

Bilateral Nephromegaly in a Child with Severe Iron-Deficiency Anemia

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Introduction

Nephromegaly is a medical entity commonly encountered in pediatrics with an extensive differential diagnosis (1). Common causes include cystic diseases, obstructive pathologies, and infiltrative and inflammatory processes (Table 1) (1). We report a child with transient bilateral nephromegaly in the context of severe anemia. Iron-deficiency anemia has not previously been associated with nephromegaly.

Case report

A 3-year-old female child presented to the emergency room with extreme fatigue. There was no past medical or family history. Her parents reported a diet consisting exclusively of cow's milk (up to 2.5 L/day). There was no history of fever, night sweats, hematuria, or gastrointestinal bleeding. On examination, the child was afebrile, mildly tachycardic and tachypneic with a normal

Abstract

Nephromegaly in childhood can result from a wide variety of causes, yet iron-deficiency anemia has not been previously described. We report a child with severe iron-deficiency anemia associated with transient bilateral nephromegaly. We hypothesize that increased renal production of erythropoietin as well as greater cardiac output with subsequent glomerular hyperfiltration secondary to critical anemia explained the observed nephromegaly. The normalization of kidney size following resolution of anemia supports this hypothesis. Our case report suggests an additional etiology of bilateral nephromegaly in the pediatric population and thus merits attention among physicians.

Keywords: Anemia; Erythropoietin; Hypoxia; Nephromegaly.

Conflict of interest: The authors declare no conflict of interest.

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blood pressure. Her anthropometry revealed a weight of 10.8 kg (<3rd percentile) and a height of 88.5 cm (3rd percentile). She was extremely pale with an otherwise unremarkable physical examination. Laboratory investigations demonstrated severe microcytic anemia (Hb=1.3 g/dL, MCV=53.3 fL) with an undetectable ferritin level and a low reticulocyte count (25x10⁹/L) for the degree of anemia. There was no evidence of hemolysis. Thrombocytopenia (68x10⁹/L) and mild neutropenia (1.4x10⁹/L) were also present. Anti-transglutaminase antibodies and fecal occult blood were negative. C-reactive protein and liver and kidney function tests were normal. There was a bland urinalysis with a normal protein to creatinine ratio, and no evidence of tubulopathy. Lead levels were marginally elevated at 0.24 µmol/L. EBV and CMV serologies were negative. Hemoglobin electrophoresis of the patient's parents revealed no anomaly.

Table 1. Causes of bilateral nephromegaly in pediatrics (1)

Obstructive	Cystic	Metabolic	Inflammatory, toxic, ischemic	Hematologic	Oncologic	Miscellaneous
Ureteropelvic junction obstruction	Autosomal dominant/recessive polycystic kidney disease	Diabetes mellitus	Acute tubulointerstitial nephritis	Sickle cell anemia	Wilms tumor	Nephrotic syndrome
Ureterovesical junction obstruction	Tuberous sclerosis	Glycogen storage disease type 1	Glomerulonephritis	Thalassemia	Acute lymphoblastic leukemia	Beckwith-Wiedemann syndrome
Posterior urethral valves	Multicystic dysplastic kidney	Hereditary tyrosinemia	Pyelonephritis	Hemophilia	Hodgkin/non-Hodgkin lymphoma	Renal amyloidosis
Prune belly syndrome	Glomerulocystic kidney disease	Fabry's disease	Renal abscess	Myelofibrosis	Neuroblastoma	Sjogren disease
Tumor		Acromegaly	Acute tubular necrosis	Renal vein thrombosis	Nephroblastomatosis	
Myoglobinuria			Kawasaki			
Hemoglobinuria						

Abdominal ultrasound showed bilateral nephromegaly of 9 cm (>99th percentile) with normal echotexture without hydronephrosis, homogeneous hepatomegaly, and no splenomegaly. Cardiac ultrasound showed left ventricle hypertrophy with diffuse coronary artery dilatation compatible with anemia.

The patient received red blood cell (RBC) transfusions (20cc/kg) along with iron and folate supplementation and nutritional counseling. Thrombocytopenia and neutropenia resolved spontaneously within four days. The patient improved clinically and was discharged at day six. At one-month follow-up, abdominal ultrasound demonstrated resolution of bilateral nephromegaly. Two months later, the patient's weight was at the 15th percentile, and her hemoglobin and ferritin levels normalized. At five-month follow-up, cardiac ultrasound normalized with the exception of mild dilatation of the left atrium.

Discussion

To our knowledge, nephromegaly secondary to severe iron-deficiency anemia has not been previously described in the literature. Iron deficiency anemia is one of the most common nutritional deficiencies found in children (2).

Several physiological adaptations are triggered in response to anemia. The kidneys upregulate their erythropoietin (Epo) production by up to 1000-fold (3). Epo is mainly produced by fibroblast-like cells in the renal cortex (4).

Epo is essential for erythropoiesis as it promotes survival, proliferation, and differentiation of RBC in order to maintain RBC mass and hemoglobin constant (4). Decreased tissue oxygen pressure resulting from anemia enhances the activation of hypoxia-inducible factors (HIF), specifically HIF-1 α and HIF-2 α , which stimulate the Epo enhancer (5). Consequently, increased HIF activity due to anemia leads to increased release of reticulocytes and greater blood oxygen capacity. Stimulation of HIF-1 α and HIF-2 α is also critical in angiogenesis (via vascular endothelial growth factor) and cell proliferation (via connective tissue growth factor, epidermal growth factor, among others) (5). HIF therefore promotes tissue growth directly and indirectly via multiple growth factors, potentially contributing to kidney enlargement.

The cardiovascular system also undergoes adaptive changes in the presence of anemia, including increased heart rate and cardiac output, causing cardiac hypertrophy and vasodilation of coronary arteries to enhance tissue perfusion. Both mechanisms were observed in our patient (6, 7).

These changes along with reduced peripheral and renal vascular resistance contribute to increased renal plasma flow (8, 9). This serves as an explanation for the increased glomerular filtration rate observed in individuals with sickle cell anemia (8-11). In the latter, it has been hypothesized that alteration of renal hemodynamics leads to increased renal growth. Altered hemodynamics in the presence of increased renal perfusion is also believed to contribute to the kidney hypertrophy observed in other conditions such as diabetes mellitus, pregnancy, increased dietary protein intake, and remnant kidney post-nephrectomy(10). In light of the literature and based on renal physiology, we hypothesize that the bilateral nephromegaly in our patient was due to increased HIF activity and Epo production, as well as greater cardiac output and glomerular hyperfiltration secondary to critical anemia. The rapid normalization of the kidney size after treatment of anemia supports this hypothesis.

Conclusion

In conclusion, our report suggests that severe iron-deficiency anemia may be a cause of nephromegaly and warrants consideration in the differential diagnosis.

Conflict of Interest

The authors declare no conflicts of interest.

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