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Case report

# Electroencephalographic (EEG) features of encephalopathy in the setting of Covid-19: A case series

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ABSTRACT

*Objective:* The Covid-19 pandemic is a global challenge presenting clinicians with an evolving diagnostic landscape. We sought to describe EEG findings observed from local experience in a typical case series of patients with severe Covid-19.
*Methods:* Ten cases of Covid-19 were identified in whom EEG recordings had been made during the course of admissions to Bristol hospitals which had required intensive care. Electro-clinical correlation between the EEG and available medical history, imaging and laboratory investigation results was explored.
*Results:* The predominant EEG features in severe Covid-19 are of generalised symmetrical slowing, consistent with encephalopathy.
*Conclusions:* The presence of focal disturbances or irritative abnormalities may be a pointer away from a pure encephalopathy and warrant further investigation.
*Significance:* A growing range of neurological sequelae from Covid-19 are now recognised to be common amongst patients hospitalised by with this condition, being seen to affect approximately one third of such cases. Electroencephalography has a unique place in the diagnostic work-up of impaired consciousness, a frequent feature of severe Covid-19. However, there is currently a paucity of literature describing typical EEG findings in this setting.


## 1. Introduction

With continuation of the Covid-19 global pandemic has come recognition of a range of neurological sequelae, affecting both the peripheral (Toscano et al., 2020; Zhao et al., 2020; Mao et al., 2020) and central (Mao et al., 2020; Manji et al., 2020; Carod-Artal, 2020; Liu et al., 2020; Moriguchi et al., 2020) components of the nervous system. Whilst examples of the former include the more prevalent muscle injury (Mao et al., 2020) and more rarely reported incidents of otherwise typical Guillain-Barre Syndrome (Toscano et al., 2020; Virani et al., 2020; Zhao et al., 2020), at this time it is perhaps the varied central disturbances which dominate (Mao et al., 2020) the neurological contribution to Covid-19 associated morbidity.

The spectrum of central features initially encountered comprised headaches, ataxia, impaired level of consciousness and seizures (Mao et al., 2020), albeit the association with the latter has more recently been called into question (Lu et al., 2020). The general likelihood of these presentations collectively appeared in proportion to the overall clinical severity of Covid-19 (Mao et al., 2020) as graded by the American Thoracic Society criteria for Community Acquired Pneumonia (Metlay et al., 2019). The occurrence of neurological features in a primary pneumonic illness related to the SARS-Cov-2 virus was not unexpected given the occurrence of similar in both of the preceding 2002 SARS (Tsai et al., 2005) and 2012 MERS (Kim et al., 2017; Algahtani et al., 2016) outbreaks caused by related coronaviruses (Manji et al., 2020). The respective SARS-CoV and MERS-CoV agents were subsequently found to invade a wide variety of cell types outwith pulmonary tissue (Ding et al., 2004; Desforges et al., 2014). A similarly broad entry of SARS-CoV-2 into many organs (via the widely distributed metallopeptidase ACE2 receptor) including neural parenchyma is also anticipated on the basis of the genetic and molecular characteristics of the virus (Baig et al., 2020; Muus et al., 2020). Early post-mortem reports have described macroscopic findings of hyperaemic and oedematous brain tissue with some degenerative features ((Mao et al., 2020) ref. 12) however whether this is an

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effect of direct viral cytopathy or an indirect consequence of severe respiratory and wider multi-organ failure remains unclear. Even the identification of viral nucleic acid within the cerebrospinal fluid and brain tissue at autopsy, as found with SARS-CoV and MERS-CoV (Arabi et al., 2017; Desforges et al., 2013) does not resolve this question but leaves open the possibility of direct neural injury. The increasing appreciation of anosmia as part of the Covid-19 syndrome has led some to posit the olfactory pathway is an important route of neuroinvasion (Baig et al., 2020) in addition to more classical haematogenous spread (Desforges et al., 2013). However, alongside the concerns of direct viral injury and neural dysfunction from systemic multi-organ compromise came the reasonable trepidation that SARS-CoV-2 may provoke parainfectious injury by triggering directed autoimmune sequelae.

Indeed, whilst a general 'cytokine storm' (not dissimilar from that of haemophagocytic lymphohistiocytosis syndrome) is currently thought to underlie most of the morbidity (Shi et al., 2020; Manji et al., 2020), which characterises severe disease and the high conversion rate of those undergoing hospital admission to requiring intensive levels of care, case reports of fortunately rare phenomena such as Acute Disseminated Encephalomyelitis (ADEM) (Zhang et al., 2020), Acute Haemorrhagic Necrotising Encephalopathy (Poyiadji et al., 2020) and meningoencephalitis (Moriguchi et al., 2020) attributed to Covid-19 infection have just been described. Although the precedent for autoimmune encephalitis following confirmed viral encephalitis has recently been set in the context of anti-NMDA disease following Herpes Simplex (even up to an interval of months after) (Dorcet et al., 2020), this has not as yet been described in the context of Covid-19. Nonetheless, the autoimmune expression of this illness continues to expand, with a Kawasaki-like hyperinflammatory syndrome amongst the paediatric population only appearing in recent weeks (Riphagen et al., 2020). Although Covid-19 appears to confer increased risk of already common cerebrovascular events (likely through an unfortunate combination of a hypercoaguable state, hypertension and direct viral injury to vascular endothelium) (Valderrama et al., 2020) clinicians will need to remain equally vigilant to the possibility of the 'recognised but rare' and 'unrecognised but possible' in those presenting with neurological impairment in the setting of Covid-19 at this time.

It is appreciated that many patients with reduced consciousness in the intensive care setting may be having subclinical seizures (Herman et al., 2015), which may have a bearing on their ultimate neurological outcome (Hahn and Jette, 2013). In the absence of evidence either way at this time, there are no reasons to suspect this is not the case in Covid-19. Accordingly, electroencephalography (EEG) remains indispensable in evaluation of the patient with impaired consciousness, particularly with a view to excluding non-convulsive seizures and status epilepticus (Herman et al., 2015). Whilst the formal consideration given to how such recordings may be most safely acquired from patients possibly suffering from Covid-19 is truly welcome (Haines et al., 2020), at this time outwith a recent brief observation of diffuse delta and theta in 20 such cases by Sethi (2020) there remains a paucity of literature describing the typical EEG appearances one might expect to encounter. Here we present the EEG characteristics of ten patients experiencing varying degrees of cerebral dysfunction (encephalopathy) in the context of a primary Covid-19 illness.

## 2. Method

Ten cases of Covid-19 were identified in whom EEG recordings had been made during the course of admissions to Bristol hospitals, between 22nd March to 10th May 2020 and which had required intensive care. EEG recordings were performed by qualified healthcare scientists (Neurophysiology) at the patient's bedside. EEGs were acquired over 20–30 min by SystemPLUS Evolution (Micromed SpA Treviso, Italy) or Polaris.one (Nihon Kohden, Japan). Recordings were obtained utilising a minimum of 9 silver/silver chloride recording electrodes, placed according to the 10–20 international system, with additional ground and reference electrodes. A limited EEG montage had been recorded in several situations where the primary clinical objective was to exclude non-convulsive status epilepticus or seizures in patients with delirium or disordered consciousness. It is an accepted limitation that discrete inter-ictal epileptic foci could be missed with such a montage. EEG channels were filtered using low and high frequency filters of 0.53 Hz and 70 Hz respectively at −3dB. A single channel ECG was recorded simultaneously. During the recordings, auditory (calling of patient's name) and somatosensory (finger nail pinching, trapezius squeeze) stimuli were applied with a minimum of 10 s intervals. EEG traces were analysed by a qualified neurophysiology consultant (N.M.K.), blinded to the patient's laboratory findings and neuroimaging results.

## 3. Results

Relevant demographic details of the ten cases including clinical features, EEG findings, imaging appearances and laboratory results are included within Table 1.

Figs. 1–4 exemplify the widespread slow activity (mainly delta) with a mild anterior emphasis, which collectively typified EEG findings in those cases when recordings were made during significant impairment of consciousness.

Eight patients had clinical diagnoses of Covid-19 confirmed by an RNA-based throat swab assay, two were diagnosed and being managed on clinical grounds alone owing to the recognised significant limitations regarding sensitivity of such testing at present.

In the face of the large and growing numbers affected by the global pandemic and the not insignificant fraction (Mao et al., 2020) who will experience impaired levels of consciousness (whether through sedation to permit ventilation or failure to appropriately rouse otherwise) the number of cases presented here is indeed small and ultimately may not be typical of larger experience. We recognise this limitation and welcome similar reports from others.

Nonetheless, the general EEG picture is consistent with an encephalopathy but non-specific for any underlying aetiology and may represent effects of hypoxia, sepsis, previous seizure or metabolic derangements. Where asymmetry was observed underlying cerebrovascular changes were apparent on the accompanying structural imaging. In this regard, the appearance of triphasic waves arose in settings of established cerebrovascular change with superimposed systemic disturbance, in keeping with previously reported structural-electrophysiological correlations (Kaplan and Sutter, 2015; Sutter and Kaplan, 2014).

## 4. Discussion

The neuropathological substrate underlying the dysfunction in this cohort is likely to be heterogenous and cannot be determined with certainty. A likely contribution from hypoxic insult is quite possible given the increasing respiratory failure that led most patients into intensive care, however its severity and duration here are unquantifiable. Imaging, where available did not demonstrate typical patterns of hypoxic injury, however it is well recognised the absence of such does not preclude its presence. Indeed, in the

**Table 1**
Clinical, EEG and other paraclinical findings in Severe COVID-19 patients undergoing evaluation to assess seizure liability and/or exclude subclinical seizures as a cause of impaired consciousness.

| No. | Age (y) & Gender | $1^0$ Diagnosis | Comorbidity | Neurologic Status | Clinical Seizure | Imaging/CSF/Lab Findings | Medication | EEG Background | Focal EEG Abnormality | Electro-graphic Seizure | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 74 M | COVID-19 [Swab + d2] | COPD, CKD, DM2, Alcohol Excess, prior SAH prior. Ischaemic. Stroke, Learning Difficulties, Essential Tremor | Delirium with visual hallucinosis and drowsiness | Y Focal motor and tonic | CT Brain: Normal CSF (d2) WCC 2, RCC 1, Prot .56 gluc 5.2, Routine viral PCR -ve | Levetiracetam, Phenytoin, carbamazepine, primodone. Lorazepam 4–5 h prior to EEG | (d4) Widespread alpha and theta frequency activity with underlying slow waves. Symmetrical, continuous and Reactive. | – | – | Died (d16) |
| 2 | 69 M | COVID-19 [Swab + d1] | Complex Mucosal Pemphigoid (Rx Rituximab) Recurrent Venous Thromboses Steroid related DM2 | Minimally responsive. Auditory stimulation provoked eye movement but not opening | N | CT Brain +Venography: Mild Small Vessel Disease CRP high, AKI | Heparin infusion, prednisolone, Bisoprolol, Citalopram No sedation For 7 days | (d23) Low amplitude with a mix of alpha and fast activity. Variable periods of generalised relative attenuation. Following stimulation, there was widespread slow and theta activity | Intermittent slow waves over both hemispheres, with anterior emphasis. | – | Ongoing admission (d50) |
| 3 | 68 M | COVID-19 [Swab + d2] | Schizophrenia | Drowsy, GCS E3, V (T), M6 | Y GTCS | CT Brain: Mild Global Volume Loss CRP high, Lymphopenia, AKI | remifentanyl, levetiracetam paliperidone | (d11) slow activity (delta and theta frequencies) with an anterior emphasis, together with and some runs of faster activity. | Occasional suspicious anterior sharp waves | – | Ongoing admission (d28) |
| 4 | 18 M | COVID-19 [Swab + d2] | Nil known (refugee) | Sedated | Y likely GTCS | CT Brain +Venography: Normal CSF (d2) WCC 8, RCC 1 prot 0.5, gluc norm, routine viral PCR −ve | propofol alfentanil acyclovir levetiracetam enoxaparin ceftriaxone docusate, senna omeprazole | (d2) Diffuse slow waves with superimposed intermittent faster activity. Some reactivity Sedation stopped at start of record | – | – | Discharged Home (d10) |
| 5 | 73F | COVID-19 [clinical, Swab – d1 and d5] | Panhypopituitarism (following previous apoplexy) HTN, GORD, AF and severe RA | Unresponsive | N | CT Brain +Venography: Mild-Moderate Small Vessel Disease Raised CRP | Azithromycin, Hydrocortizone Midazolam Hyocine Butyl Bromide, Co-amoxiclav, Cyclizine Morphine Paracetamol Furosemide | (d6) Asymmetric. Theta and irregular slow waves bilaterally (L > R) | Frequent triphasic waves with a leading sharp wave component. Of varying distribution at 1–2c/s | | Ongoing admission. (d14) |
| 6 | 29 M | COVID-19 [Clinical, Swab – d1] Admitted in Status Epilepticus | Temporal Lobe Epilepsy (5y Hx) Cannabis Abuse Poor Dietary Intake | GCS 3/15 | Y GTCS | CT Brain: Normal CSF (d2) WCC 10 (9 polymorph), RCC 2, routine viral PCR -, prot 0.6, gluc 3.8 (5.2), lact 2.2. Raised CRP and AKI | Alfentanil Propofol (on hold) Lamotrigine, Keppra, Phenytoin | (d2) Widespread Slow activity with superimposed fast. Reactive | – | – | Discharged Home (d6) |
| 7 | 62F | COVID-19 [Swab + d1] | DM1, Hypothyroidism, Pancreatic Insufficiency, CKD3, HTN, Iron deficiency Anaemia | Delirium | N | CT & MRI Brain: Moderate Multifocal Small Vessel Disease High CRP, lymphopenia, AKI | Simvastatin, Gabapentin, Omeprazole, Amitriptyline, Metformin, B12, paracetamol, Nutrizym, Insulin, Ramipril, Furosemide, Calcium Carbonate, colecalciferol | (d4) Slow and irregular with some frontal intermittent rhythmic delta activity (FIRDA) | – | – | Discharged Home (d9) |
| 8 | 74 M | COVID-19 [Swab + d1] Cardiac | RA (Rx Methotrexate), Bladder Transitional Cell Carcinoma, AF | Minimally responsive | N | CT Brain: multifocal small volume convexity SAH bilaterally; MRI Brain – Small infarcts in the left precentral gyrus and three small | Noradrenalin, Insulin, Enoxaparin Ertapenem Lansoprazole Bisoprolol Aspirin Atorvastatin | (d16) slow and irregular with an anterior emphasis | – | – | Ongoing admission. (d33) |

(*continued on next page*)

**Table 1** (*continued*)

| No. | Age (y) & Gender | 1$^{o}$ Diagnosis | Comorbidity | Neurologic Status | Clinical Seizure | Imaging/CSF/Lab Findings | Medication | EEG Background | Focal EEG Abnormality | Electro-graphic Seizure | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mass. (? Myxoma) | | | | cerebellar infarcts High CRP, Lymphopenia. CSF (d14) WCC < 5, RCC 7614, no growth, viral PCR inc. SARS-CoV-2 negative | | | | | |
| 9 | 39 M | COVID-19 [Swab + d1] | ESRF from Lithium Toxicity & DM2, Bipolar, HTN, Ankylosing Spondylitis, Alpha Thalassaemia trait | GCS 15/15 | Y GTCS when reducing sedation | CT & MRI Brain: Frontal and Medial Temporal atrophy, mild small vessel disease Raised CRP, Lymphopenia CSF (d2) prot 0.87, gluc 3.41, lac 1.5, no cells/growth. Viral PCR including SARS-CoV-2 –ve | Lacosamide, Valproate, Levetiracetam, Bisoprolol Olanzapine, Lanzoprazole | (d26) Posterior dominant rhythm slow (6 –7cps) | – | – | Discharged Home (d45) |
| 10 | 53 M | COVID-19 [Swab + d1] | Autism Schizophrenia | Drowsy | Y Tonic | CT Brain: tiny focus of L Frontal Sulcal SAH, Normal MRI Brain and follow up CT Brain with Venography High CRP, lymphopenia, CSF (d25) routine viral PCR –ve, no cells/growth, matched OCBs, Gluc 4.3, Prot 0.2, Lact 1.5 | Valproate Levetiracetam Clozapine | (1st d14) generally slow with an anterior emphasis (2nd d24) theta activity over both hemispheres; some alpha frequency activity also | (2nd d24) irregular slow waves anterior emphasis. Peaked and triphasic | – | Ongoing admission. (d30) |

[Key d = day of admission, COPD chronic obstructive pulmonary disease, SAH subarachnoid haemorrhage, DM diabetes mellitus, AKI acute kidney injury, CKD chronic kidney disease, ESRF end-stage renal failure, AF atrial fibrillation, HTN hypertension, RA rheumatoid arthritis, GORD gastro-oesophageal reflux disorder, T2RF type 2 respiratory failure, CRP C-reactive protein, OCB oligoclonal band, WCC white cell count RCC red cell count, Prot protein, Gluc glucose, Lact Lactate. Routine Viral PCR (polymerase chain reaction) included assays for Herpes simplex types 1 & 2, Varicella zoster and enterovirus.]

one subject herein who has succumbed to Covid-19 so far (patient 1, Fig. 4), the widespread alpha and theta frequency activity suggested a form of alpha coma, itself a malignant pattern often seen in the context of hypoxic ischaemic encephalopathy (Sutter and Kaplan, 2012). The dynamics of any hypoxic insult (profound anoxia of short duration vs. prolonged but milder relative hypoxia) might be important modifiers of radiological, clinical (Sasannejad et al., 2019) and electroencephalographic appearances, as may the co-occurrence of any perfusion insufficiency (Howard et al., 2012). That neurological outcomes from pure respiratory arrest are recognised to often be more favourable than hypoxic ischaemic encephalopathy arising from circulatory arrest (Howard et al., 2011) supports this proposition and practically may be something to consider when making prognostic assessments in the context of Covid-19.

Alongside a varying contribution of hypoxia many of the cases had acute kidney injury (with associated uraemia) as part of their Covid-19 syndrome and in some instances this represented an acute on chronic impairment of renal function. Such metabolic derangements, as part of the sepsis syndrome and in their own right make well recognised contributions to encephalopathic states. From our practical perspective however, even in the presence of documented clinical seizures there were no clear EEG epileptiform or periodic features which might suggest a focal destructive or irritative process, such an encephalitis *per se*. Whilst one acknowledges that more common findings in certain encephalitides are focal or more widespread slowing, we have not as yet observed electrographic (or imaging) features of a higher positive predictive value for an encephalitis (focal discharges or even delta brush) despite many of these patients having seizures *de novo* in the context of severe Covid-19. The absence of CSF PCR positivity in some cases, even in one case where the throat swab was positive for SARS-CoV-2 infection is also interesting but inconclusive in this regard.

Whilst it is not possible to make any broad practice recommendations on the basis of our findings in such a small cohort, from the consideration of the above it would seem reasonable to suggest that the presence of focal disturbances, whether periodic, typically epileptiform or localised slowing should raise suspicion of either a Covid-19 complication (e.g. cerebrovascular event or autoimmune insult) or co-existent pathology. For example, severe co-infection with other agents which may cause mengingoencephalitis, such as tuberculosis is already recognised (Liu et al., 2020) and there is no reason to suspect the confirmed presence of SAR-CoV-2 is mutually exclusive of any other neuropathology.

Indeed, whilst most of the subjects in our cohort had recognised pre-morbid risk factors for developing severe Covid-19, significantly two of them were on potent immunomodulators (one on rituximab and one methotrexate). The effects of immunosuppression during the Covid-19 pandemic are currently a matter of active large-scale surveillance (Scully, 2020; Robinson and Yazdany, 2020), driven by the as yet unverified concern that such therapies may increase vulnerability to SARS-CoV-2 (Giovannoni et al., 2020; D'Antiga, 2020). It is important to be mindful that many such agents are already associated with increased susceptibility to rare but often multifocal intracranial pathology (Berger, 2017) which is otherwise completely unrelated to Covid-19. As such, whilst much of the utility of EEG in these patients may be exclusion of non-convulsive seizures or neuroprognosis after hypoxia, a further role may be the identification of a focal EEG disturbance. Wherein, if there is no conclusive structural substrate for it on imaging in a patient with Covid-19 (even if assay confirmed) this should prompt recommending pursuit of a second pathology (i.e. with CSF sampling) – particularly if the situation is complex with concurrent risk factors including immunosuppression.

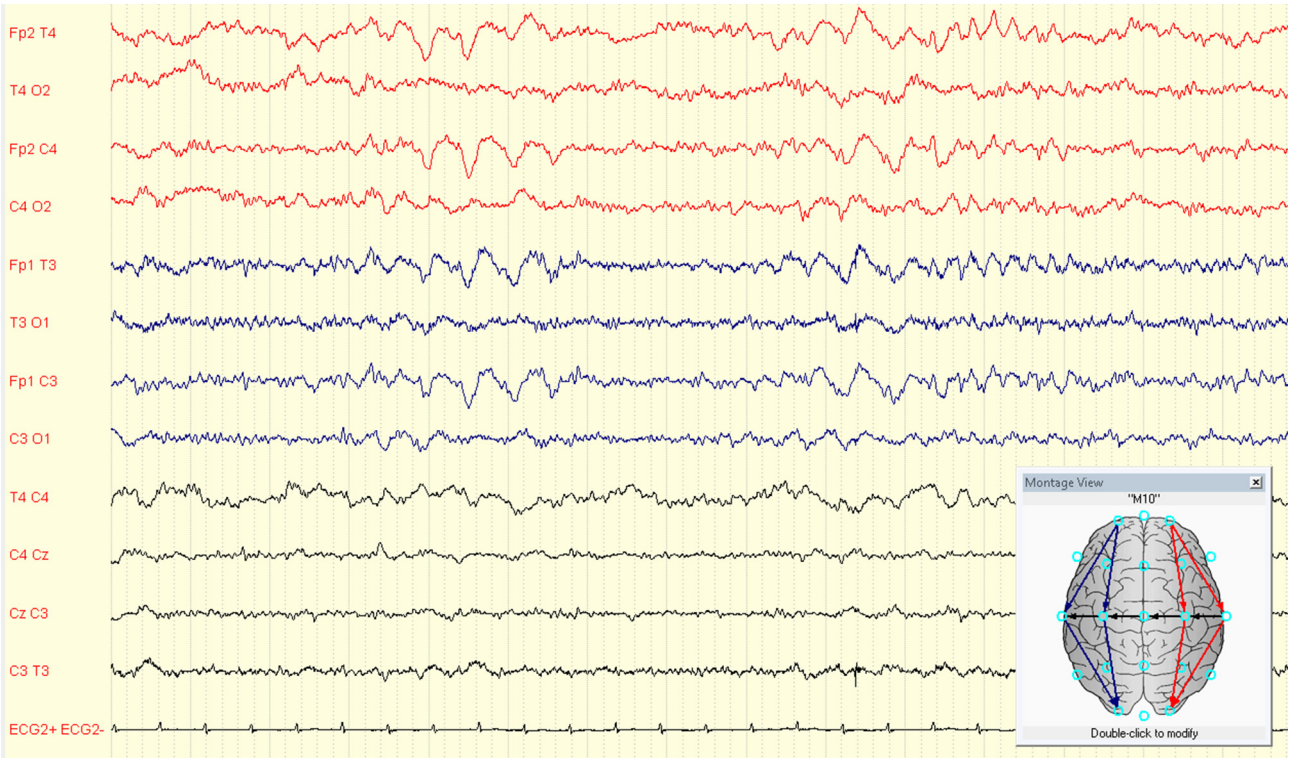


**Fig. 1.** Slow activity (delta and theta frequencies) with an anterior emphasis. From drowsy 68 year old male (patient 3) at day 11 of admission with Covid-19. [Figure is a 15 s epoch with sensitivity at 100 μV/cm.]

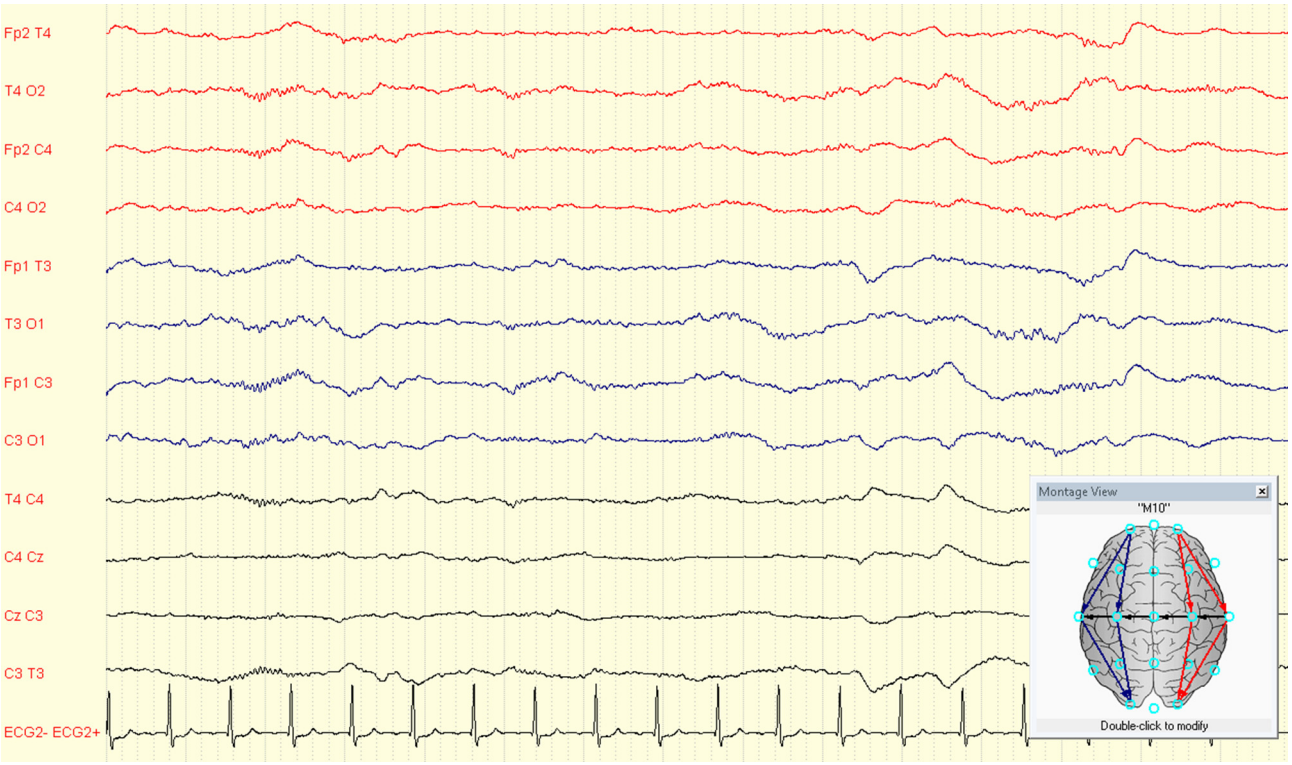


**Fig. 2.** Low amplitude intermittent slow waves over both hemispheres with anterior emphasis and a mix of alpha and fast activity. Variable periods of generalised relative attenuation were also seen. From minimally responsive 69 year old male (patient 2) at day 23 of admission with severe Covid-19. [Figure is a 15 s epoch with sensitivity at 100 μV/cm.]

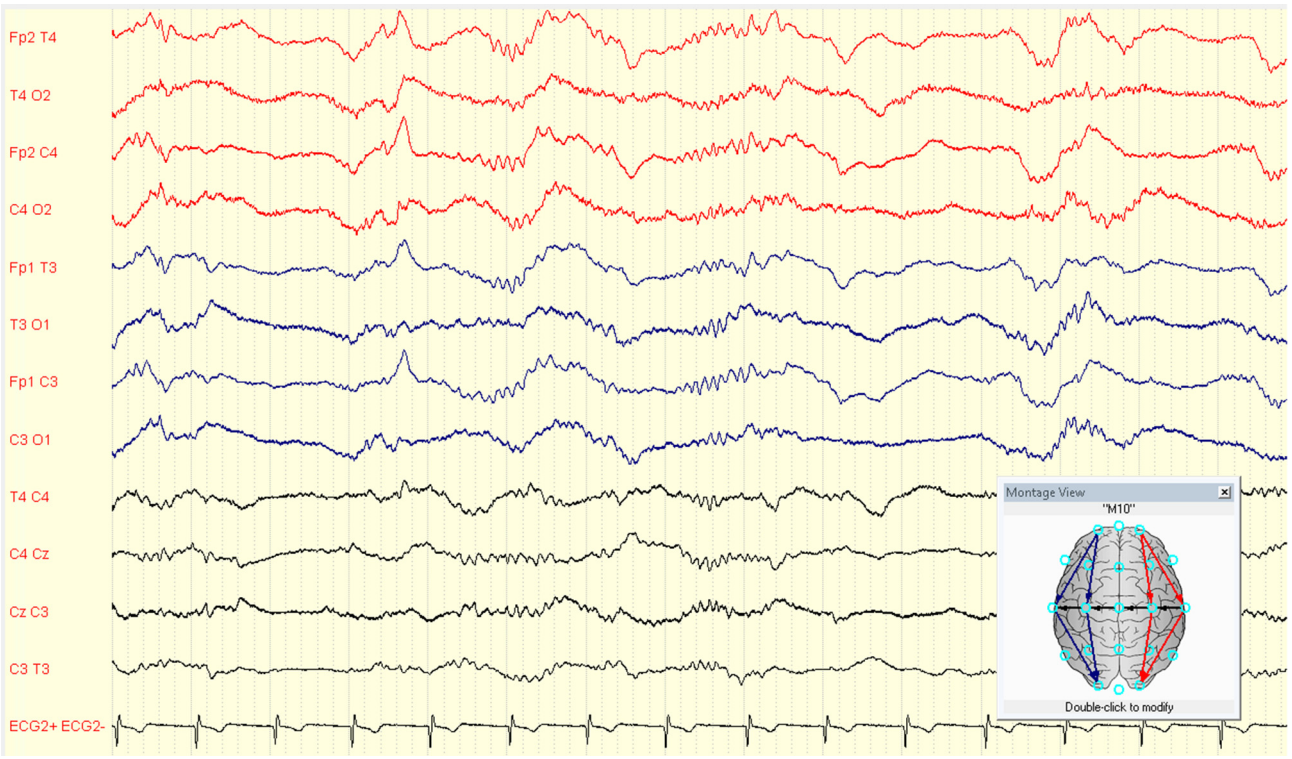


**Fig. 3.** Diffuse slow waves with superimposed intermittent faster activity (commensurate with the effects of sedation with propofol). From 18 year old male (patient 4) on day 2 of admission with severe Covid-19. Propofol sedation stopped at beginning of record. [Figure is a 15 s epoch with sensitivity at 100 μV/cm.]

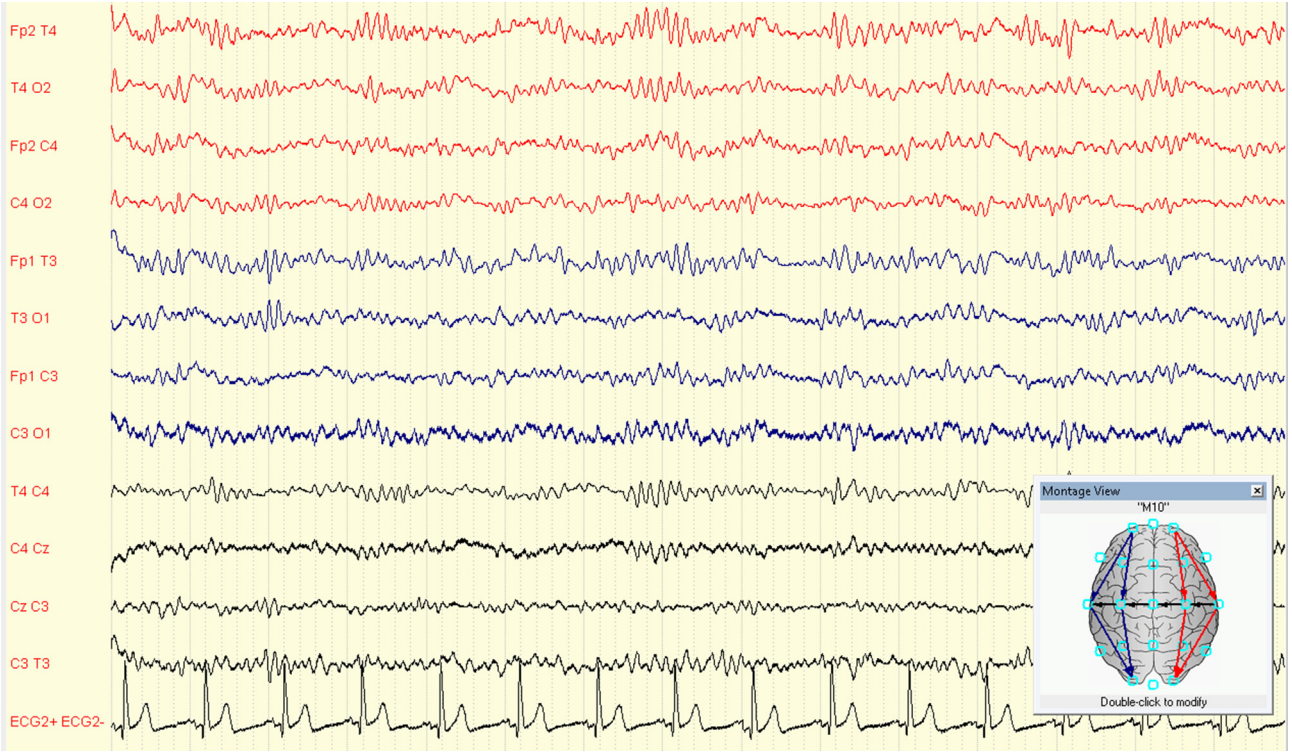


**Fig. 4.** Widespread alpha and theta frequency activity with anterior predominance and underlying slow waves. From 74 year old male (patient 1) on day 4 of admission with severe Covid-19. [Figure is a 15 s epoch with sensitivity at 100 μV/cm.]

## 5. Conclusion

The global Covid-19 pandemic is a challenge for all healthcare providers including neurophysiologists. Impaired level of consciousness and encephalopathy are not uncommon and likely multifactorial in patients with severe Covid-19, and the EEG appearances are non-specific. At this point pending further case series we suggest that focal disturbances should be accounted for, raise suspicion of other aetiologies and not be directly attributed to SARS-CoV-2 infection without exclusion of alternate causes.

## Conflicts of interest

The authors have no conflicts of interest to declare in relation to this work.

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