myoclonus in their clinical picture and assumed brainstem involvement as the pathogenic mechanism (Chaumont *et al*, 2020). There is a case report of clozapine toxicity in a COVID-19 patient who also had myoclonus (Cranshaw and Harikumar, 2020). There is report of a patient in UK-

wide surveillance study with OMS but we were not able to access data regarding encephalopathy in this case (Varatharaj *et al*, 2020). Same authors reported a patient with OMS who had been encephalopathic and assumed to have autoimmune encephalitis with brainstem involvement (Paterson *et al*, 2020). There is a recent report of a COVID-19 patient who developed generalized action myoclonus one month after respiratory disease and the authors presumed it to be post-hypoxic in nature, although there was no solid evidence for this etiology in our view (Ros-Castelló *et al*, 2020). Another similar patient with generalized action myoclonus and ataxia (with voice involvement but without opsoclonus) occurring two weeks after severe respiratory disease has been reported (Dijkstra *et al*, 2020). This latter report is very similar to our cases except the fact that it has been following severe COVID-19 respiratory phase but six out of seven cases we reported here, have been after a mild to moderate respiratory disease according to Wu and McGoogan definition (Wu and McGoogan, 2020). Their patient had been more responsive to IVIG than methylprednisolone high-dose pulse therapy, compatible with our experience.

It seems to us that the OMS merits more attention as an independent immune para-infectious syndrome, with possible relationship to COVID-19 as the initial trigger infection. The interesting point in our patients was the absence of encephalopathy and variable interval after respiratory disorder, which was very mild in the first patient. This may indicate a syndrome independent of encephalopathy or direct effect of infection. The dramatic effect of immunotherapy on recovery in cases 1, 5 and 6 in comparison to case 3 confirms the immune mediated mechanism for this myoclonic syndrome. We believe some of the reported patients in the literature may have been suffering from the same immune OMS syndrome, which was overlapped by the respiratory or encephalopthic phase of COVID-19. This alarms the possibility of under-diagnosing an autoimmune encephalitic process that further can complicate the overall outcome of COVID-19 patients. Awareness of the possibility of such disorder and becoming familiar with the features representing it such as opsoclonus or myoclonus, which are easy to recognize even in critical patients, may help to diagnosis and correctly choose the COVID-19 patients that may benefit from immunotherapy.

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Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest.

Ethics approval: This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate: All patients signed informed consent for anonymous data publication. Cases 1, 2, 5, 6 and 7 also signed informed consent for the videos to be published for scientific purposes.

Consent for publication: Not applicable.

Availability of data and material: The full data of each case is available and may be provided on request.

Code availability: Not applicable.

Authors' contributions: Conceptualization: [Mohammad Rohani]; Methodology: [Maziar Emamikhah], [Mohammad Rohani]; Formal analysis and investigation: [Maziar Emamikhah], [Mansoureh Babadi], [Mohammad Rohani]; Writing - original draft preparation: [Sharmin Aghavali], [Maziar Emamikhah], [Fahimeh Mohaghegh]; Writing - review and editing: [Mohammad Rohani]; Resources (Referring the cases and data gathering): [Mansoureh Babadi], [Mehrnoush Mehrabani], [Mehdi Jalili], [Maryam Pouranian], [Peyman Daraie] and [Maryam Zaribafian]; Supervision: [Mohammad Rohani]

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Captions to supplementary files:

Online Resource 1: Video shows Case 1 before IVIg institution. Extraocular movements examination reveals opsoclonus and secondary corrective rapid head movements. There is slightly truncal ataxia (wide-based gait) during gait examintation. Generalized myoclonic jerks which exacerbates with intentional movements are obvious during the examination.

Online Resource 2: Extraocular Examination in case 1 one week after treatment initiation. The improvement of opsoclonus showed in Online Resource 1 is noticeable.

Online Resource 3: Examination of abnormal movements and gait in case 1 one week after treatment initiation. The improvement of myoclonus and gait showed in Online Resource 1 is noticeable.

Online Resource 4: Examination of case 1 three week after treatment initiation. The improvement of opsoclonus, myoclonus and gait compared to Online Resource 1 is remarkable.

Online Resource 5: Examination of case 2 before treatment revealed generalized myoclonic jerks exacerbating with intentional movements and sudden noises.

Online Resource 6: Examination of case 5 before treatment revealed jerky movements of eyes (opsoclonus), tongue, neck, arms and interrupted voice.

Online Resource 7: Examination of case 5 before treatment shows myoclonic jerks in head, arms and trunk exacerbating with volitional movements.

Online Resource 8: Examination of case 5 two days after treatment with IVIg shows minimal changes in action generalized mycoclonus.

Online Resource 9: Examination of case 5 three days after treatment with IVIg shows considerable changes in action generalized mycoclonus.

Online Resource 10: Examination of case 6, four weeks after initial COVID-19 symptoms (one week after abnormal movements onset) shows generalized myoclonic jerks with intentional component, voice involvement, limb ataxia (intention tremor), wide-based stance, truncal ataxia and severe shuffling gait. There was no obvious opsoclonus or hypo/bradykinesia.

Online Resource 11: Examination of case 6, eight weeks after initial COVID-19 symptoms (four weeks after treatment with IVIG) shows significant improvement in myoclonus and gait. Minimal voice tremor, scanning speech, limb and truncal ataxia is still present.

Online Resource 12: Examination of case 7, revealing prominent opsoclonus, generalized myoclonus and ataxia.