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Fanconi Syndrome: Genetic and Acquired Determinants

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Abstract: Fanconi syndrome is a condition characterized by proximal tubular dysfunction of the nephron, leading to urinary loss of glucose, amino acids, and electrolytes such as phosphate, sodium, potassium, calcium, and magnesium. It often co-occurs with tubular acidosis and a decreased level of the active form of vitamin D in the blood. Fanconi syndrome is associated with various conditions, both inherited and acquired, and may also occur as a side effect of certain medications.

Inherited causes of Fanconi syndrome include conditions such as cystinosis, Wilson's disease, Dent disease type I, Lowe syndrome, tyrosinemia type I, galactosemia, and Fanconi-Bickel syndrome. Acquired forms are linked to drug toxicity, including anticancer agents, antibiotics, chelating agents, and antiviral drugs. The syndrome may also develop in the context of monoclonal gammopathies, heavy metal intoxication, or exposure to aristolochic acids present in certain herbal remedies.

The treatment of Fanconi syndrome primarily focuses on addressing the underlying cause and may involve both symptomatic management and targeted therapy. Early diagnosis in children is crucial to prevent bone damage and growth disturbances.

This article provides a comprehensive review of the pathophysiology, clinical presentation, underlying causes, and management of Fanconi syndrome, with an emphasis on both inherited

Keywords: Fanconi syndrome; acquired Fanconi syndrome; inherited Fanconi syndrome; proximal nephron tubule; drug-related Fanconi syndrome; heavy metal inducted Fanconi syndrome

Introduction:
Fanconi syndrome is a disorder characterized by dysfunction of the proximal tubule of the nephron. The dominant symptoms include urinary losses of glucose, amino acids, and phosphates. In some cases, losses may also involve other electrolytes such as sodium, potassium, calcium, and magnesium. Tubular acidosis, caused by the loss of bicarbonates and impaired tubular secretion of H+ ions, is also relatively common in the clinical presentation. Fanconi syndrome is associated with reduced levels of the active form of vitamin D3 in the

blood, which, together with phosphate loss, can lead to osteomalacia and growth disturbances in children [1][2][3].

Fanconi syndrome is associated with a range of conditions, both acquired and congenital. It is also observed as a side effect of certain drug therapies, particularly following the use of anticancer agents, antiviral drugs, and aminoglycoside antibiotics [1][4][5].

Physiology of the Proximal Tubule of the Nephron

The proximal tubule of the nephron plays a crucial role in regulating both the composition and volume of final urine. It is responsible for the reabsorption of approximately 65% of water, sodium, and potassium. Additionally, it is the only site in the nephron where proteins and amino acids that have passed through the glomerular filtration membrane are reabsorbed [6].

In the proximal tubule, glucose reabsorption from the primary urine occurs through sodium-glucose transporters SGLT1 and SGLT2 [7]. This segment of the nephron also reabsorbs 75% of phosphates [8], less than 25% of magnesium ions, about 65% of calcium ions, approximately 95% of bicarbonates [9], as well as the majority of uric acid. In the initial portion of the tubule, sodium reabsorption occurs passively via an electrochemical gradient, and along with it, lactates and bicarbonates diffuse into the proximal tubule cells. Water is reabsorbed through aquaporins, particularly AQP1 [6].

Clinical Manifestations of Fanconi Syndrome

Proteinuria and Aminoaciduria

The proximal tubule is the only segment of the nephron responsible for the uptake of amino acids and proteins from the primary urine and their reabsorption into the bloodstream. As a result, proteinuria is a fundamental symptom of Fanconi syndrome [2][10].

Glycosuria

The presence of sodium-glucose transporters SGLT1 and SGLT2 in the proximal tubule of the nephron is responsible for the reabsorption of glucose from primary urine. Proximal tubule damage in Fanconi syndrome disrupts glucose reabsorption, resulting in glycosuria. Similar to aminoaciduria, glycosuria is one of the earliest clinical manifestations observed in Fanconi syndrome [2][10].

Polydipsia and Polyuria

Polydipsia and polyuria are primarily associated with osmotic diuresis caused by an increased presence of proteins, glucose, and electrolytes in the urine [2].

Electrolyte Imbalances

The proximal tubule of the nephron is responsible for the reabsorption of various electrolytes, including sodium, potassium, phosphorus, calcium, magnesium, and bicarbonates. In Fanconi syndrome, hypophosphatemia and hypokalemia are the dominant electrolyte disturbances [2][10].

Hyperchloremic Metabolic Acidosis

Damage to the proximal tubule of the nephron disrupts the reabsorption of bicarbonate ions (HCO_3^-) as well as the active transport of hydrogen ions (H^+) from the cells into the nephron lumen. The loss of bicarbonate ions can exceed 30% of the normally filtered bicarbonates, with serum bicarbonate levels typically ranging from 12 to 18 mmol/L [11].

Growth Retardation in Children

Growth retardation in children is associated with several factors, including chronic hypophosphatemia, low levels of active forms of vitamin D3, and metabolic acidosis [2].

Hypouricemia

Damage to the proximal tubule of the nephron reduces the reabsorption of uric acid from primary urine, leading to its increased excretion in the urine. As a result, uric acid levels in the bloodstream decrease [10].

Congenital Causes of Fanconi Syndrome

Dent Disease Type I

This is an X-linked disorder caused by a mutation in the gene encoding the chloride channel CLCN5. It is characterized by calcium deposition in the kidneys, hypercalciuria, and excessive urinary excretion of low-molecular-weight plasma proteins [12].

Detailed histopathological analysis in mice with this mutation has shown, among other findings, reduced levels of Na^+/H^+ exchanger type 3 (NHE3) and sodium-phosphate cotransporter Na-Pi2a, as well as abnormalities in the endocytic function of tubular cells [13].

Lowe Syndrome (Oculocerebrorenal Syndrome)

This X-linked disorder is caused by a mutation in the **OCRL** gene, leading to the accumulation of phosphatidylinositol bisphosphate. Fanconi syndrome-related symptoms include aminoaciduria (present in approximately 80% of patients), phosphaturia (in about 40-50%), hypercalciuria, metabolic acidosis, and excessive urinary excretion of low-molecular-weight plasma proteins.

A distinguishing feature of the renal manifestations of Lowe syndrome compared to Fanconi syndrome is the absence of glycosuria in the majority of patients with Lowe syndrome [14].

Wilson's Disease

Wilson's disease is a hereditary disorder caused by a mutation in the **ATP7B** gene, leading to defects in copper metabolism and deposition. Non-ceruloplasmin-bound copper is excreted in

the urine. During filtration, excess copper accumulates in the renal parenchyma, impairing kidney function [15].

Fanconi syndrome-related symptoms of Wilson's disease include proteinuria and glycosuria [16][17].

Cystinosis

Cystinosis is an autosomal recessive disorder caused by mutations in the **CTNS** gene, leading to lysosomal dysfunction and the accumulation of cystine deposits within lysosomes. This results in cystine buildup in tissues and organs and is the most common congenital cause of Fanconi syndrome [18].

When renal cells affected by the mutation die, significant amounts of stored cystine are released into the intercellular space, attracting inflammatory monocytes and CD68(+) macrophages that engulf the released cystine. However, the storage defect also affects macrophages, which cannot process or eliminate the engulfed cystine. This triggers an inflammatory cascade and attracts additional inflammatory cells, creating a self-perpetuating cycle of inflammation that leads to damage and impaired function of renal structures [19].

Renal symptoms of cystinosis typically manifest between 4 and 6 months of age and are closely associated with Fanconi syndrome due to proximal tubular damage. These symptoms include polyuria, polydipsia, urinary loss of low- and medium-molecular-weight plasma proteins, and electrolyte loss, such as sodium, potassium, magnesium, calcium, phosphate, bicarbonates, as well as glycosuria [18][20].

Tyrosinemia Type I

Tyrosinemia type I is an autosomal recessive disorder caused by a deficiency in fumarylacetoacetate hydrolase (FAH)**,** leading to abnormal tyrosine metabolism and the accumulation of this amino acid in tissues [21].

Renal symptoms typically emerge around 6 months of age and are the predominant features of untreated tyrosinemia type I during this period. Proximal tubular damage associated with this condition includes renal tubular acidosis, urinary potassium loss, and generalized aminoaciduria [22].

Galactosemia

Galactosemia is a congenital autosomal recessive disorder of galactose metabolism. The carbohydrate processing pathway involves three key enzymes, and galactosemia can result from a deficiency in any of them: galactose-1-phosphate uridylyltransferase (GALT), galactokinase (GALK), or UDP-galactose-4-epimerase (GALE). Among these, the most common cause of inherited galactosemia is a defect in **GALT** [23].

Renal symptoms of galactosemia associated with Fanconi syndrome primarily include albuminuria and hyperaminoaciduria. Elevated levels of carbohydrates in the urine may also be observed in galactosemia. However, this is not related to defects in glucose transporters within the proximal tubule of the nephron but is instead due to the presence of galactose in the urine, which is not reabsorbed by the proximal tubule [2].

Fanconi-Bickel Syndrome

Fanconi-Bickel syndrome is a congenital autosomal recessive disorder caused by a mutation in the **SLC2A2** gene, which encodes the GLUT2 glucose transporter. GLUT2 is present in various tissues, including proximal tubular cells of the nephron, where it facilitates the release of reabsorbed glucose from primary urine into the bloodstream. In patients with Fanconi-Bickel syndrome, reabsorbed glucose accumulates within cells as glycogen in the liver and kidneys, impairing its further transport and metabolism [24].

This condition primarily manifests as glucose loss in the urine, which can be massive in some cases, with reports indicating up to 325 g/1.73 m² per day. This often leads to the frequent development of hypoglycemia in patients. Due to these symptoms, patients are frequently misdiagnosed with type I diabetes, and insulin therapy is mistakenly initiated, which further increases the risk of hypoglycemia [25].

Acquired Causes of Fanconi Syndrome

Drug-Induced Fanconi Syndrome

The list of potentially nephrotoxic pharmaceuticals capable of inducing Fanconi syndrome is extensive. This article highlights substances most frequently reported in scientific publications to cause acquired Fanconi syndrome.

Tetracycline

Tetracycline is a naphthacene carboxamide derivative and an antibiotic that reversibly binds to the 30S ribosomal subunit of bacteria. It blocks both transcription and translation of bacterial proteins and exhibits a bacteriostatic effect [26].

The use of expired tetracycline has been shown in several case studies to have nephrotoxic effects manifesting as Fanconi syndrome [27][28][29].

Gentamicin

Gentamicin is an aminoglycoside antibiotic that acts as an inhibitor of the 30S ribosomal subunit. By binding to this subunit within microorganisms, it disrupts transcription and translation of bacterial proteins. Gentamicin is also thought to have affinity for mitochondrial ribosomes in human cells, which may underlie its adverse effects, such as ototoxicity and nephrotoxicity [30].

Several case studies have demonstrated the nephrotoxic potential of gentamicin, leading to the development of Fanconi syndrome [31][32][33][34][35].

Deferasirox

Deferasirox is an iron-chelating agent used in the treatment of iron overload [36].

Numerous review articles and case studies have demonstrated its nephrotoxic potential [37][38][39][40][41][42][43][44][45][46].

Sodium Valproate

Sodium valproate is an anticonvulsant that inhibits T-type calcium channels and voltage-dependent sodium channels. It selectively increases GABA concentrations in the central nervous system [47].

Numerous review articles and case studies have highlighted its nephrotoxic potential [48][49][50][51][52][53][54][55].

Tenofovir Diphosphate (Tenofovir)

Tenofovir is an acyclic adenosine nucleotide used in the treatment of chronic hepatitis B and, in combination with didanosine, in the treatment of HIV [56].

Numerous review articles and case studies have demonstrated its nephrotoxic potential [57][58][59][60][61][62][63][64][65].

Ifosfamide (Anticancer Agent)

Ifosfamide is an alkylating cytostatic agent used in the treatment of solid tumors and leukemias [66].

Numerous case studies and review articles have demonstrated its nephrotoxic potential [67][68][69][70][71][72][73][74][75].

Fanconi Syndrome in the Context of Monoclonal Gammopathies

Fanconi syndrome often occurs alongside diseases characterized by excessive production of monoclonal immunoglobulins or their fragments, such as light chains, particularly of the kappa type. In the proximal tubule of the nephron, filtered proteins are reabsorbed. Due to their excessive quantity, these proteins accumulate in lysosomes, forming crystalline cytoplasmic inclusions or assuming the form of casts [76].

Fanconi syndrome may accompany hematological diseases such as multiple myeloma and lymphoplasmacytic lymphoma, as well as a broad range of lymphoproliferative syndromes. It can also occur in the course of amyloidosis [77][78][79][80].

Fanconi Syndrome Induced by Heavy Metal Poisoning

Among heavy metals capable of inducing Fanconi syndrome, **cadmium** is most frequently mentioned in scientific literature. Additionally, individual review articles also cite **lead** and **arsenic** as potential causes [81][82][83][84][85][86].

Fanconi Syndrome Induced by Aristolochic Acids

Numerous cases of poisoning by aristolochic acids have been reported in scientific review articles, particularly in East Asia. These acids are found in herbs commonly used in traditional

herbal medicine, especially in China. This article highlights several review publications and case studies discussing Fanconi syndrome induced by the consumption of herbal mixtures containing aristolochic acids [87][88][89][90][91][92][93].

Treatment of Fanconi Syndrome

The treatment of Fanconi syndrome varies depending on the underlying cause. In secondary Fanconi syndrome, managing the primary disease reduces symptom severity and may lead to the resolution of Fanconi syndrome [1].

Direct treatment of Fanconi syndrome involves symptomatic management and correction of electrolyte imbalances. The clinical picture frequently features hypophosphatemia, hypokalemia, and both proximal and distal renal tubular acidosis [1][2].

Phosphate Supplementation

Phosphates are administered orally in doses of 0.5–3.0 g of elemental phosphorus per day, divided into 4–6 doses. Due to impaired $1,25(OH)_2D_3$ synthesis in this syndrome, biologically active vitamin D3 analogs should be co-administered alongside phosphate supplementation to prevent bone damage. Serum and urine calcium levels should be monitored during treatment [1].

Renal Tubular Acidosis Management

Renal tubular acidosis, including proximal (HCO_3^- reabsorption defect) and distal (H^+ secretion defect) forms, is a common issue in Fanconi syndrome. Treatment involves alkalization using sodium bicarbonate ($NaHCO_3$), potassium bicarbonate ($KHCO_3$), or citrate solutions [1][94].

- **Distal Renal Tubular Acidosis**
  Sodium bicarbonate and potassium bicarbonate solutions are used at daily doses of 1–2 mmol/kg of body weight. This treatment is usually sufficient to maintain acid-base balance and correct hypokalemia. In patients with kidney stones, $KHCO_3$-containing solutions are preferred due to the increased risk of stone formation with sodium salts [94].
- **Proximal Renal Tubular Acidosis**
  Larger amounts of alkalizing solutions (10–15 mmol/kg of body weight daily) are necessary. Potassium salts are preferred due to the frequent co-occurrence of hypokalemia. However, alkalizing treatment alone is often insufficient to prevent hypokalemia in proximal renal tubular acidosis, necessitating additional potassium supplementation [94].

Treatment of Underlying Diseases Causing Fanconi Syndrome

Wilson's Disease

Pharmacological treatment involves the use of copper-chelating agents such as **D-penicillamine** and **trientine (triethylenetetramine)**. Additionally, dietary modifications to eliminate copper-rich foods are recommended [15]

Galactosemia

Treatment involves minimizing or completely eliminating galactose from the diet [95].

Tyrosinemia Type I

Treatment requires early administration of **nitisinone (NTBC)**, an inhibitor of 4-hydroxyphenylpyruvate dioxygenase, along with a diet that excludes tyrosine-containing foods [21][96].

Heavy Metal Poisoning

Treatment includes the use of chelating agents, particularly **dimercaptosuccinic acid (DMSA)** and **dimercaptopropanesulfonic acid (DMPS)** [97].

Conclusions

Fanconi syndrome has a complex etiology stemming from various pathophysiological mechanisms, both acquired and congenital. This underscores the necessity of an individualized diagnostic approach for each patient with this condition. Early diagnosis is particularly critical, especially in children, as it plays a key role in preventing permanent consequences such as growth disturbances.

Due to the diverse renal symptoms, the diagnosis of Fanconi syndrome in children is often delayed and may be mistaken for other conditions, such as diabetes. Additionally, careful monitoring of blood levels of potentially nephrotoxic drugs used in various therapies is of utmost importance, as it can reduce the risk of developing Fanconi syndrome.

Disclosure

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