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Extracorporeal Membrane Oxygenation in Dengue, Malaria, and acute Chagas disease

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Abstract

Extracorporeal Membrane Oxygenation (ECMO) is widely used in Acute Respiratory Distress Syndrome (ARDS) and myocarditis. Severe vector-mediated diseases may be complicated by ARDS or myocarditis, which are both associated with a high mortality rate. We present six cases of severe dengue, malaria, and acute Chagas disease that were treated with ECMO from September 2007 to September 2015. Patients included two pediatric and four adults (ages 12 to 48). Survival to decannulation was 83% and to discharge was 66%. Overall, the mean duration on ECMO was 25.4 days. We conclude that ECMO treatment can be beneficial in patients with severe dengue, malaria, and acute Chagas disease, if complicated by pulmonary or cardiac complications.

Keywords:

Extracorporeal membrane oxygenation, acute respiratory distress syndrome, malaria, dengue, Chagas disease

Introduction

Vector-mediated diseases such as malaria, dengue, and Chagas disease have an enormous impact on global health.[1] Dengue is a self-limiting disease caused by the Dengue Virus (DEN 1-4). When symptomatic, dengue is either classified as Dengue Fever (DF) or Severe Dengue (SD). SD is characterized by Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS).[1,2] There is a 50 times higher mortality risk in patients with DSS than with DF.[3] Acute respiratory failure is a rare complication of dengue (1.8%) with a high mortality rate (72.7%).[4]

Malaria is caused by the Plasmodium parasite, of which five subtypes are known in humans: falciparum, vivax, ovale, malariae, and knowlesi. Severe malaria is mainly caused by *P. falciparum*, but may also be introduced by *P. vivax, P. ovale,* and *P. knowlesi*.[1,5,6] Untreated severe malaria approaches a 100% mortality rate. However, prompt antimalarial treatment may reduce mortality rates to 10-20%.[6] Acute Respiratory Distress Syndrome (ARDS) is commonly seen in severe *P. falciparum* (5-25%) and *P. vivax* (1-10%) patients.[5]

Chagas disease is caused by transmission of the protozoan *Trypanosoma cruzi*.[7] Myocarditis is one of the most serious manifestations with a high mortality rate of 5-10%.[7,8] Mortality from Chagas disease is almost entirely due to cardiac involvement.[7] Extracorporeal Membrane Oxygenation (ECMO) has been shown to be a valuable addition to conventional treatment of ARDS.[9,10] Also, ECMO is used in the treatment of myocarditis, either as a bridge to recovery, Ventricular Assist Device, or heart transplant.[11,12]

Since severe dengue, malaria, and Chagas disease may be complicated by cardiac or respiratory distress, there may be an important role for additional ECMO treatment.[1-8] Here, six cases of severe dengue, malaria, and Chagas disease who were treated with ECMO in *Fundación*

Cardiovascular de Colombia (FCV), are described. Although, a number of reports have already documented the use of ECMO in severe malaria and severe dengue,[13-18] to the best of our knowledge, this is the first documentation of ECMO treatment in severe acute Chagas disease.

Materials and Methods

Since the start of the FCV ECMO program in September 2007 until September 2015, a total of 318 patients have been treated with ECMO. Six patients, two children and four adults, were treated with ECMO for dengue, malaria, or acute Chagas disease. Patient medical records and Extracorporeal Life Support (ECLS) registry forms were retrospectively reviewed. Data was collected on patients' demographics, diagnoses, and ECMO indications, characteristics, and outcomes, using the FCV electronic medical record management system.

ECMO circuit

As we describe in a previous report,[19] our ECMO care model consists of two medical directors. The first director develops protocols and provides support and advice regarding ECMO physiology and management. The co-director serves as chief of the intensive care unit and leads the treatment team. The ECMO indications are reviewed by both the director and the co-director. The ECMO coordinator, an ECMO nurse trained as a perfusionist, provides logistical support for the ECMO nurse specialists regarding priming, changing of components, transport, and so on. Furthermore the ECMO coordinator leads the skills, training, and continuous education for ECMO specialists. Eight critical care nurses were trained as ECMO specialists. They fulfilled the roles of both ECMO specialists and patient caretakers with a 1:1 staffing ratio, and were responsible for the daily circuit management. We stop deep sedation and treat abstinence syndrome and delirium in the first ECMO week in order to have a fully awake and collaborative patient. This does not only reduce patient complications, but also the team workload.

FCV has adapted the ECMO circuit due to lack of ECMO and cardiopulmonary bypass equipment in Colombia. Two centrifugal pumps (Medtronic BP-80 BioPump® and Thoratec® Centrimag®) and one ECMO membrane oxygenator (Sorin EOS ECMO) were available during the study period. To reduce complications, the ECMO circuit has been simplified. Our circuit has two stopcock connectors for priming in the venous side, a Medtronic or Centrimag pump, a pre-membrane stopcock connector for samples, an EOS ECMO membrane, and an arterial stopcock connector. Only the flow and revolutions per minute were measured. We did not measure any circuit pressure, nor did we use the circuit for administration of medications or have any permanent bridge. Minimizing circuit monitoring and interventions reduces nursing workload and risks of complications. Two models were built based on the expected duration of ECMO support. One model, the "low-cost" model, used a Medtronic BP-80 BioPump®. The "high-cost" model used a Thoratec® Centrimag® pump. Generally, treatment was started with the low-cost model. If recovery was expected to take more than four weeks, the circuit was changed to the high-cost model.

Results

Of the six patients, five were successfully weaned off ECMO and four patients survived to hospital discharge. One patient was declared brain dead during ECMO (support withdrawn) and one patient died eleven days after ECMO was discontinued. In three patients, ECMO was initiated in another hospital and the Mobile ECMO team of FCV transported these patients. The other three patients were cannulated in the operating room of FCV. Two patients received veno-arterial (VA) ECMO for cardiac support and four veno-venous (VV) ECMO for respiratory support. The mean duration of ECMO support was 25.4 days (1.2-90.9).

Pre-ECMO patients' characteristics are described in **Table 1**, while in **Table 2**, post-ECMO complications and outcomes are displayed.

Summary of dengue cases

Case 1. April 2011, a 32-year-old man presented with four days of musculoskeletal pain, fever, dry cough, and emesis. He initially required mechanical ventilation for respiratory failure and rapidly deteriorated to severe hypoxemic. (PaO2/FiO2: 44). A thorax CT scan showed diffuse ground-glass opacities and signs of multi-lobar alveolar occupation. Despite an initial partial recovery, seven days after hospital admission his respiratory status worsened (Murray score of 3.75), requiring femoro-jugular VV-ECMO. The patient tested positive for dengue IgM and antiviral treatment was initiated. The patient was successfully decannulated after 34 days of ECMO treatment and discharged after 75 days of hospitalization. Thirty-three months after discharge the patient remained asymptomatic.

Case 2. January 2014, a 31-year-old pregnant woman (29.9 weeks gestation) suffered from four days of fever, asthenia, and progressive respiratory difficulties. The patient was diagnosed with preeclampsia and preterm delivery was induced. Postpartum, she presented with refractory thrombocytopenia and hypoxemic respiratory failure, requiring invasive mechanical ventilation. Given the persistent severe hypoxemia and hemodynamic instability, the FCV Mobile ECMO team implanted femoro-jugular VV-ECMO. IgM tested positive for dengue. A brain CT scan revealed multiple foci cortical/subcortical bleeding (**Figure 1**) and anticoagulation was discontinued. The next day, the patient was declared brain dead and ECMO support was withdrawn. Autopsy confirmed multiple intraparenchymal hemorrhaging associated with microangiopathic thrombosis, brain edema, herniation of cerebellar tonsils, ARDS in proliferative phase and diffuse alveolar hemorrhaging.

Case 3. November 2014, an 11-year-old obese (BMI: 29.4, 98th percentile) male, was admitted after five days of general malaise and persistent fever. The patient progressed to ARDS requiring mechanical ventilation. IgM tested positive for dengue. On day 12 of IMV, the patient presented refractory hypoxemia and hemodynamic instability. The FCV Mobile ECMO Team initiated femoral-jugular VV- ECMO (**Figure 2**). The patient was weaned off ECMO on day fifteen, extubated at day eighteen and discharged at day 31. Eight months after discharge the patient presented with NYHA functional class II. The spirometry showed a mixed pattern, without changes in spite of bronchodilator.

Summary of malaria case

Case 4. February 2013, a 15-year-old primigravida was admitted at 26 weeks of gestation, for periodic fever during the previous six months. Four days before admission, the patient developed intense fever (>39°C) associated with cold chills, back pain, rash and asthenia. Pancytopenia was identified and a Thick Blood Smear (TBS) revealed *P. vivax* that was treated with chloroquine. On day five, the patient developed ARDS and hemodynamic instability requiring invasive mechanical ventilation. Urgent caesarean section was performed at 28 weeks due to refractory hypoxemia. Five days after caesarean section patient´s respiratory status worsened (PaO2/FiO2: 46.8). The FCV Mobile ECMO Team initiated femoral–jugular VV-ECMO. The patient presented Multiple Organ Failure (MOF) with cardiac, hepatic and renal compromise. Lung biopsy showed edema, bleeding, mononuclear cells infiltration in the interstitial space, and low fibrotic remodeling. After eight weeks on ECMO patient´s condition did not improve, she was evaluated according to the Lung Transplantation Program but was rejected as a candidate. Subsequently, pulmonary surfactant was used as a rescue treatment. ECMO was successfully weaned off at 90 days and total hospital stay was 134 days. Twenty-nine months after discharge

patient remains with severe restrictive compromise in spirometry and moderate functional compromise in the six-minute walk test (508m).

Summary of Chagas cases

Case 5. February 2010, a 24-year-old woman from a high-risk zone for Chagas disease, was admitted with 20 days of fever, asthenia, headache, dyspnea, and leg edema. Echocardiogram revealed severe pericarditis, pericardial effusion and signs of imminent tamponade with Left Ventricular Ejection Fraction (LVEF) 60%, requiring pericardial emergency window. Pericardial biopsy showed a moderate lymphocytic pericarditis. The patient became hemodynamic instable requiring resuscitation and inotropic support. Acute Chagasic myocarditis was suspected, and empiric antiparasitic management was initiated. Echocardiography reported lower ventricular akinesia, and LVEF less than 10%. The patient developed arrhythmia requiring resuscitation and femoro-femoral VA-ECMO was started as a bridge to heart transplantation. Two days after, an orthotopic heart transplant was performed. Enzyme-linked immunosorbent assay (ELISA) was positive for *T. Cruzi*. The diagnosis of severe acute Chagasic myocarditis was confirmed by endomyocardial biopsy. The patient was discharged after 150 days. Following 62 months the patient was asymptomatic with NYHA functional class I and LVEF of 60%.

Case 6. September 2012, a 46-year-old woman was admitted with 20 days of fever, asthenia, dysuria, lumbalgia, emesis, diffuse-nonspecific abdominal pain, dyspnea, and lower limbs edema. General infection diseases were discarded. Echocardiogram revealed LVEF of 55% and pericardial effusion, requiring emergency pericardial window. ELISA was positive for *T. Cruzi.* Severe acute Chagasic myocarditis was confirmed by endomyocardial biopsy and antiparasitic management with nifurtimox was initiated. Despite antiparasitic treatment the patient deteriorated to cardiogenic and septic shock with MOF with a LVEF of 20-25% and a poor right ventricular contractility. Therefore, femoro-femoral VA-ECMO was started as a bridge to recovery. The

patient remained on ECMO for eight days. Echocardiogram reported LVEF of 60% with a normal heart size. After 55 days in the ICU the patient died due to severe sepsis caused by ventilation associated pneumonia, catheter-related infection, and inguinal area infection.

Consent

Our ethics committee approved this article and any accompanying images for publication.

Discussion

With this case report we demonstrate the additional value of ECMO therapy in the treatment of severe dengue, malaria, and acute Chagas disease. Although these vector-borne diseases are endemic in several continents, literature on ECMO treatment is lacking. This is, to the best of our knowledge, the biggest case report of vector-mediated diseases and ECMO, and the first description of ECMO being implemented in the treatment of acute Chagas disease.

According to the World Health Organization, every year 50 to 100 million people are infected with the dengue virus, whereas 198 million people are annually infected with malaria causing approximately 548000 deaths every year. As for Chagas disease, year by year 7 to 8 million people are infected.[1,6] Aforementioned, these vector-mediated diseases may be complicated by respiratory distress and/or cardiac failure.[2-8,18] Due to significant technical improvements ECMO is currently globally used as a salvage therapy for patients with refractory hypoxemia and cardiogenic shock who fail to respond to conventional therapy and have an estimated mortality rate over 80%.[9-12,20] Unfortunately, the most advanced ECMO devices are expensive, hampering its use in underdeveloped countries.[19] FCV has adapted the ECMO system in two ways; using less expensive cardiopulmonary bypass devices and reducing the workload by simplifying the ECMO care process. This case report demonstrates that these adaptations are successful, given that five (~83%) were successfully weaned off ECMO and four (~66%) were

successfully discharged. Furthermore this demonstrates that ECMO therapy can be beneficial in the treatment of severe vector-borne diseases like dengue, malaria, and Chagas disease.

Still, ECMO remains a high-risk treatment with severe complications such as bleeding, hemolysis, and infection.[10] Extra precautions should be taken in severe dengue patients when treated with ECMO, especially with regards to coagulation parameters. We described two patients, one dengue and one malaria, that were pregnant when admitted to the hospital. During pregnancy the immunity is modified;[6] therefore, pregnant women are more vulnerable to develop severe dengue or malaria. Extra caution should be taken to prevent this. In 1993, Neurath et al. already reported successful ECMO treatment in a pregnant patient with malaria.[13]

In case five, ECMO was initiated as a bridge to heart transplantation. At that time, it was not known that patients with acute Chagas disease would recover. Since FCV was able to receive an organ donor within two days it was decided to threat the acute Chagas infection with a heart transplant and immunosuppression simultaneously. Despite this chosen treatment Chagas reactivated seven months later, requiring additional antiparasitic treatment. Five years since, there has not been any further Chagas reactivation in the patient. In case six ECMO was initiated as a bridge to recovery, showing heart function improvement in the first week of ECMO and antiparasitic treatment. Based on this comparison, for future consideration FCV will try to recover acute Chagas patients within one to two weeks before listing them for heart transplantation.

As stated before, ARDS and refractory cardiogenic shock can be caused by vector-mediated diseases, especially in tropical areas. Since ECMO remains a bridging therapy, early disease detection is of imminent importance to start the specific and effective therapy as soon as possible.

In four cases the definite diagnoses were confirmed after ECMO was initiated, thus the right treatment plan was initiated later than ideally required.

In conclusion, we successfully weaned ~83% off ECMO and ~66% were successfully discharged, using our adapted ECMO system. ECMO could be a rescue therapy in severe dengue, malaria, and acute Chagas disease, either as a bridge to recovery or to transplantation. However, ECMO remains a high-risk therapy that should only be considered in specialized ECMO centers.

Limitations

In this study we retrospectively reported six patients. No hard conclusions can be extracted from these results due to the small number of patients. Furthermore, because five of our patients were primarily admitted to another hospital, a complete medical history was difficult to obtain and therefore some information could be incomplete.

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Figure Legends

Figure 1: Cerebral computed tomography (CT) the day after cannulation.

Figure 2: Chest X-ray four days after ECMO cannulation.

Table 1. Pre-ECMO Characteristics

Tropical disease	Dengue			Malaria (*P. vivax*)	Chagas	
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)/gender	32/M	31/F	11/M	15/M	24/F	46/F
Diagnosis at admission	ARDS, atypical pneumonia, septic shock	ARDS, pre-eclampsia	ARDS, septic shock	Severe malaria, ARDS, MOF	Cardiac tamponade, acute heart failure (pre-transplant)	UTI, cardiac tamponade, polyserositis
Initial approach	IMV, norepinephrine IV, ABT	NIMV, IMV, ABT, prone position	IMV, prone position, blood transfusions, ABT	Chloroquine, blood transfusions, IMV, ABT	Pericardial window, intra aortic balloon pump	ABT, pericardial window
Pre-ECMO complications	Hypokalemia	Pancytopenia, coagulopathy	Bacteremia (*Acinetobacter ursingii*)	UTI (*Candida albicans*)	Progressive ventricular dysfunction	Progessive ventricular dysfunction, mixed shock, MOF,

						vasoplegia
Definite diagnosis	Severe dengue	Severe dengue	Severe dengue	Refractory ARDS secondary to severe malaria and sepsis	Severe acute Chagas myocarditis	Severe acute Chagas myocarditis
Diagnostic test (positive)	IgM*	IgM*	IgM*	TBS (schizonts, young and adult trophozoites)	IgG* Microstrout blood smear (post-transplant)	Endomyocardial biopsy

* Enzyme-Linked ImmunoSorbent Assay. ECMO: extracorporeal membrane oxygenation; M: male; F: female; (N)IMV: (non) invasive mechanical ventilation; ARDS: acute respiratory distress syndrome; MOF: multiple organ failure; UTI: urinary tract infection; IV: intravenous; ABT: antibiotic therapy;TBS: thick blood smear.

Table 2. ECMO and Post-ECMO Characteristics

	ECMO											
Case	Initiated	Indication	Mode	Complications	Actions taken	Post-ECMO complications	IMV (days)	ECMO (days)	Hospital stay (days)	ICU (days)	ECMO survival	Hospital survival
1	OR*	Refractory hypoxemia	VV	Severe refractory hypoxemia	Change of membrane oxygenator	Small apical left pneumothorax, nosocomial sepsis (MDRKP, MDRPA)	55	34.8	75	57	Yes	Yes
2	Mobile†	Refractory hypoxemia	VV	Bradycardia during cannulation	Atropine and epinephrine	Multiple intraparenchymal brain hemorrhage – brain death	5	1.5	2	2	No	No
3	Mobile†	Refractory hypoxemi	VV	Macroscopic hematuria	Urinary tract ultrasonography (normal), follow-	UTI (*Candida tropicalis*), VAP (*Acinetobacter ursingii*),	18	15.7	31	26	Yes	Yes

		a			up	Miller Fisher Syndrome						
4	Mobile†	Refractory hypoxemia	VV	Tracheal bleeding through tracheostomy tube	Revision surgery and hemostasis, fibrobronchoscopy	Right hemothorax, VAP (*MDRPA*), Hamman Rich Syndrome	110	90.9	134	100	Yes	Yes
5	OR*	Cardiac arrest	VA	None	-	Acute cellular rejection, MOF, soft tissue infection (*Proteus mibralis*), cryptogenic organizing pneumonia, PRES	UNK	1.2	150	41	Yes	Yes
6	OR*	Cardiogenic shock	VA	Incipient left lower limb ischemia	Recannulation (smaller cannula)	Prolonged mechanical ventilation, Hypoxic-ischemic encephalopathy, Fungemia (*Candida tropicalis*), VAP	55	8.4	59	55	Yes	No
				Right inguinal hematoma at cannulation site	None							

				Sub-optimal blood flow	Additional cannulation	(*Burkholderia cepacia*), catheter-related infection (*MDRKP*)						
				Hemolysis	Pump change							
				Bilateral inguinal area infection (*Klebsiella pneumoniae)* with femoral vessels exposition	Two surgical debridement procedures							

ECMO: extracorporeal membrane oxygenation; OR: operating room; IMV: invasive mechanical ventilation; ICU: intensive care unit; VV: veno-venous; VA: veno-arterial; MDRKP: multidrug-resistant Klebsiella pneumoniae; MDRPA: multi-drug resistant Pseudomonas aeruginosa; UTI: urinary tract infection; VAP: ventilator-associated pneumonia; MOF: multiple organ failure; PRES: posterior reversible encephalopathy syndrome; UNK: unknown. * in FCV; † FCV mobile ECMO team.

Figure 1.

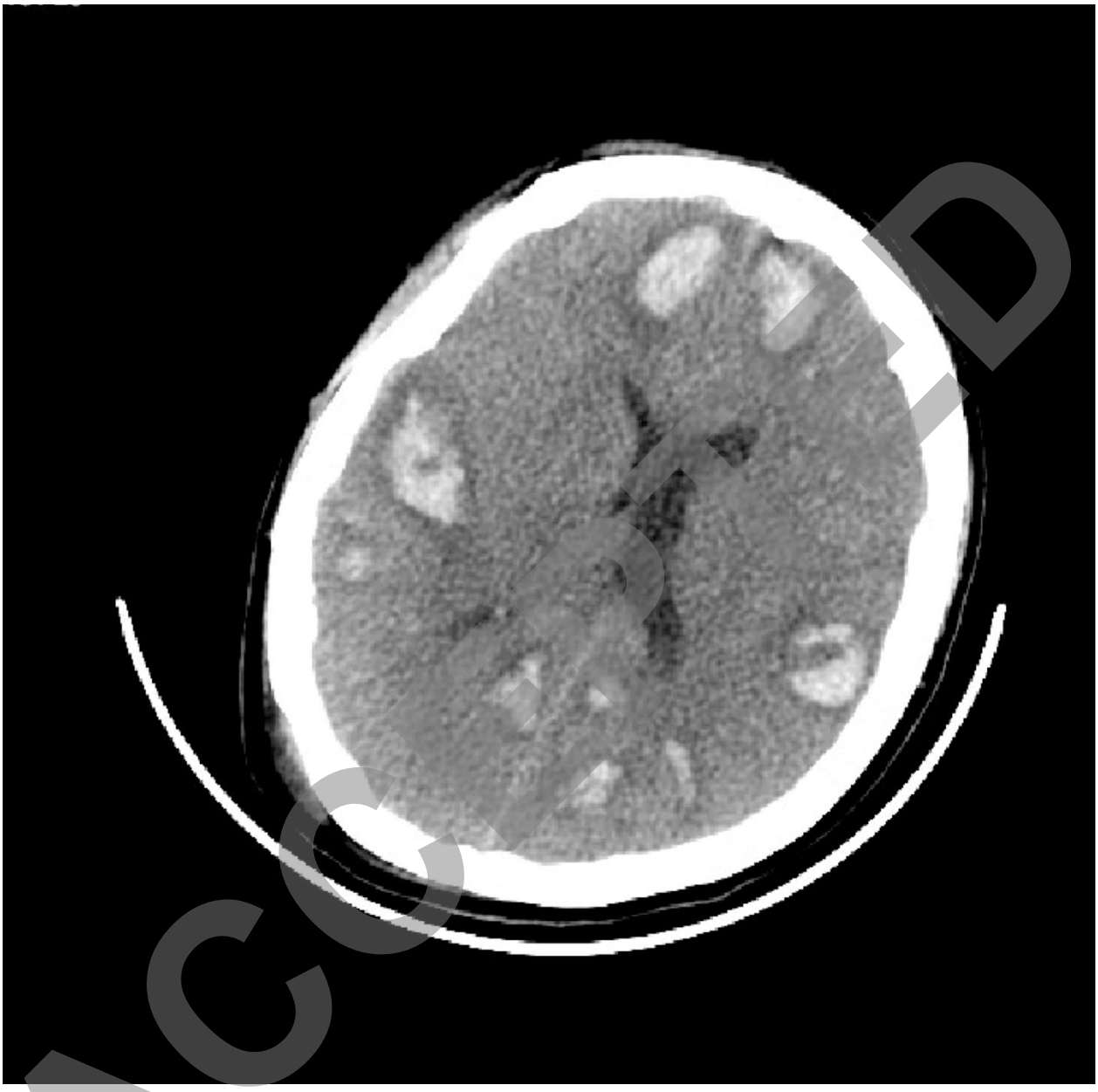

Figure 2.