Efficacy of Rasburicase in Hyperuricemia Secondary to Lesch-Nyhan Syndrome

Ana Roche, MD,[1] Belén Pérez-Dueñas, MD, PhD,[1,2] Juan Antonio Camacho, MD,[3] Rosa J. Torres, MD, PhD,[2,4,5] Juan G. Puig, MD, PhD,[2,4,5] Angels García-Cazorla, MD, PhD,[1,2] and Rafael Artuch, PhD[2,5]

We report on a 16-day-old male with metabolic acidosis, hyperuricemia, hyperuricosuria, and nephrocalcinosis caused by Lesch-Nyhan syndrome. Activity of the hypoxanthine-guanine phosphoribosyl transferase (HPRT) enzyme in lysed erythrocytes was undetectable, and molecular DNA analysis confirmed the presence of a 4–base pair deletion at the 5′ end of intervening sequence 8 in the *HPRT1* gene, a change that affects a 5' splice site consensus sequence. Rasburicase, a urate oxidase enzyme, was administered on day 26 of life, with an endovenous dose of 0.20 mg/kg/d for 3 days. Plasma urate concentrations normalized (2.96 mg/dL) at 38 days of life. Kidney function was preserved in our patient. In summary, rasburicase proved to be a safe and effective treatment in a patient with Lesch-Nyhan syndrome with uric acid nephropathy in the neonatal period.
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INDEX WORDS: Rasburicase; Lesch-Nyhan disease; hyperuricemia; acute kidney disease; nephrolithiasis; uric acid.

Lesch-Nyhan syndrome is a rare disorder (prevalence, 1/235,000 live births in Spain)[1] caused by a deficit in the hypoxanthine-guanine phosphoribosyl transferase (HPRT) enzyme. The *HPRT1* gene is located in the X chromosome (locus q26-q27.2; OMIM [Online Mendelian Inheritance in Man] entry no. *308000, #300322, and #300323), and more than 300 mutations have been identified to date.[2]

The lack of the enzyme activity causes increased turnover of the uric acid pool and overproduction of de novo purine synthesis (Fig 1), leading to hyperuricemia, uricaciduria, and nephrolithiasis. When enzymatic activity is undetectable, defective motor development, dyskinesias, and compulsive automutilation usually appear in the first years of life.[3] Subtle abnormalities in urine, such as crystalluria and hematuria, may be present in the first months of life, and a few cases of acute kidney injury as the first manifestation of the disease have been described.[4-9] In this report, we describe a patient who presented with vomiting, metabolic acidosis, and nephrocalcinosis in the neonatal period, which led to the diagnosis of Lesch-Nyhan syndrome in the first month of life. To our knowledge, this is the first patient with Lesch-Nyhan syndrome to have received treatment with rasburicase, a recombinant urate oxidase enzyme (Fig 1) otherwise used in the treatment or prophylaxis of hyperuricemia in pediatric patients with cancer at high risk of tumor lysis syndrome.[10]

CASE REPORT

A 16-day-old male was admitted to the emergency department because of vomiting and weight loss after the introduction of artificial formula. He was the second child of a nonconsanguinous healthy family of Moroccan origin. The child was delivered normally at 40 weeks after a normal pregnancy. On admission, his weight was 3.540 kg (6% body weight loss), examination findings were normal, and there were no signs of dehydration.

Plasma biochemical analysis detected metabolic acidosis (pH 7.14; bicarbonate, 14 mEq/L [14 mmol/L; base excess, −15'4 mEq/L]; P_{CO_2}, 20 mm Hg; potassium, 6.5 mEq/L [6.5 mmol/L]; and anion gap, 26 mEq/L [26 mmol/L]), serum creatinine concentration of 1.2 mg/dL (92 μmol/L), and urate concentration of 16.5 mg/dL (981 μmol/L; Table 1). Other metabolite (urea, ions, lactate, pyruvate, and amino acids) levels were within normal limits. Urine analysis detected pH 6, urinary density less than 1,005, and hyperuricosuria (uric acid, 1.73 mmol/d; reference values, 0.1 to 0.7 mmol/d); no

From the [1]Department of Neurology, Hospital Sant Joan de Déu; [2]Center for Biomedical Research on Rare Diseases, Instituto de Salud Carlos III; [3]Department of Nephrology, Hospital Sant Joan de Déu; Departments of [4]Biochemistry and [5]Internal Medicine, Metabolic and Vascular Diseases Unit, La Paz Hospital; and [6]Department of Biochemistry, Hospital Sant Joan de Déu, Barcelona, Spain.

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Address correspondence to Belén Pérez-Dueñas, MD, PhD, Department of Neurology and Center for Biomedical Research on Rare Diseases (CIBERER), Hospital Sant Joan de Déu, Barcelona, Spain. E-mail: bperez@hsjdbcn.org

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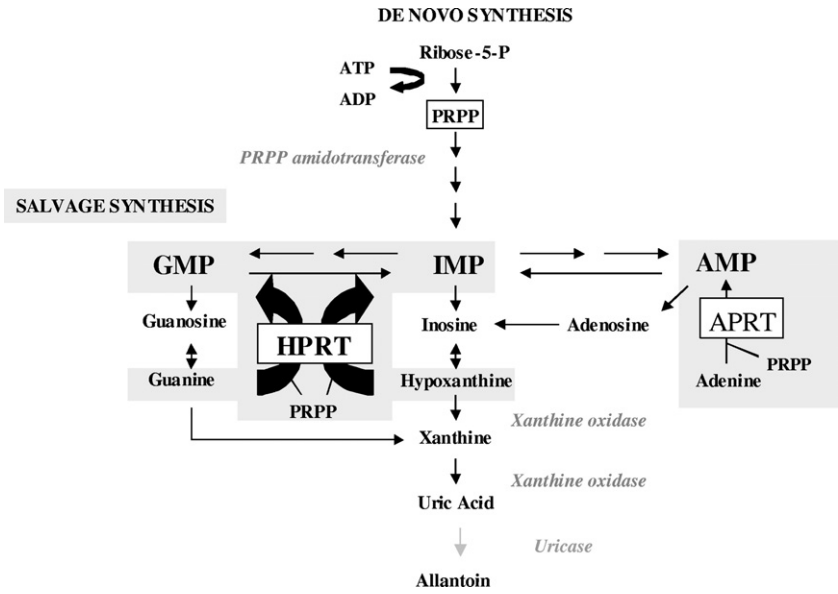

Figure 1. Purine metabolism. The metabolic scheme shows the first and rate-limiting step of de novo purine synthesis mediated by the enzyme 5′-phosphoribosyl-1-pyrophosphate (PRPP) amidotransferase and the salvage pathway mediated by hypoxanthine phosphoribosyltransferase (HPRT) and adenine phosphoribosyltransferase (APRT). The de novo synthesis occurs through a multistep process and requires the contribution of 4 amino acids, 1 PRPP, 2 folates, and 3 adenosine triphosphates (ATPs) to synthesize an inosine monophosphate (IMP) molecule. HPRT catalyzes the salvage synthesis of IMP and guanosine monophosphate (GMP) from the purine bases hypoxanthine and guanine using PRPP as a cosubstrate, respectively. The HPRT defect results in the accumulation of its substrates, hypoxanthine and guanine, which are converted into uric acid by means of xanthine oxidase. The enzyme uricase, not present in humans, converted uric acid to the more soluble allantoin. Abbreviations: ADP, adenosine diphosphate; AMP, adenosine monophosphate.

crystals of uric acid were observed on microscopy. An abdominal-renal ultrasound showed bilateral nephrocalcinosis. Differential diagnoses of hyperuricosuria and hyperuricemia with nephrocalcinosis included neoplasic disorders and inborn errors of metabolism of purines, such as Lesch-Nyhan syndrome. HPRT activity in erythrocyte lysates was determined by means of a high-performance liquid chromatography method.[12] The low detection limit was 0.01 nmol/h/mg hemoglobin. Activity of the HPRT enzyme in lysed erythrocytes was undetectable (<0.01 nmol/h/mg hemoglobin) in our patient, suggesting the diagnosis of Lesch-Nyhan syndrome when the baby was 26 days old.

The RNA-free genomic DNA sample was isolated from whole blood by using a Puregene DNA Purification Kit (Gentra Systems, Minneapolis, MN). All 9 exons of the human *HPRT* gene and its flanking sequences were amplified as 8 separate DNA fragments of different lengths, as previously described.[1] Each amplified DNA fragment was sequenced using the BigDye Terminator Cycle Sequencing kit (Applied Biosystems, Nieuwerkerk, The Netherlands) in

Table 1. Baseline and Serial Parameters of Kidney Function and Uric Acid Metabolism in the Patient on Treatment With Rasburicase

	Baseline	1 Week Posttreatment	4 Weeks Posttreatment
Parameters of kidney function			
Serum creatinine (μmol/L; NV <45)	92	86	54
Creatinine clearance (mL/min/1.73 m^2; NV 40-65)	13.8	19	40.5
Parameters of uric acid metabolism			
Serum urate (μmol/L; NV 100-330)	981	779	168
Uric acid FE* (%; NV 0.8-21.5)	42	52	17
Urinary uric acid-creatinine ratio (mmol/mmol; NV 0.03-1.03)	6.53	7.03	2.10

Note: NVs for uric acid FE and urinary uric acid-creatinine ratio are from Grivna et al.[11] Serum creatinine in μmol/L may be converted to mg/dL by dividing by 88.4, creatinine clearance in mL/min to mL/s by multiplying by 0.0167.

Abbreviations: FE, fractional excretion; NV, normal value; S, serum; U, urinary.

*The following formula was used to calculate the FE of uric acid: $FE_{uric\ acid} = U_{uric\ acid} \times S_{creatinine}/S_{uric\ acid} \times U_{creatinine}$.

an ABI Prism 377 DNA Sequencer (Applied Biosystems). Molecular DNA analysis confirmed the presence of a 4–base pair deletion in intervening sequence 8. This deletion (NM_000194.2:c.776+1_776+4delGTAA) occurs at the extreme 5' terminus of an intron, thereby removing the nearly invariant GT dinucleotide of the 5' splice site, as well as the highly conserved RA (ie, purine [A or G]-adeninine dinucleotide) of the downstream consensus sequence. We infer that this sequence change causes abnormal posttranscriptional processing of HPRT messenger RNA.

Acidosis persisted despite bicarbonate corrections and rehydration. Rasburicase was administered on day 26 of life, after written consent of the family. Rasburicase was infused when urinary pH was greater than 7, with an endovenous dose of 0.20 mg/kg/d during 3 consecutive days. On day 4, rasburicase was replaced by oral administration of allopurinol (10 mg/kg/d). Hyperhydration (180 mL/kg/d) and urinary alkalinization with sodium bicarbonate (1.2 mEq/kg/d) were continued throughout treatment to maintain urinary pH greater than 7 and facilitate crystal dissolution. Plasma urate concentrations normalized (2.96 mg/dL) at 38 days of life. Renal ultrasound after 2 weeks of treatment did not show any variation, with continued images of bilateral nephrocalcinosis. However, kidney function progressively improved to normal (Table 1).

DISCUSSION

In this report, we describe a neonate who presented with uric acid nephropathy as the first symptom of Lesch-Nyhan syndrome. The disease is often overlooked until late infancy or early childhood, when neurological abnormalities become apparent, although crystalluria and hematuria may be present in the first months of life.[13] During the last decade, a few patients with acute kidney disease as the first symptom of Lesch-Nyhan syndrome have been described.[4-8] Most of these patients were younger than 2 months, and some had associated articular tophi.[6,8] They were successfully treated with allopurinol or dialysis. We report the first patient with Lesch-Nyhan syndrome to have received treatment with rasburicase, which proved to be effective in reducing urate concentrations in plasma to normal levels in 12 days. No side effects were registered, and kidney function progressively improved to normal in our patient throughout the treatment period.

Acute kidney injury is believed to be caused by crystallization of urate and obstruction of the tubular lumina, resulting in local granulomatous inflammation associated with macrophage and T-cell infiltration.[14] However, experimental data support the theory that uric acid may contribute to acute kidney injury by additional pathogenic mechanisms independent of crystal deposition, including renal vasoconstriction, endothelial dysfunction, inflammatory response, oxidative stress, and disturbances in renal autoregulation.[15]

In summary, this case report and others should encourage physicians to think of Lesch-Nyhan syndrome in neonates with vomiting and metabolic acidemia, especially if hyperuricemia, hyperuricosuria, and nephrocalcinosis are present. In our experience, rasburicase proved to be a safe and effective treatment in this patient with Lesch-Nyhan syndrome who had hyperuricemia and acute kidney disease in the neonatal period. Prompt diagnosis and treatment appeared to be essential for a favorable outcome.

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