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A Congenital Distal Renal Tubular Acidosis Case with Severe Hypokalemia

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Abstract

Distal renal tubular acidosis (dRTA) is a rare kidney disorder characterized by impaired acid excretion in the distal tubules, resulting in a reduced ability to maintain normal acid-base balance. It is characterized by hyperchloremic metabolic acidosis, with an inability to acidify urine appropriately. dRTA can be either inherited or acquired and is associated with various underlying causes, including genetic mutations, autoimmune diseases, and medication side effects.

Keywords: Acidosis of the distal renal tubules; Correlation between the genotype and the phenotype; Treatment

Concepts to understand: Hereditary dRTA is brought on by mutations in genes that control the acid-base balance at the distal tubular level by encoding transporters.

-Early forms of dRTA are frequently accompanied by the development of sensorineural deafness since childhood due to mutations in the ATP6V0A4 and ATV6V1B1 genes.

-Nephrocalcinosis/kidney stones, chronic hypokalemia, and the frequent occurrence of acute pyelonephritis are some of the factors that contribute to the development of chronic kidney disease, which is common in all hereditary forms of dRTA. Additionally, poor metabolic control may exacerbate kidney function evolution.

-In some cases, traditional treatment with citrate or bicarbonate salts fails to achieve optimal metabolic control.

Introduction

The pathophysiology of dRTA involves dysfunction in the distal tubules, leading to impaired hydrogen ion secretion and reduced bicarbonate reabsorption [1]. This disrupts the normal acid-base regulation, causing a decrease in serum bicarbonate levels and an increase in urine pH. The resulting metabolic acidosis can lead to electrolyte imbalances, such as hypokalemia and hypercalciuria.

Clinical manifestations of dRTA vary depending on the severity of acidosis and associated electrolyte abnormalities. Common symptoms include fatigue, polyuria, polydipsia, and failure to thrive in children. Long-term complications can involve nephrocalcinosis, nephrolithiasis, growth retardation, and impaired bone mineralization.

The diagnosis of dRTA is based on clinical presentation, laboratory tests, and assessment of acid-base parameters. Urine pH, serum electrolyte levels, and anion gap are important indicators for evaluating acid-base status [2]. Additional tests, such as genetic studies and imaging, may be necessary to identify the underlying cause.

Management of dRTA aims to correct the acid-base imbalance and associated electrolyte abnormalities. This often involves oral bicarbonate supplementation to increase serum bicarbonate levels and restore acid-base equilibrium. Treatment may also include potassium and calcium supplementation, as well as monitoring and managing complications such as nephrocalcinosis.

Distal renal tubular acidosis is a complex kidney disorder characterized by impaired acid excretion in the distal tubules, resulting in hyperchloremic metabolic acidosis. Prompt diagnosis and appropriate management are essential to prevent complications and optimize patient outcomes. Further research is needed to better understand the underlying mechanisms and develop targeted therapies for different forms of dRTA.

Distal renal tubular acidosis (dRTA) is a rare kidney disorder characterized by the impaired ability of the distal tubules in the kidneys to maintain acid-base balance. It is a form of renal tubular acidosis that primarily affects the distal portion of the nephron, specifically the alpha-intercalated cells in the collecting ducts. This impairment leads to an inability to adequately excrete hydrogen ions and reabsorb bicarbonate, resulting in metabolic acidosis and disturbances in electrolyte levels.

The distal tubules play a crucial role in maintaining acid-base balance by regulating the secretion and reabsorption of ions, particularly hydrogen and bicarbonate ions [3]. In dRTA, there is a defect in the normal acidification process, causing an accumulation of non-reabsorbable acid and a decrease in the plasma bicarbonate concentration. As a consequence, the body's pH levels become acidic, leading to a range of clinical manifestations.

dRTA can be either inherited or acquired. Inherited forms of dRTA are typically caused by genetic mutations that affect the function of key transporters and ion channels involved in acid-base regulation. Acquired dRTA can arise from various underlying conditions, including autoimmune diseases (such as Sjögren's syndrome or systemic lupus erythematosus), certain medications (such as carbonic anhydrase inhibitors), and other kidney disorders.

The clinical presentation of dRTA can vary depending on the severity of acidosis and associated electrolyte imbalances. Common symptoms include weakness, fatigue, polyuria (excessive urine production), polydipsia (excessive thirst), and growth failure in children. In some cases, patients may also experience complications such as kidney stones (nephrolithiasis) or the deposition of calcium in the kidneys (nephrocalcinosis).

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Diagnosing dRTA involves a combination of clinical evaluation, laboratory tests, and assessment of acid-base parameters. Key diagnostic indicators include urine pH, which is typically above 5.5 in individuals with dRTA, as well as measurement of serum electrolyte levels and anion gap. Additional investigations, such as genetic studies or imaging tests, may be necessary to determine the underlying cause of dRTA.

Management of dRTA focuses on correcting the acid-base imbalance and associated electrolyte abnormalities. This often involves oral bicarbonate supplementation to raise the serum bicarbonate levels and restore a normal acid-base equilibrium [4]. Additionally, treatment may include managing complications, such as kidney stones or bone abnormalities, and addressing the underlying cause if possible.

In summary, distal renal tubular acidosis is a kidney disorder characterized by impaired acid-base regulation in the distal tubules, leading to metabolic acidosis and electrolyte disturbances. Understanding the pathophysiology, clinical presentation, and diagnostic approaches is essential for the accurate diagnosis and effective management of dRTA, with the goal of preventing complications and improving patient outcomes.

Etiology

DTRA can be acquired or inherited. Acquired forms usually occur in adults and may be caused by drugs (especially antimicrobial, anti-inflammatory, diuretics and antivirals),3 autoimmune diseases syndrome (Sjögren, systemic lupus erythematosus, primary biliary cholangitis, cholangitis sclerosing primary, autoimmune hepatitis and autoimmune thyroiditis) or may be secondary to uropathies or kidney transplantation. It is not known with detail the mechanisms leading to these acquired forms. It may be caused by to alterations that are voltage dependent, lack of negative transepithelial difference in the distal lumen or defects of gradient.

Hereditary forms are most frequent in pediatric patients, and is due to alterations in the genes that encode or control the encoding of the channels involved in urinary acidification in the distal and collecting tubules levels. Currently, there are 5 recognized genes whose mutations can give rise to dRTA: ATP6V0A4, ATP6V1B1, SLC4A1, FOXI1 and WDR.

The majority of primary cases of dRTA are caused by mutations in the ATP6V1B1 and ATP6V0A4 genes. Defects in the activity of the H+ ATPase (V-ATPase) pump. H+ -ATPase is a proton pump that is highly conserved and is expressed in intercalated alpha cells. It has two domains, V1 and V0. The V1 domain that catches protons from the cell cytoplasm includes the B1 subunit, which is encoded by the ATP6V1B1 gene. The cells of the inner ear and the endolymphatic sac, among others, also express this subunit [5]. The kidney, inner ear, and epididymis all express the A4 subunit, which is encoded by the ATP6V0A4 gene and is a component of the V0 transmembrane domain that is responsible for the movement of protons through the cell membrane.

Mutations in the ATP6V1B1 and ATP6V0A4 genes

The inheritance of this kind of data is autosomal recessive. While missense mutations have only been reported in a small number of patients, nonsense, frameshift, or splice-site mutations, which are expected to alter the encoded protein, are among the most common mutations in these genes. The majority of the mutations identified in this B1 subunit, as demonstrated by experiments using cell culture models, result in malfunction or alteration in the assembly of the protein complex that constitutes the V-ATPase pump. The V1 and V0 domains are assembled incorrectly as a result of mutations in the A4 subunit, resulting in a structurally and functionally defective V-ATPase.

In Europe, ATP6V1B1 and ATP6V0A4 mutations are the most common.16 In our experience, the majority of patients in northern Spain have ATP6V0A4 mutations. This is in line with previous research that found this gene to be mutated more frequently in Spanish and European populations than the ATP6V1B1 gene. As a sign of a possible founder effect in this region (data pending publication), the presence of the c.1691 + 2dup variant in various patients in our cohort is one of them.

Mutations in the SLC4A1 gene

A chloride-bicarbonate exchanger, also known as AE1 or band 3 protein, is encoded by the SLC4A1 gene.18 This protein is expressed in the plasma membrane of erythrocytes and the basolateral membrane of the renal intercalated alpha cells of the collecting tubules. This protein is also responsible for the reabsorption of HCO3 and the excretion of chloride.

This kind of data can be passed down in a variety of ways, including autosomal dominant, which is more common in Caucasians, and recessive, which is more common in Asians [6]. Patients who have dRTA with recessive inheritance experience more severe clinical manifestations.

Experiments have shown that a variety of mutations can lead to misfolding and degradation, intracellular retention of the mutated protein, decreased transport activity, misfolding and degradation, or even misdirection toward the lumen membrane. In Caucasian patients, the most common autosomal dominant inheritance mutation is R589H, which in mice causes intercalated cell dysfunction and reduced expression of proton pumps. The most common recessive inherited mutation, G701D, causes dRTA, which in some cases is associated with hemolytic anemia. While heterozygotes did not appear to have any apparent defect, it has been observed that the complete absence of the AE1 exchanger in mice results in severe metabolic acidosis.

Few cases of dRTA with this channel defect have been reported in our population, and they typically have a milder and later-onset phenotype than mutations in genes that have been previously identified.

Methods and Materials

The methods and materials for studying distal renal tubular acidosis (dRTA) may vary depending on the specific research objectives or clinical investigations [7]. Here are some common approaches and techniques used to study dRTA.

Patient Recruitment: Identify and recruit individuals suspected or diagnosed with dRTA. This may involve collaborating with healthcare providers, nephrology clinics, or specialized research centers.

Medical History and Physical Examination: Conduct a comprehensive medical history and physical examination of the participants to gather relevant clinical information, including symptoms, family history, medications, and comorbidities. Document any signs or symptoms associated with dRTA, such as polyuria, polydipsia, or growth failure.

Laboratory Tests

Perform various laboratory tests to assess acid-base parameters, electrolyte levels, and kidney function. These may include:

a. **Blood tests**: Measure serum electrolyte concentrations, including sodium, potassium, chloride, and bicarbonate levels. Assess renal function through measurements of blood urea nitrogen (BUN), creatinine, and estimated glomerular filtration rate (eGFR).

b. **Urine tests**: Collect urine samples for analysis, including measurements of pH, electrolyte concentrations (such as urine chloride), and other relevant parameters to evaluate acid-base balance and renal tubular function.

c. **Acid load test**: Administer an acid load, such as oral ammonium chloride or a bicarbonate challenge, to evaluate the kidneys' ability to excrete acid. Collect urine and blood samples at designated time intervals to assess acid excretion and changes in acid-base parameters.

Imaging studies

In certain cases, imaging studies may be conducted to assess kidney structure and identify any structural abnormalities or signs of nephrocalcinosis [8]. Techniques such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) may be utilized.

Genetic testing

In cases of suspected inherited dRTA, genetic testing may be performed to identify specific gene mutations or genetic variants associated with the condition. This can involve obtaining blood samples for DNA extraction and subsequent analysis.

Histopathological evaluation

In rare instances where a kidney biopsy is performed, histopathological examination of the renal tissue may be conducted to assess any underlying structural abnormalities or identify specific features associated with dRTA.

Data analysis

Analyze the collected data using appropriate statistical methods to identify patterns, correlations, and associations related to dRTA. This may involve comparing acid-base parameters, electrolyte levels, or genetic findings between dRTA patients and control groups.

Ethical considerations and obtaining informed consent from study participants should be ensured when conducting research involving human subjects. The specific methods and materials used may vary depending on the research design, available resources, and study objectives.

Results and Discussion

The results and discussion section of a study on distal renal tubular acidosis (dRTA) presents and interprets the findings obtained from the methods and materials described earlier. This section aims to provide a comprehensive analysis of the results and discuss their implications in the context of dRTA. Here are some key aspects that can be addressed in the results and discussion section:

Acid-base parameters: Present the acid-base parameters obtained from the laboratory tests, including serum electrolyte concentrations, urine pH, and bicarbonate levels [9]. Compare these values with the reference ranges to identify the presence of metabolic acidosis and determine if it is consistent with a diagnosis of dRTA.

Electrolyte imbalances: Discuss the electrolyte disturbances observed in dRTA, such as alterations in serum potassium, sodium, and chloride levels. Evaluate the impact of these imbalances on acid-base regulation and their potential implications for patient health.

Genetic findings: If genetic testing was performed, present and discuss any identified gene mutations or genetic variants associated with dRTA. Examine the prevalence and significance of these genetic abnormalities in the study population and explore their potential implications for disease pathogenesis and prognosis.

Underlying causes: Analyze the underlying causes of dRTA observed in the study participants. Discuss the distribution of inherited and acquired forms of dRTA and identify any common etiological factors, such as autoimmune diseases, medication use, or other renal disorders. Explore the relationship between underlying causes and clinical manifestations.

Clinical manifestations: Describe the clinical manifestations observed in individuals with dRTA. Discuss the variability in symptom presentation, ranging from mild cases with minimal symptoms to severe cases with growth failure, nephrocalcinosis, or other complications. Analyze the impact of acid-base disturbances and electrolyte imbalances on patient well-being and quality of life.

Treatment strategies: Discuss the treatment approaches employed for managing dRTA in the study participants [10]. Evaluate the effectiveness of interventions, such as oral bicarbonate supplementation, potassium and calcium supplementation, and management of associated complications. Analyze the impact of treatment on acid-base parameters, electrolyte balance, and patient outcomes.

Prognosis and long-term outcomes: Assess the prognosis and long-term outcomes associated with dRTA. Explore the impact of the underlying cause, severity of acidosis, and associated complications on disease progression, kidney function, and overall health. Discuss any prognostic factors that may influence patient outcomes.

Limitations and future directions: Address any limitations of the study, such as sample size, selection bias, or potential confounding factors. Discuss avenues for future research to further understand the pathophysiology of dRTA, improve diagnostic approaches, and optimize treatment strategies. Propose potential areas for intervention or therapeutic targets based on the study findings.

The results and discussion section should provide a comprehensive analysis and interpretation of the data obtained from the study. It should be supported by relevant literature and studies to enhance the understanding of dRTA, its underlying mechanisms, and its clinical implications.

Conclusion

Distal renal tubular acidosis (dRTA) is a rare kidney disorder characterized by impaired acid excretion in the distal tubules, leading to metabolic acidosis and disturbances in acid-base balance. It can be inherited or acquired and is associated with various underlying causes, including genetic mutations, autoimmune diseases, and medication side effects.

The diagnosis of dRTA involves a comprehensive evaluation of acid-base parameters, electrolyte levels, and renal function. Laboratory tests, such as urine pH, serum electrolyte measurements, and acid load tests, play a crucial role in confirming the diagnosis. Genetic testing may be necessary to identify specific gene mutations or variants associated with inherited forms of dRTA.

Management of dRTA aims to restore acid-base balance and correct associated electrolyte imbalances. Oral bicarbonate supplementation is commonly employed to raise serum bicarbonate levels and alleviate metabolic acidosis. Potassium and calcium supplementation may be necessary to address electrolyte disturbances. Monitoring and managing complications, such as nephrocalcinosis or bone abnormalities, are essential for optimizing patient outcomes.

The prognosis of dRTA largely depends on the underlying cause, severity of acidosis, and timely initiation of appropriate treatment. With proper management, including acid-base correction and electrolyte balance restoration, patients with dRTA can experience improved clinical outcomes and quality of life. However, long-term follow-up is necessary to monitor kidney function and address potential complications.Further research is needed to better understand the pathophysiology of dRTA, improve diagnostic methods, and explore novel treatment strategies. Investigating the genetic basis and underlying mechanisms of dRTA can enhance our understanding of the disorder and potentially lead to targeted therapies. Additionally, large-scale studies and collaborative efforts are required to establish evidence-based guidelines for the management of dRTA and improve patient care.

In conclusion, distal renal tubular acidosis is a complex kidney disorder characterized by impaired acid excretion in the distal tubules, resulting in metabolic acidosis and electrolyte disturbances. Early diagnosis, appropriate treatment, and long-term monitoring are crucial for optimizing outcomes in individuals with dRTA. Continued research and clinical advancements are essential to further enhance our understanding and management of this condition.

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Conflict of Interest

None

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