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**Review Article**

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# Fanconi Syndrome

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## Abstract

The renal syndrome that is associated with the Swiss pediatrician Guido Fanconi was actually described in parts and under various names by several researchers who followed him. Several mechanisms can cause Fanconi syndrome, some of which may not be fully known. These mechanisms include decreased influx of solute into the blood from the tubular epithelium, increased back flux of solute across the tight junctions separating the cells that line the tubular epithelium from the blood to the glomerular filtrate, defective solute influx into the tubular epithelium, and leakage of the solute back into the lumen from the tubular epithelium. This could be due to a larger problem associated with generating the energy that is needed by the cells to accomplish the task of bringing solutes in through the brush border membrane or in transferring solutes out through the basolateral membrane.

**Keywords:** renal syndrome, Fanconi syndrome, glomerular filtrate, basolateral membrane.

## Introduction

The renal syndrome that is associated with the Swiss pediatrician Guido Fanconi was actually described in parts and under various names by several researchers who followed him. The first researcher was Abderhalden; in 1903, he discovered cystine crystals in the liver and spleen of a 21-month-old infant and called the disease "a familial cystine diathesis." In 1924, Lignac described 3 such children who presented with severe rickets and growth retardation. In 1931, Fanconi described a child who had glucosuria and albuminuria in addition to rickets and dwarfism. Two years later, de Toni added hypophosphatemia to the clinical picture; soon after, Debre et al found large amounts of organic acids in the urine of an 11-year-old girl.

Fanconi's further contribution to the subject came in 1936, when he recognized the similarities between these cases, added 2 new patients to the list, named the disease nephrotic-glucosuric dwarfism with hypophosphatemic rickets, and suggested that the organic acids found in the urine may be amino acids. Fanconi's results were confirmed in 1943 by McCune et al and in 1947 by Dent, who established that the organic acids originated in the kidneys (Sahar *et al.*, 2018).

## Pathophysiology

Several mechanisms can cause Fanconi syndrome, some of which may not be fully known. These mechanisms include decreased influx of solute into the blood from the tubular epithelium, increased back flux of solute across the tight junctions separating the cells that line the tubular epithelium from the blood to the glomerular filtrate, defective solute influx into the tubular epithelium, and leakage of the solute back into the lumen from the tubular epithelium. This could be due to a larger problem associated with generating the energy that is needed by the cells to accomplish the task of bringing solutes in through the brush border membrane or in transferring solutes out through the basolateral membrane. For example, heavy metal poisoning can compromise the utilization of energy by mitochondria (Yoshida *et al*., 2019).

**Symptoms of inherited FS can be seen as early as infancy. They include**:

- excessive thirst
- excessive urination
- vomiting
- failure to thrive
- slow growth
- frailty
- ricket
- low muscle tone
- corneal abnormalities
- kidney disease

Symptoms of acquired FS include:

- bone disease
- muscle weakness
- low blood phosphate concentration (Hypophosphatemia)
- low blood potassium levels (Hypokalemia)
- excess amino acids in urine (hyperaminoaciduria)

**The clinical features of proximal renal tubular acidosis are:**

- Polyuria, polydypsia and dehydration
- Hypophosphatemic rickets (in children) and osteomalasia (in adults)
- Growth failure
- Acidosis
- Hypokalemia
- Hyperchloremia

- Other features of the generalized proximal tubular dysfunction of the Fanconi syndrome are:

- Hypophosphatemia/hyperphosphaturia
- Glycosuria
- Proteinuria/aminoaciduria
- Hyperuricosuria

## Causes

In contrast to Hartnup disease and related tubular conditions, Fanconi syndrome affects the transport of many different substances, so is not considered to be a defect in a specific channel, but a more general defect in the function of the proximal tubules.Different diseases underlie Fanconi syndrome; they can be inherited, congenital, or acquired.

## Inherited

Cystinosis is the most common cause of Fanconi syndrome in children. Other recognised causes are Wilson's disease, Lowe syndrome, tyrosinemia , galactosemia, glycogen storage diseases, and hereditary fructose intolerance.Two forms, Dent's disease and Lowe syndrome, are X linked (Cochat *et al*., 2010). This mutation misdirects the EHHADH to the mitochondria. This interferes with respiratory complex I and with beta oxidation of fatty acids. The end result is a decrease in the ability of the mitochondria to produce ATP.It was shown that a specific mutation (R76W) of *HNF4A*, a gene encoding a transcription factor, causes Fanconi syndrome in human (Hametin *et al*., 2014). In the kidney, *HNF4A* is expressed in the proximal tubules specifically. Deletion of *Hnf4a* in the developing mouse kidney caused Fanconi syndrome phenotypes including polyruia, polydipsia, glycosuria, and phosphaturia. The *Hnf4a* mutant kidney showed a defect in the formation of proximal tubules. Other inherited metabolic diseases that can be involved with FS include:

- Lowe syndrome
- Wilson’s disease
- inherited fructose intolerance

## Acquired

It is possible to acquire this disease later in life.

Causes include ingesting expired tetracyclines (where tetracycline changes to form epitetracycline and anhydrotetracycline which damage the proximal tubule), and as a side effect of tenofovir in cases of pre-existing renal impairment (Irizarry *et al*., 2009). In the HIV population, Fanconi syndrome can develop secondary to the use of an antiretroviral regimen containing tenofovir and didanosine (Tu *et al*., 2018). Lead poisoning also leads to Fanconi syndrome. Multiple myeloma or monoclonal gammopathy of undetermined significance can also cause the condition. Additionally, Fanconi Syndrome can develop as a secondary or tertiary effect of certain autoimmune disorders. The causes of acquired FS are varied. They include:

- exposure to some chemotherapy
- use of antiretroviral drugs
- use of antibiotic drugs

Toxic side effects from therapeutic drugs are the most common cause. Usually the symptoms can be treated or reversed; sometimes the cause of acquired FS is unknown. The anticancer drugs associated with FS include:

- ifosfamide
- cisplatin and carboplatin
- azacitidine
- mercaptopurine
- suramin (also used to treat parasitic diseases)

Other drugs cause FS in some people, depending on dosage and other conditions. These include:

- **Expired tetracyclines.** The breakdown products of expired antibiotics in the tetracycline family (anhydrotetracycline and epitetracycline) can cause FS symptoms within days.
- **Aminoglycoside antibiotics.** These include gentamicin, tobramycin, and amikacin. Up to 25 percent of people treated with these antibiotics develop FS symptoms, notes a 2013 review.
- **Anticonvulsants.** Valproic acid is one example.
- **Antivirals.** Theseinclude didanosine (ddI), cidofovir, and adefovir.
- **Fumaric acid.** This drug treatspsoriasis.
- **Ranitidine.** This drug treats peptic ulcers.
- **Boui-ougi-tou.** This is a Chinese drug used for obesity (Sahar *et al*., 2017).

Other conditions associated with FS symptoms include:

- chronic, heavy alcohol use
- glue sniffing
- exposure to heavy metals and occupational chemicals
- vitamin D deficiency
- kidney transplantation
- multiple myeloma
- amyloidosis

## Diagnosis

Urine routine, might not be completely reliable but is an important indicator, Diabetes mellitus and diabetes insipidus can cause the polydipsia and polyuria and are often observed in Fanconi syndrome. Vitamin D or calcium deficiencies can give rise to rickets or osteomalacia (Koda *et al*., 2019).

## Laboratory studies

The diagnosis of Fanconi syndrome is made based on tests that document the excessive loss of substances in the urine (eg, amino acids, glucose, phosphate, bicarbonate) in the absence of high plasma concentrations. More elaborate tests are designed to determine the renal threshold for these substances (ie, the concentration in the blood at which these substances appear in the urine) or their fractional reabsorption (ie, the percentage of the filtered load that is reabsorbed by the renal tubule). The results are compared with normal levels for age. Recently, an increased urinary lactate-to-creatinine ratio has been postulated as a sensitive test for disordered proximal tubular function. Moreover, urinary retinol-binding protein 4 is thought to be a functional biomarker of the proximal tubule and elevated levels appears to be an excellent screening test for Fanconi syndrome ( Koda *et al*., 2019). Tests that can be carried out are
Urine test

Renal function tests : Creatinin test
Bicarbonate test
Urea test
Electrolyte test

## Conclusion

Several mechanisms can cause Fanconi syndrome, some of which may not be fully known. These mechanisms include decreased influx of solute into the blood from the tubular epithelium, increased back flux of solute across the tight junctions separating the cells that line the tubular epithelium from the blood to the glomerular filtrate, defective solute influx into the tubular epithelium, and leakage of the solute back into the lumen from the tubular epithelium.

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