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Case Report

Generalized arterial calcification of infancy in a neonate with acute kidney injury: A rare case report☆,☆☆

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ABSTRACT

Generalized arterial calcification of infancy (GACI) is a rare condition characterized by diffuse arterial calcification within the internal elastic lamina associated with intimal proliferation leading to stenosis of great and medium-sized vessels, which causes end-organ damage and loss of life during infancy. The clinical presentation of acute renal failure with normal cardiac function is rare. A 7-day-old female neonate was admitted with a clinical impression of late-onset neonatal sepsis, meningitis, and acute kidney injury after developing a high-grade fever, abnormal body movements, and vomiting of the ingested matter associated with decreased urinary output. On laboratory tests, she had abnormal urea and creatinine levels, multiple electrolyte abnormalities, and a negative septic workup. Ultrasonography revealed diffuse arterial calcification that also involved the renal arteries and renal parenchyma bilaterally. She was clinically diagnosed with GACI and initiated on supportive care including renal replacement therapy. However, she died at the age of 42 days. This case highlights that GACI can present as unexplained acute kidney injury associated with generalized arterial calcification. Ultrasound can be optimized to aid in diagnosis in resource-limited settings.

Abbreviations: ABCC6, ATP-binding cassette subfamily C member 6; CT, computed tomography; ENPP1, ecto-nucleotide pyrophosphatase/phosphodiesterase-1; GACI, generalized arterial calcification of infancy; MRI, magnetic resonance imaging; US, ultrasound.

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Introduction

Generalized arterial calcification of infancy (GACI) is a rare autosomal recessive genetic disorder characterized by diffuse calcification of large and medium-sized arteries like the aorta, renal, pulmonary, cerebral, and mesenteric arteries [1,2]. Although cases of prenatal diagnosis have been reported, some patients are diagnosed postmortem at the earliest [3,4]. Most patients die within the first 6 months of life despite intensive therapy due to the rapid progression of arterial stenosis and heart failure [3,5,6]. There are rare reports of spontaneous resolution of the calcifications and cases of successful treatment with bisphosphonates and other experimental drugs [1,2]. Although the clinical presentation of GACI varies widely, a predominant feature of acute kidney injury has rarely been reported in the literature.

Case presentation

A female neonate born to a 25-year-old mother presented to our hospital- Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia- with meningeal symptoms. The antenatal course was uneventful, and no history of maternal medication use, harmful drug use, or exposure to radiation during pregnancy was reported. The mode of delivery was C-section for an indication of fetal distress, giving birth to a 3.2 kg female neonate. At 7 days of life, she developed high-grade fever, abnormal body movement, and vomiting of ingested matter associated with a decrease in urine output. She was admitted with a clinical impression of late-onset neonatal sepsis, meningitis, and acute kidney injury.

A physical examination at the presentation revealed tachycardia. The laboratory investigations showed derangement of renal function tests: the creatinine at admission was 11 mg/dL, the lowest record during the hospital stay was 2.3 mg/dL, reference value (0.3-1.2 mg/dL), and the BUN level ranged from 140 to 163 mg/dL, reference value (3-12 mg/dL). The clinical chemistry study revealed multiple electrolyte derangements, including hyponatremia, hyperkalemia, and hypocalcemia. Complete blood count and urinalysis were normal. Workup for neonatal sepsis and meningitis including blood and cerebrospinal fluid cultures were nonrevealing. We couldn't do genetic testing since it is not available in our setup.

Ultrasound (US) showed extensive calcification of the walls of the abdominal aorta and bilateral common and external iliac arteries. The celiac trunk and hepatic artery extending up to its lobar branches, the superior mesenteric artery, both renal arteries, the inferior mesenteric artery, and the median sacral artery were calcified. In addition, external carotid arteries, the distal extracranial portion of internal carotid arteries, and vertebral arteries were also involved bilaterally. All the above-mentioned arteries had luminal narrowing or stenosis (Fig. 1). The aortic arch and its 3 major branches were spared.

The kidneys were normal in size, with the right and left measuring 4.06 × 1.53 cm and 4.03 × 1.76 cm, respectively. However, there was a surface irregularity and extensive calcification of the kidneys involving the cortex and medulla on the right side and the medulla on the left side (Fig. 2). The rest of the intra-abdominal solid organs and hollow viscera were normal. Computed tomography (CT) scan was not done as the patient was in respiratory distress with deteriorating renal function.

The patient was presumptively diagnosed with GACI on a clinical basis. Although the patient was receiving medical care, such as antibiotics, cardiovascular support, and renal maintenance therapy, she passed away at 42 days of age due to cardiorespiratory failure. Bisphosphonates were not

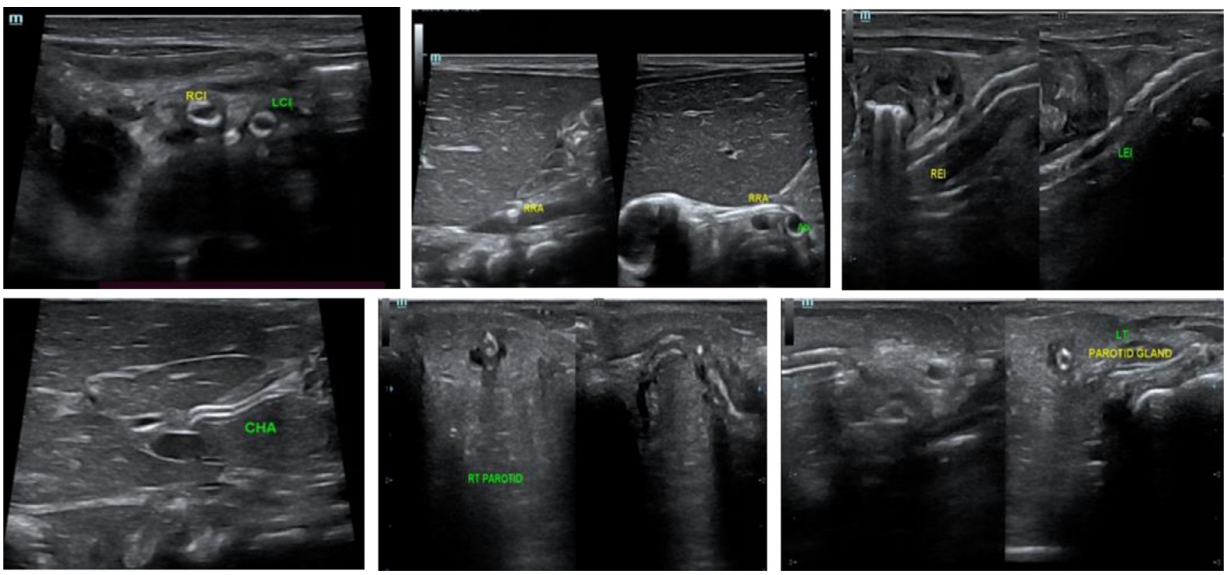

Fig. 1 – Ultrasound images showing calcified arteries (Ao, aorta; RRA, right renal artery; RCI, right common iliac artery; LCI, left common iliac artery; REI, right external iliac artery; LEI, left external iliac artery; and CHA, common hepatic artery).

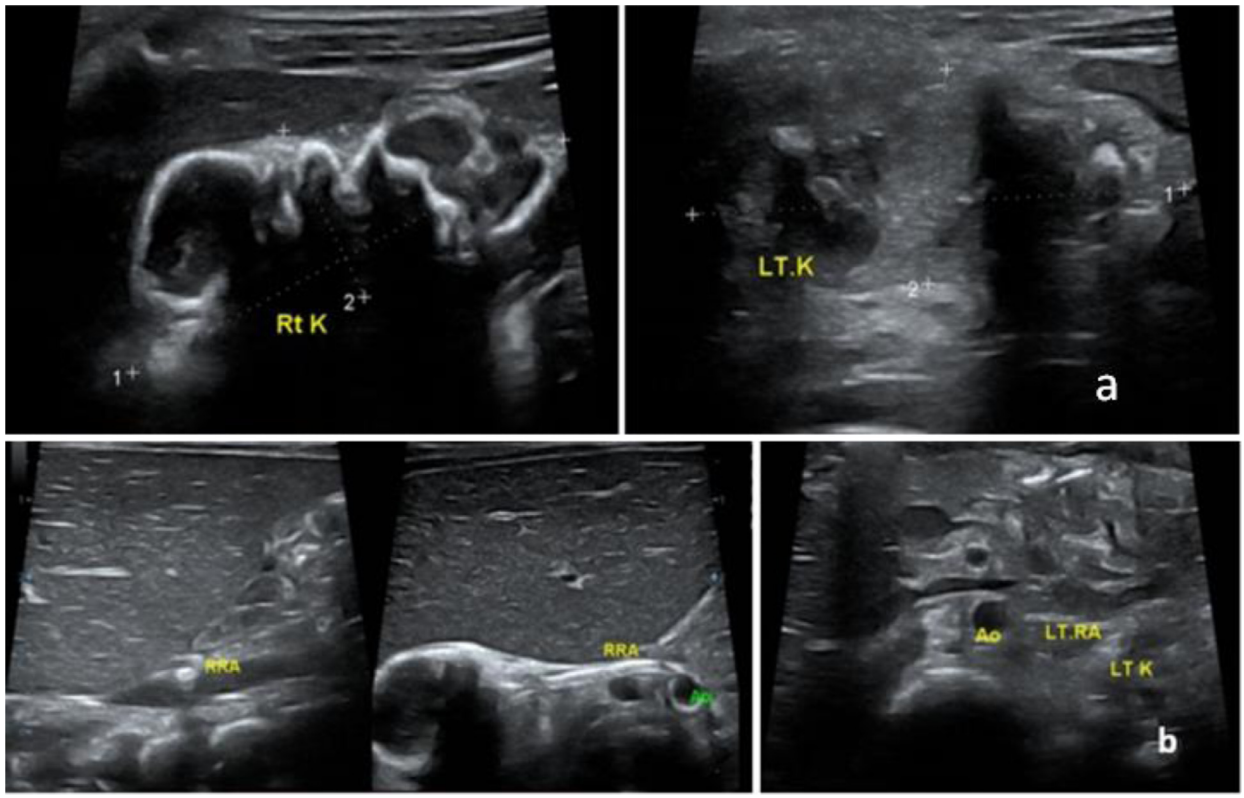

Fig. 2 – Ultrasound images showing the right and the left kidneys with parenchymal calcifications (A) and renal artery wall calcification with stenosis (B).

initiated. An autopsy was suggested, but the parents did not consent.

Discussion

GACI is an inherited autosomal recessive disease with an estimated frequency of 1 in 200,000 people [1]. GACI type 1, which is seen in 75% of cases, is caused by mutations in the ENPP1 gene, and GACI type 2 is caused by mutations in ABCC6 gene, seen in 10% of cases [1,2,6]. Novel variations in these genes are increasinglt being reported in the literature [7]. Mutations in these genes result in reduced levels of endogenous inhibitors of bone mineralization, which results in ectopic mineralization of arteries and other tissues [8–10]. Diffuse calcification of large and medium-sized arteries is usually present during the neonatal period [3,4]. There is also vascular smooth muscle cell proliferation, further decreasing lumen diameter and compromising blood flow [5]

The most frequently calcified artery in early-onset GACI, encompassing prenatal and first week of life, is the hepatic artery (81%), followed by the aorta (80%), pulmonary artery (67%), coronary artery (53%), and renal artery (39%) [2,3]. The vascular calcification pattern we found was atypical in that great vessels near the heart were spared while most major branches of the aorta in the abdomen were involved [11]. The extracranial parts of internal and external carotid arteries and vertebral arteries were calcified which is a common finding [4,11]. Our patient also had calcification of the kidneys, which are the most commonly affected organs in GACI next to the heart valves [3].

Diagnosis of GACI is suspected based on clinical and imaging findings and confirmed by genetic testing or arterial biopsy [4,7,8]. Within the first week of life, neonatal respiratory distress, severe heart failure, and systemic hypertension are the main clinical features, while fever, vomiting, irritability, and convulsions dominate after the first week [2,4,5]. Our patient's presentation with features of neonatal meningitis and renal insult in the first week of life suggests possible ranges of presentation at any period of life. However, renal, osseous, parathyroid, and metabolic disorders associated with generalized arterial calcification should be ruled out first before suspecting GACI [11]. Genetic testing was required to make a definitive diagnosis and to detect potential novel mutations in the ENPP1 gene associated with an atypical presentation [1,7,8,10]. The identification of new mutations can potentially enable genotype/phenotype associations that will ultimately impact the clinical management and prognosis of the disease [7]. In addition, targeted therapies such as ENPP1 replacement are also on the horizon [1,5]. However, genetic testing requires infrastructure that is not available in our setup in Ethiopia.

Imaging plays an important role in diagnosis given the rarity of this entity and its nonspecific presentation, which make clinical suspicion low [2]. US and CT are the most common

modalities for initial imaging evaluation and follow-up [5]. Arterial calcifications tend to be circumferential and contiguously involve the length of the vessel, visualized as increased echogenicity of the vessel wall on US [1,2]. An echocardiogram is helpful to assess arteries near the heart, including the coronary and pulmonary arteries, the ascending aorta, and its major branches [3]. Antenatal US can help to visualize diffuse cardiac and arterial calcification and associated complications such as polyhydramnios and hydrops fetalis [11–13]. Although calcification is detected as a subtle radiopaque area on radiographic films, these findings are often overlooked [3].

A CT scan combined with CT angiography is usually the preferred modality to assess the extent of calcifications, intimal thickening, and stenosis in the arteries [4,8]. In our case, CT was deferred as the renal function of the patient was deteriorating consistently. Recently, MRI and MR angiography have been used to avoid radiation exposure and potential contrast-induced renal toxicity. In addition, monitoring for arterial calcification with a low-dose CT scan every 3-4 months and echocardiography to detect cardiovascular issues has been suggested [8].

The management of GACI is evolving, with multidisciplinary care suggested to have better outcomes [5]. Medical treatment with bisphosphonates, which are nonhydrolyzable inorganic pyrophosphate analogs of osteoclast inhibitors and calcium chelators such as sodium thiosulfate, had variable outcomes in preventing new calcifications and reversing existing lesions [5,6,8,9]. However, their effect on the prevention of subsequent stenosis is not promising [1,3,8]. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor blockers (ARBs) may be helpful in the treatment of renal artery stenosis-associated renovascular hypertension [5,10]. In some patients, Spontaneous resolution of arterial calcifications can be observed as a natural course of the disease without bisphosphonate therapy [6].

Conclusion

This report highlights that radiologists and pediatricians should be familiar with generalized arterial calcification of infancy and have a high index of suspicion for this entity in unexplained cases of neonatal renal failure with diffuse arterial calcification in US in order to timely diagnose and treat patients.

Authors' contributions

All authors contributed to the conduct of this research and read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent

Written informed consent was obtained from the patient's parents for anonymized patient information to be published in this article.

Availability of supporting data

The datasets supporting the current study will be available from the corresponding author on reasonable request.

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