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A Comprehensive Review on Fanconi Syndrome and Its Treatment Strategies

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ABSTRACT

Fanconi syndrome refers to a global dysfunction of the proximal tubule leading to excessive urinary excretion of amino acids, glucose, phosphate, bicarbonate, uric acid, and other solutes reabsorbed by this nephron segment. Fanconi syndrome, not to be confused with Fanconi anemia, this review literature describes briefly about the origin, causes, pathophysiology and treatment strategies of falconi syndrome. Studies of amino acid excretion in the urine should be made in all cases of refractory rickets or osteomalacia if the problem is to be accurately classified since marked generalized aminoaciduria is one of the constant diagnostic characteristics of the Fanconi syndrome. When severe, these losses lead to acidosis, dehydration, electrolyte imbalances, rickets, osteomalacia, and growth failure. Numerous inherited or acquired disorders are associated with Fanconi syndrome.

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INTRODUCTION

Fanconi syndrome is a disease that is associated with dysfunction of the proximal tubule of the kidney. It is characterized by the wasting of phosphate, amino acids, glucose, and bicarbonate in varying degrees [1,2]. This loss can cause a range of symptoms such as dehydration, bone disorders, and electrolyte imbalances [3]. Clinical manifestations stem from direct or indirect disturbances of the tubule system [4]. In children, this principally caused by inborn errors of metabolism and in adults it is usually caused by drugs and toxins. Treatment consists of treating the underlying disorder or removal of the toxin and replacing the lost electrolytes and volume [1].

EPIDEMIOLOGY

Fanconi syndrome is a rare disease with sporadic incidence and reporting of newly diagnosed cases [5]. In studies reviewed, individuals at risk are most often young Caucasian children. For other forms of Fanconi syndrome, both acquired and exogenous, there are no significant populations adversely affected. The age of those affected varies because the etiology is diverse. If the disease was acquired from medications, metal toxicity, or exposure to other noxious agents, it can present itself at any age. However, if Fanconi syndrome was inherited in an autosomal recessive pattern, the onset is usually evident in early development [6].

ETIOLOGY

There are at least 10 inherited causes that include cystinosis, galactosemia, hereditary fructose intolerance, tyrosinemia, Wilson disease, Lowe syndrome, Dent disease, glycogenosis, mitochondrial cytopathies, and idiopathic. There are several acquired causes as well that includes certain antivirals (nucleoside reverse transcriptase inhibitors [NRTIs]), chemotherapeutic agents (cisplatin), immunosuppressive (azathioprine), antibiotics (gentamicin), or several other medications. In addition, the condition may be due to monoclonal gammopathy, lead poisoning, and other toxins [7].More generalized kidney injury such as that secondary to renal transplant, certain causes of nephrotic syndrome, and acute tubular necrosis. Honeybee stings can also give rise to Fanconi syndrome[8]. Legionella pneumonia may also cause Fanconi syndrome for unknown reasons [9].

PATHOPHYSIOLOGY

Proteins and solutes are reabsorbed by the proximal tubules using specialized transporters and channels. These are localized in the tubular cell membranes, located on the luminal or basolateral membrane. The tubules are also responsible for the regulation of acid-base balance, mineral homeostasis, and drug elimination. Adult humans typically filter 180 l of fluid per day through the kidneys; more than 98% of this has to be reclaimed before excretion, and the bulk of reabsorption occurs in the PT. Most solute transport in the PT is coupled directly, or indirectly, to sodium transport. Plasma proteins smaller than albumin (LMWPs) are filtered by the glomerulus and reabsorbed in the Proximal Tubule via receptor-mediated endocytosis. PT cells are densely packed with mitochondria and are dependent on aerobic metabolism to generate sufficient ATP to power solute transport [10]. In Fanconi syndrome, the solutes are prevented from crossing the apical network of the proximal renal tubule cell [11]. Cystinosis is the most common genetic cause of Fanconi syndrome due to the defective function of cystinosin resulting from the mutation of the gene CTNS, which leads to intralysosomal cystine accumulation [12]. Drugs that induce mitochondrial dysfunction have the potential to cause Fanconi syndrome [13,14]. The most common drugs are outdated tetracycline antibiotics, chemotherapy agents, antiviral drugs, aminoglycosides, and anticonvulsants. Tetracycline metabolites can cause renal tubular disease with electrolyte imbalance and induce tubular damage within 2 to 8 days after beginning treatment. Cisplatin is a direct toxin to the proximal tubular cells, resulting in an increase in b_2-microglobulin and/or aminoaciduria and/or proteinuria [13]. Tenofovir and adefovir induce Fanconi syndrome in AIDS/HIV patients [15]. Nephrotoxicity is a consequence of aminoglycoside administration in hospitalized patients [16]. Aminoglycosides are reabsorbed in the proximal tubule, causing a decreased glomerular filtration rate. The pathophysiology is uncertain, but it is believed that aminoglycosides irreversibly bind to the cellular membranes causing lysosomal swelling [17]. Fanconi syndrome represents the extreme end of the spectrum of valproic acid–induced renal impairment. Previous studies have shown that the renal impairment stems from the epilepsy itself, not the drug. Additionally, valproic acid–induced Fanconi syndrome appears to be exclusive to children and usually abates on the discontinuation of the drug [18].

CLINICAL FEATURES

Clinical presentations of Fanconi syndrome are due to various defects in proximal tubular transport. These include impaired reabsorption of glucose, phosphate, amino acids, bicarbonate, uric acid, water, potassium, and sodium. Hereditary Fanconi syndrome features proximal tubular renal acidosis, hypophosphatemic rickets, hypokalemia, polyuria, and polydipsia (usually in infancy). Acquired Fanconi syndrome presents with slightly different abnormalities such as renal tubular acidosis, hypophosphatemia, hypokalemia, osteomalacia, and muscle weakness [19].Hypertension and diabetes mellitus were found to be the major comorbidities in valvular heart disease patients in some studies [20], multiple ill-defined areas of erythema with multiple bullae over face And chin can be seen in few cases but, in Falconi syndrome these symptoms are not seen [21].

DIAGNOSIS

Urinary LMWPs such as retinol-binding protein and beta-2-microglobulin are the most sensitive markers of proximal tubule dysfunction and provide a quantitative readout of severity [10]. Comparison with urinary albumin excretion can help to classify proteinuria as being predominantly of either tubular or glomerular origin[10]. Urine protein/creatinine ratio (PCR) does not distinguish the origin of proteinuria, but is more widely available and is typically raised in patients with Falconi Syndrome. In some cases, a renal biopsy is performed to assess the extent of acute tubular damage and irreversible tubulointerstitial scarring[10].

TREATMENT

The primary therapy for Fanconi syndrome is to treat the underlying causes and replace substances wasted in the urine. Fluids and electrolytes are administered via oral or parenteral routes due to dehydration resulting from polyuria, which may exceed 2 to 6 liters per day of dilute urine in cystinosis patients [22]. Metabolic acidosis is caused by the impaired capacity of the kidney to absorb normal levels of bicarbonate. In an acute setting, small boluses of IV sodium bicarbonate may be utilized to raise blood pH [23]. Chronic metabolic acidosis probably also contributes to bone disease in Falconi Syndrome and is easily corrected with oral sodium bicarbonate [10]. Citrate salts are dosed based on the amount of bicarbonate equivalents they generate. For example, Cytra-K, which contains potassium citrate and citric acid, generates 2 mEq of potassium and 2 mEq of bicarbonate per mL [24]. The use of

thiazide diuretics, which can help reduce the loss of bicarbonate in the urine, may also be helpful in certain cases [25]. Falconi Syndrome may also require treatment with alfacalcidol or calcitriol [10]. Underlying genetic causes usually involve a defective enzyme in nutrient metabolism resulting in damage to the proximal tubule. Patients with hereditary galactosemia, fructose intolerance, and tyrosinemia would benefit from limiting the amount of galactose, fructose, and tyrosine or phenylalanine, respectively, from their diets [26]. Patients with Wilson's disease should be encouraged to ingest a low-copper diet (such as restricting organ meats, shellfish, and whole wheat) and take D-penicillamine due to studies suggesting beneficial outcomes. Cysteamine (Cystagon) is an FDA-approved medication used to treat cystinosis [27]. It functions by reacting with and then exporting the cystine trapped within lysosomes, thus reducing the load available to induce cellular damage. Initial doses are one-fourth to one-sixth of the maintenance dose and should be titrated up to the initial maintenance dose over 4 to 6 weeks. For pediatric patients, the initial maintenance dose is 1.3 g/m^2/day divided four times per day. For patients over 12 years old and greater than 110 lb, the initial maintenance dose is 500 mg four times per day. The goal of therapy is to keep leukocyte cystine levels below 1 nmol of half-cystine/mg protein when measured 5 to 6 hours after drug administration. The doses for both age groups may be titrated to a maximum dose of 1.95 g/m^2/day to reach this goal. Side effects include lethargy, diarrhea, seizures, GI toxicity, anemia, and tremor. There are no known drug interactions with cysteamine. Patients allergic to penicillamine should be carefully monitored for adverse events when given cysteamine [28].

MONITORING

Widely used tests for CKD such as serum creatinine and eGFR are not sensitive markers of PT dysfunction. This point has been illustrated by the story of tenofovir, in which original safety studies using these parameters reported no evidence of renal toxicity, but multiple cases of tubular toxicity were steadily reported over time [29]. Monitoring should be focused on more appropriate markers, such as tubular proteinuria (if available), urine PCR, phosphate reabsorption and glycosuria [10].

PROGNOSIS

Patient prognosis is dependent upon the cause of the syndrome and the severity of renal and extrarenal manifestations. Genetic forms are difficult to manage, are usually associated with

disruptions in growth, and involve other organs [11]. The Proximal Tubule has a remarkable capacity to regenerate itself following an insult, and substantial improvement in function can occur after drug-induced FS, provided that the offending agent is withdrawn. However, recovery of function can take months and is not always complete, leaving some patients with residual tubular defects [10].

CONCLUSION

Fanconi is a rare and complex disease characterized by the dysfunction of proximal tubule which results in excessive loss of essential substances in the urine. This leads to a number of symptoms and complications like bone disorders, acidosis, electrolyte imbalances, dehydration and growth failure. Early diagnosis is important to prevent its further progression as it is not completely curable. There is still not much understanding about this disease. Further research is required to acquire more knowledge about its pathophysiology and to find newer therapies with better outcomes.

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