

Neonatal arterial thrombosis associated with maternal paraganglioma: a case report

Trombose arterial neonatal associada a paraganglioma materno: relato de caso

Trombosis arterial neonatal asociada a paraganglioma materno: reporte de un caso

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ABSTRACT

Introduction: Neonatal arterial thrombosis is a rare but life-threatening condition, most often associated with umbilical catheterization, congenital thrombophilia, or perinatal complications. Maternal pheochromocytomas and paragangliomas (PPGLs) are rare during pregnancy, and their impact on neonatal hemostasis remains poorly understood. **Objective:** To describe a case of neonatal arterial thrombosis associated with maternal PPGL and its implications for neonatal care. **Case description:** We report a case of neonatal arterial thrombosis associated with maternal paraganglioma. A female neonate was born at 37 weeks via cesarean section to a 29-year-old woman with a 9.4 cm retroperitoneal paraganglioma. The infant had normal Apgar scores (9/9) and birth weight of 2,922g. On admission to the neonatal intensive care unit, she exhibited pallor, cyanosis, and decreased temperature of the left lower limb. Doppler ultrasound revealed a thrombus extending from the common femoral artery to the superficial femoral artery origin. Thrombophilia screening was negative. The mother experienced severe postpartum hypertension requiring nitroprusside, suggesting massive catecholamine release during delivery. The infant was treated with intravenous heparin followed by subcutaneous enoxaparin. Follow-up Doppler ultrasound at 20 days showed complete thrombus resolution and the infant was discharged without complications. **Discussion:** Excessive maternal catecholamine release during delivery may overwhelm placental metabolic capacity, leading to fetal exposure and subsequent arterial thrombosis. Pediatric healthcare providers should be aware of this potential risk, as early recognition and prompt anticoagulation therapy can lead to favorable outcomes.

Keywords: Thrombosis; Newborn; Paraganglioma; Catecholamines; Pregnancy; Anticoagulation.

RESUMO

Introdução: A trombose arterial neonatal é uma condição rara, porém potencialmente fatal, frequentemente associada à cateterização umbilical, trombofilia congênita ou complicações perinatais. Feocromocitomas e paragangliomas maternos são raros durante a gravidez e seu impacto na hemostasia neonatal permanece pouco compreendido. **Objetivo:** Descrever um caso de trombose arterial neonatal associada a paraganglioma materno e suas implicações para o cuidado neonatal. **Descrição do caso:** Recém-nascida do sexo feminino, nascida com 37 semanas de gestação por cesariana, filha de uma mulher de 29 anos com um paraganglioma retroperitoneal de 9,4 cm. A criança apresentou escores de Apgar normais (9/9) e peso ao nascer adequado (2.922 g). Na admissão à unidade de terapia intensiva neonatal, apresentou palidez, cianose e hipotermia no membro inferior esquerdo. O ultrassom Doppler revelou um trombo estendendo-se da artéria femoral comum até a origem da artéria femoral superficial. O rastreio de trombofilia foi negativo. A mãe apresentou hipertensão pós-parto grave, necessitando de nitroprussiato, o que sugere uma liberação maciça de catecolaminas durante a cirurgia. A recém-nascida foi tratada com heparina intravenosa, seguida de enoxaparina subcutânea, com resolução completa do trombo após 20 dias e alta sem complicações. **Discussão:** A liberação excessiva de catecolaminas maternas durante o parto pode sobrecarregar a capacidade metabólica da placenta, levando à exposição fetal e subsequente trombose arterial. Os profissionais de saúde pediátricos devem estar cientes desse risco potencial, pois o reconhecimento precoce e a terapia anticoagulante imediata podem levar a desfechos favoráveis.

Palavras-Chave: Trombose; Recém-nascido; Paraganglioma; Catecolaminas; Gravidez; Anticoagulação.

RESUMEN

Introducción La trombosis arterial neonatal es una afección rara pero potencialmente mortal, frecuentemente asociada con la cateterización umbilical, trombofilia congénita o complicaciones perinatales. Los feocromocitomas y paragangliomas maternos son raros durante el embarazo, y su impacto en la hemostasia neonatal aún no se comprende completamente. **Objetivo:** Describir un caso de trombosis arterial neonatal asociada con un paraganglioma materno y sus implicaciones para la atención neonatal. **Descripción del caso:** Una recién nacida, nacida a las 37 semanas de gestación por cesárea, era hija de una mujer de 29 años con un paraganglioma retroperitoneal de 9,4 cm. La niña presentó puntuaciones de Apgar normales (9/9) y un peso al nacer adecuado (2922 g). Al ingresar a la unidad de cuidados intensivos neonatales, presentó palidez, cianosis e hipotermia en la extremidad inferior izquierda. La ecografía Doppler reveló un trombo que se extendía desde la arteria femoral común hasta el origen de la arteria femoral superficial. El cribado de trombofilia fue negativo. La madre presentó hipertensión posparto grave, que requirió nitroprusiato, lo que sugiere una liberación masiva de catecolaminas durante la cirugía. El recién nacido fue tratado con heparina intravenosa, seguida de enoxaparina subcutánea, con resolución completa del trombo a los 20 días y alta sin complicaciones. **Discusión:** La liberación excesiva de catecolaminas maternas durante el parto puede sobrepasar la capacidad metabólica de la placenta, lo que conlleva la exposición fetal y la consiguiente trombosis arterial. Los profesionales de la salud pediátrica deben estar al tanto de este riesgo potencial, ya que el reconocimiento precoz y la terapia anticoagulante inmediata pueden conducir a resultados favorables.

Palabras Clave: Trombosis; Recién nacido; Paraganglioma; Catecolaminas; Embarazo; Anticoagulación.

INTRODUCTION

Neonatal thrombotic events are rare but potentially serious complications that can result in significant morbidity when not recognized and treated early. The incidence of neonatal thrombosis ranges from 0.7 to 0.14 per 10,000 live births,¹ with arterial thrombosis being less frequent than venous thrombosis.^{2,3}

Risk factors for neonatal thrombosis include the presence of venous or arterial catheters, prematurity, maternal diabetes and hypertension, perinatal asphyxia, congenital heart disease, and other conditions affecting fetal circulation.^{1,4} However, episodes of arterial thrombosis can also occur in the absence of these traditional triggers, suggesting the involvement of additional perinatal mechanisms possibly associated with endothelial dysfunction and the particularities of the neonatal hemostatic system.⁵

In addition to the maternal conditions mentioned, some others can impact fetal circulation. Although they are rare tumors, pheochromocytomas and paragangliomas sometimes occur in the obstetric population, posing challenges in the management of the maternal-fetal dyad. These catecholamine-secreting neuroendocrine tumors have an estimated incidence of between 1 in 15,000 and 54,000 pregnancies and may have significant implications for neonatal health and well-being.^{6,7} Although maternal catecholamines typically do not cross the placental barrier, extreme elevations -during paroxysmal episodes or at delivery - can exceed placental metabolic capacity. Under these circumstances, fetal exposure to high concentrations of these vasoactive substances can result in growth restriction, premature birth, and, in rare cases, cardiovascular complications.^{8,9}

This report describes a case of femoral artery thrombosis in a newborn girl whose mother had an uncontrolled retroperitoneal paraganglioma, discussing possible pathophysiological mechanisms and implications for neonatal management.

The case report was approved by the

Research Ethics Committee on 08/11/2024 (CAAE 83447324.0.0000.5243), and the Informed Consent Form was obtained from the patient and legal guardian of the newborn.

CASE REPORT

A female newborn (NB), born at 37 weeks of gestation via elective cesarean section, was the daughter of a 29-year-old woman with a prior diagnosis of left retroperitoneal paraganglioma. At birth, she had an Apgar score of 9/9 and weighed 2,922 grams, appropriate for her gestational age. She was admitted to the neonatal intensive care unit for observation due to her mother's condition.

The mother had been diagnosed with a left retroperitoneal paraganglioma measuring 9.4 x 5.9 x 9.5 cm, confirmed by elevated urinary catecholamine levels (dopamine: 1,192 µg/24h, reference value: < 500 µg/24h; metanephrines: 6,726 µg/24h, reference value < 1,000 µg/24h; normetanephrines: 5,741 µg/24h, reference value < 390 µg/24h). During the preoperative assessment for surgical removal of the tumor, pregnancy was diagnosed, and considering this high-risk prenatal context, surgery was postponed.

During pregnancy, the patient presented with gestational diabetes mellitus, in addition to episodes of paroxysms with sweating, tremors, and palpitations. Treatment with NPH insulin and doxazosin was initiated to control blood glucose and blood pressure, respectively. Doxazosin was titrated to a dose of 3 mg/day, at which point the patient began to present with postural hypotension. The pregnancy progressed to 37 weeks, when an elective cesarean section was performed. In the postoperative period, she developed severe hypertension, requiring sodium nitroprusside, probably due to massive release of catecholamines by the tumor during the surgical procedure.

Upon admission to the neonatal intensive care unit, the newborn presented with pallor, cyanosis, and decreased temperature in

the lower left limb. Physical examination revealed an absence of peripheral pulses in the affected limb, with a clear demarcation between the ischemic and well-perfused areas, raising immediate suspicion of vascular compromise.

Doppler ultrasound of the lower limbs showed a thrombus extending from the common femoral artery to the origin of the superficial femoral artery. The contralateral limb showed normal vascular flow. Additional images, including computed tomography angiography of the carotid, vertebral, and cranial arteries, showed no abnormalities, ruling out systemic thrombotic disease. In addition, an investigation for thrombophilia was carried out, including screening for antiphospholipid syndrome, antithrombin III deficiency, and protein C and S deficiency. All results were negative, suggesting that the thrombotic event was not due to a hereditary or acquired thrombophilic condition.

After the diagnosis, anticoagulation with intravenous unfractionated heparin was initiated for five days, followed by subcutaneous enoxaparin at a dose of 1.7 mg/kg twice daily for 23 days. During hospitalization, the newborn presented with mild and transient physiological jaundice, without associated hypoglycemia or other complications. Throughout the treatment, she was regularly monitored for signs of hemorrhagic complications and therapeutic response.

A follow-up Doppler ultrasound performed 20 days after the initial diagnosis confirmed complete resolution of the thrombosis, with restoration of arterial flow, perfusion, color, temperature, and pulses in the affected limb. Anticoagulation was discontinued, and the child was discharged from the hospital in stable condition with a normal neurological examination. Long-term follow-up plans included consultations with pediatric cardiology and vascular surgery to monitor possible late repercussions of the thrombotic event.

DISCUSSION

To our knowledge, this is the first case report of arterial thrombosis in a newborn whose mother had paraganglioma. Although this is a complication described in adult patients with pheochromocytoma and/or paraganglioma, due to chronic excess of catecholamines, which results in endothelial dysfunction, platelet activation and altered coagulation,^{10,11} the occurrence of this phenomenon in the neonatal period is still poorly understood. Neonatal arterial thrombosis in this context is possibly due to the interaction of multiple pathophysiological mechanisms.

First, it is worth highlighting the unique hemostatic system of neonates, which differs from the adult system. Newborns have physiologically reduced levels of most coagulation factors, especially those dependent on vitamin K (II, VII, IX and X), as well as natural anticoagulants, such as protein C and S, antithrombin and heparin cofactor II. These changes are counterbalanced by higher hematocrit and von Willebrand factor levels, as well as larger red blood cells.^{1,5}

However, this balance has limited adaptive capacity. Once the coagulation cascade is activated, even small amounts of tissue factor can generate thrombin more rapidly in neonatal plasma. This occurs due to reduced concentrations of tissue factor pathway inhibitor and antithrombin.¹ Elevated von Willebrand factor, particularly in ultra-high molecular weight multimers, promotes platelet adhesion to damaged endothelium under high shear stress conditions present in constricted arteries. Furthermore, the pro-inflammatory environment associated with endothelial injury can further activate platelets through pathways that differ from traditional agonist stimulation,⁵ predisposing the neonatal circulation to thrombus formation.

These mechanisms can be interpreted within Virchow's triad, in which catecholamine-induced vasoconstriction, associated with endothelial injury and altered blood flow, facilitates thrombus formation in a

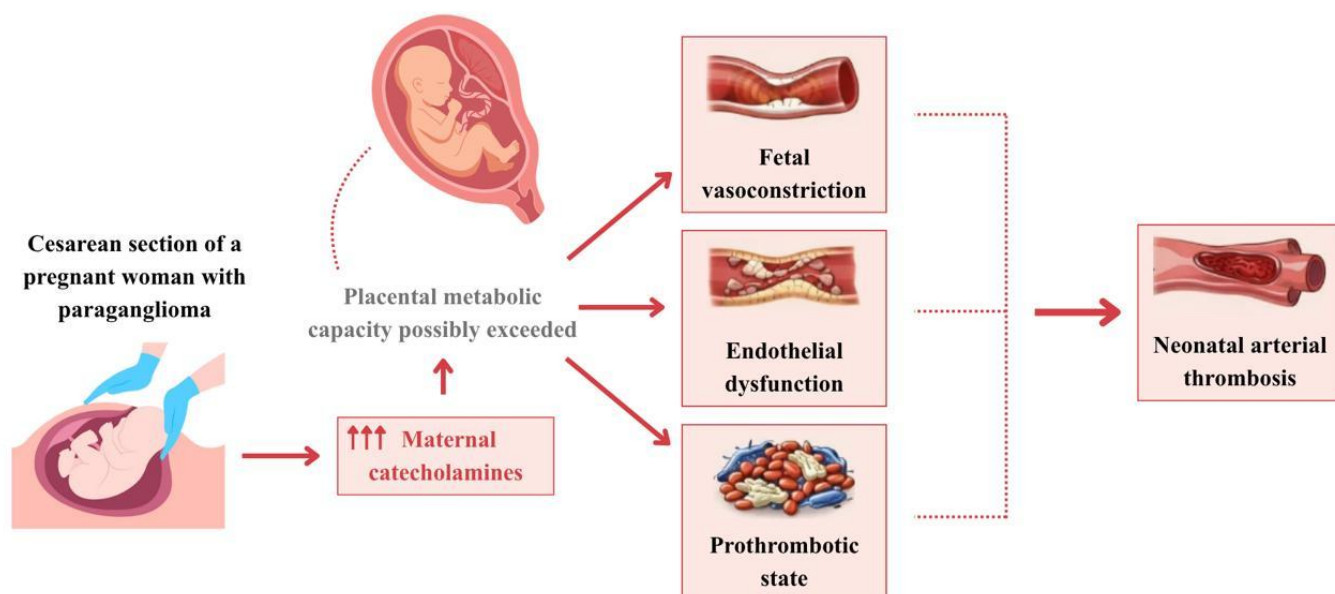
physiologically vulnerable neonatal coagulation system.¹²

In addition, the maternal condition should also be considered as a possible contributing factor to arterial thrombosis in this child. Under normal circumstances, maternal catecholamines rarely cross the placental barrier due to efficient placental metabolism by catechol-O-methyltransferase and monoamine oxidase.^{13,14} Still, given the absence of other explanations for the newborn's arterial thrombosis and considering the mother's history of paraganglioma, the possibility has been raised that, during labor, the marked release of catecholamines may have exceeded the placental metabolism capacity. This is, however, a speculative hypothesis, not directly described in the literature, although it is a biologically plausible event. It should also be considered that pheochromocytomas and

paragangliomas in pregnancy are rare events, and even more uncommon is their manifestation during labor, which limits the availability of clinical data capable of consistently evaluating this type of mechanism.

Severe maternal hypertension in the postpartum period, which required nitroprusside in this case, suggests a massive release of catecholamines during labor, the peak of which may have exceeded placental metabolic capacity, resulting in fetal exposure to elevated levels of norepinephrine and epinephrine. Prolonged exposure to these vasoactive substances can cause severe vasoconstriction, endothelial dysfunction, and activation of the coagulation cascade, ultimately leading to thrombotic complications.^{6,8}

Figure 1: Hypothetical pathophysiological scheme of neonatal arterial thrombosis associated with maternal paraganglioma



In this sense, this case presents important implications for neonatal care. Newborns of mothers with known or suspected paraganglioma should undergo careful cardiovascular evaluation, including assessment of peripheral perfusion and pulse examination, and the presence of signs suggestive of vascular compromise should raise suspicion of thrombotic complications. In these cases, Doppler ultrasound should be performed early, as early detection and treatment can prevent irreversible tissue damage.

Furthermore, the successful management of neonatal arterial thrombosis in this report is consistent with recent pediatric literature, which shows favorable outcomes with early anticoagulant therapy. The use of unfractionated heparin followed by low molecular weight heparin is a well-established approach in the management of neonatal thrombosis.¹⁵

Despite the suspicion of a causal relationship between excess maternal catecholamines and neonatal arterial thrombosis in this case, definitive proof of causality is limited by the inability to directly measure fetal exposure to catecholamines. The absence of measurements of these substances in the newborn is a relevant limitation, even though their usefulness would probably be reduced due to their short half-life.⁷ Similarly, metanephrines (plasma or urinary) were not measured, which are more indicated because they have greater sensitivity for detecting catecholamine excess, since they more stably reflect its production.^{4,7} Furthermore, although reference values for metanephrines exist, their interpretation in the neonatal period requires caution, due to the physiological variations of this phase and the influence of perinatal stress.

Due to these and other limitations, and because this is a single case report, it is not possible to establish a causal relationship between maternal paraganglioma and neonatal arterial thrombosis, nor can the contribution of unidentified factors be excluded, including possible uninvestigated maternal or neonatal prothrombotic conditions and other perinatal factors that may have influenced the observed outcome.

Future research should focus on understanding the mechanisms of catecholamine transport and metabolism in the placenta in the context of maternal paraganglioma. Long-term follow-up studies are also needed to determine whether children exposed to excess maternal catecholamines in utero have an increased risk of cardiovascular complications in adulthood.

In conclusion, this report describes a case of neonatal arterial thrombosis associated with maternal paraganglioma, a condition not yet documented in the literature. The case reinforces the importance of clinical surveillance of newborns exposed to catecholamine-secreting maternal tumors, as well as the early recognition of signs of vascular compromise. Rapid diagnosis and successful management with anticoagulant therapy resulted in complete resolution of the thrombosis, without sequelae. These findings highlight the need for a multidisciplinary approach, involving neonatologists, pediatric cardiologists, and vascular surgeons, and suggest that fetal exposure to elevated levels of catecholamines may be an additional risk factor for neonatal thrombotic events.

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Scientific Editor:

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Publisher:

Sociedade de Pediatria do Rio de Janeiro – SOPERJ

E-mail de contato: secretaria@soperj.org.br

Financial support:

None.

Availability of research data:

The underlying content of the research text is contained in the article.

Conflict of interests:

None.

Authors' contributions:

GV Bon., TP Felix and VNK Pessôa: data collection and manuscript preparation.

VNK Pessôa and GAB Lima: methodological analysis and critical review of the intellectual content.

DA Bulzico, GAB Lima and GF Taboada: supervision of the study, guidance, and manuscript review.

All authors contributed to the discussion of the results, final revision of the text, and approved the final version of the manuscript.