Report of EEG Finding on Critically Ill Patients with COVID-19

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Running Head: Report of EEG Finding on Patients with COVID-19

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Abstract

In March 2020, we treated a cohort of 26 critically ill hospitalized SARS-CoV-2 infected patients who received EEGs to assess unexplained altered mental status, loss of consciousness, or poor arousal and responsiveness. Of the 26 patients studied, 5 patients had EEGs that showed Periodic Discharges (PD) consisting of high amplitude frontal monomorphic delta waves with

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absence of epileptic activity. These findings may suggest CNS injury potentially related to COVID-19 in these patients.

Introduction

The new Coronavirus, SARS-CoV-2, is the latest of the coronavirus diseases (COVID-19) found to afflict humans with severe respiratory infection, respiratory distress, and possibly death. However, as we gain more knowledge about this particular virus, we recognize potentially devastating involvement of other organs such as the heart and the brain[1,2]. While genetically related to the other forms of coronavirus, particularly the previous SARS coronavirus (SARS-COV-1) that resulted in severe acute respiratory distress, COVID-19 has proven to be far more contagious than the other coronaviruses[3,4]. Other coronaviruses have been reported to be neurotropic[5,6,7]. For example, like SARS-CoV-1 virus, the SARS-COV-2 virus has an affinity to the Angiotensin Converting Enzyme 2 receptors (ACE2) that allow entry of the virus into the cells coated with such receptors[8]. ACE2 receptors are naturally found in the heart, lungs, kidneys, and CNS in particular[8]. It has been suggested that the SARS-CoV-2 virus may enter the brain through the olfactory epithelium deep in the nasal passages and other tissues possessing the ACE2 receptors[8,9]. However, only a single case of presumed SARS-CoV-2 encephalitis has been reported in which the analysis of the cerebrospinal fluid (CSF) revealed the presence of SARS-CoV-2 RNA sequences. The brain CT scan in that case was normal and no EEG was performed. The patient was discharged from the ICU without evidence of any neurological sequalae[10].

COVID-19 may be strongly associated with various neurological symptoms including hyposmia/anosmia (30% to 33% of patients[11,12]), dysgeusia, headache, and myalgia. Unexplained altered mental status or consciousness disturbances are observed in 13% of the patients[8]. Despite the high frequency of encephalopathy associated with SARS-CoV-2, no EEG abnormalities were recorded in early reports[13]. We therefore wish to place our observations

on record of an unusual number of cases of SARS-CoV-2 encephalopathy with focal EEG findings suggesting brain injury.

Methods

Between March 18 and 31, 2020, EEGs were performed on 26 severe COVID-19 infected patients hospitalized in several ICU departments in the Paris area. The patients were diagnosed as being COVID-19 positive by semi-quantitative reverse-transcriptase polymerase chain reaction (RT-PCR) analysis from nasopharyngeal swab specimens obtained in the emergency department or at the time of hospitalization. The EEGs were requested to assess the etiology of mental status changes or poor responsiveness of the patients, or to determine the presence of status epilepticus in non-arousable patients.

The clinical data and EEGs presented were based upon retrospective chart review and descriptive assessment of the patients during their hospitalization. The patient data collected for this report was performed as a "Health Data Study" referred by the code MR-004 (CNIL), which is a French National Centralized Authority (IRB equivalent) for this type of study report. The authors also confirm that informed consent for all medical exams and use of the anonymized data have been obtained by the patients' health care providers from either the patient or, in the majority of the cases, by a family member.

The EEGs were performed over a 30-minute period in accordance with the international 10-20 system using a 9-electrode placement configuration. The 9 electrodes consisted of: Cz, FP2, C4, O2, T4, FP1, C3, O1, T3 and Reference in FPz, with ground in Oz. The EEG recording was obtained with intermittent light (photic) stimulation with the EEG recording parameters consisting of low filter at 0.530 HZ, high filter at 70 HZ, recording speed at 30 sec, and gain at 100 µV. Due to the patients' COVID-19 infection, disposable needle electrodes were used for the EEGs.

Results

Of the original cohort of 26 patients, 19 showed EEGs consisting of diffuse and nonspecific theta and alpha wave activity, with some including diffuse delta wave activity without focal or periodic features, and two had isoelectric EEGs consistent with brain death (see supplementary Table 1). Five patients, however, had evidence of generalized periodic discharges. The 5 patients highlighted in this report consisted of 4 men (patient 1, 2, 3, and 4) and 1 woman (patient 5) with the mean age of 67, with the ages ranging from 58 to 70 years old (table 1).

Four of the five patients were intubated and poorly responsive or unresponsive, and the EEGs were obtained from 4 days to 12 days after they were intubated (patient 1, 2, 3, and 4). Two of the patients were deeply sedated with propofol and fentanyl (patient 1, and 4) and one patient was mildly sedated with midazolam (patient 3). The other 2 patients were not sedated (patient 2, and 5). One of the patients (patient 2) had anoxia associated with a cardiac arrest prior to intubation. The other 3 patients on ventilators were intubated because of unresponsiveness in combination with hypoxia (patient 1, 3, and 4). The fifth patient (patient 5) was not intubated and received the EEG study after presenting with sudden unexplained confusion, lethargy, and significant cognitive impairment. In addition, 3 of the patients (patient 1, 3, and 4) demonstrated brief myoclonic seizure activity while sedated. Lumbar punctures were obtained in 2 of the patients (patient 1 and 5) that were reported to be "normal" (opening pressure and protein quantification were not available) with no evidence of cells, or presence of coronavirus or HSV on PCR. A brain CT scan was performed on one patient (patient 3) reporting no specific abnormalities other than "a cyst in the occipital area" and a brain MRI was performed in another patient (patient 5) that was reported to show diffuse white matter hyperintensity (both image results were by report, and the actual images were not available). One patient (patient 1) was receiving extracorporeal membrane oxygenation (ECMO) for severe hypoxemia, and another patient (patient 4) was receiving dialysis for acute renal failure. Three of the patients died in the ICU (patient 1, 2, and 4), while 2 patients remained hospitalized as of 20 April 2020 (patient 3 and 5).

EEG Interpretation

The EEG recordings (Figure 1) reveal a background rhythm that is clearly abnormal, showing generalized slowing and theta activity consistent with sedation. They also show bilateral diffuse frontocentral slow wave activity with high amplitude generalized periodic discharges (GPD) with frontal involvement. The EEGs display monomorphic biphasic delta activity or generalized rhythmic delta activity (GRDA) of less than 4 second intervals (Panels A,B,D,E representing patient 1, 2, 4, 5 respectively), or lateralized periodic discharge (LPD) of a 1 to 2 second period with right frontal predominance (Panel C representing patient 3).

The EEG abnormalities can be summarized as generalized or lateralized periodic discharges that primarily consist of symmetric slow monomorphic biphasic delta waves of high amplitude occurring in short repetition of less than 4 seconds. The periodic discharges are located primarily in the frontal region without evidence of paroxysmal epileptic activity.

Discussion

The significance of GRDA and LPD EEG findings in the presence of mental status abnormalities may be related to a host of etiologies. Clearly the background slowing and theta activity demonstrated in the EEGs could be related to sedation, somnolence, coma, anoxia or hypoxia, and other CNS depressive entities. However, the presence of the monomorphic biphasic high amplitude delta waves associated with occasional myoclonic muscular activity could also possibly be indicative of brain injury either related to anoxia, severe hypoxia, anesthesia, or the direct effects of COVID-19 itself. The reported onset of loss of consciousness or confusion and cognitive impairment in COVID-19 infected patients with EEGs revealing biphasic delta PDs may suggest an injury or localized brain defect attributed to encephalopathy related to a unique and acute CNS process. While potentially complicated by the severity of multiorgan disfunction, the focal encephalopathy may be due to possible vascular, infectious, or parainfectious inflammatory processes in the brain[14]. However, the lack of pleiomorphism in the CSF and lack of evidence of viral infection of the brain by PCR would suggest that the discharges are not the result of direct brain infection or autoimmune encephalitis (although

such EEG patterns, most prominent in patient 1 and 5, have been seen in subacute sclerosing panencephalitis (SSPE) due to measles[15,16]).

Another possible source of focal brain injury could be the vasculopathy and coagulopathy that is seen in many COVID-19 patients[17]. Unfortunately, unless patients have evidence of focal brain injury on examination, many hospitals are not performing routine MR imaging on COVID-19 patients, as this risks increased exposure and requires subsequent decontamination of the scanner. Therefore, while EEG assessment alone may not directly provide a diagnosis or confirm the etiology for the unexplained alteration of a patient's mental state or lack of responsiveness, the appearance of lateralized frontal or bilateral frontal PDs with abnormal background may be an important clue that the patient has in fact suffered from a brain injury[18].

When hospitalized patients infected with SARS-CoV-2 (COVID-19) present with an unexplained loss of consciousness, confusion or altered mental status, impaired arousal, and abnormal paroxysmal movements (myoclonus), it is suggested that an EEG be performed as part of the diagnostic assessment of the patient to determine an etiology and to identify potentially treatable CNS disorders. Such studies will also further enhance our knowledge to better understand the growing number of new and unusual neurologic illnesses possibly associated with COVID-19.

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Author Contributions

HV contributed to the conception and design of the study
HV, DC, BL, CS, VP, LM, OP, and SM contributed to the acquisition and analysis of the data
HV, DC, BL, and PF contributed to drafting the text and preparaing the figures

Potential Conflicts of Interest

Professor Hervé Vespignani, Dr. Bruce Lavin, Dr. Damien Colas, Dr. Samir Medjebar, and Mr. Pierre-Yves Frouin, are employees of Bioserenity, the company that performed the EEG recordings and collected the EEG recording data at the Paris hospital units.

There are no other conflicts of interest to report.

References

1. Steardo L, Steardo Jr L, Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiologica. 2020 Mar 29:e13473.
2. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D, Gavazzi E, Maroldi R. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA cardiology. 2020 Mar 27.
3. Fauci A.S., Lane H.C., Redfield R.R. Covid-19 - navigating the uncharted. N Engl J Med. 2020 ; 382:1268-1269. doi: 10.1056/NEJMe2002387
4. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nature medicine. 2020 Apr;26(4):450-2.
5. Talbot P, Jouvenne P. Neurotropic potential of coronaviruses. Medecine/Sciences. 1992 Jan 1;8(2).
6. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, Talbot PJ. Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System?. Viruses. 2020 Jan;12(1):14.
7. Arbour N, Day R, Newcombe J, Talbot PJ. Neuroinvasion by Human Respiratory Coronaviruses. J Virol 2000;74(19):8913–21.
8. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS chemical neuroscience. 2020 Mar 13;11(7):995-8.
9. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. Journal of virology. 2008 Aug 1;82(15):7264-75.
10. Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. Brain, behavior, and immunity. 2020 Apr 10.
11. Hopkins C, Kumar N. Loss of sense of smell as marker of COVID-19 infection. Ear, Nose and Throat surgery body of United Kingdom. Retrieved. 2020 Mar 21;28.
12. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, Rusconi S, Gervasoni C, Ridolfo AL, Rizzardini G, Antinori S. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. Clinical Infectious Diseases. 2020 Mar 26.
13. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Hu Y, Li Y. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study.
14. Reichard, R. Ross, Kianoush B. Kashani, Nicholas A. Boire, Eleni Constantopoulos, Yong Guo, and Claudia F. Lucchinetti. "Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology." Acta Neuropathologica (2020): 1-6.
15. Markand ON, Panszi JG. The electroencephalogram in subacute sclerosing panencephalitis. Archives of neurology. 1975 Nov 1;32(11):719-26.

16. Honarmand S, Glaser CA, Chow E, Sejvar JJ, Preas CP, Cosentino GC, Hutchison HT, Bellini WJ. Subacute sclerosing panencephalitis in the differential diagnosis of encephalitis. Neurology. 2004 Oct 26;63(8):1489-93.
17. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, Baxter-Stoltzfus A, Laurence J. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Translational Research. 2020 Apr 15.
18. Smith SJ. EEG in neurological conditions other than epilepsy: when does it help, what does it add?. Journal of Neurology, Neurosurgery & Psychiatry. 2005 Jun 1;76(suppl 2):ii8-12.

Figure Legends

Figure 1:
EEG recordings of Patients 1 through 5.
The panels display EEG recordings of 20 seconds for each patient. In each panel, the EEG channels are shown with an ECG recording at the bottom. Nomenclature is in accordance with the international 10/20 montage. The EEGs reveal a pattern of slow waves with periodic discharges in the frontal regions.

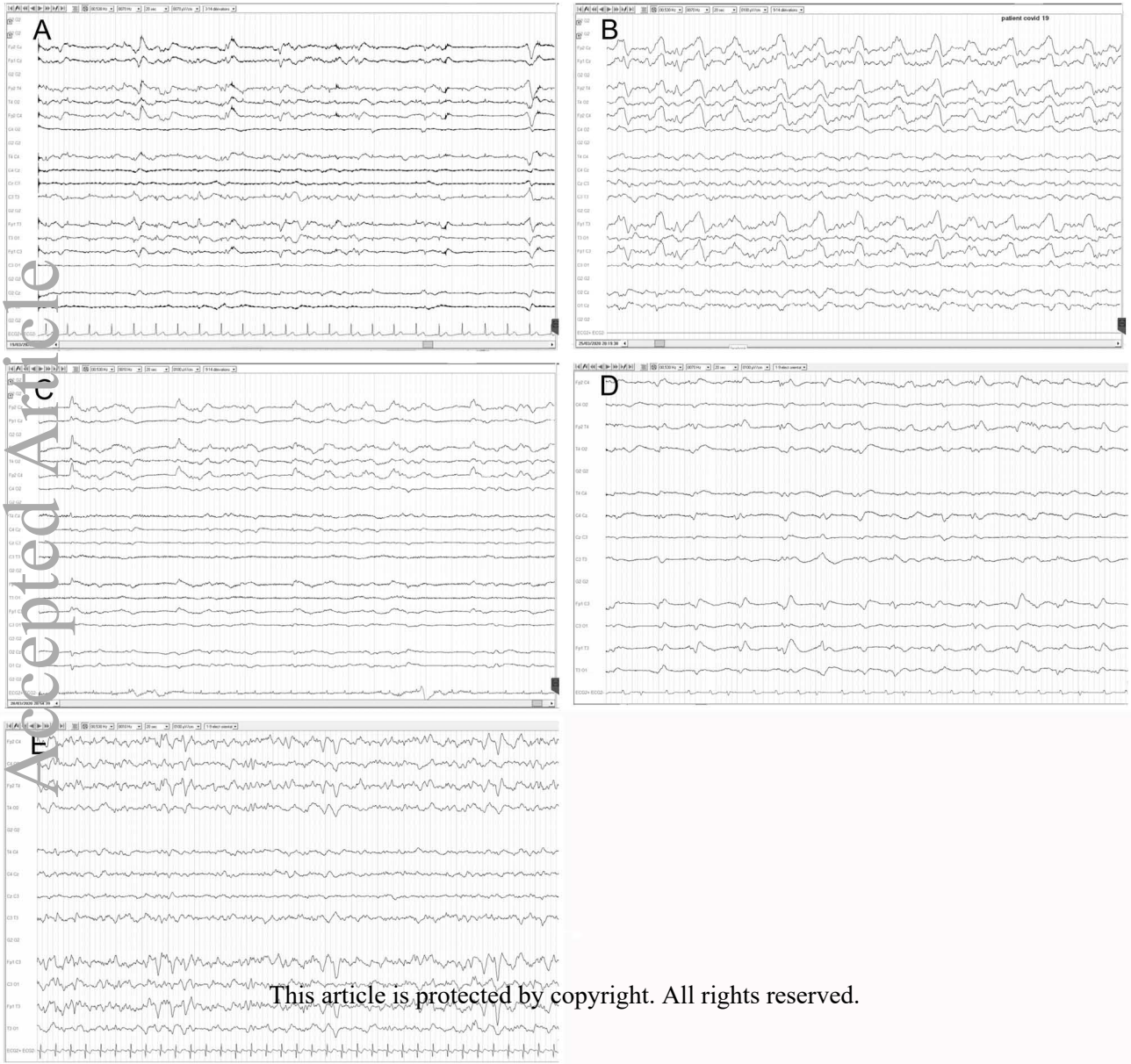
Panel A: Scalp EEG in a reference montage from patient #1 reveals generalized rhythmic delta activity (GRDA) with intermittent biphasic delta waves in bilateral frontal regions that are symmetric and monomorphic with low voltage rhythmic background activity

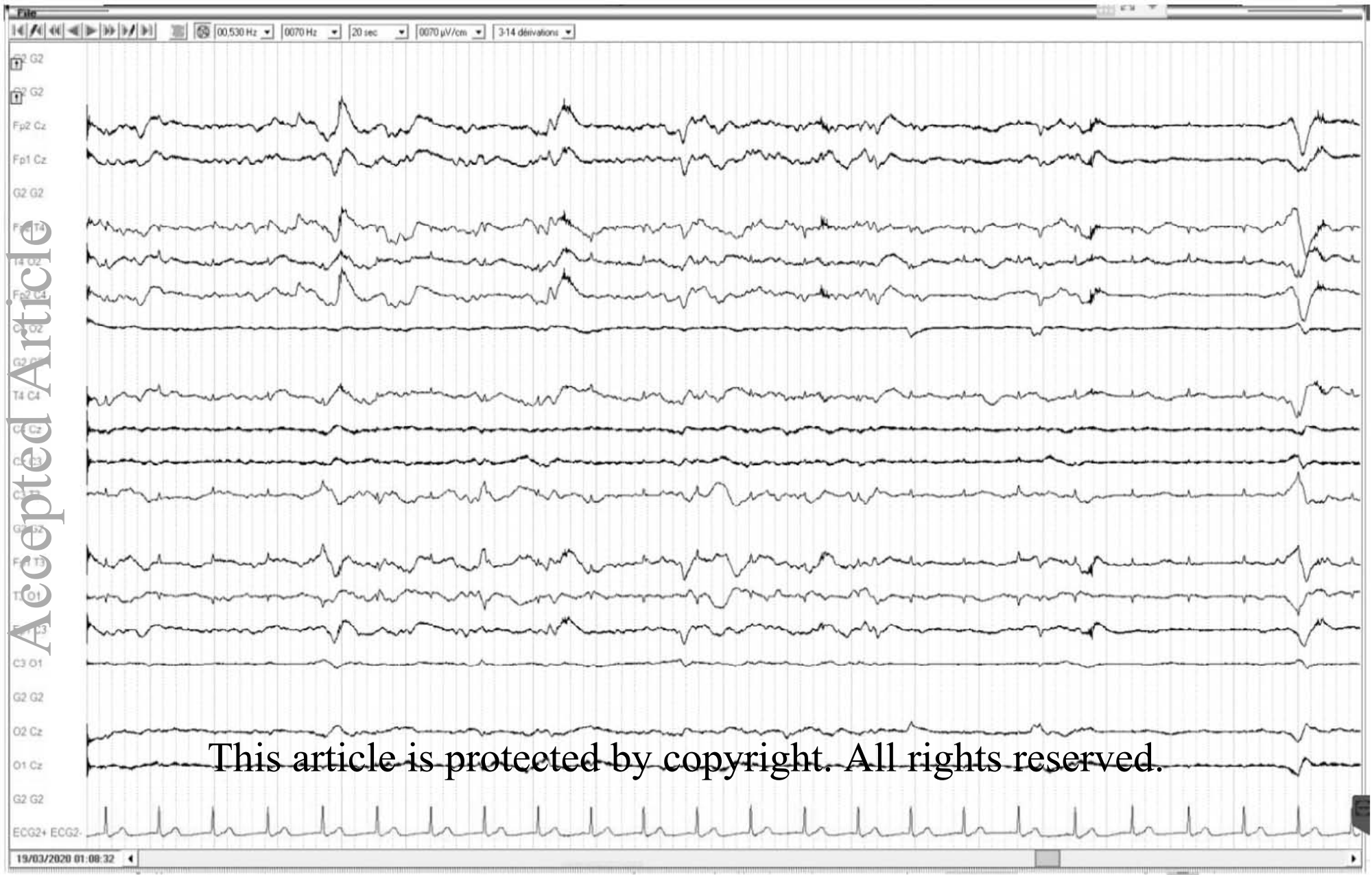
Panel B: Scalp EEG in a reference montage from patient #2 reveals generalized rhythmic delta activity (GRDA) with frequent high amplitude biphasic delta waves in bilateral frontal regions that are symmetric and polymorphic with low voltage rhythmic theta background activity

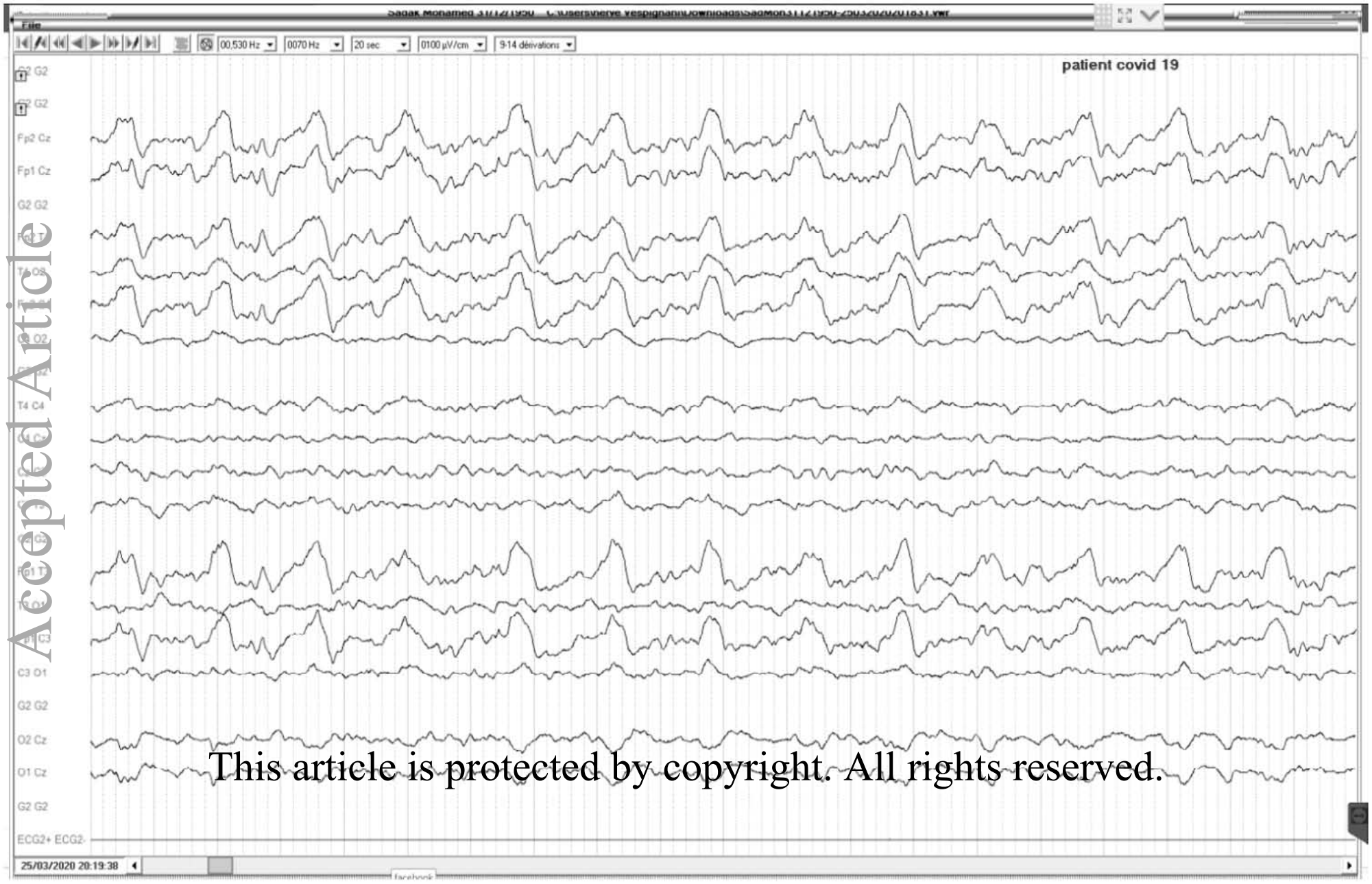
Panel C: Scalp EEG in a reference montage from patient #3 reveals lateralized periodic discharges (LPD) of high amplitude monomorphic delta activity with right frontal region predominance and low voltage rhythmic theta background activity

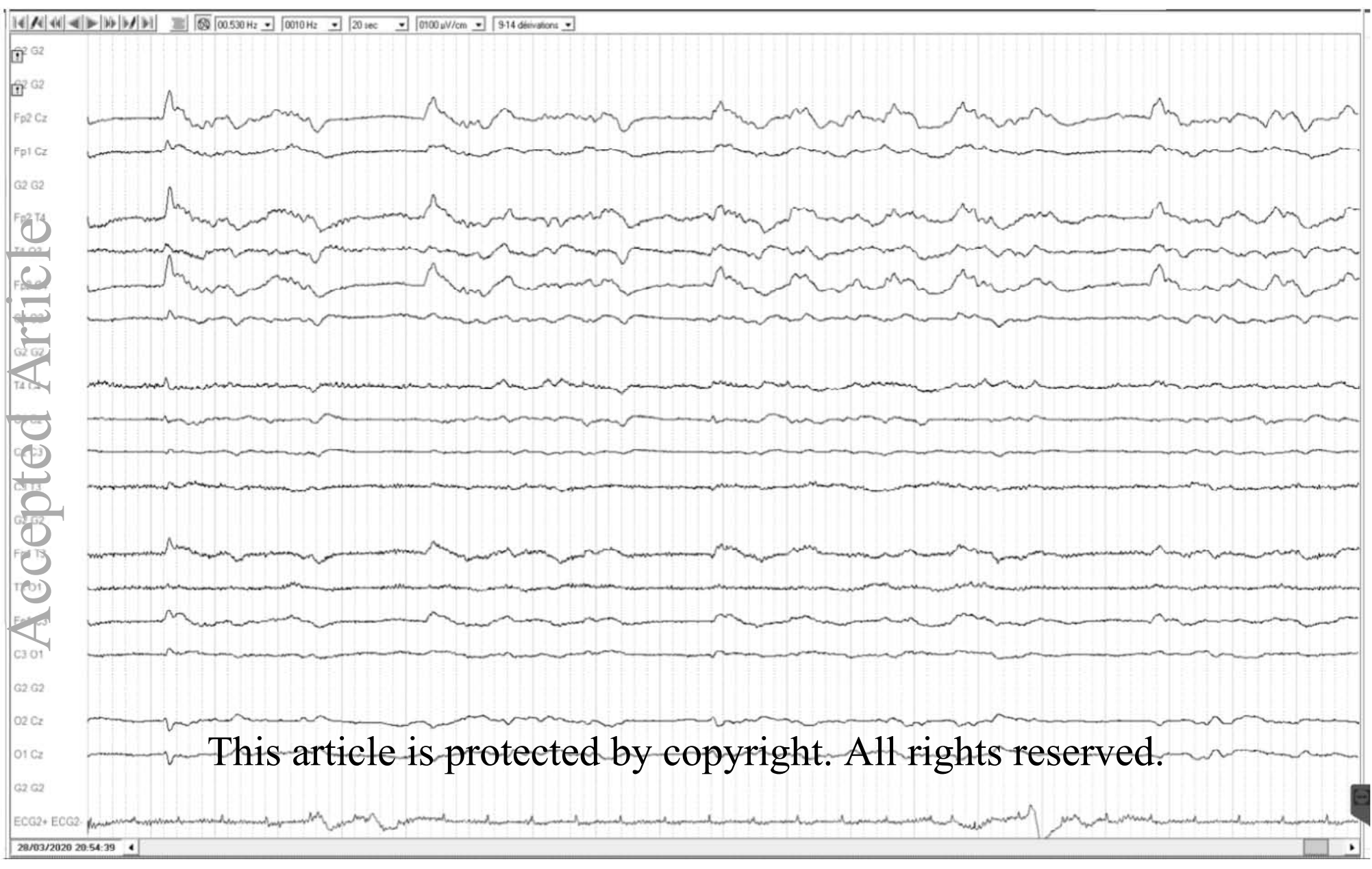
Panel D: Scalp EEG in a reference montage from patient #4 reveals generalized rhythmic delta activity (GRDA) with intermittent low amplitude slow biphasic delta waves in bilateral frontal regions that are slightly asymmetric and monomorphic with low voltage continuous background activity

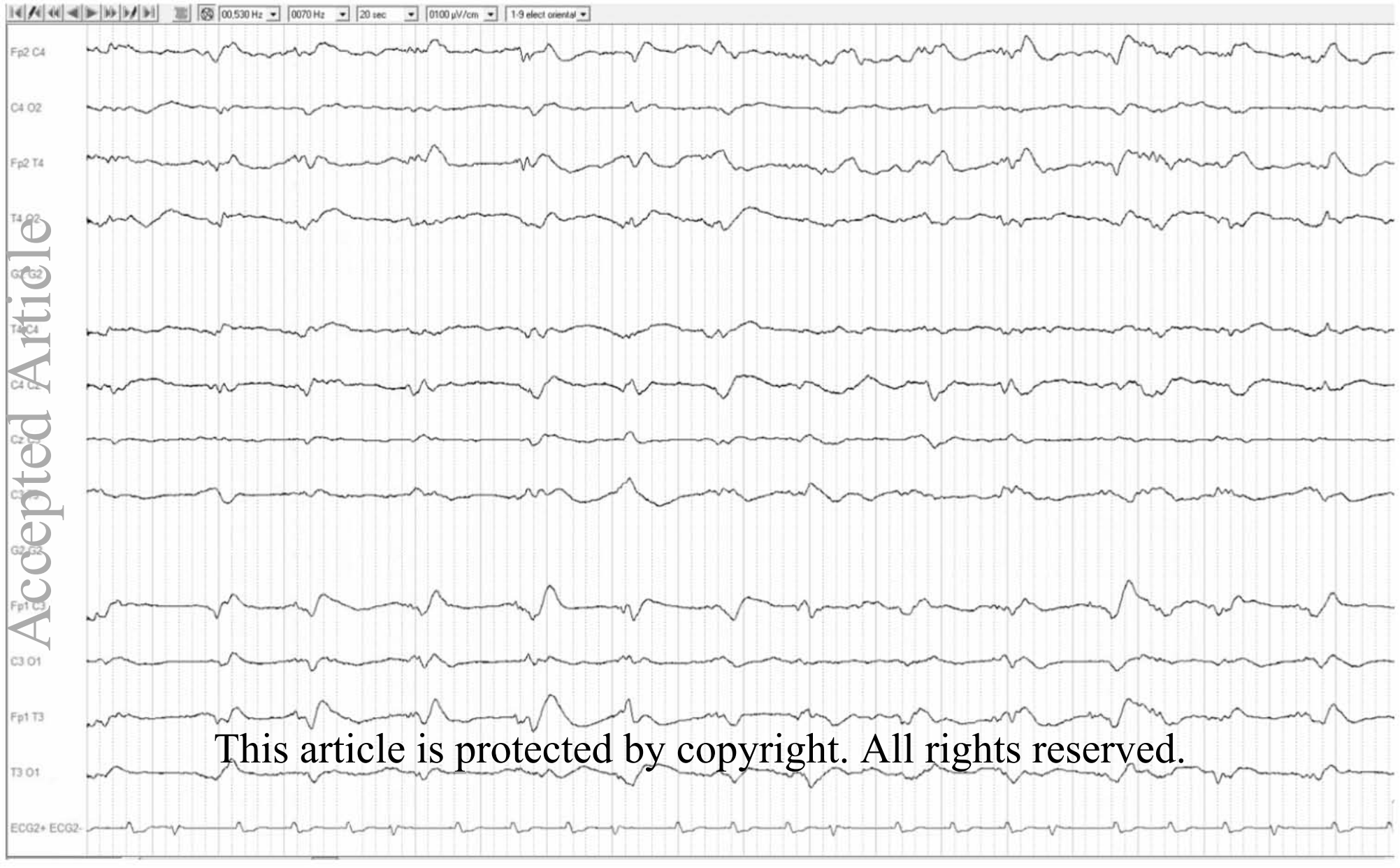
Panel E: Scalp EEG in a reference montage from patient #5 reveals generalized rhythmic delta activity (GRDA) with intermittent high amplitude biphasic delta waves in bilateral frontal regions that are symmetric and monomorphic with intermittent low voltage rhythmic theta background activity











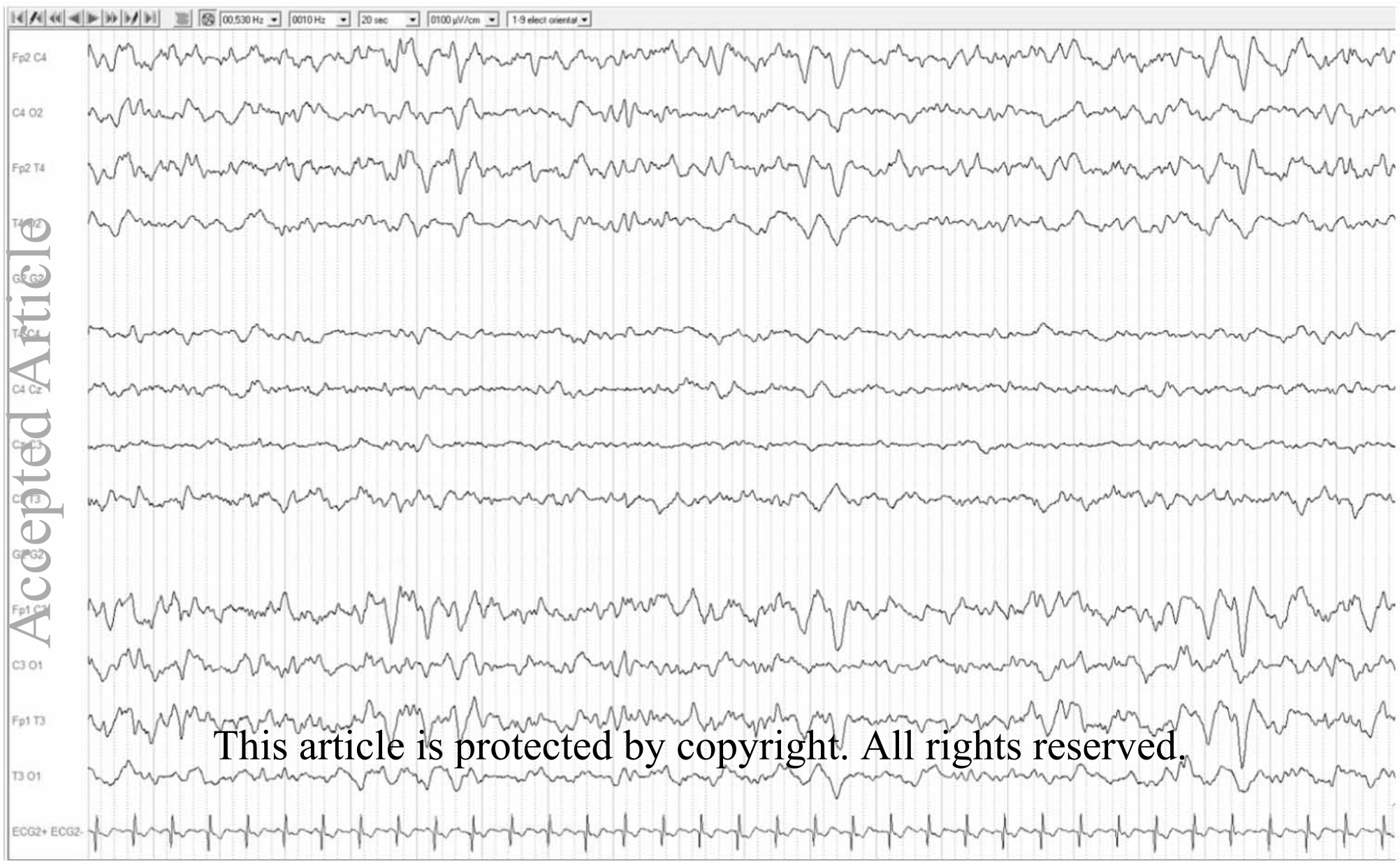


Table 1 Clinical Profile of Patients With Evidence of EEG Periodic Discharge

Patient	Age	Gender	Medical History	Intervention	*Days Intubated at time of EEG*	EEG Interpretation		Clinical Outcome
1	58	M	Coma, Face and Eye myoclonus	Ventilator Deep Sedation (propofol,fentanyl) ECMO Lumbar Puncture	4	Generalized Bilateral Frontal intermittent Symmetric Biphasic delta Theta activity		Died 8 days after EEG performed
2	70	M	Delayed Awakening, Cardiac Arrest	Ventilator Not Sedated	8	Generalized Bilateral Frontal high amplitude Symmetric Biphasic delta theta activity		Died 3 days after EEG performed
3	70	M	Poor Arousal Epilepsy?	Ventilator Mild Sedation (Midazolam) CT Scan	6	Lateralized Right Focal Frontal high amplitude Symmetric Biphasic delta Symmetric		Remains Hospitalized in ICU
4	70	M	Coma, Face Myoclonus	Ventilator Deep Sedation (propofol, fentanyl) Renal Dialysis	12	Generalized Biphasic delta Asymmetric Frontal predominance		Died 9 days after EEG performed
5	67	F	Confusion, Lethargy	MRI Lumbar Puncture	N/A	Generalized Frontal slowing Symmetric Biphasic delta theta activity		Remains Hospitalized on Ward Significant cognitive deficit