Fanconi’s Syndrome -I
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Introduction
Fanconi Syndrome, also known as Lignac-de Toni-Debré-Fanconi syndrome is named after a Swiss Pediatrician Guido Fanconi who initially described the syndrome in 1924, presented with growth retardation, glycosuria and hypophosphatemia. It is either hereditary or acquired. Usual presentation in children is due to hereditary causes, whereas as adults present with one of the acquired causes. Fanconi syndrome or Fanconi’s syndrome (FS) is a syndrome of inadequate reabsorption in the proximal renal tubules of the kidney. After the fluid is filtered through Glomerulus, proximal convulated tubule (PCT) is the first part of the kidney to process the reabsorption of fluid containing nutrients and metabolites. In FS there is a defect in PCT which results in various small metabolites being passed into the urine instead of being reabsorbed from the tubular fluid (for example, glucose, amino acids, uric acid, phosphate, and bicarbonate). In FS the reabsorption of other solutes like sodium, calcium, magnesium, chloride, and potassium is also compromised but distal convulated tubule compensates for these losses.

Etiology
The cause of Fanconi Syndrome can be inherited and acquired. Secondary FS is due to idiopathic diseases, Alport Disease, Lowe Syndrome and Dent Wrong Disease. It can also be associated with other inherited metabolic diseases such as Cystinosis, Wilson’s disease, Hereditary fructose intolerance, Galactosemia. The most common inherited cause of FS is cystinosis. The acquired causes of FS include vitamin D deficiency, amyloidosis, sarcoidosis, multiple myeloma, acute Lymphoblastic leukemia, paroxysmal nocturnal hemoglobinuria, renal transplantation, Maleic Acid, drugs and some exogenous toxins that affect PCT (cadmium, mercury, lead). The most common acquired cause of FS is drug toxicity. It includes chemotherapeutic agents, outdated tetracycline, antibiotics, immunosuppressants, anticonvulsant, aminoglycoside. Valproic Acid used in treatment of epilepsy causes FS. It is seen mainly in children and the disease settles when the use of drug is discontinued. Ifosfamide and Carboplatin are chemotherapeutic agents proven (by trials on animals) to cause FS by increasing resistance in renal blood vessels and ultimately affecting the reabsorption in PCT. Lesser-known causes include Monoclonal gammopathy, honeybee and Legionella pneumonia for unknown reasons.

Pathogenesis
Glomerulus filters 180 liters per day out of which 99% is reabsorbed by kidney and 1% is excreted in the form of urine. 65% of the reabsorption is done via PCT using specialized transporters and channels present on the basolateral cell membrane (towards interstitium) and apical membrane (towards tubular lumen). It reabsorbs about 65% of water, sodium, potassium, and chloride, 100% of glucose, 100% amino acids, and 85-90% of bicarbonate. The transportation takes place via two routes in PCT either through intracellular or paracellular. Defect in channels across PCT lead to Fanconi Syndrome. Multiple theories have been described regarding the pathogenesis. One such theory involves, defect in energy dependent carriers leading to decrease influx of solutes across the proximal tubules.

Genetic cause in most types of isolated Fanconi’s syndrome has been unknown. A mutation in mitochondria has been linked to genetic cause of Fanconi’s syndrome. A mutation in HNF4A has been linked to Fanconi’s in Drosophila nephrocytes.
References:


