J Extra Corpor Technol. 2019;51:88–93
The Journal of ExtraCorporeal Technology

Management Strategies during a VA ECMO Run in a Neonate with *E. Coli* Septic Shock Masquerading as Hypoxic Ischemic Encephalopathy

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Case report presented at the ELSO 29th Annual Meeting, Scottsdale, Arizona, September 14–16, 2018.

Abstract: Advances in neonatal care for hypoxic respiratory failure, with high-frequency ventilation and inhaled nitric oxide, have led to a decreased need for extracorporeal membrane oxygenation (ECMO). However, neonates resistant to such therapies are more complex and at higher risk of mortality. One such population includes those with hypoxic ischemic encephalopathy (HIE) undergoing controlled hypothermia (CH). We present a challenging case of a full-term neonate with inotrope-resistant *Escherichia coli* septic shock, profound coagulopathy, hypoxic respiratory failure, and HIE requiring CH and venoarterial (VA) ECMO. We illustrate that family-centered decision-making, ECMO, primary team, and subspecialist support is critical to success. In addition, we share the strategic medical interventions concomitantly used with VA ECMO to aid in the survival of this high-risk infant such as continuous venovenous hemofiltration with AN69 membrane for cytokine and fluid removal, prostaglandin use to relieve right ventricular strain in malignant pulmonary hypertension, and cautious use of bronchoscopy to assist in lung recruitment. **Keywords:** ECMO (extracorporeal membrane oxygenation), neonate, hypoxia, hypothermia, shock. *J Extra Corpor Technol. 2019;51:88–93*

OVERVIEW

Hypoxic ischemic encephalopathy (HIE) affects one to two infants per 1,000 live term births and accounts for 23% of neonatal deaths worldwide (1). Advances in neonatal care for hypoxic respiratory failure, with high-frequency ventilation and inhaled nitric oxide (iNO), have led to a decreased need for extracorporeal membrane oxygenation (ECMO); however, neonates resistant to such therapies are more complex and at higher risk of mortality (2). One such population includes those with HIE undergoing controlled hypothermia (CH). Historical data from our tertiary institution indicates 10% of neonates with HIE require ECMO support. Although CH has become the mainstay for HIE management because of its benefits in mitigating reperfusion injury and improving neurodevelopmental outcomes, the effects of hypothermia on other organ systems can be problematic (3). We present a challenging case of a term neonate with *Escherichia coli* (*E. coli*) septic shock, hypoxic respiratory failure, and HIE requiring CH and venoarterial (VA) ECMO.

DESCRIPTION

A term 2,816-g female was born at 40 weeks and 2 days of gestation via vaginal delivery to a 30-year-old primigravid

Received for publication November 30, 2018; accepted April 3, 2019.
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The senior author has stated that the authors have reported no material, financial, or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.
Contributors' Statement: Dr. Quinones Cardona obtained IRB approval, acquired and interpreted case report data, and drafted, reviewed, and revised the manuscript. Dr. Menkiti obtained IRB approval, interpreted case report data, and critically reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

female with noncontributory prenatal laboratories. Delivery was complicated by maternal chorioamnionitis, meconium stained amniotic fluid, nuchal cord, and prolonged rupture of membranes. At birth, the infant was lethargic, hypotonic, and poorly perfused requiring intubation and FiO_2 1.0. Apgar scores were 2 and 7, at 1 and 5 minutes, respectively. Initial laboratory tests revealed metabolic acidosis and leucopenia (white blood cells [WBC] 4.8 10×3 cells/mcL). iNO was started at 20 ppm for suspected persistent pulmonary hypertension (PPHN) and required significant volume resuscitation with crystalloids for severe metabolic acidosis and poor perfusion. Sepsis evaluation was performed and the infant was started on ampicillin and gentamicin while undergoing passive cooling in preparation for transfer to our institution for CH in the setting of HIE.

Over the course of 18 hours while on CH protocol, the infant developed worsening hypoxemia, systemic hypotension, and lactic acidosis requiring maximum intravenous inotropic support with dopamine, epinephrine, and hydrocortisone every 6 hours. Concurrently, the infant required multiple blood products to treat pancytopenia and severe coagulopathy (Figure 1). Meropenem was added when the blood culture revealed Gram-negative rods, later speciated to gentamicin-resistant *E. coli*. Initial echocardiography confirmed severe PPHN, patent ductus arteriosus with predominant right to left shunt, and normal biventricular function. Screening head ultrasound (HUS) was unremarkable.

Fluid- and inotrope-resistant septic shock complicated by hypoxic respiratory failure, despite maximal therapy, led to the consideration of ECMO as rescue therapy for this profoundly coagulopathic infant. Despite the high risks, the family agreed to proceed with ECMO. The right carotid artery and right internal jugular vein were cannulated with Medtronic 10-French arterial and 12-French venous cannulas, respectively. The infant was successfully placed on VA ECMO at 24 hours of life after a modified heparin bolus dose of 50 units/kg using a S5 roller pump (Sorin Group, Deutschland GMBH Munchen, Germany) with a venous compliance reservoir, Quadrox-i pediatrics and

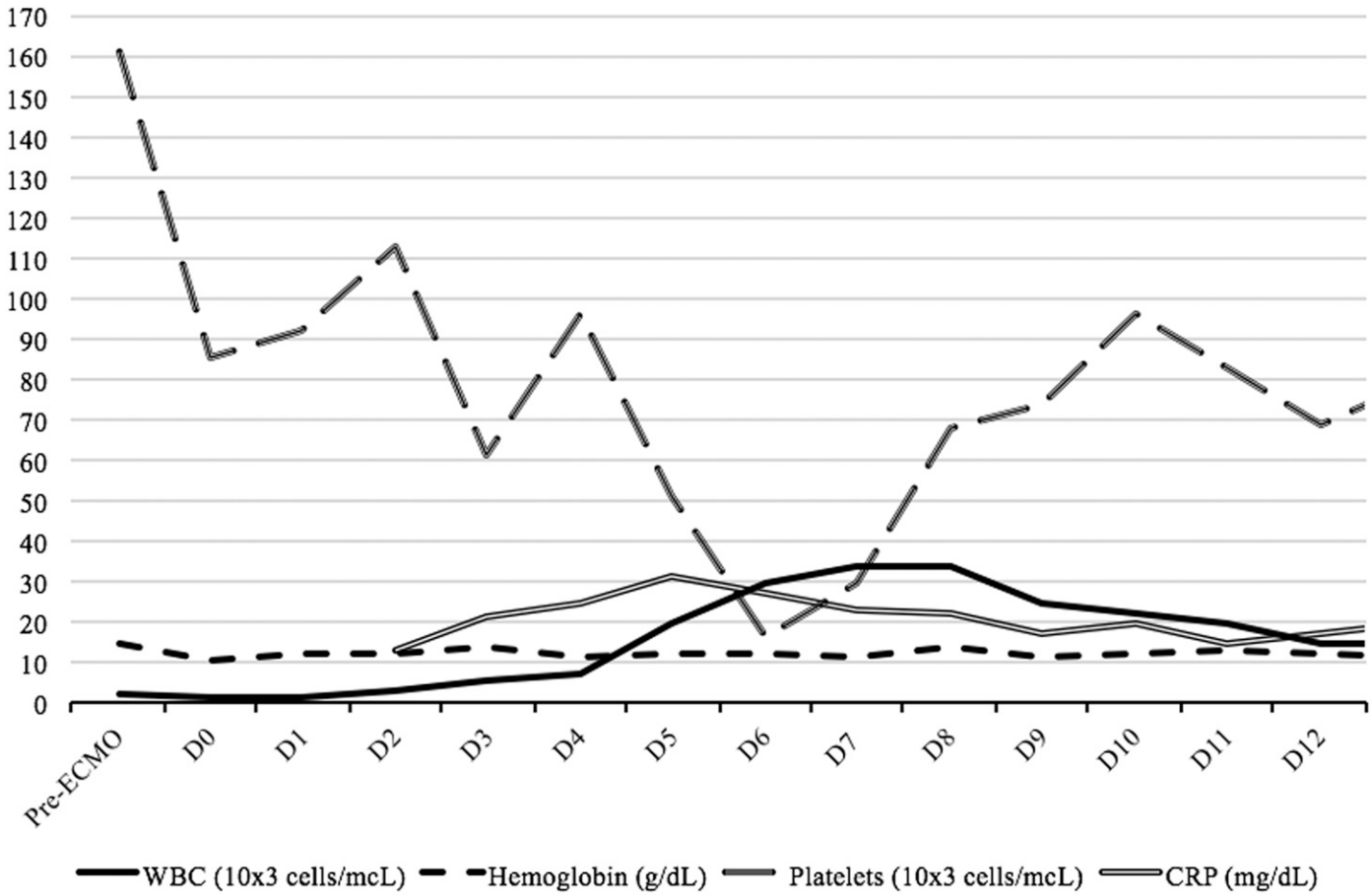

Figure 1. Blood counts and CRP trends per ECMO day. This figure illustrates the downward trend in platelets, lowest on ECMO D5-6, which correlated with initiation of CRRT, followed by slow recovery with transfusions. CRP had an upward trend until ECMO day 5, followed by a decrease. WBC trend showed the infant initially had leukopenia followed by leukocytosis, with normalization after D8. Hemoglobin levels remained relatively stable with transfusions as needed. CRP, C-reactive protein; D, day.

neonatal oxygenator (Maquet Getinge Group, Rastatt, Germany), and a Tygon S-95-E ¼ inch tubing. The circuit was primed with Plasma-Lyte A, pH 7.4, albumin, sodium bicarbonate, calcium gluconate, and blood. She required ECMO pump flows of up to 196 mL/kg/min in addition to ongoing fluid resuscitation and inotrope therapy, sweep gas flow .55–.9 L/min and FiO_2 of 1.0 for the first 10 days of the run (Figure 2). Her coagulation profile was closely monitored, and coagulopathy was aggressively corrected (Table 1). Lungs were rested until ECMO day 5 when conditioning was introduced simultaneously with continuous renal replacement therapy (CRRT) using the Prismaflex 2000 system (Baxter International, Deerfield, IL) with an AN69 membrane to aid in cytokine removal and treatment of severe fluid overload. The CRRT inlet was connected post-pump and the outlet connected pre-oxygenator. Vasopressors were successfully weaned off by ECMO day 6.

Despite lung recruitment maneuvers, chest x-ray revealed significant consolidation and atelectasis likely due to congenital *E. coli* pneumonia (Figure 3). Malignant pulmonary hypertension ensued on ECMO day 7 with bilateral lung collapse despite recruitment maneuvers. Because of worsening right ventricle (RV) failure and inability to recruit lungs, the infant was started on milrinone to aid RV function and prostaglandins to re-open the ductus arteriosus and relieve RV strain. Bronchoscopy was performed on ECMO day 8. Bronchial alveolar lavage culture was positive for *E. coli* and *Candida albicans*. The infant received dornase alfa and fluconazole and continued on meropenem with doses adjusted based on drug levels. These maneuvers resulted in modest improvement in lung recruitment, PPHN, and RV function by ECMO day 12, resulting in successful discontinuation of prostaglandins and milrinone infusions. Pulmonary recovery lagged behind heart recovery forcing undesired discussions around the risks and benefits of conversion to VV ECMO vs. VV-A ECMO. This was deemed too risky and the infant continued on VA ECMO while weaning pump flow. After a successful trial off, she was de-cannulated, and CRRT was discontinued simultaneously on ECMO day 14.

Post-ECMO, she developed systemic hypertension requiring intravenous and later oral therapy and direct hyperbilirubinemia, which resolved gradually. The brain magnetic resonance imaging (MRI) performed at day of life 23 did not reveal findings consistent with HIE; however,

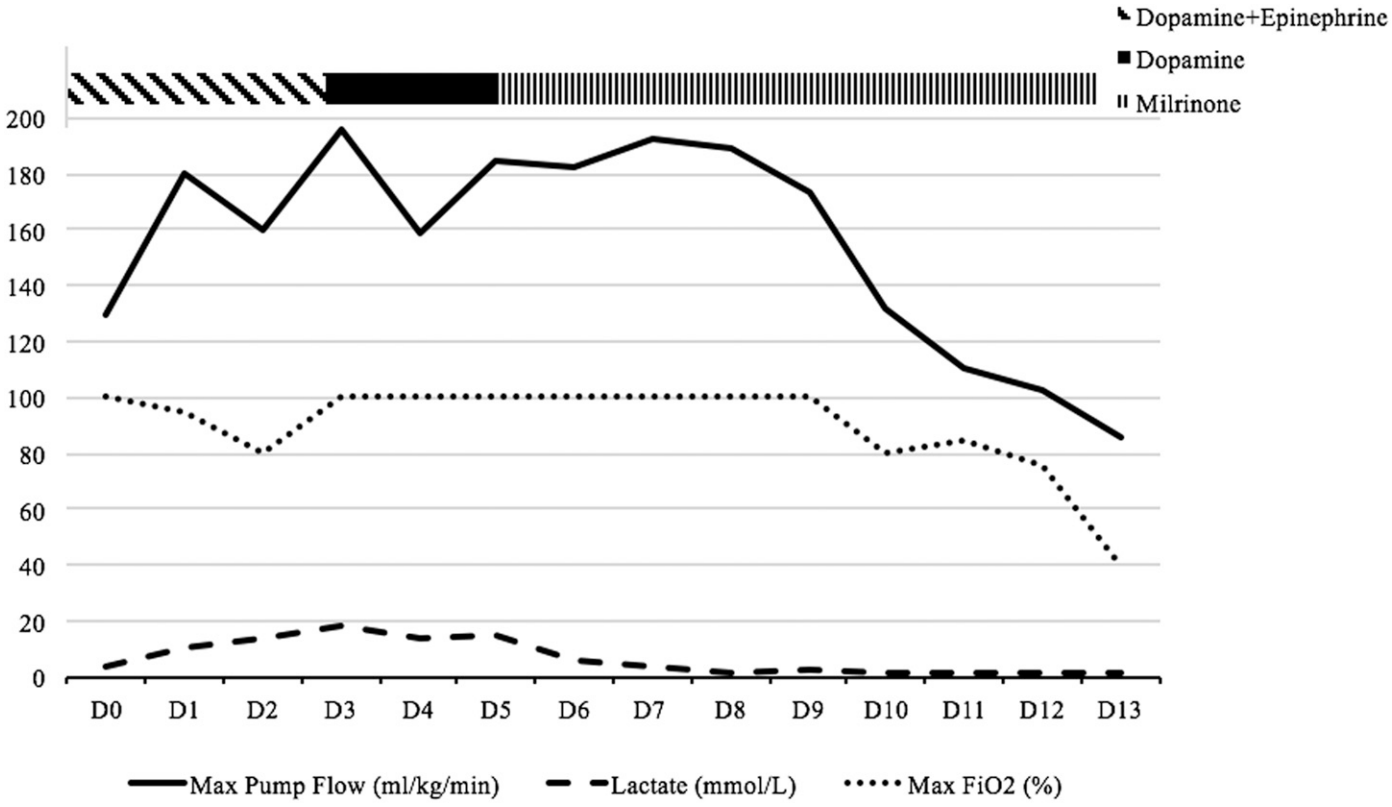

Figure 2. ECMO pump flow, FiO_2, lactate, and inotrope trends. The top bar chart represents the inotropes the infant was on during the ECMO run. The line chart demonstrates the duration and range of ECMO pump flow and FiO_2 required in relationship to lactate clearance. Epinephrine was weaned by D3 and dopamine by D5; however, the infant was maintained on milrinone from D5 to D12 to improve cardiac function. Modest lactate clearance was achieved starting on D5. Pump flow and FiO_2 wean began on D9 until decannulation on D13.

Table 1. Coagulation profile and heparin requirements.

	Pre-ECMO	DO	D1	D2	D3	D4	D5	D6	D7	D8	D9	Dll	D12	D13	D14
INR	7.45*	2.33*	1.78*	1.74*	1.61*	1.45	1.38	1.27	1.23	1.15	1.22	1.12	1.1	1.09	1.15
ACT (sec)	–	289	188–239	192–223	192–220	185–240	186–221	171–222	197–217	184–214	180–220	197–221	194–238	182–234	179–231
PTT (sec)	>120	57.1	>120	>120	70.6	43.4	45.1	54	78.8	54.8	61.3	65.4	76.3	70.1	93.9
Anti-Xa (IU/mL)	–	–	–	0.14	<0.1	<0.1	<0.1	<0.1	0.2	<0.1	<0.1	<0.1	<0.1	<0.1	0.16
AT3 activity (%)	–	–	–	75	54	61	51†	74	89	70	71	71	73	64†	70
Heparin (units/kg/h)	–	9–20	9–20	3–13	8–16	27–56	30–63‡	49–103‡	80–125‡	82–128‡	89–133‡	95–147‡	78–143‡	69–126‡	73–111‡

ACT, activated clotting time; anti-Xa, anti-Xa factor assay; AT3, antithrombin III activity; D, day; INR, international normalized ratio; PTT, partial thromboplastin time.
*Fresh frozen plasma transfused.
†Thrombate replaced.
‡Concomitantly on CRRT.

it demonstrated a retro-cerebellar bleed with hydrocephalus despite multiple negative HUS during the ECMO run, which did not require intervention (Figure 4). She was eventually discharged home in room air with fortified oral and gastrostomy tube feeds. Follow-up at 1 year of age demonstrated a developmentally appropriate infant feeding orally with plans for gastrostomy tube removal.

COMMENT

According to ELSO, neonates with sepsis have a 55% survival rate because of disease severity with associated respiratory failure, shock, PPHN, cardiac failure, and profound coagulopathy (4). Some of these conditions can be further worsened by CH, making ECMO a risky proposition in this group. However, it is important to recall that death is almost certain with inaction.

Sepsis masquerading as fetal intolerance of labor and HIE may delay the timely initiation and/or adjustment of antibiotics which may prove fatal for this patient population. *E. coli* resistance to first-line antibiotics in the neonatal intensive care unit (ampicillin and gentamicin) for early onset sepsis is not uncommon (5). This case presented with findings suggestive of HIE prompting CH therapy with simultaneous treatment for suspected sepsis. However, clinical deterioration prompted broadening antibiotic coverage, which was critical in the setting of gentamicin-resistant *E. coli* sepsis. High index of suspicion for sepsis is urged in severe cases of HIE for timely broadening of antibiotics.

Elevated lactate levels have been well documented as a strong predictor of poor outcomes (6). Failure to normalize lactate levels (<2 mmol/L) in the first 24–48 hours of VA ECMO assistance in cardiogenic shock is a predictive marker for 30-day mortality (7). Our case had a peak lactate level of 18.6 mmol/L on ECMO day 3, and the lactate levels did not normalize until ECMO day 7. Extrapolating from this case demonstrated that although lactate trends correlated with severity of illness, it did not necessarily correlate with the outcome. The sequence of events from CRRT to prostaglandin therapy, dornase alfa, bronchoscopy, and aggressive treatment of the coagulopathy improved the odds in this patient's favor.

CRRT not only aided in fluid removal of a severely fluid-overloaded infant but also in cytokine removal by using the AN69 membrane. The AN69 membrane adsorbs cytokines via ionic bonding between its sulfonate group and the amino group on the surface of a cytokine molecule (8). Caution is advised as the AN69 membrane can lead to bradykinin release when blood passes through the membrane leading to hypotension, especially in patients on angiotensin-converting enzyme inhibitors. Two case reports also highlight the sensitivity of the membrane to pH,

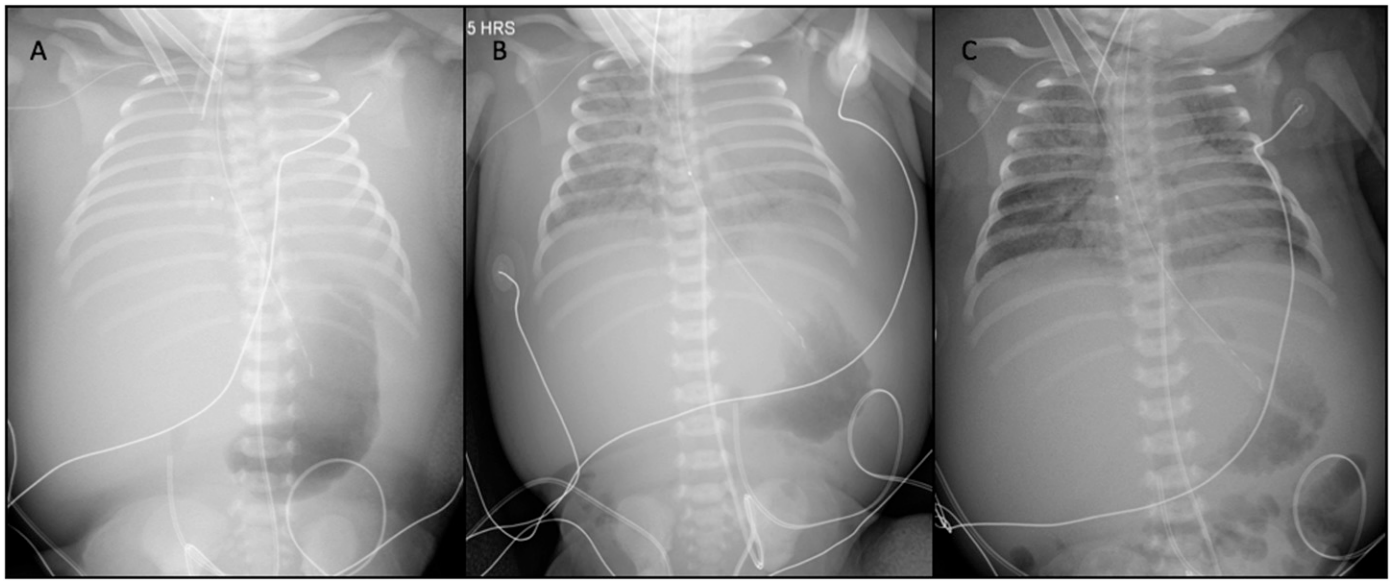

Figure 3. Pre- and post-bronchoscopy radiographs. (A) Radiograph on ECMO D8 showed bilateral haziness of lungs suggestive of lung consolidation despite lung recruitment maneuvers. (B) Radiograph post-bronchoscopy, lung recruitment, and dornase alfa therapy on ECMO D9 revealed slight improvement in aeration; right greater than left. (C) Radiograph on ECMO D10 demonstrated modest improvement in aeration bilaterally with persistent signs of pneumonia. D, day.

with lower pH blood increasing the risk and severity of hypotensive episodes. Particularly, this can be seen in infants <10 kg with blood bank primed circuits as this blood tends to be acidotic, hyperkalemic, and hypocalcemic if citrate is used as an anticoagulant (9). To mitigate the potential side effects of hypotension and hypocalcemia, nephrology primed the circuit with 5% albumin while neonatology gave packed red blood cells for volume, calcium gluconate and transiently increased the dopamine infusion for a successful CRRT initiation.

The unusual use of prostaglandin therapy in this infant without a ductal-dependent cardiac lesion on VA ECMO was to substantially reduce the right-side afterload by providing a pop-off valve, thereby relieving the RV strain given malignant PPHN in spite of a week of ECMO support. This strategy bought time while lung recruitment maneuvers were optimized with bronchoscopy and aggressive pulmonary toilet.

ECMO-related mortality in this population is often related to severe intracranial hemorrhage (ICH) resulting in discontinuation of ECMO. ICH has been associated with prematurity, thrombocytopenia, low fibrinogen, and elevated mean arterial pressures (10). Despite severe coagulopathy and persistent thrombocytopenia during the ECMO run, necessitating numerous blood transfusions, serial HUS remained negative. However, it is important to note that HUS during neck approach cannulation can be limited because of positioning of ECMO cannulas. Transmastoid views in this patient were limited, which may have masked the retro-cerebellar bleed later identified. Another possible explanation of ICH in this case can be from the systemic hypertension that ensued post-ECMO, necessitating medical therapy.

This case demonstrates that effective and timely deployment of strategic medical interventions while on VA

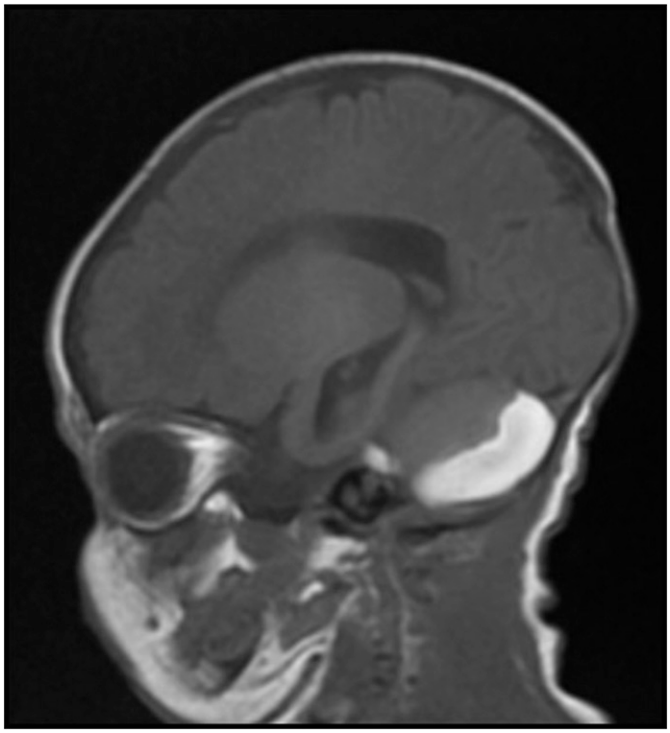

Figure 4. Post-ECMO brain MRI. T1-weighted image of obstructive hydrocephalus secondary to a large retro-cerebellar hemorrhage extending into the right cerebellopontine angle causing mass effect on inferior cerebellum.

ECMO were necessary to aid in the survival of this extremely high-risk infant. ICH remains a concern; therefore, close monitoring and aggressive management of coagulopathy, thrombocytopenia, and avoiding systemic hypertension cannot be overstated. Clearly defined goals with expectations for family and ECMO team, intermingled with proactive subspecialists, are also critical for success.

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