



Case Report

Neonatal Renovascular Hypertension in a Pediatric Patient due to Occult Renal Artery Thrombosis: A Case Report

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Abstract

Neonatal hypertension has an incidence of 1-2% in the Neonatal Intensive Care Unit (NICU) with renovascular disease and renal parenchymal disease being the most common etiology. Renovascular Hypertension (RVH) accounts for 5-25% of childhood hypertension and is the most common cause of surgically correctable hypertension. Here we report a case of neonatal RVH presenting at 3 weeks of life. A 3-week-old infant with a history of Hypoxic-Ischemic Encephalopathy (HIE) and seizures presented to the emergency department with systolic blood pressure in the 160s. On admission CT Angiography (CTA) was significant for right renal artery occlusion with absence of right kidney perfusion, narrowing of the distal left renal artery with maintained left kidney perfusion, celiac artery narrowing, tortuosity of the great vessels as they arise from the aortic arch, and tortuosity of the femoral vessels within the groin. DMSA scan revealed a relative uptake of 79% in the left kidney and 21% in the right kidney with generalized decreased activity throughout the right kidney. Laboratory workup was significant for elevated plasma renin (258.3 ng/mL/hr, nl 2-37 ng/mL/hr) and aldosterone (137 ng/dL, nl < 23.2 ng/dL). Hypertension was managed with a Nicardipine drip initially, which was transitioned to oral Amlodipine, with Amlodipine continued for 4 months after admission. The patient was treated with unfractionated heparin drip which was transitioned to enoxaparin. The kidney function has been within normal range throughout. 5 months after admission, both plasma renin (4.4 ng/mL/hr) and aldosterone (35.8 ng/dL) have returned to normal. 8 months after admission, repeat CTA revealed normal contrast enhancement suggesting perfusion to both kidneys. Repeat MAG3 scan demonstrated symmetric perfusion of both kidneys (54% left kidney, 46% right kidney), with improved uptake and excretion of the radionuclide in the right kidney compared to the prior study. This case of neonatal hypertension due to renal artery thrombosis, a common etiology, was complicated by extensive radiographic changes and severe presentation. Significantly, after treatment with enoxaparin there was complete reversal of radiographic findings, the patient's renal perfusion improved, and antihypertensive therapy was no longer required.

Keywords: COVID-19; Lovenox; Neonatal hypertension; Renovascular hypertension; SARS-CoV-2

Introduction

Renovascular Hypertension (RVH) is the most common cause of neonatal hypertension seen in Neonatal Intensive Units (NICU) [1]. It accounts for 5-25% of childhood hypertension [2] and is the most common cause of surgically correctable hypertension [3]. Neonatal hypertension can be difficult to diagnose as the

range of normal blood pressures rapidly changes in the neonatal period, with pressures increasing by 20% over the first month in full-term neonates and 50% over the first month of life in neonates born before 28 weeks [4]. The incidence of neonatal hypertension in the NICU is about 1-2%, and neonates with hypertension commonly have associated risk factors. Maternal risk factors include hypertension, diabetes mellitus, and antenatal steroid exposure. Neonatal risk factors for hypertension are most commonly due to renal vascular abnormalities. The second most common cause of neonatal HTN is congenital renal abnormalities,

and bronchopulmonary dysplasia associated HTN being the third [5]. The most common renovascular abnormality associated with HTN in neonates is thrombus formation associated with Umbilical Artery Catheter (UAC) placement [5,6].

RVH occurs when decreased blood flow to the kidneys, unilaterally or bilaterally, results in activation of the renin-angiotensin-aldosterone system [7]. There are many known etiologies of renovascular hypertension which can be divided into intrinsic and extrinsic causes. In North America and Europe, the most common intrinsic cause in children is Fibromuscular Dysplasia (FMD) [7], an arterial disease manifesting with characteristic alternating areas of stenosis and dilation on CTA [8]. However, in Asia and South America, Takayasu Arteritis is the most common intrinsic cause [9]. Other intrinsic etiologies include inflammatory conditions like Kawasaki disease and Polyarteritis Nodosa; syndromic causes like Neurofibromatosis Type 1, Williams Syndrome, Alagille Syndrome, Turner Syndrome, Marfan Syndrome, and Tuberous Sclerosis; intraluminal causes like umbilical catheter-related thrombosis and hypercoagulable states; and surgical causes like transplant related renal artery stenosis [10]. Extrinsic causes include conditions that lead to compromised renal blood flow through external compression, such as Wilms Tumor, Neuroblastoma, Pheochromocytoma, Lymphoma, hematomas, and retroperitoneal fibrosis.

Umbilical artery catheter-related thrombosis occurs at a rate of approximately 25% [11], with an incidence of symptomatic thrombosis ranging from 1-3% [12]. The etiology of thrombosis is thought to be due to damage to the vascular endothelium during catheter placement, small caliber of the vessel in relation to the catheter, composition of materials infused through the catheter, and altered blood flow leading to venous stasis [5]. In a prospective cohort study of 61 neonates undergoing umbilical artery catheterization, 19 developed umbilical artery catheter-related thrombosis, but events were asymptomatic and all resolved spontaneously [13]. Neonates in this study did not require treatment, but pharmacologic intervention is recommended for any symptomatic thrombosis or if there is evidence of renal failure [14]. Factors associated with an increased risk of thrombosis in the setting of UAC include increased duration of catheter use, low position of the catheter between vertebrae L3-L4, and catheter use in the setting of hypothermia, as utilized in management of Hypoxic-Ischemic Encephalopathy (HIE) [12].

Case Presentation

A 3 week old full-term female with a past medical history of HIE, patent ductus arteriosus, patent foramen ovale, pulmonary Hypertension, and seizures presented to the emergency department with tachypnea, tachycardia, mottling, and erythema and swelling of her hands and feet. The patient's Mother was a 32 year old G1P0 with negative prenatal infectious screening labs. The pregnancy was complicated by thrombocytopenia and COVID infection in the second trimester. The patient was delivered by urgent cesarean

section at 38 weeks 5 days gestation due to non-reassuring fetal heart tracing. The mother received steroids just prior to the delivery given her history of thrombocytopenia, and the patient's platelets were normal at birth. APGARs at delivery were 2 at 1 minute, 3 at 5 minutes, and 5 at 10 minutes. Initial neurologic exam demonstrated no spontaneous activity, extension of all four limbs, absent suck and moro reflexes, nonreactive pupils, and periodic breathing, all of which were concerning for HIE. She was subsequently intubated and transferred from an outside hospital to a level III NICU. She met criteria for hypothermia protocol for management HIE and passive cooling was initiated with core temperature reaching 33.5 °C at 2 hours of life. Umbilical artery and vein catheters were placed. 7 hours after delivery, she was noted to have lip smacking with associated desaturation and electrical seizure noted on EEG. She was started on Keppra and Phenobarbital for seizure management. Echocardiogram the day after delivery demonstrated PFO and PDA. She required 2 days of nitric oxide for management of pulmonary hypertension. She was intubated for 2 days after delivery and extubated to room air without complications. UVC was removed after 2 days, and UAC was removed after 5 days. Brain MRI performed 5 days after delivery demonstrated diffuse restricted diffusion in the subcortical and central white matter of all lobes consistent with a diffuse supratentorial ischemic insult. Throughout the patient's NICU course she remained normotensive. She was discharged from the NICU on 13th day of life on Keppra (80 mg/kg/day, q8h) and Phenobarbital (5 mg/kg/day, q12h).

On post hospital discharge day 7, patient's mother noted change from baseline with decreased feeding, mottling, swelling and erythema of hands and feet and was referred to a local emergency department. In the emergency department, vitals were significant for hypothermia (34.8 °C) and tachycardia (180-220 bpm). Blood pressure ranged 120-90s Systolic and 100-70s Diastolic. Review of systems was positive for fever, tachypnea, mottling, but negative for seizures, URI symptoms, cough, diarrhea, or hematuria. Physical exam revealed diffuse mottling and erythema of the extremities. Initial creatinine prior to fluid resuscitation was 0.7 mg/dL. Given concern for sepsis, cultures of the blood, urine and cerebrospinal fluid were obtained and Ampicillin, Gentamycin and Acyclovir were administered. The patient was transferred for a higher level of care.

On admission, the patient was intubated for concerns of shock and end-organ failure. Labs on admission were significant for elevated procalcitonin, elevated BNP, D-dimer 1.64 mcg/mL (nl 0-0.45 mcg/mL). An arterial line was placed and blood pressures measured through A line were significantly elevated, with systolic pressures up to the 160s (Figure 1). CT Angiography on admission was significant for right renal artery occlusion with absence of right kidney perfusion and kidney atrophy, narrowing of the distal left renal artery with maintained left kidney perfusion, narrowing of the celiac artery, tortuosity of the great vessels as they arise from the aortic arch, and tortuosity of the femoral vessels within

the groin. As a result, the right kidney was under-perfused (Figure 2A, left). A DMSA scan to assess kidney function was completed and revealed a relative uptake of 79% in the left kidney and 21% in the right kidney with generalized decreased activity throughout the right kidney (Figure 2B, left). Echo demonstrated known PFO and a mobile echodensity in the right atrium attached to a stalk, concerning for a thrombus versus vegetation. Bilateral upper and lower extremity arterial and venous Doppler ultrasounds did not have any evidence of additional thrombosis.

Multiple subspecialties were consulted including Hematology, Rheumatology, Nephrology, Neurology, Vascular Surgery and Genetics. Nephrology was consulted for severe renovascular hypertension. Labs on admission revealed stable creatinine (0.55 - 0.57 mg/dL) and normal electrolytes. For management of hypertension, the patient was started on a Nicardipine drip to target systolic blood pressures to 140s for the first 8 hours of treatment, then to gradually reduce systolic pressures to a goal of less than 110 over the next 24 to 36 hours (Figure 1). Additional evaluations were significant for elevated plasma renin 258.3 ng/mL/hr (nl 2-37 ng/mL/hr) and aldosterone 137 ng/dL (nl < 23.2 ng/dL) (Table 1). Hematology was consulted for concomitant arterial and venous thromboses and unfractionated heparin drip was started on the day of admission with goal of anti-Xa levels of 0.3-0.7 IU/mL.

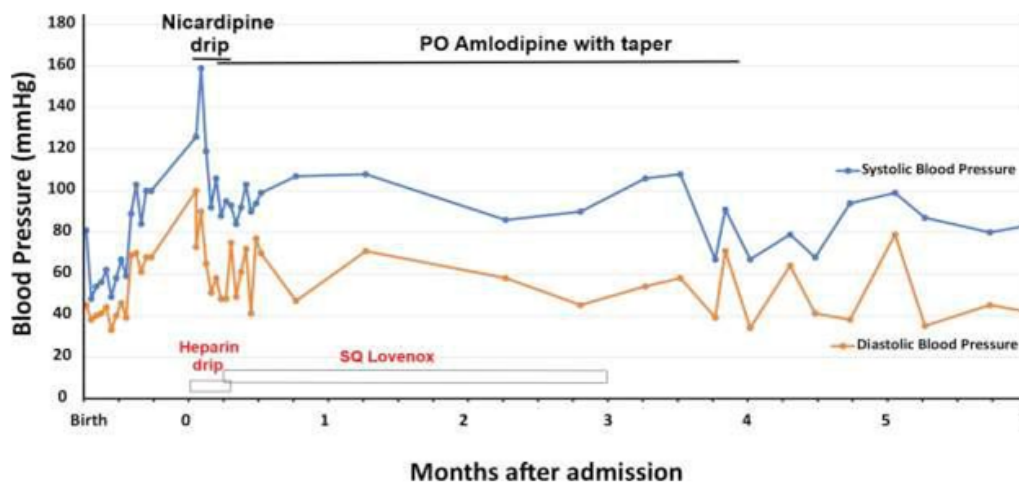


Figure 1: Changes in blood pressure from birth to 6 months of age. As indicated, patient started on Nicardipine drip and Heparin drip on admission (time 0). Nicardipine drip was continued for 6 days then discontinued. Patient remained on oral amlodipine with taper for 4 months. Blood pressure has been within normal range in the absence of antihypertensive medication. As for systemic anticoagulation, Heparin drip was continued for 3 days then discontinued. Patient remained on Sq Lovenox for 3 months. On her 6-month follow up, patient remains normotensive.

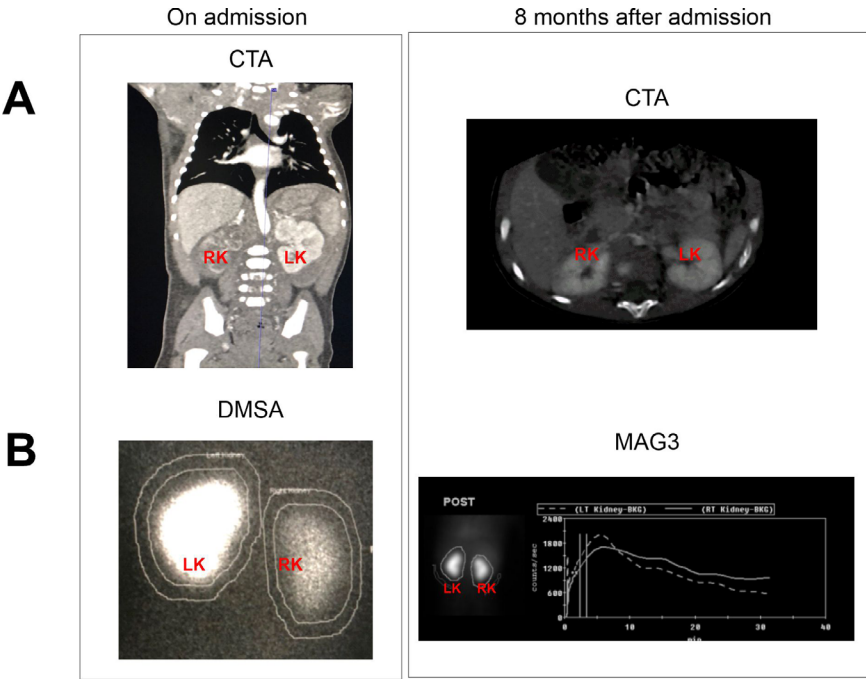


Figure 2: Image studies on admission and 8 months after admission. As indicated: CTA (A, left) on admission demonstrated absence of perfusion in the right kidney (RK) compared to the left kidney (LK) as a result of right renal artery occlusion. Repeat CTA (A, right) after treatment of anticoagulation and antihypertensives demonstrated normal contrast enhancement seen in both RK and LK. DMSA scan (B, left) on admission demonstrating relative uptake of 79% in the LK and 21% in the RK with generalized decreased activity throughout the RK. MAG-3 scan (B, right) after treatment with anticoagulation and antihypertensives demonstrating symmetric perfusion of the kidneys (54% of LK, 46% of RK), with improved uptake and excretion of the radionucleotide in the RK compared to the prior study.

	On admission	5 months after admission	Reference range
Aldosterone (ng/dL)	137	35.8	21-65
Plasma renin activity (ng/ml/hr)	258.299	4.4	2.4-37

Table 1: Plasma renin and aldosterone levels on admission prior to initiation of anticoagulation and antihypertensive therapy and 5 months after treatment. As indicated, serum plasma renin activity and serum aldosterone level returned to normal after completion of therapy.

The patient was successfully extubated on hospital day 4 and transferred to the floor on hospital day 8. Her hypertension was managed with a Nicardipine drip for a total of 6 days with Amlodipine (0.1 mg/kg/day) starting on hospital day 2. She was transitioned from unfractionated heparin to Lovenox (4.5 mg, q12) on hospital day 3. Renal ultrasound 11 days after admission demonstrated flow in the renal artery and vein bilaterally, with slightly decreased blood flow to the right kidney and decreased right kidney volume (10 mL) compared to the left kidney (18.6 mL). CTA 13 days after admission demonstrated resolution of the right renal artery occlusion with increased right kidney perfusion and patency of the celiac artery and femoral artery without evidence of the previously noted narrowing or tortuosity. The patient’s condition continued to improve, and she was discharged on hospital day 13. Discharge medications included Keppra (0.7 mL, q8), Phenobarbitol (1.6 mL, q12), Lovenox (4.5 mg, q12), and Amlodipine (1 mg/mL, 1.9 mL, qD).

The patient was able to discontinue Lovenox 3 months after admission following resolution of the right atrial thrombus. Amlodipine dose was weaned and discontinued 4 months after admission. In follow up 5 months after admission, renin and aldosterone were within normal limits (Table 1). 8 months after admission, repeat CTA demonstrated normal contrast enhancement of the kidneys bilaterally (Figure 2A, right). Repeat MAG3 demonstrated symmetric perfusion of the kidneys (54% left kidney, 46% right kidney), with improved uptake and excretion of the radionuclide in the right kidney compared to the prior study (Figure 2B, right).

Work up for inherited thrombophilias including Antithrombin III, Protein C, Protein S, Factor VIII activity, Factor IX activity, homocysteine, lipoprotein (a), Factor V Leiden, Prothrombin gene mutation were all unremarkable. Evaluations for autoimmune and inherited vasculitis and collagen vascular disorders were unremarkable including testing for Adenosine deaminase 2 deficiency, amino acid disorders, Antiphospholipid Syndrome (beta-2 glycoprotein, cardiolipin antibodies, and phosphatidylserine antibodies), and vasculitis (ESR, CRP, ANA, ANCA, PR-3, MPO).

Discussion

Neonatal hypertension is difficult to define as it is impacted by a multitude of infant characteristics and blood pressure patterns that change throughout the newborn period. While the underlying etiology is unknown in approximately half of the cases, the most common identified etiologies are renovascular abnormalities, renal parenchyma disease, and chronic lung disease [5]. The most common cause of RVH is thrombotic occlusion of the renal vessels following placement of umbilical catheters. It can also occur in the setting of congenital renal anomalies, acquired renal parenchymal disease [5].

Hypertension due to renovascular disease occurs through activation of the Renin-Angiotensin-Aldosterone System (RAAS). The pathogenesis of RVH occurs in three phases. Phase I is characterized by activation of RAAS. Decreased renal perfusion leads to increased renin secretion and increased levels of angiotensin II, which is responsible for the subsequent elevation in blood pressure [15]. Angiotensin II exerts effects through the Angiotensin receptor type 1 (AT1) and Angiotensin receptor type 2 (AT2). The AT1 receptor mediates Angiotensin's vasoconstrictive effects, aldosterone secretion, ADH secretion, decreased renal perfusion, decreased renin secretion, and increased tubular sodium absorption. The AT2 receptor in effect opposes the actions of the AT1 receptor, stimulating nitric oxide production and leading to vasodilation and renal sodium excretion [16]. During this phase, if perfusion is restored, blood pressure will quickly normalize. Phase II is characterized by salt retention by the inadequately perfused kidney and hypertension. Hypertension is more dependent on volume expansion and less so on Angiotensin II during this phase,

as renal perfusion pressure is maintained through the effects of sodium and water retention and secretion of renin declines. In a patient like ours with a perfused functional contralateral kidney, the response to increased systemic pressure is suppression of renin secretion and pressure natriuresis. As in Phase I, if perfusion is restored the blood pressure will normalize. Phase III is characterized by hypertension that persists independent of the systemic RAAS. Long-term under perfusion may lead to irreversible renal disease that results in the persistence of hypertension even if perfusion is restored [15]. At the time of presentation, our patient was likely in pathogenesis Phase I as her renin level was markedly elevated.

Our patient's renovascular hypertension was of multifactorial etiology. Right renal artery thrombotic occlusion was likely an unrecognized provoked event that occurred during her initial NICU hospitalization and stabilization after birth. She had numerous risk factors for thromboembolism including fetal distress, respiratory failure and intubation, HIE, cooling protocol (which causes numerous derangements of the hemostatic system) and umbilical venous and arterial catheters. Concomitant maternal COVID-19 infection while in utero cannot be excluded as a potential association, but the mildness of mom's illness and the timing from infection to birth makes a potential association less likely.

Renal vascular thrombosis in neonates is a rare entity, with renal vein thrombosis being much more common than renal artery thrombosis. Risk factors for renal vein thrombosis include prematurity, respiratory distress syndrome, asphyxia, inherited thrombophilia, congenital heart disease, and umbilical vein catheterization. Risk factors for renal artery thrombosis include prematurity, low birth weight, sepsis, and, most commonly, umbilical artery catheterization [17]. The risk of thrombosis is further exacerbated by the unique dynamics of hemostasis in the neonatal period that place newborns at increased risk of thromboembolism, and are particularly susceptible to further derangements when hypoxic or septic [18]. The reported incidence of umbilical artery catheter related thrombosis varies based on whether thrombosis is identified by clinical signs or an imaging based surveillance strategy. The incidence of symptomatic renal artery thrombosis is 1-3% and by active ultrasound surveillance is 14-35% [17,19]. While the rates of symptomatic thrombosis associated with UACs are low, umbilical catheterization associated thrombosis is more common in neonates with either an UAC or both a UAC and UVC when compared to neonates who only had a UVC. In a prospective observational study by Boo et al, the risk of thrombosis was found to be related to the duration of UAC placement, with an adjusted odds ratio of developing thrombosis of 1.2 for every additional day that the UAC was in situ. This study determined the risk of thrombus development in an infant with UAC in situ to be 16.3% at 1 day, 31.8% at 7 days, and 56.5% at 14 days [20]. This was also demonstrated in a prospective cohort study by Z Ergaz et al, who found that the duration of UAC in situ

was the only risk factor that significantly increased incidence of thrombosis [19]. Our patient had a UAC in situ for 5 days.

Renal vascular thrombosis can have a wide variety of clinical presentation ranging from asymptomatic to life-threatening depending on thrombus size and venous versus arterial involvement. Renal vein thrombosis has a characteristic triad of a palpable flank mass, thrombocytopenia, and macroscopic hematuria but these features are only present in 22% of neonates on presentation [17]. Renal artery thrombosis is typically diagnosed based on a high index of suspicion in the setting of recent umbilical catheterization as the clinical presentation can be subtle [17]. In a cohort study by Z Ergaz et al, none of the infants with umbilical catheter associated thrombosis displayed persistent hypertension or signs of vascular compromise. However other cases in the literature have described dramatic presentations including cardiogenic shock, congestive heart failure and nephrotic syndrome [5,21,22,23]. The presentation is often delayed from UAC placement, with thrombosed identified 2-3 weeks after line placement, including after hospital discharge as in our case. Often, hypertension in neonates is accompanied by nonspecific signs such as irritability, lethargy, poor feeding, unexplained tachypnea or seizures and these symptoms may only be appreciated in retrospect [17]. Our patient presented in cardiogenic shock with tachypnea, mottling, swelling and erythema of hands and feet. Blood pressure measured through an arterial line demonstrated significantly elevated blood pressures, with systolic pressures in the 160s. Additionally, our patient had extensive radiographic changes with narrowing and tortuosity at multiple locations that initially raised concern for a diffuse vasculopathy like vasculitis or a collagen vascular disease-with time and treatment these disorders were ruled out.

Treatment in this case required a dual approach - antihypertensive medications to reduce severely elevated blood pressures and systemic anticoagulation to prevent propagation of thrombosis. Criteria for the use of pharmacologic therapy in the management of neonatal hypertension is not well defined outside of the setting of severe hypertension with manifestations of end-organ damage [4]. For moderately elevated blood pressure, Isradipine provides a more rapid onset of action than other calcium channel blockers and can be administered in small doses, making it especially useful in neonates [24]. Controversy surrounds the use of other antihypertensives in the neonatal population, especially when coexisting diseases often found in this population are present. ACE inhibitors are typically avoided in premature infants due to concerns of their impact on nephrogenesis [25]. In the setting of chronic lung disease, beta-blockers should be avoided. Treatment of acute severe hypertension requires the use of intravenous antihypertensives, often through continuous infusion so as to allow for easier titration. In this setting, Nicardipine is the drug of choice [4].

In the treatment of RVH, a multifaceted approach is often required. Medical management with antihypertensives alone does

not typically result in blood pressure normalization. Angioplasty can be used with the benefits of improving renal perfusion while decreasing the number of antihypertensives required for blood pressure management. Angioplasty is preferred over stenting in children as long-term studies provide evidence that the frequency of restenosis in children is greater after stenting compared to angioplasty [2]. However, when RVH is secondary to renal vascular thrombosis, treatment is uniquely challenging due to the variability of individual neonates' responses to pharmacologic management. Treatment options include anticoagulation therapy with unfractionated heparin or Low Molecular Weight Heparin (LMWH) and catheter directed or systemic thrombolysis in certain cases [17]. The American College of Chest Physicians clinical practice guidelines recommend that unfractionated heparin be titrated to an anti-Xa activity range of 0.35 to 0.7 units/mL and LMWH be titrated to an anti-Xa activity range of 0.5 to 1 units/mL [12]. Our patient remarkably had complete restoration of renal flow and perfusion, recovery of renal function, and reversal of radiographic findings following treatment with anticoagulation therapy and was subsequently able to discontinue antihypertensive therapy.

Conclusion

We present a rare, complicated case of neonatal renovascular hypertension due to renal artery thrombosis with extensive radiographic changes that resolved following administration of anticoagulant therapy. The cause of renal artery thrombosis in our patient is likely multifactorial, with risk factors including umbilical artery and vein catheterization, fetal distress, respiratory failure requiring intubation, and cooling protocol for HIE. After medical management with 3 months of Lovenox and 4 months of Amlodipine, the patient is now 9 months out from hospitalization and remains normotensive with normal renal vasculature and normal renal function.

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