

Erythropoietin Resistant Anemia in An Infant with End Stage Renal Disease

Son Dönem Böbrek Hastalığı Olan Bir Süt Çocuğunda Eritropoietine Dirençli Anemi

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Only a few disorder cause severe nephrocalcinosis with end stage renal disease (ESRD) in infancy. Bartter syndrome and the primary hyperoxalurias (PH) are the main causes of severe nephrocalcinosis with ESRD in infancy period. Bartter syndrome was ruled out because of the absence of hyponatremic hypokalemic metabolic alkalosis and recurrent dehydration attacks in our patient. Urinary chloride level was normal. Furthermore, SLC12A1 and CLCNKB gene analyses showed no mutation. Therefore, the most likely etiology in this infant with ESRD was the primary hyperoxalurias. The primary hyperoxalurias are autosomal recessive and rare metabolic disorders resulting from deficiencies of the hepatic peroxisomal enzyme alanine-glyoxlate aminotransferase (PH-1) and the enzyme glyoxylate reductase/hydroxypyruvate reductase (PH-2) which cause excessive oxalate formation and calcium oxalate deposition in various organs.^{1,2} The most common type of primary hyperoxaluria is type 1. Diagnosis relies on detection of increased levels of oxalate in urine (N: < 0.5 mmol/l/1.73m² per day) and either assay enzyme activity from liver biopsy or molecular genetic testing of associated gene. Liver biopsy is still considered as the gold standard, but it is an invasive process and bears some risks. Genetic analysis provides some additional non-diagnostic information.^{1,2} However, the diagnosis of PH-1 was mainly established on the basis of clinical and radiologic findings in our case. Urine oxalate level could not be measured on admission due to financial problems of the family, and then urine output abruptly decreased.

Erythropoietin (EPO) resistance is defined as failure to achieve target hemoglobin/hematocrit levels in the presence of adequate iron stores at a dose of 450 IU/kg/week intravenous or 300 IU/kg/week subcutaneously within 4-6 months, or failure to maintain hemoglobin/hematocrit levels subsequently at the same dose.^{2,3} The main reason for EPO resistance is iron deficiency. Other reasons are chronic blood loss, infection, inflammation, hyperparathyroidism, osteitis fibrosa, aluminum toxicity, hemoglobinopat-

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hies, folic acid and B₁₂ vitamin deficiencies, malnutrition, hemolysis, use of high-dose angiotensin-converting enzyme inhibitor and insufficient dialysis.^{2,3} In the present case, the patient did not respond to EPO treatment and required recurrent blood transfusions. The etiology of EPO resistance in our patient was not revealed. National Kidney Foundation suggests that bone marrow biopsy should be performed if the etiology of EPO resistant anemia was not revealed.³⁻⁵ Therefore, due to ongoing macrocytic anemia and bone marrow aspiration findings, the patient underwent bone marrow biopsy. Bone marrow biopsy showed extensive deposition of oxalate crystals, decreased hematopoietic cells and increased histiocytic cells. Based on current data, we decided that, bone marrow replacement with oxalate crystals and histiocytes or vitamin B12 deficiency might be the cause of EPO resistant anemia the present case.

Treatment modality is still challenging. A large daily fluid intake (> 3 l/1.73 m² per day) is essential. Dietary oxalate restriction is of limited benefit.^{1,2} The alkali citrate treatment is aimed to reduce the urinary calcium oxalate saturation. Daily dose of alkali citrate is 0.1-0.15 g/kg or 0.3-0.5 mmol/kg of sodium or sodium/potassium citrate preparation.^{1,2} Pyridoxine treatment must be tried at daily dose of 3-5 mg/kg, with stepwise increase to 15 mg/kg. Response to pyridoxine may delay the progression to ESRD.^{1,2} This is a very rare metabo-

lic disorder without brain involvement. Hence, systemic oxalosis is a good model for gene therapy. The AGT gene transfection into hepatocytes has provided encouraging results *in vitro*.¹ Many years of research will be required before considering its potential use in humans. *Oxalobacter formigenes* is a gram negative, anaerobic bacterium which metabolizes oxalate in intestinal tract. There are limited studies showing us that oral administration of this bacterium may decrease oxalate absorption. It is a promising trend, but further investigations needed to clarify this issue.^{1,2} Renal replacement therapy is of very limited benefit. Clearance of oxalate with peritoneal or hemodialysis is not enough. There are limited indications for dialysis in children with primary hyperoxaluria.¹ The important indication of dialysis is preparation for transplantation. Any kind of transplantation should be a preemptive procedure. Current transplantation modality is combined liver and kidney transplantation or preemptive liver transplantation. Palliative treatment is required when bone marrow involvement occurs.^{1,2}

CONCLUSION

Primary hyperoxaluria shows a wide range of clinical symptoms. It should be kept in mind that oxalate deposition in bone marrow should be considered in infants with end stage renal disease due to nephrocalcinosis, especially when they present with EPO resistant anemia.

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