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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[1], presented with growth retardation, glycosuria and hypohphosphatemia. It is either hereditary or acquired. Usual presentation in children is due to hereditary causes, where 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[2]. 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[3].

Etiology

The cause of Fanconi Syndrome can be inherited and acquired. Secondary FS is due to idiopathic diseases, Alport Disease, Lowe Syndrome[4] and Dent Wrong Disease[5].It can also be assosiated with other inherited metabolic diseases such as Cystinosis ,Wilson' s disease[6], Heriditarory fructose intolerence[7],Galactosemia. The most common inherited cause of FS is cystinosis[8].

The acquired causes of FS include vitamin D deficiency[9], amyloidosis[10], sarcoidosis[11], multiple myeloma[12], acute Lymphoblastic leukemia[13], paroxysmal nocturnal hemoglobinuria[14], renal transplantation[15], Maleic Acid[16], drugs[17] and some exogenous toxins[18] that affect PCT (cadmium, mercury, lead)[19].The most common acquired cause of FS is drug toxicity[20].It includes chemotherapeutic agents, outdated tetracycline, antibiotics, immunosuppressants, anticonvulsant, aminoglycoside.

Valproic Acid used in treatment of epilepsy causes FS[21]. It is seen mainly in children and the disease settles when the use of drug is discontinued[22].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[23]. Lesser-known causes include Monoclonal gammopathy[24], honeybee [25] and Legionella pneumonia for unknown reasons[26].

Pathogenesis

Glomerulus filters 180 liters per day out of which 99% is reabsorbed by kidney and 1% is excreted in the form of urine[27]. 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)[28]. It reabsorbs about 65% of water, sodium, potassium, and chloride, 100% of glucose, 100% amino acids, and 85-90% of bicarbonate[29]. 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 [30].

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 [31]. A mutation in HNF4A has been linked to Fanconi' s in Drosophilia nephrocytes [32].

References:

1. Bakx CJ. Renalrickets, renal diabetes and cystine metabolism. Toni-Fan-coni-Debre'syndrome. Nederlands tijdschrift voor geneeskunde. 1950;94:2326-35.

2. Rehberg PB. Studies on kidney function: the rate of filtration and reabsorption in the human kidney. Biochemical Journal. 1926;20(3):447.

3. Hall AM, Bass P, Unwin RJ. Drug-induced renal Fanconi syndrome. QJM: An International Journal of Medicine. 2014 Apr 1;107(4):261-9.

4. Kleta R. Fanconi or not Fanconi? Lowe syndrome revisited.

5. Solano A, Lew SQ, Ing TS. Dent – Wrong disease and other rare causes of the Fanconi syndrome. Clinical kidney journal. 2014 Aug 1;7(4):344-7.

6. Morgan HG, Stewart WK, Lowe KG, Stowers JM, Johnstone JH. Wilson's disease and the Fanconi syndrome. Quarterly Journal of Medicine. 1962;31:361-84.

7. Morris RC. An experimental renal acidification defect in patients with hereditary fructose intolerance: II. Its distinction from classic renal tubular acidosis; its resemblance to the renal acidification defect associated with the fanconi syndrome of children with cystinosis. The Journal of clinical investigation. 1968 Jul 1;47(7):1648-63.

8. Haque SK, Ariceta G, Batlle D. Proximal renal tubular acidosis: a not so rare disorder of multiple etiologies. Nephrology Dialysis Transplantation. 2012 Dec 1;27(12):4273-87.

9. Bando H, Hashimoto N, Hirota Y, Sakaguchi K, Hisa I, Inoue Y, Imanishi Y, Seino S, Kaji H. Severe hypophosphatemic osteomalacia with Fanconi syndrome, renal tubular acidosis, vitamin D deficiency and primary biliary cirrhosis. Internal Medicine. 2009;48(5):353-8.

10. Finkel PN, Kronenberg K, Pesce AJ, Pollak VE, Pirani CL. Adult Fanconi Syndrome, Amyloidosis and Marked x-Light Chain Proteinuria. Nephron. 1973;10(1):1-24.

11. Correia FA, Marchini GS, Torricelli FC, Danilovic A, Vicentini FC, Srougi M, Nahas WC, Mazzucchi E. Renal manifestations of sarcoidosis: from accurate diagnosis to specific treatment. International braz j urol. 2020 Feb;46(1):15-25.

12. Costanza DJ, Smoller M. Multiple myeloma with the Fanconi syndrome: study of a case, with electron microscopy of the kidney. The American Journal of Medicine. 1963 Jan 1;34(1):125-33.

13. Sahu KK, Law AD, Jain N, Khadwal A, Suri V, Malhotra P, Varma SC. Fanconi syndrome: a rare initial presentation of acute lymphoblastic leukemia. Indian Journal of Hematology and Blood Transfusion. 2016 Jun;32(1):5-7.

14. Hsiao PJ, Wang SC, Wen MC, Diang LK, Lin SH. Fanconi syndrome and CKD in a patient with paroxysmal nocturnal hemoglobinuria and hemosiderosis. American Journal of Kidney Diseases. 2010 Jan 1;55(1):e1-5.

15. Sahu KK, Law AD, Jain N, Khadwal A, Suri V, Malhotra P, Varma SC. Fanconi syndrome: a rare initial presentation of acute lymphoblastic leukemia. Indian Journal of Hematology and Blood Transfusion. 2016 Jun;32(1):5-7.

16. Reynolds R, McNamara PD, Segal S. On the maleic acid induced Fanconi syndrome: effects on transport by isolated rat kidney brushborder membrane vesicles. Life sciences. 1978 Jan 1;22(1):39-43.

17. Hall AM, Bass P, Unwin RJ. Drug-induced renal Fanconi syndrome. QJM: An International Journal of Medicine. 2014 Apr 1;107(4):261-9.

18. Román AV, Rodríguez MS, Arias BP. Fanconi syndrome following an accident at work. Nefrologia: publicacion oficial de la Sociedad Espanola Nefrologia. 2009;29(5):491-2.

19. Gonick HC. Nephrotoxicity of cadmium & lead. Indian J Med Res. 2008 Oct 1;128(4):335-52.
20. Hall AM, Bass P, Unwin RJ. Drug-induced renal Fanconi syndrome. QJM: An International Journal of Medicine. 2014 Apr 1;107(4):261-9.

21. Endo A, Fujita Y, Fuchigami T, Takahashi S, Mugishima H. Fanconi syndrome caused by valproic acid. Pediatric neurology. 2010 Apr 1;42(4):287-90.

22. Zaki EL, Springate JE. Renal injury from valproic acid: case report and literature review. Pediatric neurology. 2002 Oct 1;27(4):318-9.

23. Rossi R, Rath B, Ullrich K, Ehrich JH. Ifosfamide-induced nephrotoxicity. Monatsschrift Kinderheilkunde. 1993 Jul 1;141(7):594-601.

24. Tu H, Mou L, Zhu L, Jiang Q, Gao DS, Hu Y. Acquired Fanconi syndrome secondary to light chain deposition disease associated with monoclonal gammopathy of renal significance: A case report. Medicine. 2018 Sep;97(36).

25. Ram R, Swarnalatha G, Ashok KK, Madhuri HR, Dakshinamurty KV. Fanconi syndrome following honeybee stings. International urology and nephrology. 2012 Feb 1;44(1):315-8.

26. Koda R, Itoh R, Tsuchida M, Ohashi K, Iino N, Takada T, Narita I. Legionella Pneumonia Complicated with Acquired Fanconi Syndrome: A Case Report. Internal Medicine. 2018:0942-18.

27. Macías-Núñez JF, López-Novoa JM. Physiology of the healthy aging kidney. InThe aging kidney in health and disease 2008 (pp. 93-112). Springer, Boston, MA.

28. Zhuo JL, Li XC. Proximal nephron. Comprehensive Physiology. 2013 Jan;3(3):1079-123.

29. Curthoys NP, Moe OW. Proximal tubule function and response to acidosis. Clinical Journal of the American Society of Nephrology. 2014 Sep 5;9(9):1627-38.

30. Klootwijk ED, Reichold M, Helip-Wooley A, Tolaymat A, Broeker C, Robinette SL, Reinders J, Peindl D, Renner K, Eberhart K, Assmann N. Mistargeting of peroxisomal EHHADH and inherited renal Fanconi's syndrome. New England Journal of Medicine. 2014 Jan 9;370(2):129-38.

31. Marchesin V, Pérez-Martí A, Le Meur G, Pichler R, Grand K, Klootwijk ED, Kesselheim A, Kleta R, Lienkamp S, Simons M. Molecular basis for autosomal-dominant renal Fanconi syndrome caused by HNF4A. Cell reports. 2019 Dec 24;29(13):4407-21.