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Case Report

Bilateral Adrenal Hemorrhage Complicating Neonatal Encephalopathy

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Abstract

Bilateral adrenal hematomas are a rare finding in neonates. Premature delivery, hypoxic ischemic encephalopathy, fetal acidemia, sepsis and infection can increase the risk for adrenal hemorrhage. We present a case of neonate with hypotension unresponsive to vasopressors, profound anemia and electrolyte abnormalities found to have bilateral adrenal hematomas. This infant was stabilized after initiation of hydrocortisone and the hematomas were followed by ultrasound. After discontinuing hydrocortisone, he was restarted on the medication at 4 months of age due to concern for persistent adrenal insufficiency. Bilateral adrenal hemorrhages must be considered in infants with extreme hypotension, particularly if unresponsive to vasopressors and transfusion of blood products.

Keywords: Adrenal hemorrhage; Adrenal hematoma; Hypoxic ischemic encephalopathy; Adrenal insufficiency

Abbreviations

NICU: Neonatal Intensive Care Unit; HIE: Hypoxic Ischemic Encephalopathy; iNO: inhaled Nitric Oxide; FFP: Fresh Frozen Plasma; HOL: Hour of Life; DOL: Day of Life; CMV: Cytomegalovirus; ACTH: Adrenocorticotropic Hormone; BMP: Basic Metabolic Panel

Introduction

Bilateral neonatal adrenal hematomas are an uncommon finding in the first week of life. Infants' adrenal glands are highly susceptible to adrenal hemorrhage due to their high vascularity and large anatomic size. Prematurity, traumatic delivery, fetal acidemia, sepsis and infection can increase the risk for adrenal hemorrhages. We present a case of bilateral adrenal hematomas confirmed by ultrasound in a term infant requiring therapeutic hypothermia for Hypoxic-Ischemic Encephalopathy (HIE) who developed pressor-resistant profound hypotension and required a partial exchange transfusion for severe anemia. Bilateral adrenal hemorrhages may result in life threatening hypotension if not diagnosed and treated appropriately. Adrenal hemorrhages should be considered in cases of acute idiopathic anemia, electrolyte disturbance and hypotension unresponsiveness to vasopressors.

Case Presentation

A male infant was born to a now G1P1 Caucasian woman at 38w1d via vaginal delivery. Pregnancy was complicated by maternal asymptomatic COVID-19 infection (14 days prior to delivery), chorioamnionitis, and GBS unknown without intrapartum prophylaxis. Delivery was complicated by vacuum assist, meconium-stained amniotic fluid, shoulder dystocia, and nuchal cord. The infant was cyanotic, hypotonic, and had no spontaneous respiratory effort at birth. APGARS were 1, 4, 5, and 6 at 1, 5, 10 and 15 minutes of life, respectively and he was intubated for hypoxic respiratory failure shortly after admission. Cord gases were notable for mixed metabolic and respiratory acidosis (Table 1) and his initial neurologic exam was consistent with severe hypoxic ischemic encephalopathy. He was given 3 normal saline boluses (10 mL/kg each) and transferred to a level IV NICU for therapeutic hypothermia. At the referring hospital, therapeutic hypothermia was initiated, and he was transitioned to the high frequency jet ventilator and started on dopamine for hypotension. Echocardiogram was consistent with pulmonary hypertension and he was started on inhaled nitric oxide (iNO). Labs were notable for elevated white blood cell count, transaminitis, coagulopathy and anemia for which he received fresh frozen plasma (FFP) and packed red blood cells. Initial sodium was 131 (Table 1).

At approximately 24 hours of life, he tolerated de-escalation of care to the conventional ventilator, weaning iNO and dopamine when he developed sudden worsening hypotension that did not respond to increasing dopamine and adding epinephrine. Hydrocortisone was bolused at 25 mg/m^2 and maintenance of 50 mg/m^2/day was started. At that time, he was noted to have an acute drop in his hematocrit from 41.9% to 27% (HOL 24) to 14.8% (HOL 47) and profound hyponatremia – sodium decreased from 131 to 120 over 12 hours to a nadir of 115 (49 HOL) (Table 1). Coagulation studies improved, but were still abnormal (Table 1). Ultrasound of the kidneys showed bilateral nonvascular, heterogenous suprarenal masses, suspected to be adrenal hematomas. The right adrenal hematoma measured 4.6x2.7x3.5 cm and the left adrenal hematoma measured 4.2x3.5x4.1 cm, containing approximately 104 mL of blood total (Figure 1). He received 142 mL of packed red blood cells, 33 mL of platelets and 105 mL of FFP. Therapeutic hypothermia was discontinued early given the profound hemorrhage and concerns for coagulopathy. His urine output decreased from 1.1 mL/kg/day to 0.3 mL/kg/day. He underwent a partial volume exchange transfusion (HOL 50) to correct the hematocrit to 26.3% (Table 1). At this time, another 1 mg/kg bolus of hydrocortisone was administered and maintenance dosing was increased to 75 mg/m^2/day due to overall electrolyte abnormalities and concern for adrenal insufficiency. Over the next 24 hours he required multiple boluses of 3% hypertonic saline,

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Table 1: Laboratory values during hospital admission from day of life 0 to day of life 6.

	Cord Gas	HOL 1	HOL 8	HOL 24	HOL 36	HOL 47	HOL 49	DOL 3	DOL 4	DOL 5	DOL 6
Blood Gas											
pH, a	6.85	7.059	7.28	7.27	7.31	7.32	-	7.33	7.39	7.47	-
CO_2, a (mmHg)	97.3	32.6	23	31	34	36	-	34	35	37	-
PO_2, a (mmHg)	<30	48.1	41.6	118	199	44	-	73	79	51	-
HCO_3, a (mmHg)	17.2	9.2	-	15	17	20	-	18	22	27	-
Base excess (mmol/L)	-16.5	-21.1	-15	-12	-8	-7	-	-8	-3	4	-
Lactate, a (mmol/L)	-	15.11	10.8	7.3	5.6	2.5	-	2.1	2.3	-	-
Complete Blood Count											
WBC (14x10^9)	-	37.3	34.3	19.7	-	-	13.5	12.4	17.9	17.4	20.1
Hemoglobin (g/dL)	-	18.1	14.9	9.6	10.6*	-	5.7	9.3	13.3	12.8	13.3
Hematocrit (%)	-	55	41.9	27	-	14.8	15.3	26.3	37.6	35.4	37
Platelet (400x10^9/L)	-	201	114	119	-	55	53	218	85	50	93
Metabolic Panel											
Sodium (mmol/L)	-	-	131	124*	120	109†	115	120	133	137	140
Potassium (mmol/L)	-	-	4.2	3.8	4.4	5.7†	6.3	5.7	3.2	2.3	3.7
Carbon Dioxide (mmol/L)	-	-	13	15	16	-	19	17	18	25	25
Creatinine (mg/dL)	-	-	2.2	2.4	2.4	-	2.4	2.4	2.3	2.3	2.1
AST (U/L)	-	-	1461	1570	1392	-		984	1032	560	260
Calcium, ionized (mmol/L)	-	-	-	1.19	1.01	-	-	-	-	0.98	-
ALT (U/L)	-	-	456	357	334	-	-	274	372	443	370
Coagulation Studies											
PT (seconds)	-	27.5	64.7	31.6	30.8	14	16.5	13.6	11.4	-	-
aPTT (seconds)	-	-	75.2	38	33.4	38.6	33.3	30.1	27.9	-	-
INR	-	2.39	5.4	2.7	2.6	1.2	1.4	1.2	1	-	-
Fibrinogen (mg/dL)	-	-	37	90	104	102	109	131	182	-	-

aPTT - Activated Partial Thromboplastin Time, ALT - Alanine Aminotransferase, AST - Aspartate Aminotransferase, DOL - Day of Life, HOL - Hour of Life, INR - International Normalized Ratio, PT - Prothrombin Ntime, WBC - White Blood Cell Count,
*First dose of hydrocortisone administered
†From arterial blood gas.

calcium gluconate and normal saline. He was weaned off vasopressors shortly after these interventions, his electrolytes stabilized and urine output improved over the next 24 hours. He was extubated on DOL 5 and weaned to room air on DOL 9. His MRI post re-warming (DOL 5) was significant for small infarcts on the right frontal and bilateral occipital lobes, and genu/splenium of the corpus callosum. Repeat echocardiogram on DOL 8 showed resolution of pulmonary hypertension.

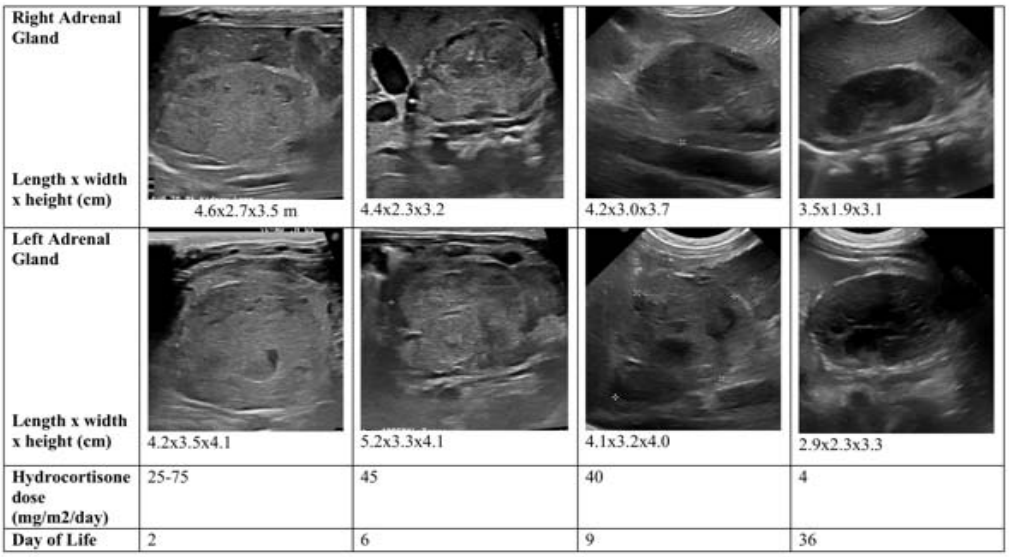
Infectious disease service was consulted to rule out an infectious cause for his clinical presentation. Blood culture and virologic studies were negative (Figure 2). Lumbar puncture was not done due to clinical instability. He was treated with Ampicillin and Cefotaxime for 14 days for presumed sepsis. Acyclovir was discontinued after negative HSV studies (Figure 2). Urine was positive for cytomegalovirus (CMV), and he was started on valganciclovir.

The adrenal hematomas were monitored every 1 to 3 weeks during hospitalization. At discharge (DOL 61), his ultrasound showed interval progressive cystic degeneration of the bilateral hematomas, measuring 3.5x1.9x3.1 cm on the right and 2.9x2.3x3.3 cm on the left (Figure 1). Imaging continued to show no internal vascularity or apparent color doppler signal to suggest a neuroblastoma. Hydrocortisone was slowly weaned off (over 6.5 weeks). ACTH and cortisol levels were 9.2 ug/dL(reference range 15-66 pg/mL) and 225 pg/mL (5-25 ug/dL) respectively 4 days after discontinuation of

Table 2: ACTH level, cortisol level and hydrocortisone dose, sodium, potassium and bicarbonate at and post-discharge.

Day of Life	50	127	190
ACTH (pg/mL)	225	124	50
Cortisol (ug/dL)	9.2	9.3	--
Hydrocortisone Dose (mg/m^2/day)	none	16	18
Sodium (mmol/L)	137	136	138
Potassium (mmol/L)	4.6	4.6	4.6
Bicarbonate (mmol/L)	25	22	25

ACTH: Adrenocorticotropic Hormone.



Right Adrenal Gland				
Length x width x height (cm)	4.6x2.7x3.5 m	4.4x2.3x3.2	4.2x3.0x3.7	3.5x1.9x3.1
Left Adrenal Gland				
Length x width x height (cm)	4.2x3.5x4.1	5.2x3.3x4.1	4.1x3.2x4.0	2.9x2.3x3.3
Hydrocortisone dose (mg/m2/day)	25-75	45	40	4
Day of Life	2	6	9	36

Figure 1: Adrenal gland hematoma size and hydrocortisone dose progression throughout patient's hospital stay. Ultrasound images are in the transverse view of the adrenal gland.

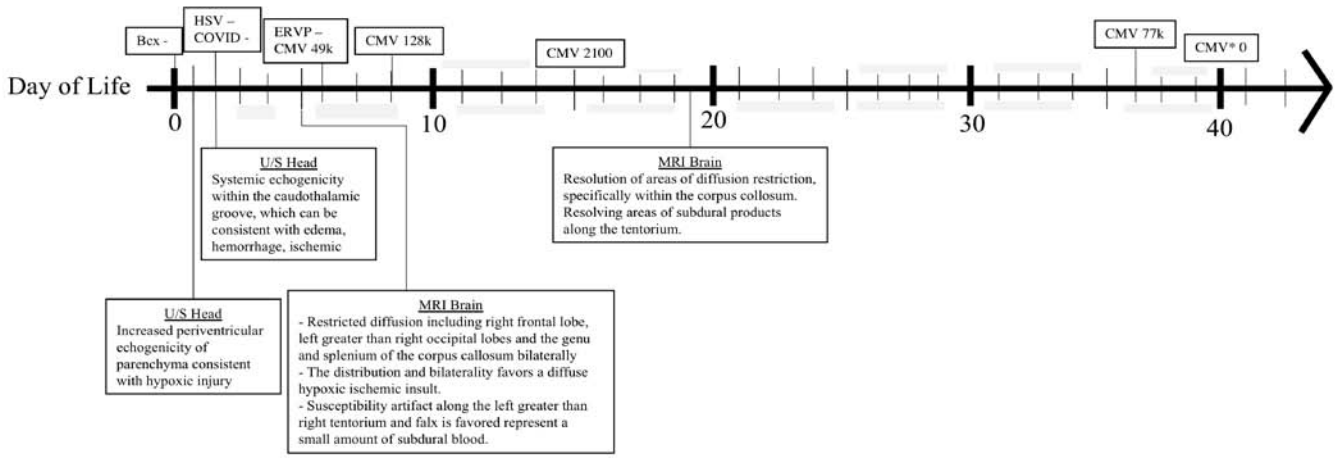


Figure 2: Infectious disease and neurological studies throughout patient's stay in the neonatal intensive care unit.
Abbreviations: Herpes Simplex Virus (HSV): Skin/Eyes/Mouth Swab and Serum PCR; COVID: Coronavirus SARS-CoV-2 Rapid Test; Extended Respiratory Viral Panel (ERVP): Includes Influenza A, Influenza B, Respiratory Syncytial Virus RNA, Parainfluenza 1, Parainfluenza 2, Parainfluenza 3, Parainfluenza 4, Human Metapneumovirus, Adenovirus, Human Rhinovirus/Enterovirus; Cytomegalovirus (CMV) qPCR (Urine); Bcx: Blood Culture; U/S: Ultrasound; MRI: Magnetic Resonance Imaging

hydrocortisone. Newborn screens were not suggestive of congenital adrenal hyperplasia.

He was discharged home on DOL 61 on room air with a gastrostomy tube, valganciclovir for congenital CMV (6-month course), ferrous sulfate and as needed stress dose hydrocortisone. He is followed by Pediatric Endocrinology, Pediatric Infectious Disease and the Special Infant Care Clinic. At 4 months he was taking all feeds by mouth and meeting social, motor and language milestones appropriate for his age, although he continues to have hypertonicity. ACTH and cortisol were rechecked at his 4-month visit and his ACTH was elevated to 124 pg/mL in the afternoon, though cortisol and BMP were normal (Table 2). Endocrinology restarted physiologic hydrocortisone due to this persistent elevation in ACTH, which suggested primary adrenal insufficiency. His sodium and potassium remained within normal limits with no evidence of mineralocorticoid deficiency (renin activity level 5.8 ng/mL/hr).

Discussion

Unilateral adrenal hemorrhage occurs in approximately 1.7 to 2.1 per 1000 births, with bilateral hemorrhages even less common [1-4]. The most common risk factors for adrenal hemorrhage are fetal acidemia (31%) and macrosomia (22%); other risk factors include: vaginal delivery, traumatic delivery, sepsis, and coagulation disorders [1-6]. Infants may present with anemia, persistent jaundice, abdominal mass, or painful swelling/bluish discoloration of the scrotum [1-3,5]. In acute stress, blood shifts toward the heart, brain, and adrenal glands. Venous sinusoids of the adrenal cortex can become distended and congested. Additionally, hypoxia may damage

the endothelial lining of the adrenal gland [3,6]. This combination puts the adrenal cortex at risk for hemorrhage. In 70% of cases, adrenal hemorrhage only affects the right adrenal gland [3]. The right adrenal gland is primarily impacted and larger because of its anatomic compression between the liver and ribs and hemodynamic variability from pressure changes within the inferior vena cava [3]. Adrenal insufficiency is uncommon with unilateral hemorrhage, due to compensation from the unaffected adrenal gland.

Our patient had multiple risk factors for adrenal hemorrhage, including instrumented vaginal delivery, fetal acidemia (cord pH 6.85), sepsis and coagulopathy. It is unclear if the adrenal hemorrhages started at birth or DOL 1, but he had significant bleeding into the adrenal glands leading to hypotension and anemia. He presented with findings concerning for adrenal insufficiency (hypotension, hyponatremia and hyperkalemia) that resolved with high dose hydrocortisone [2,3,6]. ACTH and cortisol were not measured prior to the initiation of hydrocortisone. Interestingly, our case presented with bilateral adrenal hemorrhages with the left adrenal hematoma larger than the right.

Early identification of adrenal hemorrhage is critical and monitoring with ultrasound is the mainstay of management [1-6]. Serial ultrasounds are the most effective modality for monitoring adrenal hematomas and avoiding unnecessary surgical interventions. Current guidelines endorse serial ultrasounds every one week to three months until resolution [3]. Adrenal hematomas are solid, enlarged, echogenic and have no flow on doppler [4]. They first appear with mixed echogenicity and a central hypoechoic region, then gradually transition to cystic forms, which spontaneously regress [4]. Another cause of adrenal mass in neonates is neuroblastoma. Neuroblastomas typically present as highly vascularized structures with high velocity doppler shifts, which rarely regress and are rarely bilateral (<10%) and do not normally present with laboratory evidence of adrenal insufficiency [4]. They also present with lymphadenopathy and infiltration of surrounding structures with small punctate echogenic areas4. Other causes of adrenal masses to consider in the neonate include: Wilm's tumor, hydronephrosis, cystic renal disease and vascular thrombus. If ultrasound findings are non-diagnostic, further work up, including collection of urine catecholamines and/or MRI abdomen must be considered [4].

Due to the adrenal glands' high regenerative capacity, prolonged adrenal insufficiency after adrenal hemorrhages is relatively rare [5,7]. Adrenal insufficiency is rare because most adrenal hemorrhages are unilateral and are subcapsular, which spare the glucocorticoid-producing cortex6. High doses of hydrocortisone are recommended in cases of bilateral hemorrhages and when vital signs are not adequately responding to blood products and intravenous fluids [2]. Most cases of adrenal insufficiency after acute hemorrhages resolve and patients only require stress dose steroids as needed for illness. Interestingly, our patient restarted hydrocortisone at 4 months of age, suggesting persistent adrenal insufficiency.

Conclusion

In conclusion, adrenal hemorrhage should be considered in newborns with sepsis or hypoxic ischemic injury and unresolving/unexplained anemia, hypotension and/or electrolyte abnormalities. Other underlying causes for prolonged adrenal insufficiency must be considered, including infection and congenital adrenal hyperplasia. HIE and acidosis significantly increase the risk for adrenal hemorrhage in the highly vascularized adrenal glands during the neonatal period. Serial ultrasounds are the preferred imaging modality for diagnosis and monitoring of adrenal hemorrhages to avoid unnecessary intervention. Close follow up with endocrinology is recommended for treatment and monitoring.

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