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Clinical short communication

Special considerations in the assessment of catastrophic brain injury and determination of brain death in patients with SARS-CoV-2

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ABSTRACT

Introduction: The coronavirus disease 2019 (Covid-19) pandemic has led to challenges in provision of care, clinical assessment and communication with families. The unique considerations associated with evaluation of catastrophic brain injury and death by neurologic criteria in patients with Covid-19 infection have not been examined.

Methods: We describe the evaluation of six patients hospitalized at a health network in New York City in April 2020 who had Covid-19, were comatose and had absent brainstem reflexes.

Results: Four males and two females with a median age of 58.5 (IQR 47–68) were evaluated for catastrophic brain injury due to stroke and/or global anoxic injury at a median of 14 days (IQR 13–18) after admission for acute respiratory failure due to Covid-19. All patients had hypotension requiring vasopressors and had been treated with sedative/narcotic drips for ventilator dyssynchrony. Among these patients, 5 had received paralytics. Apnea testing was performed for 1 patient due to the decision to withdraw treatment ($n = 2$), concern for inability to tolerate testing (n = 2) and observation of spontaneous respirations ($n = 1$). The apnea test was aborted due to hypoxia and hypotension. After ancillary testing, death was declared in three patients based on neurologic criteria and in three patients based on cardiopulmonary criteria (after withdrawal of support ($n = 2$) or cardiopulmonary arrest ($n = 1$)). A family member was able to visit 5/6 patients prior to cardiopulmonary arrest/discontinuation of organ support.

Conclusion: It is feasible to evaluate patients with catastrophic brain injury and declare brain death despite the Covid-19 pandemic, but this requires unique considerations.

1. Introduction

The coronavirus disease 2019 (Covid-19) pandemic has led to a number of challenges in provision of patient care, performance of clinical assessment and communication with families [1]. Protocols have been developed to prioritize safety, maximize efficiency, and focus on judicious use of resources without compromising quality of care [1].

Covid-19 is currently a prominent cause of death worldwide, with a death toll of over 320,000 reported as of May 22, 2020 [2]. Although Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection has been associated with conditions that can lead to brain death such as multi-organ damage, anoxic brain injury, and ischemic and hemorrhagic stroke [3,4], the unique considerations associated with catastrophic brain injury and death by neurologic criteria in this patient population have not been examined.

Here, we discuss our experience assessing patients with Covid-19 with catastrophic brain injuries and declaring brain death.

2. Methods

We describe the evaluation of six patients hospitalized at New York University Langone Health associated hospitals in April 2020 who had Covid-19, were comatose and had absent brainstem reflexes. Of note, two of these patients were previously described by Carroll and Lewis in

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Table 1
Characteristics of patients with Covid-19 who had catastrophic brain injury.

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	46	68	66	37	74	51
Sex	M	F	F	M	M	M
Cause of catastrophic brain injury	Brainstem and cerebellar infarction followed by global hypoxic-ischemic injury	Global anoxic injury due to cardiac arrest	Global anoxic injury due to cardiac arrest	Multifocal intracerebral hemorrhage with diffuse cerebral edema and brain compression	Multifocal intracerebral hemorrhage with diffuse cerebral edema and brain compression	Global anoxic injury due to cardiac arrest and catastrophic cerebellar hemorrhage with diffuse cerebral edema and brain compression
Number of days from viral symptom onset to consult for catastrophic brain injury	7	20	16	31	21	32
Number of days from admission to consult for catastrophic brain injury	7	14	13	28	18	26
Sedative/narcotic drips	Fentanyl, Midazolam	Dexmedetomidine, Fentanyl, Midazolam	Fentanyl	Hydromorphone, Ketamine, Propofol, Midazolam	Dexmedetomidine, Fentanyl, Ketamine, Midazolam, Propofol	Dexmedetomidine, Hydromorphone, Ketamine, Midazolam
Number of days on sedative/ narcotic drips	7	7	1	21	14	18
Number of days off sedative/ narcotic drips prior to consult for catastrophic brain injury	1.5	4	1	2	4	1
Paralytics	Rocuronium	Rocuronium	N/A	Rocuronium	Rocuronium	Rocuronium, Cisatracurium
Number of days off paralytics prior to consult for catastrophic brain injury	5	8	N/A	19	8	3
Blood pressure prior to final neurologic examination (mm Hg)	130/56	110/62	115/52	88/30	141/60	96/56
Vasopressors prior to final neurologic examination	Norepinephrine, Vasopressin, Phenylephrine	Epinephrine, Norepinephrine, Vasopressin	Norepinephrine	Norepinephrine, Phenylephrine, Vasopressin	Norepinephrine	Norepinephrine, Vasopressin, Dopamine
Temperature prior to final neurologic examination (°C)	36.6	35	37.4	37.8	37.1	36.5
pH prior to final neurologic examination	7.23	7.46	7.34	6.95	7.36	7.39
$PaCO_2$ prior to final neurologic examination (mm Hg)	40	39	43.6	40	43	44
PaO_2 prior to final neurologic examination (mm Hg)	106	182	125	100	148	81
FiO2 prior to final neurologic examination (%)	40	100	60	100	60	50
Creatinine prior to final neurologic examination (mg/ dl)	15.4	1.4	5.5	1.45	1.66	2.68
Peak D-Dimer (ng/ml)	> 10,000	11,402	47,803	9887	4488	> 10,000
Peak C-reactive protein (mg/l)	226	136	446	307	416	368
Peak IL-6 (pg/ml)	N/A	61.7	152.4	569	N/A	126
Evaluation for spontaneous breathing	No spontaneous breaths seen; formal testing deferred due to acidosis	No spontaneous breaths seen; formal testing deferred due to hemodynamic instability	Attempted using t-piece and PEEP valve, but aborted after 90 seconds due to hypoxia to 85% and MAP of 55mm Hg	No spontaneous breaths seen; formal testing deferred due to decision to withdraw treatment	Occasional spontaneous breaths seen with respiratory rate on ventilator adjusted to 4 breaths/ minute	No spontaneous breaths seen; formal testing deferred due to decision to withdraw treatment
Formal assessment for brain death performed	Yes	Yes	Yes	No: prerequisites not met (acidemia, hypothermia, hypotension); cardiac arrest	No: family withdrew care prior to brain death testing	No: family withdrew care prior to brain death testing
Time between consult for catastrophic brain injury and	8 days		1 day	N/A	N/A	N/A

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
formal brain death assessment		3 days: delay waiting for family to be ready to accept this determination				
Ancillary testing	TCDs	EEG and CT angiography	EEG	N/A	N/A	N/A
Criteria to declare death	Neurologic	Neurologic	Neurologic	Cardiopulmonary	Cardiopulmonary	Cardiopulmonary
Family visitation prior to brain death assessment	No	Yes	Yes	N/A	N/A	N/A
Family visitation prior to cardiopulmonary arrest/after brain death assessment and prior to discontinuation of organ support	Yes	N/A	N/A	No in-person visit, but family was able to see patient via video	Yes	Yes
Time between brain death declaration and discontinuation of organ support	32 h: Accommodation of family's request to delay pending their visit	3 h	2 days: Accommodation of religious objections	N/A	N/A	N/A

a case series on multifocal intracerebral hemorrhage in patients with Covid-19 who were treated with empiric anticoagulation [5].

3. Description of cases

Four men and two women with a median age of 58.5 (IQR 47–68) were admitted to the hospital for respiratory distress secondary to Covid-19 and were intubated (see Table. 1). Neurology was consulted for catastrophic brain injury at a median of 14 days (IQR 13–18) after admission due to 1) global anoxic injury after cardiac arrest (n = 2); 2) multifocal intracerebral hemorrhage with diffuse cerebral edema and brain compression (n = 2); 3) global anoxic injury after cardiac arrest and catastrophic cerebellar hemorrhage with diffuse cerebral edema and brain compression (n = 1); and 4) brainstem and cerebellar infarction followed by global hypoxic-ischemic injury (n = 1). All patients had been on sedatives or narcotics due to ventilator dyssynchrony and these had been discontinued for a median of 2.5 days (IQR 1–4) at the time of neurology consultation. Five patients had received paralytics previously, but no paralytics had been administered for a median of 8 days (IQR 5–8) prior to the consult. All patients were on vasopressors at the time of the consult. Labs were notable for a median creatinine of 2.17 mg/dL (IQR 1.5–4.8), pH of 7.35 (IQR 7.26–7.38), PaO_2 of 125 mmHg (IQR 106–148) and $PaCO_2$ of 41.5 mmHg (IQR 40–43.5). All patients were unresponsive; had absent pupillary, corneal, oculovestibular, cough, and gag reflexes; and did not move their extremities to any stimuli. Non-contrast computed tomography (CT) of the head was obtained in five patients, but one patient who had anoxic injury after cardiac arrest was too unstable to be transported for brain imaging. Formal apnea testing was performed for only one patient and was aborted due to hypoxia and hypotension; it was not attempted for the remaining 5 patients due to concern for inability to tolerate testing (n = 2), decision to withdraw support (n = 2) and observation of spontaneous respirations (n = 1). Ancillary testing was performed in three patients after which death by neurological criteria was declared. Death was declared by cardiopulmonary criteria in the other three patients (two of whom had support withdrawn and one of whom had a cardiopulmonary arrest). Despite pandemic conditions, a family member was able to visit five of the six patients prior to cardiopulmonary arrest/discontinuation of organ support.

4. Discussion

Assessment of patients with catastrophic brain injuries and determination of brain death can be challenging under ordinary conditions, but the unique medical and social circumstances of the Covid-19 pandemic exacerbate this further. Here, we discuss the issues we faced in assessing six patients with Covid-19 who developed catastrophic brain injuries. While only 3 of these patients were ultimately declared dead based on neurologic criteria, the other 3 had catastrophic irreversible brain damage prompting us to carefully consider whether they could be declared dead using neurologic criteria.

5. Determination of irreversible brain damage

A prerequisite to the determination of brain death is the identification of the proximate cause and irreversibility of injury. The exact mechanism by which Covid-19 affects the central nervous system remains largely unknown, but direct and indirect pathways of injury have been proposed. SARS-CoV-2 enters cells using ACE2 receptors, which are expressed in the brain and may facilitate direct damage to the cardiorespiratory center in the brainstem through trans-synaptic migration of the virus from the respiratory system [6,7]. Indirect damage to the central nervous system may occur from induction of pro-inflammatory cytokines in the glial cells of the brain and spinal cord, disruption to the coagulation cascade or cerebral hypoxic and ischemic injury secondary to prolonged shock and refractory hypoxia [8,9]. All

of our patients had some component of anoxic injury; four also had severe edema and brain compression due to ischemic or hemorrhagic stroke. Notably, while knowledge of the mechanism for catastrophic brain injury is required to make a determination of brain death, neuroimaging is not mandated [10]. Due to hemodynamic instability, we were only able to obtain imaging in five of the six patients; one patient had anoxic injury after cardiac arrest and was too unstable to be transported for brain imaging.

Prior to the assessment of catastrophic brain injury and determination of brain death, it is necessary to ensure the condition is irreversible by excluding confounding factors such as hypothermia, drug intoxication, neuromuscular blockade, or metabolic abnormalities. Although patients with Covid-19 are often febrile, hypothermia is uncommon and less likely to be a confounding factor [11]. In contrast, the impact of drugs on patients with Covid-19 is an important consideration; a large proportion of Covid-19 patients have unusually high sedation requirements and receive multiple sedating agents for prolonged periods of time [12]. There are no uniform recommendations for the use of toxicology tests in patients who have previously received sedating drugs to ensure these medications are no longer impacting the neurologic assessment, but the American Academy of Neurology advises clinicians to wait at least 5 half-lives (assuming normothermia and normal hepatic and renal function) after discontinuation of sedation prior to evaluating a patient for brain death [10]. Similarly, patients with Covid-19 often require paralytics to manage ventilator dyssynchrony. The ongoing effects of paralytics can be excluded using train-of-four testing or by assessing for the presence of deep tendon reflexes [13]. Patients with Covid-19 also develop multiorgan failure which must be considered prior to assessment for catastrophic brain injury and determination of brain death [14]. Alterations in hepatic and renal function can change the pharmacokinetics of drugs resulting in protracted effects of sedative and paralytic agents [15]. Moreover, metabolic acidosis and hyperkalemia secondary to kidney injury increase the likelihood for hemodynamic instability and cardiac arrhythmias during apnea testing [16].

6. Neurological examination

The diagnosis of brain death is primarily clinical, and consists of three essential findings: irreversible coma, absence of brainstem reflexes, and apnea [17]. Although we were able to perform the neurological examination of our patients, it should be noted that, in the setting of the pandemic, performance of a neurological examination may be impacted by limitations in personal protective equipment and fear of spreading infection.

7. Apnea test

The apnea test is used to assess for loss of function of the medullary chemoreceptors when performing a determination of brain death. In a positive apnea test, there is no respiratory response to hypercarbia, defined as a $PaCO2 > 60$ mmHg or 20 mmHg greater than baseline [10]. Although there is no international consensus on the apnea test procedure, most protocols require disconnection of a patient from the ventilator prior to observation for spontaneous respirations. This procedure is safe if a patient has a normal pH, is preoxygenated well, is euvolemic and is normotensive [18].

There are two major concerns when considering performance of the apnea test in patients with Covid-19. First, many patients with acute respiratory failure due to Covid-19 require high positive end-expiratory pressures (PEEP) to maintain adequate alveolar recruitment and oxygen exchange. Disconnecting the ventilator can lead to de-recruitment of alveoli leading to hypoxia and hypotension and may even result in lung collapse. Second, the primary method of transmission of SARS-CoV-2 is by droplet spread, and disconnection of the ventilator system generates aerosols, thus increasing the risk of transmission of viral particles [19]. A modified apnea test that does not require disconnection from the ventilator system, such as the one proposed by Ahlawat et al., is therefore preferred in these patients, as it prevents high-risk aerosolization of viral particles during this procedure [20].

Due to concern for hemodynamic instability, apnea testing was deferred in two of the three patients who were determined dead by neurologic criteria. In the third, apnea testing was attempted using a t-piece and PEEP valve, but it needed to be aborted after 90 s because the patient developed hypoxia and hypotension, likely caused by de-recruitment of alveoli after disconnecting the ventilator.

8. Ancillary tests

An ancillary test is not routinely required for brain death determination, but it may be indicated to supplement the clinical examination and apnea test when extenuating circumstances preclude performance of a complete brain death examination. The ancillary tests used in the confirmation of brain death represent two principles: confirmation of loss of bioelectrical activity of the brain using electroencephalography (EEG) or demonstration of cerebral circulatory arrest using neuroimaging (transcranial Doppler ultrasonography [TCD], 4-vessel diagnostic digital subtraction angiography [DSA], or cerebral scintigraphy [radionuclide brain scan]) [10,21,22]. These tests require considerable technical expertise and are prone to artifact. However, these tests are necessary to declare brain death in patients with Covid-19 who cannot complete apnea testing.

8.1. Electro-diagnostic tests

Cerebral cortical inactivity can be confirmed when a 30 min EEG recording of good quality shows complete electrocerebral silence, defined as no cerebral activity greater than 2 μV [23]. There are several disadvantages to interpretation of an EEG in a critically ill patient with Covid–19. Heavy sedation used in these patients to prevent ventilator dyssynchrony can produce unreliable false positive readings. Other factors which may lead to false positive readings in this population include toxic or metabolic abnormalities and electrical artifacts caused by ambient electromagnetic fields [22]. EEG has also been criticized due to the potential failure to detect subcortical and brainstem activity resulting in a flat EEG in patients with preserved brainstem function [22]. Additionally, care must be taken when bringing an EEG into the room of a patient who has COVID-19 due to the risk of contamination of equipment and nosocomial spread of disease.

Despite these deficiencies, an EEG can readily be obtained at the bedside and does not require transport of the patient out of the ICU. As a result, an EEG was used as an ancillary test for brain death determination for two of our patients.

8.2. Neuroimaging

The gold standard test to assess for cerebral blood flow is invasive 4-vessel angiography, but non-invasive modalities are available. Patients with Covid–19 are frequently too hemodynamically unstable to be out of the ICU for a protracted period, if at all. TCD can conveniently be performed at the bedside, so this test was utilized for one of our patients. Other imaging modalities such as computed tomography perfusion (CTP) or angiography (CTA) are sometimes used to assess for cerebral blood flow, but these studies have pitfalls so they are not included in the American Academy of Neurology Practice Parameter on Determination of Death by Neurologic Criteria; however, CTA is included in the New York State Department of Health Guidelines for Determining Brain Death [10,24]. One of our patients had a CTA and a CTP.

9. Communication with families about catastrophic brain injury

In ordinary circumstances, it can be daunting to discuss catastrophic brain injury and introduce the potential for brain death determination with a patient's family. A family's acceptance of brain death is dependent upon their understanding of brain death. Clear effective communication is imperative; having a poor comprehension of brain death and the impact of catastrophic brain injuries can put families at increased risk for complicated grief [25,26]. Before the Covid-19 pandemic, these conversations were held face-to-face with a patient's family, and family members were allowed time to grieve with their loved one at the bedside. In response to the highly contagious nature of Covid-19, the New York State Department of Health established new security protocols which prohibited visitors to hospitalized patients as a disease containment measure except in the setting of imminent death [27]. Under these new regulations, clinicians had no choice but to deliver all news via telephone, adding an additional layer of complexity and uncertainty to this already complicated and disheartening task. Under normal circumstances, palliative care, social work and chaplaincy often mediate these discussions, but due to the surge of deaths during the pandemic, these services became strained and scarcely available.

Limited interaction between the clinical staff and a patient's family, as well as between the family and the patient themselves, may result in delayed acceptance of catastrophic brain injury and brain death. For the families of the three patients who were declared dead by cardiopulmonary criteria, education about catastrophic brain injury and the concern for brain death through serial conversations over the phone culminated in the decision to proceed with palliative extubation for two patients and to change code status to do-not-resuscitate and await cardiopulmonary arrest in the third patient who was still taking spontaneous respirations. The families of the three patients who were declared dead by neurologic criteria doubted the dismal neurological prognosis relayed to them over the phone, expressed that they did not believe this assessment and requested further testing prompting performance of ancillary testing and delay in discontinuation of organ support after brain death determination.

Comprehension can be improved by allowing families to observe the neurological examination on a patient with catastrophic brain injury [26,28], but in the current environment, this is not easy to facilitate. Of the three patients who were declared brain dead, the family was able to see two in-person before the brain death determination and one prior to discontinuation of organ support. Of the three patients who were declared dead by cardiopulmonary criteria, the family was able to see two in-person before cardiopulmonary arrest.

10. Organ donation

The impetus for brain death determination, just like determination of death by cardiopulmonary criteria, is the need to make a distinction between whether a patient is alive or dead [29]. A determination of death eliminates the need for decision-making about withdrawal of treatment and instead provides a concrete finding which is followed by distinct next steps. There are numerous consequences of a determination of death including the initiation of mourning and performance of ritualistic procedures. Additionally, determination of death impacts taxation and criminal prosecution. Following a determination of brain death, organ support is discontinued. This facilitates allocation of resources, including an ICU bed, a ventilator, medications, and nursing and clinician time, to living patients, in lieu of a dead patient. However, it is worth noting that organ support is continued after brain death if a patient, or their surrogate, has indicated they would want to be an organ donor.

In March 2020, multiple national and international organizations issued recommendations against the use of organs from donors with SARS-CoV-2 based on the assumption that viral particles could be inadvertently transplanted from a positive donor and result in severe manifestations in immunosuppressed recipients [30]. Referral for organ donation of patients with COVID-19 to our organ procurement organization (OPO) was temporarily suspended between March 31st and May 6th, 2020 due to compelling, data-driven, requests from front line workers to be released from the obligation to refer COVID-19 patients, the high volume of deaths in hospitals across New York City, the critical shortage of ventilators and a physically and emotionally overwhelmed OPO staff [31]. Although routine referral of all patients, including those with COVID-19 positive tests, has resumed, there is still limited evidence to support or reject the use of organs from SARS-CoV-2 infected donors [30].

11. Conclusion

Covid-19 can cause devastating injury to the central nervous system that may ultimately result in brain death. Assessment of catastrophic brain injuries, determination of brain death and communication with families during the pandemic necessitates unique considerations.

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