42 Fanconi Syndrome

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Fanconi syndrome (FS) is a generalized dysfunction of the renal proximal tubules leading to excessive urinary wasting of amino acids, glucose, phosphate, uric acid, bicarbonate, and other solutes. The patients develop failure to thrive, polyuria, polydipsia, dehydration, and rickets in children, and osteoporosis and osteomalacia in adults. The patients also manifest renal salt wasting, hypokalemia, metabolic acidosis, hypercalciuria, and low-molecular-weight (LMW) proteinuria. De Toni, Debré, and Fanconi described children with renal rickets and glucosuria in the 1930s (1, 2, 3). FS is named after Guido Fanconi, a Swiss pediatrician or it is called as de Toni-Debré-Fanconi syndrome.

Pathophysiology

The renal proximal tubules reabsorb almost all of the physiologically filtered load of proteins including of albumin, LMW proteins, amino acids, glucose, bicarbonate, sodium, chloride, phosphate, and uric acid. The transport processes in the proximal tubule can be characterized broadly as megalin/cubilin-mediated endocytic pathways and sodium (Na^+) gradient-dependent transport systems.

The proximal tubule cells have extensive luminal receptors and endocytic apparatus such as megalin and cubilin that are critical for the reabsorption and degradation of proteins that traverse the glomerular filtration barrier (4) (◉ *Fig. 42-1*) as well as for the extensive recycling of many functionally important membrane proteins (5). Numerous filtered proteins including albumin, LMW proteins, polypeptide hormones, vitamin-binding proteins, and polybasic drugs such as aminoglycosides from glomerulus are bound to megalin and cubilin in the luminal membrane of proximal tubules. Then, the protein-receptor complex is incorporated into the endosome. The ligand and receptor are disassociated in the endosome; the receptor is recycled back to the luminal membrane and the reabsorbed proteins go into lysosome for further processing (◉ *Fig. 42-2*). This disassociation is dependent on acidification of the endosome by increased concentration of H^+ and Cl^- due to the function of H^+-ATPase (proton pump) and ClC-5 chloride channel. An abnormal endocytosis pathway may affect the recycling of transport proteins (megalin and cubilin), the back to the luminal membrane, and the expression of megalin and cubilin in the luminal membrane, leading to decreased solute reabsorption. Perturbation of endosomal acidification in proximal tubule cells leads to diminished reabsorption and increased urinary wasting of albumin, LMW proteins, electrolytes, and solutes. Cadmium inhibits H^+-ATPase and mitochondria, which results in a Fanconi-like syndrome (6). Folimycin, a H^+-ATPase inhibitor, abolishes albumin uptake by proximal tubules (7). Moreover, a defect of ClC-5 chloride channel in patients with Dent disease manifests Fanconi syndrome (8). Acidification defect in the endosome in Dent disease leads to recycling from intracellular endosome into luminal membrane resulting in megalin deficiency in the luminal membrane of the proximal tubule. Analysis of normal human urine samples identified megalin as a physiologically excreted protein. The presence of megalin in normal human urine is due to shedding from the proximal tubule cells into the lumen. Patients with Dent disease demonstrate an almost complete absence of urinary megalin (9). This megalin-shedding deficiency in the urine is also observed in patients with Lowe syndrome (9).

Reabsorption of filtered solutes including glucose, phosphate, amino acids, and bicarbonate by proximal tubule cells is accomplished by transport system at the brush border membrane that are directly or indirectly coupled to Na^+ movement, by energy production and transport from the mitochondria, and by the Na^+, K^+-ATPase at the basolateral membrane. The Na^+, K^+-ATPase lowers intracellular Na^+ concentration and provides the electrochemical gradient that allows Na^+-coupled solute entry into the cell. Disturbances in energy generation could impair net transepithelial transport in the proximal tubule. Energy is necessary for the operation of Na^+, K^+-ATPase and other membrane carriers that are involved with solute reabsorption of amino acid, glucose, phosphate, uric acid, and bicarbonate. Although the weight of bilateral kidneys is less than 1% of total body weight, kidneys consume about 10% of the total energy consumed by the whole body in a static condition. Moreover, most of the energy is consumed in the proximal tubule cells to operate multiple

⬛ Figure 42-1

Structure of megalin and cubilin. (Veroust PJ, Birn H, Nielsen R et al. The tandem endocytic receptors megalin and cubilin are important proteins in renal pathology. *Kidney Int* 2002;62:745–756).
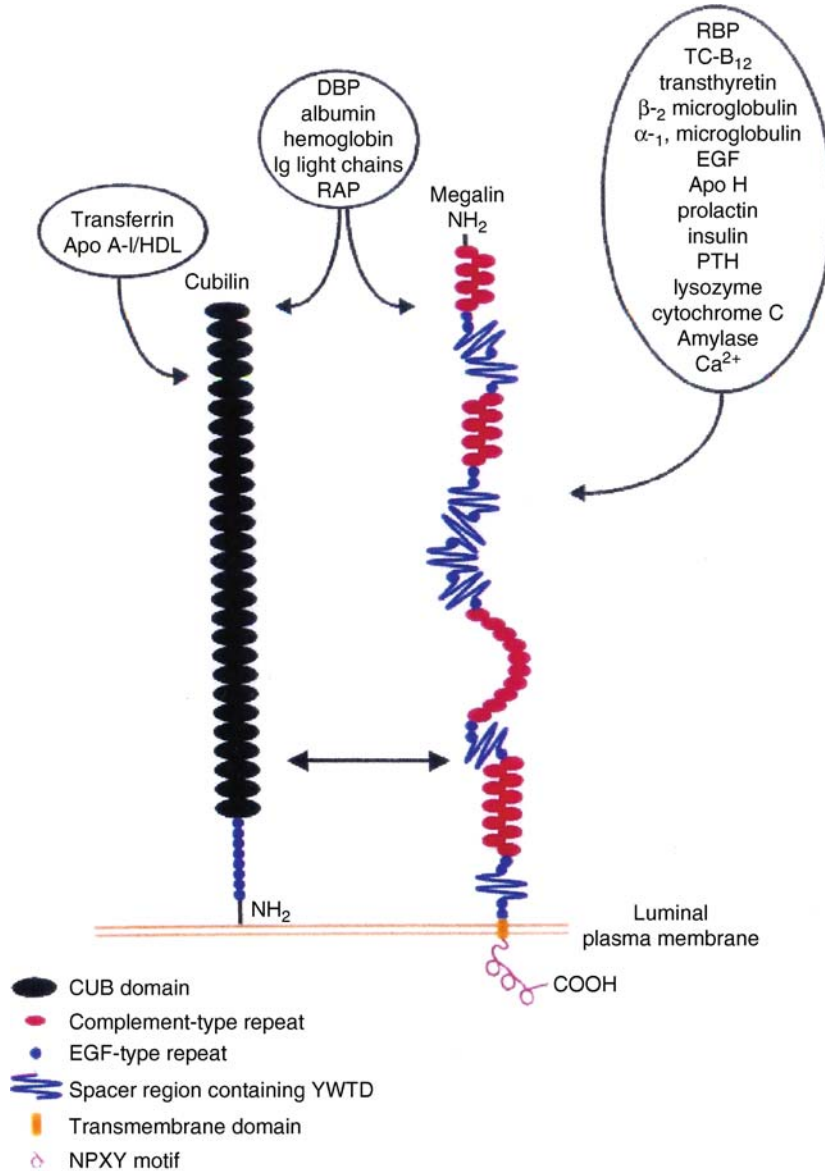

membrane and intracellular transporter proteins. A defect in energy generation in the proximal tubule cells produces multiple transport anomalies of the proximal tubule that characterize the FS. The ATP production is severely compromised in cystine-loaded tubule in cystinosis (10). Thiol-containing enzymes are critical for renal energy metabolism. Cystine inhibits in vivo and in vitro the thiol-containing enzyme activity resulting in multiple renal transport anomalies (11). The mitochondrial respiratory chain has a major role in ATP production during aerobic respiration. Genetic defects of enzyme complexes of the oxidative phosphorylation system or toxic substances including of drugs in the proximal tubule cells can produce mitochondrial respiratory chain defect leading to multiple renal transport anomalies (12, 13). In contrast, isolated dysfunction of transporter proteins in proximal tubule cells results in the selective wasting of amino acids, glucose, phosphate, bicarbonate, or uric

◼ **Figure 42-2**

Schematic model of endocytosis in the proximal tubule cells. Albumin and low molecular weight proteins are filtered into the primary urine and endocytosed by proximal tubule cells via the megalin-cubilin receptor pathway. (a) The receptor-ligand complexes progress along the endocytic pathway. The endosomes undergo a progressive, ATP-dependent acidification that results in the dissociation of the receptor-ligand complexes, with megalin and cubilin being recycled in the luminal membrane, whereas the ligand is directed to lysosomes for degradation. (b) Vesicular acidification is mediated by the vacuolar H^+-ATPase, which requires a net Cl^- conductance to functions as an electrogenic nCl^-/H^+ exchanger, which is predicted to facilitate acidification and to play a role in keeping high vesicular Cl^- concentration. (Devuyst O, Pirson Y. Genetics of hypercalciuric stone forming disease. *Kidney Int* **2007:72:1065–1092).**
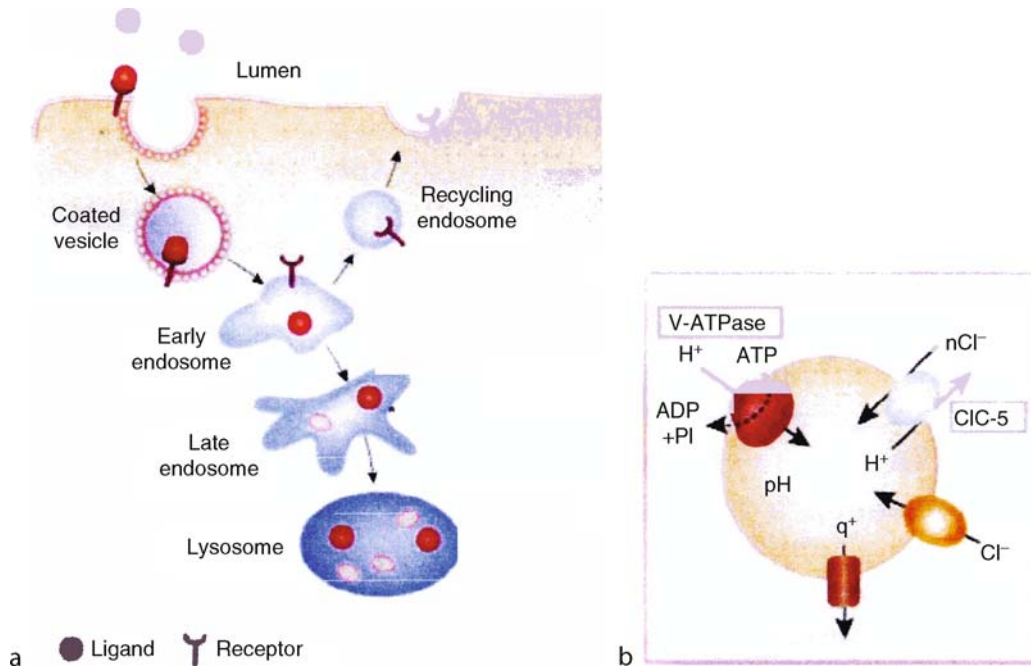
acids. However, glucosuria and aminoaciduria are seen in some patients with defective isolated proteins. They are familial renal glucosuria resulting from the mutations in the kidney-specific low affinity/high capacity Na^+/glucose cotransporter gene (*SLC5A2*) and maturity-onset diabetes of young age type 3 (MODY3) resulting from the mutations in hepatocyte nuclear factor-1 alpha gene that acts as a regulator of transcription for *SLC5A2* (14, 15). Generalized aminoaciduria seen in these patients is considered as a consequence of the impairment in tubular glucose reabsorption, whereas the precise mechanism is not known.

Signs and Symptoms

Growth Retardation (Failure to Thrive)

Growth retardation (failure to thrive) is a common feature of FS in children (16). Patients with FS present severe growth failure at the time of diagnosis that persists into adult life. The pathomechanism of growth failure in FS is complex. Malnutrition, hypokalemia, hypophosphatemia, and metabolic acidosis can lead to growth retardation in patients with FS (17). Potassium deficiency induces growth retardation through reduced circulating levels of growth hormone (GH) and insulin-like growth factor I (IGF-I) (18, 19). Hypokalemia can induce appetite decrease leading to malnutrition and extracellular volume contraction. Metabolic acidosis inhibits growth hormone secretion, the expression of IGF-I and GH receptor (20). Hypophosphatemia is related to severe bone changes leading to rickets and growth retardation in children with FS (21). In patients with adult onset FS, osteomalacia is thought to result from hypophosphatemia due to renal phosphate loss and relative 1,25-dihydroxyvitamin D3 deficiency (22, 23). Metabolic acidosis impairs the conversion of 25-vitamin D3 to 1,25-dihydroxy vitamin D3. The patients present bone and joint pain in the hips,

shoulders, and trunk and difficulty of walking due to multiple bone fracture. Hypomineralization of dentin structure and immature formation of craniofacial bones are seen in patients with FS (24). Specific forms of FS are associated with endocytotosis pathway dysfunction; disruption of megalin-mediated uptake vitamin D-binding protein/25-vitamin D3 complex produces metabolic bone disease in affected individuals (25).

Earlier diagnosis and efficient correction of acidosis and electrolyte balances by supportive therapy can contribute to improve growth and final height in patients with FS (17, 21). However, supportive therapy is frequently unable to prevent further loss of relative height in patients with FS, especially those with cystinosis.

Polyuria, Polydipsia, and Dehydration

Polyuria, polydipsia, and dehydration are frequently seen in patients with FS. Polyuria is secondary to the osmotic diuresis from the excessive urinary solute losses and urine concentration defect in the collecting ducts due to chronic hypokalemia. Recurrent acute fever due to dehydration is a frequent manifestation in infants with FS. In the most common type of cystinosis, Fanconi syndrome occurs at 6–12 months of age. Recurrent febrile episodes are often the first sign of FS in infantile patients with cystinosis (26).

Generalized Aminoaciduria (Generalized Hyperaminoaciduria)

Molecular weight (MW) of 20 different amino acids is small; the largest amino acid is tryptophan [MW = 204 D (daltons)]. Amino acids are not bound to proteins in the plasma. Thus, amino acids are freely filtered from glomerulus. Then, 95–99% of filtered load of amino acids are reabsorbed in the proximal tubules. More than one transporter in the proximal tubule cells absorbs amino acids. Fractional excretion of amino acid is usually less than 3% in the controls except for neonate or premature babies. However, only histidine has a fractional excretion of 5% in the controls.

$$\text{Fractional excretion of amino acid } (\%) = [(U_{aa}/P_{aa})/(U_{cr}/P_{cr})] \times 100$$

(aa; amino acid, cr; creatinine, U; urine, P; plasma)

Therefore, the excretion more than 5% of the filtered load of amino acid is termed aminoaciduria or hyperaminoaciduria. Every amino acid is highly excreted in patients with FS, and this phenomenon is called as *generalized aminoaciduria.*

Glucosuria

Filtered load of glucose (D-glucose, MW = 180 D) is almost completely absorbed by a sodium-coupled active transport located in the brush border membrane of the proximal tubule in the normal condition. Glucose reabsorption involves a couple of transporters at the luminal and basolateral membranes of the proximal tubules. The driving force for glucose reabsorption is provided by Na^+, K^+-ATPase in the plasma membrane. Thus, very small amount of glucose are present in the urine in the normal condition. Glucosuria is a common manifestation in FS. It is derived from impaired reabsorption of glucose when serum glucose is normal. Renal threshold of glucose is reduced in FS. Glucosuria is one of the originally described clinical features of FS (1, 2, 3). 0.5–20 g of glucose a day is lost in the urine in patients with FS.

Hypophosphatemia

Most of the patients with FS manifest a low tubular reabsorption of phosphate (percent tubular reabsorption of phosphate: %TRP, >80–85% in the control) and decreased serum phosphate. Rickets and osteomalacia are produced by the increased urinary wasting of phosphate as well as by impaired 1α-hydroxylation of 25-hydroxy vitamin D3 by proximal tubule cells (27).

$$\%TRP = [1-(U_p/S_p)/(U_{cr}/S_{cr})] \times 100$$

(p; phosphate, cr; creatinine, U; urine, S; serum)

The maximal threshold of phosphate (TmP/GFR) is a very sensitive indicator that reflects the reabsorption of phosphate in the renal tubules.

$$TmP/GFR = TRP \times S_p$$

(GFR; glomerular filtration rate, p; phosphate, S; serum)

The Tm/GFR is usually very low (2.3–4.3 in the control) in patients with FS. Rickets manifests bowing deformity of the lower limbs, distal femur, the ulna, and the radius.

Phosphate handling in the kidney is affected by a couple of factors including parathyroid hormone (PTH) and vitamin D. PTH level is normal or elevated in patients with FS. Serum 1, 25-dihydroxy vitamin D3 is variable in patients with FS (28, 29).

Metabolic Acidosis

More than 85% of filtered load of bicarbonate ($HCO3^-$) is reabsorbed by the proximal tubule cells. This is accomplished by the coordinated function of luminal membrane Na^+/H^+ exchanger, luminal membrane carbonic anhydrase IV and XIV, and basolateral membrane $Na^+/HCO3^-$ cotransporter (30). Hyperchloremic metabolic acidosis is a common feature of FS resulting from defective bicarbonate reabsorption in the proximal tubules. Anion gap is normal. More than 30% of filtered load of $HCO3^-$ is not reabsorbed in patients with FS, and they manifest low plasma $HCO3^-$ levels between 12–18 mEq L^{-1}. Fractional excretion of $HCO3^-$ ($FEHCO3^-$) under the alkali treatment to increase plasma $HCO3^-$ to the normal ranges is >15% in patients with FS.

$$\text{Fractional excretion of } HCO_3^- \% = [(UHCO_3^-/PHCO_3^-)/(Ucr/Pcr)] \times 100$$

($HCO3^-$; bicarbonate, cr; creatinine, U; urine, P; plasma)

Acidification in the distal tubule is usually normal or impaired in association with chronic hypokalemia or toxic effect on distal tubules due to the original disorder in patients with FS.

Sodium and Potassium Losses

60–80% of filtered load of Na^+ is reabsorbed in the proximal tubules in the normal condition. Renal Na^+ reabsorption in the proximal tubules decreased in patients with FS. It leads to hyponatremia, hypotension, and dehydration. Hypokalemia is a secondary phenomenon. Increased delivery of Na^+ into the distal tubules and activation of the renin-angiotensin system secondary to hypovolemia cause potassium (K^+) wasting in the distal tubules. Severe hypokalemia can cause sudden death.

Hypercalciuria

Hypercalciuria is a common finding in patients with FS due to several original diseases. Defective endocytosis of parathyroid hormone (PTH) in patients with Dent disease resulting in its persistence in the lumen of the proximal tubule stimulates 25-hyroxyvitamin D3 1-hydroxylase to produce more 1,25-dihydroxyvitamin D3, raising serum levels of this vitamin. 25-hydroxyvitamin D3 is presented to 25-hydroxyvitamin D3 1-hydroxylase in the form of a complex with the vitamin D3-binding protein. As this complex is lost in the urine as a result of defective endocytosis leading to LMW proteinuria, the precursor 25-hydroxyvitamin D3 could be in short supply. The overall outcome of increased 1, 25-dihydroxyvitamin D3 levels may depend on the delicate balance between these processes. The slightly elevated serum levels of 1, 25-dihydroxyvitamin D3 in patients with FS can lead to increased intestinal Ca^{2+} reabsorption which will lead to hypercalciuria (*absorptive hypercalciuria*) (29). Hypercalciuria is rarely associated with nephrolithiasis in FS, possibly because of the polyuria and alkalized urine. However, patients with Dent disease manifest hypercalciuria and nephrolithiasis.

Hyperuricosuria (Uricosuria)

Uric acid (urate) is the end product of purine metabolism in humans. Because of its small molecular size (MW = 126 D), uric acid is freely filtered from the glomerulus. Then, 90–95% of filtered load of uric acid is eventually reabsorbed in the proximal tubules. A four-component hypothesis has been proposed to explain the renal uric acid transport mechanism; it includes glomerular filtration, presecretory reabsorption, secretion, and postsecretory reabsorption (31). Hyperuricosuria is often present in FS, leading to secondary hypouricemia (<2 mg dL^{-1}) (32). A voltage-sensitive uric acid pathway and uric acid exchangers are located at both luminal and basolateral membranes of proximal tubule cells (33). Uric acid-anion exchanger (URAT1) that reabsorbs uric acid from the lumen of the proximal tubules in the luminal membrane of proximal tubules regulates serum uric acid levels. This uric acid-anion exchanger can be disturbed in patients with FS. Defective URAT1 is a predominant cause of the patients with renal hypouricemia who manifest acute renal failure after exercise (34, 35). Hexose transporter gene (*SLC2A9*) is identified as a cause of gout and hyperuricemia (36). This transporter transports both fructose and uric acid. *SLC2A9* produces two isoforms by alternative splicing; the long isoform is expressed in basolateral membrane of proximal tubular cells and the short isoform is expressed in apical membrane of proximal tubular cells. This hexose transporter can be affected in patients with FS. Uric acid is a selective antioxidant, capable especially of reaction with hydroxyradicals and hypochlorous acid, itself being converted to innocuous products such as allantoin, allantoate, glyoxylate, urea, and oxalate (37).

Proteinuria (LMW Proteinuria)

The proximal tubules have a high capacity for uptake of filtered proteins from the glomerulus. The cut off molecular weight for filtration of plasma proteins is assumed to be in the range of 65 KD (kilodaltons) that corresponds to the molecular weight of serum albumin. However, small amount of larger weight proteins including gammaglobulin are filtered from glomerulus in the normal condition. Albumin and LMW proteins (MW<45,000 D) filtered in the glomerulus are considered to be the major source of urinary albumin and LMW proteins. Filtration of albumin and LMW proteins are followed by tubular reabsorption, and thus the resulting albuminuria and LMW proteinuria reflect the combined contribution of these two processes. Dysfunction of both these processes may result in increased urinary excretion of albumin and LMW proteins, and both glomerular injury and tubular impairment have been implicated in the initial events leading to proteinuria. In FS, proteinuria is predominantly caused by the dysfunction of reabsorption in the proximal tubules. Adolescent patients with FS due to Dent disease or Lowe syndrome excrete greatly increased amounts of proteins (1,740 ± 660 mg/day) and peptide (446 ± 145 mg/day). LMW proteins ranging from 2 to 5 KD were present in 12.9 ± 3.9-fold excess in FS compared with normal urine (38). The micropuncture technique in dogs revealed that the filtered load of albumin was $50\mu g\ m^{-2}$ suggesting that a filtered load of albumin is 9 g/day in normal humans (39). However, urinary excretion of protein is less than 0.1–0.15 g/day in the normal condition. Numerous filtered proteins including albumin and LMW proteins from glomerulus are bound to megalin and cubilin in the luminal membrane of proximal tubules. Then, the protein-receptor complex is incorporated into the endosome. The ligand and receptor are disassociated in the endosome; the receptor is recycled back to the luminal membrane and the reabsorbed proteins go into lysosome for further processing. Megalin is a 600 KD glycoprotein and a member of the low-density lipoprotein receptor family. Megalin is expressed in the proximal tubule brush-border and luminal endocytic apparatus. Megalin binds to a number of structurally very different proteins. It contains a large amino-terminal, extracellular domain, a single transmembrane domain and a short carboxy-terminal cytoplasmic tail (❯ Fig. 42-1). Cubilin is a multiligand, endocytic receptor. It is a 460 KD protein with little structural homology to known, endocytic receptor (❯ Fig. 42-1). Cubilin is expressed in the proximal tubule brush-border and luminal endocytic apparatus. Megalin involved in albumin reabsorption directly as a receptor for albumin, and/or indirectly by affecting the expression and/or endocytic function of cubilin (40, 41). Megalin's expression was decreased in patients with Dent disease. Acidification defect due to endosomal defective ClC-5 in patients with Dent disease disturbs the recycling from intracellular endosome into luminal membrane of the proximal tubule resulting in megalin and cubilin deficiency in the luminal membrane of the proximal tubule.

Etiologies

The causes of FS are divided into three main categories; hereditary, acquired, and exogenous substances (❯ Table 42-1). Most of the hereditary FS occurs as one of the manifestations of congenital metabolic disorders or as sporadic or familial disorders. Acquired forms are derived from immunological reactions, nephrotic syndrome or accumulated abnormal proteins. Exogenous substances are composed of drugs, chemical compounds, and heavy metals.

Hereditary Fanconi Syndrome

Dent Disease

Dent disease is an X-linked proximal tubulopathy characterized by LMW protinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, and eventual end stage renal failure. Hypophosphatemic rickets and metabolic acidosis are sometimes seen (42, 43). Almost all of the patients are males. Adult patients with Dent disease manifest FS. However, children with Dent disease often manifest LMW proteinuria and one or two of the manifestations due to proximal tubular dysfunction and this is called partial FS (44). They usually fall into end stage renal failure by the age of 40s. However, this is highly variable, and one third of patients with Dent disease will not develop end stage renal failure. Patients with Dent disease never manifest extrarenal manifestations, except for rickets, which may itself be a consequence of phosphaturia. School children with Dent disease manifest proteinuria. A lot of school children with Dent disease are detected as proteinuria by school urine mass screening program in Japan, and it was called as idiopathic low molecular weight proteinuria (45, 46). Carrier females are often manifest less severe LMW proteinuria and hypercalciuria, depending on X-chromosome inactivation, but they rarely develop clinically significant problems.

Table 42-1

Causes of Fanconi syndrome

Hereditary
• Dent disease
• Lowe syndrome
• Mitochondriopathies
• Cystinosis
• Galactosemia
• Hereditary fructose intolerance
• Glycogen storage disease type I (von Gierke disease)
• Fanconi-Bickel syndrome
• Tyrosinemia
• Wilson disease
• Idiopathic Fanconi syndrome
Acquired
• Nephrotic syndrome
• Myeloma
• Sjögren syndrome
• Renal transplantation
• Acute tubulointerstitial nephritis with uveitis (TINU) syndrome
• Autoimmune interstitial nephritis and membranous nephropathy
• Anorexia nervosa
• Untreated condition of distal renal tubular acidosis
Exogenous substances
• Drugs
• Chemical compounds
• Heavy metals

Dent disease is associated with inactivating mutations in *CLCN5* gene, which encodes 746 amino acids renal specific chloride channel-5 (ClC-5) (8, 47–49). ClC-5 belongs to the family of voltage-dependent chloride channels, which function as homodimeric proteins. ClC-5 is co-expressed with the vacuolar H^+-ATPase and plays a key role in endosomal acidification that is a crucial function in the receptor-mediated endocytic pathway (50). More than 80 distinct *CLCN5* mutations are reported in patients with Dent disease. They are nonsense, missense, frameshift, splice-site, insertional, and deletional mutations, which result in total or partial loss of function. There are no genotype-phenotype correlations as various mutations are associated with different clinical phenotypes, even within the same family.

Numerous filtered proteins are bound to megalin and cubilin in the luminal membrane of proximal tubules, and the protein-receptor complex is incorporated into the endosome. The ligand and receptor are disassociated in the endosome; the receptor is recycled back to the luminal membrane and the reabsorbed proteins go into lysosome for further processing. This disassociation is dependent on acidification of the lumen of endosome by increased concentration of H^+ and Cl^- due to the function of H^+-ATPase and ClC-5 chloride channel. An abnormal endocytosis pathway due to ClC-5 dysfunction disturbs the recycling of megalin and cubilin, the back to the luminal membrane, and the expression of megalin and cubilin in the luminal membrane of proximal tubules, leading to LMW proteinuria, hypercalciuria, hyperphosphaturia, and nephrolithiasis. Proper acidification is also important for protein degradation in the endosome. Immunohistochemical analysis of proximal tubule cells in patients with Dent disease revealed an inverted polarity of the H^+-ATPase, with redistribution to basolateral regions, suggesting that the loss of ClC-5 channel alters the function of components that co-distribute and physically interact with it (51).

Total urine protein ranges from 0.5–2.5 g a day, but may reach 4 g or higher in patients with Dent disease (45, 52). More than 60% of the filtered proteins are LMW proteins with molecular weight less than 45 KD (❯ *Fig. 42-3*). Nephrotic syndrome does not occur. LMW proteinuria is the most consistent and one of the earliest presenting abnormalities. Urinary beta 2-microglobulin, a LMW protein (MW = 11.6 KD), is excreted in amounts 100–300 times the upper limit of the normal. Albumin is also excreted in the urine. The pattern of proteins representing the increased excretion of several LMW proteins as well as albumin (MW = 65 KD) is termed as *tubular proteinuria* (52, 53). The terms of LMW proteinuria and tubular proteinuria have usually been used interchangeably (53).

Patients with Dent disease manifest hypercalciuria in the range of 4–10 mg kg^{-1} of body weight a day in children and 4–6 mg kg^{-1} of body weight a day in adults (54). Nephrocalcinosis is also found in children (❯ *Fig. 42-4*). Defective endocytosis of parathyroid hormone (PTH) in patients with Dent disease resulting in its persistence in the lumen of the proximal tubule stimulates 25-hydroxyvitamin D3 1-hydroxylase to produce more 1,25-dihydroxyvitamin D3 resulting in the increased serum levels of this vitamin. 25-hydroxyvitamin D3 is presented to 25-hydroxyvitamin D3 1-hydroxylase in the form of a complex with the vitamin D3-binding protein. As this complex is lost in the urine as a result of defective endocytosis leading to LMW proteinuria, the precursor

Electrophoresis of urine from the family members of Dent disease on the polyacrylamide gel and stained by sliver representing LMW proteinuria. Lanes 1 and 2, molecular markers; Lane 3, 12-year-old boy with Dent disease; Lane 4, his mother; Lane 5, his father.
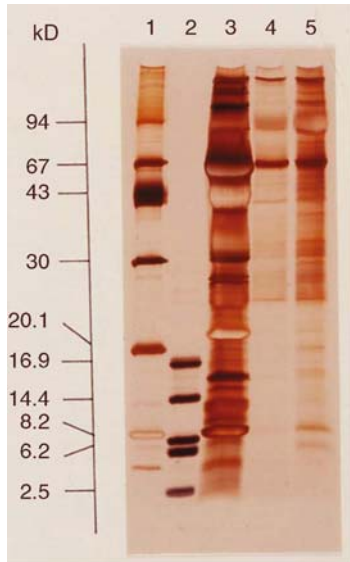

25-hydroxyvitamin D3 could be in short supply. The overall outcome of increased 1, 25-dihydroxyvitamin D3 levels may depend on the delicate balance between these processes. The slightly elevated serum levels of 1, 25-dihydroxyvitamin D3 in patients with Dent disease can lead to increased intestinal Ca^{2+} reabsorption resulting in hypercalciuria (*absorptive hypercalciuria*). In fact, 70% of the patients with *CLCN5* mutations manifest hypercalciuria, even though some of these do exhibit nephrocalcinosis ([55]). This may be explained by the *CLCN5* knock-out mice model; ClC-5 disruption promotes calcium crystal agglomeration, as well as a redistribution of the crystal-binding molecule annexin A2, in collecting duct epithelial cells ([56]).

The onset of renal insufficiency and progression to end-stage renal failure are quite variable. Significant decrease of glomerular filtration rate is seen in children with Dent disease, and the patients fall into end-stage renal failure by the end of the age of 40s. Renal biopsy demonstrates normal or focal global glomerulosclerosis with tubular atrophy, tubular dilatation, and interstitial infiltration of monocytes. Medullary nephrocalcinosis is a significant feature in patients with Dent disease. Patients less than 5 years of age manifest medullary nephrocalcinosis. The precise mechanism of progressive renal failure

is not known in patients with Dent disease. Nephrocalcinosis can be a candidate to disturb the glomerular filtration rate. High urinary concentrations of potentially bioactive proteins including insulin, insulin like growth factor-1 (IGF-1), and the chemokine monocyte chemoattractant protein-1 (MCP-1) may contribute to interstitial fibrosis that will lead to progressive renal failure in patients with Dent disease ([57]). Generalized proximal tubule dysfunction is associated with increased cell proliferation, dedifferentiation, and oxidative stress resulting in interstitial fibrosis and eventual renal failure ([58]). Patients and carrier females often manifest nephrolithiasis, and renal stone is calcium phosphate stone that is also seen in patients with distal renal tubular acidosis.

Dent disease is genetically heterogeneous. Mutations in the *OCRL1* gene are identified in a subset of patients with the Dent disease phenotype ([59]). Unlike patients with typical Lowe syndrome, typical facial features, mental retardation, metabolic acidosis, and ocular abnormalities are usually absent in patients with Dent disease who have *OCRL1* mutation. The phosphoinositol 4,5-bisphosphate phosphatase (PIP_2 5-phosphatase) activity is markedly reduced in skin fibroblasts cultured from patients with Dent disease due to *OCRL1* mutations, and protein expression, measured by Western blotting, is reduced or absent. PIP_2 5-phosphatase participates the trafficking and recycling of endosome in the proximal tubules. Defective PIP_2 5-phosphatase activity can lead to endosomal dysfunction leading to LMW proteinuria. Unlike the patients with typical Lowe syndrome, none of patients have metabolic acidosis. These observations and findings suggest that *OCRL1* mutations can cause the isolated renal phenotype of Dent disease and affected individuals lack the cataracts, typical facial features, renal tubular acidosis, and neurologic abnormalities that are characteristic to Lowe syndrome. It is difficult to explain that *OCRL1* mutations can cause the isolated renal phenotype of Dent disease. However, it is possible that another phosphatase, *INPP5B*, which shares amino acid homology with *OCRL1*, can compensate phosphatase activity in patients with Dent disease due to *OCRL1* mutations.

There are no specific interventions at present that will change the natural course of renal manifestations and progressive renal failure in patients with Dent disease. Hypercalciuria is corrected by thiazide diuretics therapy in doses similar to effective doses for idiopathic hypercalciuria, presumably by stimulating the reabsorption of calcium in the distal convoluted tubule, where ClC-5 channel is not expressed ([60]). However, this is not a long-term study which provides the evidence that it is

Abdominal CT demonstrating bilateral medullary nephrocalcinosis in a 12-year-old boy with Dent disease.
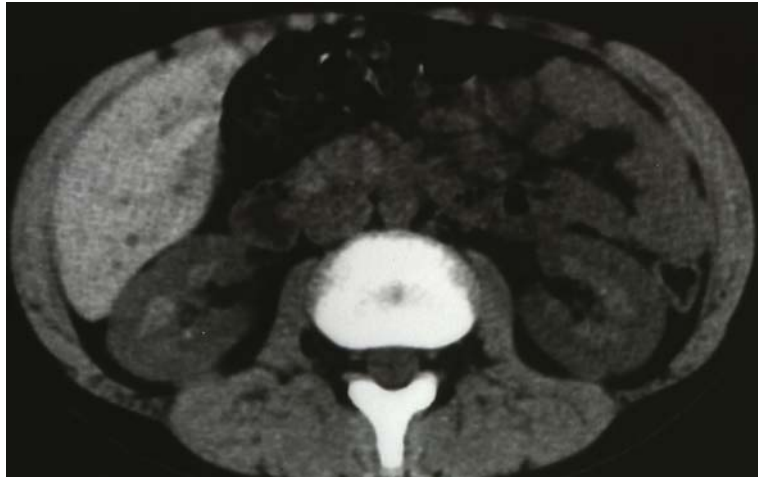
effective to prevent or delay the progression of end stage renal failure. In animal experiment using *clcn5* (mouse chloride channel 5 gene) knock-out mice, high citrate diets can delay the progression of nephrocalcinosis and end stage renal failure (61, 62). Treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) may delay progression of end stage renal failure (63).

Lowe Syndrome

The oculocerebrorenal syndrome of Lowe (OCRL) is a rare X-linked disorder that is characterized by a complex phenotype that involves major abnormalities of the eyes (particularly congenital cataracts), central nervous system abnormality and FS (64). Cataracts are recognized in all the male patients. Lens opacities are present in all carriers of females by slit-lamp examination and this is a reliable screen for carriers (65). Other ocular abnormalities include glaucoma, microphthalmos, and corneal keloid formation. Visual acuity is frequently disturbed. Central nervous system abnormalities include infantile hypotonia (floppy infant), areflexia, and mental retardation. The patients manifest mild ventriculomegaly and cysts in the periventricular regions in the brain. Status epilepticus is sometimes recognized. FS is a major clinical feature and occurs in the 1st year of life, but the severity and age of onset vary. The patients manifest LMW proteinuria, glucosuria, aminoaciduria, hyperphosphaturia, hypercalciuria, hypophosphatemic rickets, hypercholoremic

metabolic acidosis, and progressive renal insufficiency (66). Renal insufficiency progresses at variable rate among patients, and it progresses to end-stage renal failure by 30s or 40s.

Like in patients with Dent disease, megalin is nearly absent from the urine in patients with Lowe syndrome suggesting of the decreased expression of megalin in the luminal membrane of the proximal tubule cells. Thus, urinary excretion of retinol-binding protein and the lysosomal enzyme N-acetyl-glucosaminidase are significantly increased in young boys with OCRL (67).

The gene (*OCRL1*) that is responsible for OCRL encodes a 105 KD Golgi protein with phosphoinositol 4,5-bisphosphate phosphatase (PIP$_2$ 5-phosphatase) activity (68). PIP$_2$ 5-phosphatase is mainly a lipid phosphatase that may control cellular levels of a critical metabolite, phosphatidylinositol 4,5-bisphosphate, and is involved in the inositol phosphatase signaling pathway (69). PIP$_2$ 5-phosphatase is present in cultured skin fibroblast and it is not present in peripheral blood cells. PIP$_2$ 5-phosphatase activity is markedly reduced in fibroblasts from patients with Lowe syndrome (70). However, this biochemical test for carrier diagnosis is not reliable; lyonization produces a highly variable pattern of tissue expression in females.

Deficiency of PIP$_2$ 5-phosphatase leads to cellular accumulation of its substrate PIP$_2$. PIP$_2$ accumulates in lysosomal membrane (71). PIP$_2$ is involved in signal transduction, vesicle trafficking and actin polymerization. Absence of PIP$_2$ 5-phosphatase activity leads to a reduction in the number and length of actin stress fibers, a tendency of actin fibers to depolymerize when provoked,

and an abnormal distribution of two actin-binding protein gelsolin and alpha-actinin. This disruption of actin function has significant effects on epithelial function through disrupting cell–cell contacts such as tight junctions or adherent junctions or by altering membrane trafficking such as transport proteins (72). Trans-Golgi dysfunction or altered actin polymerization can explain FS in patients with Lowe syndrome. PIP$_2$ 5-phosphatase is localized to endosome and Golgi membranes along with clathrin, giantin, the mannose 6-phosphate receptor, transferrin, and the early endosomal antigen 1 marker. PIP$_2$ 5-phosphatase interacts with clathrin terminal domain and the clathrin adaptor protein AP-2. This suggests a role for PIP$_2$ 5-phosphatase in endosomal receptor trafficking and sorting (73, 74). OCRL1 is present throughout the early endocytic pathway, including in endocytic clathirin-coated pits, and demonstrate a connection between OCRL1 and adaptor molecules implicated in the endocytic trafficking of receptor in the kidney (75).

OCRL1 has a C-terminal RhoGAP domain. *OCRL1* encodes a PIP$_2$ 5-phosphatase activity that binds to Rac GTPase. Activated Rac GTPase stably associates with the *OCRL1* RhoGAP domain. In this sense, the protein encoded in *OCRL1* can play a bifunctional role. Loss of *OCRL1* RhoGAP domain and the resulting alteration in Rho pathways may contribute to mental retardation in Lowe syndrome, as observed in other forms of X-linked mental retardation (76).

OCRL1 mutations can cause the isolated renal phenotype of Dent disease and affected individuals lack the cataracts, typical facial features, renal tubular acidosis, and neurologic abnormalities that are characteristic to Lowe syndrome. It is difficult to explain that *OCRL1* mutations can cause the isolated renal phenotype of Dent disease. However, another phosphatase, *INPP5B*, which shares amino acid homology with *OCRL1,* can compensate phosphatase activity in patients with Dent disease due to *OCRL* mutations.

More than 70 *OCRL1* mutations have been described in patients with Lowe syndrome; nearly all are clustered in exons 10–23, especially exon 15, and almost none are found in exons 1–9 (70).

Treatment is supportive and includes taking care of ocular manifestations, anticonvulsants, speech therapy, and dental complications. The eye abnormalities usually require therapy early in life. Bicarbonate therapy is usually necessary at a dose of 2–3 mmol kg^{-1} of body weight a day every 6–8 h. Sodium or potassium phosphate can be given in amounts of 1–4 g a day for phosphate depletion and if unsuccessful, vitamin D can be given.

Mitochondriopathies

The mitochondria (mt) have a major role in fatty acid oxidation, tricarboxylic acid cycle, urea cycle, and ATP production through the process of oxidative phosphorylation. Oxidative phosphorylation occurs at the level of the respiratory chain in the inner membrane of the mt (77). The respiratory chain comprises five components (◗ *Fig. 42-5*). Complex I (NADH-coenzyme Q reductase) carries reducing equivalents from NADH to coenzyme Q and consists of different polypeptides, seven of which are encoded by mitochondrial DNA (mtDNA). Complex II (succinate-coenzyme Q reductase) carries reducing equivalents from FADH$_2$ to coenzyme Q and contains five polypeptides that are all encoded only by mtDNA. Complex III (reduced coenzyme Q-cytochrome c reductase) carries reducing equivalents from coenzyme Q to cytochrome c and contains 11 subunits, one of which is encoded by mtDNA. Complex IV (cytochrome c oxidase) transfers reducing equivalents from cytochrome c to oxygen. This complex is composed of cytochromes a and a3, and 13 protein subunits, three of which are encoded by mtDNA. The fifth complex is ATP synthetase.

Oxidative phosphorylation consists of oxidative reactions that lead to oxygen consumption and phosphorylation of ADP to ATP. Each mt have its own 2–10 mtDNA. MtDNA genome is a 16.5 kb circular double stranded DNA with an asymmetrical base composition. The heavy strand contains more guanine residues while the light strand contains more cytosine residues. The mtDNA contains 37 genes; 13 encode for polypeptides of the respiratory chain, 2 for the ribosomal RNAs and 22 for transfer RNAs (78). Mitochondrial injury is due to congenital insults or may be the result of secondary events. Genetic defects of one or several polypeptide enzyme complexes of the oxidative phosphorylation system in the mt DNA or nuclear DNA which encodes structural or functional mitochondrial proteins can give rise to mitochondriopathies (mitochondrial cytopathies, mitochondrial diseases) (79).

Mitochondriopathies are multi-systemic disease and may begin at any age. Affected organs are diverse including central nervous system, muscle, liver, heart, kidney, gut, endocrine system, bone marrow, ear, eye, and skin (◗ *Table 42-2*). They display extreme heterogeneity, and make unpredictable the extent and manifestations of disease presentation (80). With the course of the disease, the numbers of organs involved are increased.

The screening for mitochondriopathies includes the determination of plasma lactate, pyruvate, keton bodies and their ratios in fasted and fed patients, polarographic, and spectrometric studies to evaluate the different

◘ **Figure 42-5**

Map of mitochondria genome. Regions encoding cytochrome b (ctb b), various subunits of NADH-coenzyme Q reductase (ND), cytochrome c oxidase (COX), ATPase, and ribosomal RNAs (rRNA) are indicated (Niaudet P, Rötig A. The kidney in mitochondrial cytopathies. *Kidney Int* **1997;51:1000–1007).**
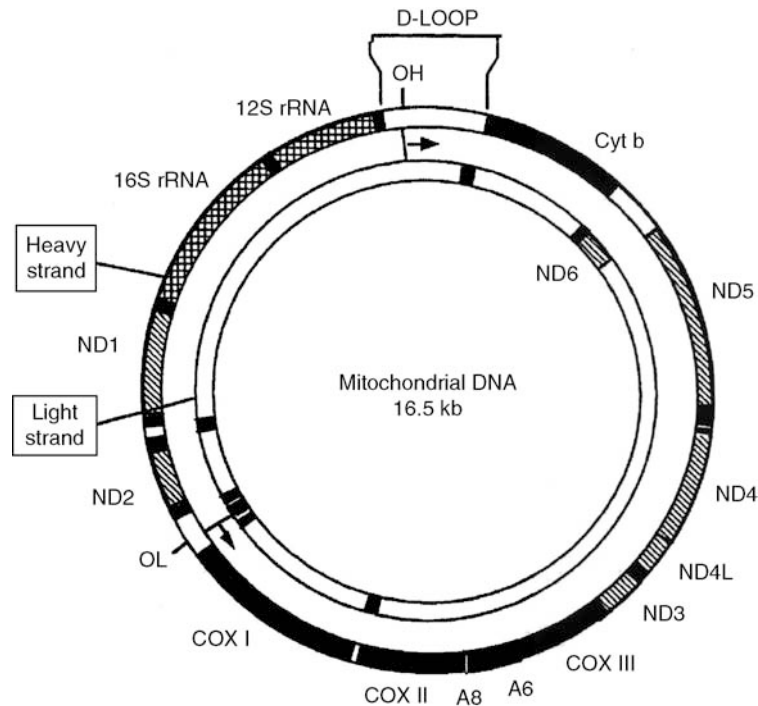
enzymatic complexes of the respiratory chain, muscle histologic studies, and genetic analysis (4).

Renal disease may be the first sign of mitochondriopathies, or it may appear simultaneously with neurological and neuromuscular signs (81). FS is particularly frequent in newborns, infants, and young children (82–84), whereas tubulointerstitial nephropathy is more frequent in children and young adults (85, 86), and can be associated with hereditary focal segmental glomerulosclerosis due to the mitochondrial transfer RNA gene mutation (87–89) and collapsing glomerulopathy due to the mutations in the gene *COQ2* encoding the para-hydroxybenzoate-polyprenyl-transferase enzyme of the CoQ10 synthesis pathway (CoQ2 nephropathy) and in the gene *PDSS2* encoding for decaprenyl diphosphate synthase (90, 91).

Most patients with FS due to mitochondriopathies manifest moderate FS including failure to thrive, dehydration, aminoaciduria, glucosuria, proteinuria, LMW proteinuria, phoshaturia, uricosuria, hypercalciuria, and bicarbonaturia. Many patients manifest FS by the age of 2 years. Extra-renal manifestations including neurological symptoms, myopathy, hepatic dysfunction, clinical features of Pearson syndrome, partial adrenal insufficiency, cardiac involvement, diabetes mellitus, deafness, and ophthalmoplegia often manifest in the patients (12, 92, 93). Patients who manifested proximal tubular acidosis with hypercalciuria or Bartter syndrome were described (94, 95). Some patients manifest progressive renal failure (96). Histological analysis reveals tubular dilatations, tubular atrophy and cytoplasmic vacuolization of the tubules. Bizarre giant mitochondria are frequently observed (97).

No satisfactory treatment is presently available to alter the course of mitochondriopathies. The treatment is mainly symptomatic: supplements of sodium bicarbonate, potassium, vitamin D3, phosphate, and water are necessary. Carnitine is given in case of secondary carnitine deficiency. It includes avoidance of drugs that interfere with the respiratory chain such as valproate and barbiturates, or that inhibit mitochondrial protein synthesis such as tetracyclines and chloramphenicol. Dietary recommendations include a high lipid and low carbohydrate diet in patients with complex I deficiency. Hypercaloric diet and parenteral nutrition should be avoided in these patients.

⬛ Table 42-2

Clinical symptoms in patients with mitochondriopathies

Affected organs	Symptoms
Central nervous system	Apnea, lethargy, hypotonia, coma, pshycomotor retardation, cerebellar ataxia, stroke-like episodes, myoclonus, seizures, dementia, spasticity, headache, hemiparesis
Muscle	Myopathy, poor head control, limb weakness, myalgia, exercise intolerance
Liver	Hepatomegaly, liver dysfunction
Heart	Cardiomyopathy, arrhythmia
Kidney	Fanconi syndrome, tubulointerstitial nephropathy, nephrotic syndrome (focal segmental glomerulosclerosis, collapsing nephropathy), renal failure
Gut	Vomiting, diarrhea, villous atrophy, cholonic pseudoobstruction, pancreatic dysfunction
Endocrine	Diabetes mellitus, growth hormone deficiency, hypoparathyroidism, hypothyroidism, adrenal insufficiency
Bone marrow	Sideroblastic anemia, neutorpenia, thrombocytopenia
Ear	Hearing loss
Eye	Progressive extrarenal ophthalmoplegia, pigmentary retinal degeneration, ptosis, diplogia, cataract
Skin	Mottled pigmentation, trichothiodystrophy

Cystinosis

Cystinosis is reviewed in detail in Chapter 41 of this textbook, and therefore only a short description is included here. Cystinosis is an autosomal recessive lysosomal storage disorder characterized by an accumulation of cystine, the disulfide of the amino acid cysteine, in the systemic organs, notably kidney, cornea, bone marrow, thyroid, lymph nodes, liver, and spleen (98). Renal manifestations dominate the clinical presentation and course in infantile cystinosis. Cystinosis is the most common familial form of the FS in Western countries. Many patients, particularly in North America, have blonde or reddish-blonde hair. Other organs frequently affected include the cornea and thyroid, causing painful photophobia and hypothyroidism respectively.

Various clinical forms of the disease exist and are based on age at onset and severity of the symptoms (⊙ *Table 42-3*). The most severe form, infantile cystinosis, is manifested by failure to thrive, polyuria, polydypsia, dehydration, fluid and electrolyte loss, aminoaciduria, glucosuria, phosphaturia, renal tubular acidosis between 6 and 12 months of age. Some of the patients may develop vitamin D-resistant rickets due to phosphaturia and manifest severe growth failure. Renal function is generally normal at presentation. However, subsequent glomerular impairment leads to focal segmental glomerulosclerosis and eventually to end stage renal failure by 10 years of age without treatment (99).

Patients with infantile cystinosis manifest FS, including hyperchloremic metabolic acidosis, aminoaciduria, hypokalemia, hypophosphatemia, glucosuria, and phosphaturia. There have been several patients of nephropathic cystinosis presenting with features of secondary Bartter syndrome (hypokalemia, hyperchloremic metabolic alkalosis, hyperreninemia, and hyperaldosteronism), suggesting abnormalities of Na^+ and Cl^- reabsorption (100, 101). Patients with cystinosis often manifest medullary nephrocalcinosis (102).

Renal histopathologic changes in infantile cystinosis include severe lesions of proximal tubules; typical alterations to the glomerular podocytes, which become multinucleated giant cells; and the presence of cystine crystals, mostly in interstitial cells and podocytes (103). The proximal tubule is the first clinical target of the disease, but cystine crystals are rarely found in the tubular cells of patients with cystinosis. Cystine crystal deposition in the cornea leads to photophobia. Continuous widespread cystine accumulation eventually leads to rickets and retinal, endocrinologic (hypothyroidism and impaired glucose tolerance), hepatic, gastrointestinal, muscular, and neurological abnormalities.

Two less severe and less common form of cystinosis are juvenile (or late-onset) and ocular cystinosis. Patients with juvenile cystinosis manifest glomerular impairment between 12 and 15 years of age but do not suffer from severe tubulopathy or growth failure. Progression to end stage renal failure is slow and occurs at

◼ Table 42-3

Clinical manifestations of infantile cystinosis

At presentation
Common
Failure to thrive
Polyuria and polydipsia
Fanconi syndrome
Vitamin D resistant rickets
Progressive renal failure
Photophobia
Hypothyroidism
Uncommon[a]
Bartter syndrome
Nephrotic syndrome
Diabetes insipidus
Pot-renal transplantation
Dysphagia
Myopathy
Exocrine pancreatic insufficiency
Diabetes mellitus
Central nervous system deterioration
Primary hypogonadism

Adapted from Gahl et al. (114)
[a]may be transient and coexist with common manifestations

variable ages (104). Patients with ocular cystinosis do not involve kidney.

Infantile cystinosis is caused by mutations of the *CNTS* gene encoding cystinosin, a lysosomal transport protein, leading to complete abolition of cystine transport (105). Cystinosin has 367 amino acids and seven transmembrane domains. Cystine transport is dependent on the pH gradient, and the transport of cystine out of the lysosome is driven by the high H^+ content within the lysosomal lumen that is produced by the activity of the H^+-ATPase. A range of mutations in *CNTS* gene has been described, but a single mutation, a 57-kb intragenic deletion, accounts for as many as three quarters of all European cases (105). The adolescent and ocular forms have one severe and one mild *CTNS* mutation, leading to reduced transport activity. The sparing of the kidney in patients with ocular cystinosis reflects tissue-specific expression of splicing factors, or the increased endogenous level of *CTNS* mRNA normally seen in the kidney (106). Individuals who are heterozygous for severe *CTNS* mutations reveal elevated levels of leukocyte cystine but are completely asymptomatic.

The pathophysiology of tubular cystine transport defects in patients with cystinosis is poorly understood, reflecting of an animal model for the disease. Knock-out mice model lacking cystinosin gene do not manifest signs of FS, despite accumulation of lysosomal cystine in the proximal tubules (107). Cystine-loaded proximal tubular cells demonstrate loss of free phosphate and defective ATP production and inhibition of Na^+-dependent transporters (108). ATP depletion can reduce proximal tubular Na^+, K^+-ATPase activity leading to increased Na^+ delivery into the distal tubules and Bartter syndrome (101). A cell culture demonstrated that cells accumulated with intracellular cystine undergo apoptosis at a rate two- to fourfold higher than controls (109). Another works suggests that increased oxidative stress and altered redox status in proximal tubule cells cultured from the urine of patients with cystinosis are associated with proximal tubule dysfunction (110).

The diagnosis of cystinosis is confirmed by demonstrating elevated cystine levels in peripheral leukocytes (97). Corneal crystals detected by slit-lamp examination are diagnostic in childhood cystinosis because these crystals are not seen in patients with other hereditary FS. However, this finding is not sensitive for early diagnosis. The renal pathologic findings in infantile cystinosis consist of a chronic tubulointerstitial nephropathy, with characteristic multinucleated podocytes and intracellular crystalline inclusions in interstitial histiocytes (111). Although numerous multinucleated podocytes are the most characteristic pathologic findings, they are not found in the sclerotic glomeruli and detected only in low frequency (<4%). The cystine crystals are birefringent under polarized light in only alcohol-fixed tissue or in unfixed frozen tissue, because they are water-soluble and not retained in the tissue after routine histologic preparation with aqueous solutions (112).

The management and treatment for infantile cystinosis involve supportive therapy to maintain fluid balance and replace electrolyte losses at initial presentation. Early diagnosis and oral cysteamine, a cystine-depleting agent, can delay the progression of end stage renal failure and other organ involvement. Oral cysteamine therapy given at doses of 60–90 mg kg^{-1} of body weight (or between 1.3 and 1.95 g m^{-2}) a day divided every 6 h generally achieves approximately 90% depletion of cellular cystine, as measured in circulating leukocytes (<1.0 nmol half-cystine/mg protein) (113). The dosage recommended for adults is 500 mg every 6 h, but higher dosages are often required to achieve satisfactory cystine depletion. On the basis of its beneficial effects in maintaining thyroid function and depleting muscle of cystine, oral cysteamine

therapy should continue in patients after renal transplantation to help preserve other organs. Administration of 0.55% cysteamine eye-drops, given 6–12 times a day, can dissolve corneal cystine crystals and lessen visual symptoms (114). Other therapies to supply potassium, alkalinizing agents including citrate or bicarbonate, phosphate, and vitamin D3 are required. When the growth velocity has not improved and the patient remains below the 3rd percentile for height after one year of therapy, growth hormone therapy may be considered.

Galactosemia

Galactosemia is an autosomal recessive disease of galactose metabolism. Nursing infants must move large amounts of galactose through Leloir pathway in order to utilize the carbon skeletons for energy (❯ *Fig. 42-6*). Galactose is the preferred carbon source in mammalian neonates, since it is incorporated into glycogen more efficiently than is glucose (115).

The most frequent form is classic galactosemia that is due to the deficient activity of galactose-1-phosphate uridyl-transferase (GALT) encoded by *GALT1* (116). GALT catalyzes the reaction of galactose-1-phosphate (gal-1-p) plus uridine diphosphate glucose to uridine diphosphate galactose plus glucose-phosphate. Uridine diphophate galactose can be further metabolized to either glucose or CO_2 and H_2O via glycolysis. Milk is a major source of galactose. Accumulated gal-1-p due to defective GALT and exposure to galactose lead to acute deterioration of multiple organ systems, including liver, kidney, ovary, brain, and eye. Affected infant patients manifest vomiting, diarrhea, failure to thrive, developmental delay, liver dysfunction, coagulopathy, renal tubular dysfunction, cerebral edema, vitreous hemorrhage, and *Escherichia coli* sepsis. They sometimes manifest jaundice and unconjugated hyperbilirubinemia and may have severe hemolysis. Liver damage leads to hepatomegaly and cirrhosis that is potentially lethal. Neonatal screening program includes galactosemia, anticipating that early detection and intervention would prevent long-term complications such as mental retardation, premature ovarian failure, and speech delay. Although a galactose-restricted diet prevents the neonatal death, many well-treated patients continue to develop debilitating complications (117, 118). Clinically evident speech delay and cerebellar signs are more frequent than other findings. Premature ovarian failure is nearly universal in females with galactosemia. The predominant manifestation due to

kidney damage is FS including hyperaminoaciduria, LMW proteinuria, hyperphosphaturia, and bicarbonaturia (118). Patients placed on a galactose-restricted diet are never truly free of galactose insult, as a significant amount of galactose is found in non-dairy foodstuffs such as vegetables and fruits (119, 120). More importantly, galctose moieties can be produced endogenously from UDP-glucose via the UDP-4-galactose epimerase reaction, and natural turnover of glycoproteins/glycolipid; the rate of endogenous galactose synthesis ranges from 0.53–1.05 mg kg^{-1} of body weight a day (121, 122). Once the lactose is formed intracellularly, it will be converted to gal-1-p by GALT. The less common form of galactosemia is a deficiency of galactose kinase (GALK), which forms gal-1-p from galactose. These patients do not manifest either the acute toxicity syndrome or chronic complications seen in patients with classic galactosemia. They manifest cataracts. Since GALK-deficient patients do not accumulate gal-1-p in their tissues, gal-1-p is considered to play a significant role in the pathogenesis of classic galactosemia (123, 124). GALT deficiency results in accumulation of toxic galactose leading to the unfolded proteins, altered calcium homeostasis and subsequently endoplasmic reticulum (ER) stress (125). ER stress caused by GALT-deficiency might contribute to accelerated apoptosis seen in the granulose cells maturing follicles in galactosemic females, leading to premature ovarian failure (126). Formation of galactitol from galactose by aldose reductase has been proposed as a pathogenetic mechanism and is at least responsible for cataract formation.

The diagnosis is suggested by galactose or galactose 1-phosphate in serum, or in the urine. The diagnosis is confirmed by demonstrating deficient GALT activity in red blood cells, fibroblasts, leukocytes, or hepatocytes.

Treatment of this disorder is elimination of galactose from the diet. Acute symptoms and signs resolve within a few days after starting the diet therapy. However, developmental delay, speech disturbance, ovarian dysfunction, and growth retardation are common outcomes in this disorder (127).

Hereditary Fructose Intolerance

Hereditary fructose intolerance (HFI) is an autosomal recessive disorder caused by a deficiency of aldolase B, an enzyme of liver, intestine, and renal cortex catalyzing the metabolism of fructose of exogenous origin (128). Frequency of HFI is estimated at 1 in 20,000 live births. Aldolase B catalyses the specific and reversible cleavage of

⬛ **Figure 42-6**

Composite diagram of the Leloir pathway and uridine diphosphate (UDP)-glucose pyrophosphorylase pathway. *Galk*, galactokinase; *galt*, galactose-1-phosphate uridyltransferase; *Gale*, UDP-galactose 4-epimerase; *Hex*, hexokinase; *Pgm*, phosphoglucomutase; *Ugp*, UDP-glucose pyrophosphorylase (Leslie ND. Insights into pathogenesis of galatosemia. *Annu Rev Nutr* 2003;23:59–80).
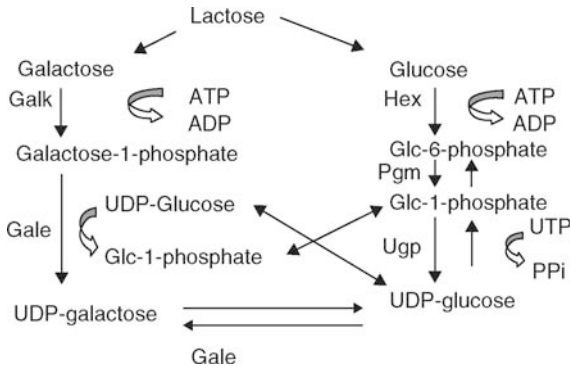
fructose-1,6-bisphophate (FBP) and fructose-1-phosphate (F1P) into dihydroxyacetone phosphate and D-glyceraldehyde-3-phophate, or D-glyceraldehyde, respectively. Aldolase B is equally active with FBP and F1P, whereas aldolase A and aldolase C, the other two vertebrate isozymes, are more active with FBP than with F1P. Aldolase B is encoded in Aldolase B gene *(ALDOB)* mapped to chromosome 9q21.3–q22.2 (129, 130). Missense and nonsense mutations, large and small gene deletions and mutations in the splicing region have been identified in *ALDOB* of HFI patients (131).

Affected individuals manifest symptomatic hypoglycemia, vomiting and life-threatening episodes shortly after the intake of fructose or related sugars including sucrose and sorbitol (132). Prolonged ingestion leads to failure to thrive, hepatomegaly, jaundice, hepatic cirrhosis, and nephrocalcinosis, and may lead to convulsions, coma, and death from severe liver and kidney failure. Symptoms of HFI appear during infancy when infants with HFI are fed a formula or foods including fruits, vegetables, and sweetened cereals that contain sucrose. Patients with HFI may develop a protective aversion to sweets and fruits, which is a reason that diagnosis is frequently missed, and which also explains that reliable prevalence numbers for different populations do not exist.

HFI is associated with proximal tubule dysfunction leading to aminoaciduria, bicarbonaturia, phosphaturia, and lactic acidosis. These manifestations appear rapidly after the ingestion of fructose (133, 134).

The development of lactic acidosis adds significantly to the metabolic acidosis (135). Chronic fructose ingestion leads to nephrocalcinosis and impaired distal tubular function. In contrast, resolution of proximal tubule dysfunction can take days or weeks with strict restriction of fructose and sucrose (136).

Aldolase B coexists abundantly in endocytosis zones of the proximal tubule cells with H^+-ATPase (137). Nonfunctional aldolase B impairs the coupling of H^+-ATPase to glycolysis and endosomal acidification that will lead to FS.

Diagnosis includes the metabolic response to an intravenous fructose load or an enzymatic assay of liver or intestinal biopsy samples. However, both of them are bothering and invasive (138). Fructose breath hydrogen test is one of the standard procedures for the diagnosis. However, it can develop life-threatening adverse effects during the test (139). Molecular analysis is available for the diagnosis.

Strict avoidance of foods or drugs containing fructose, sucrose, and sorbitol is the predominant treatment.

Glycogen Storage Disease Type I (von Gierke Disease)

Glycogen storage disease type I (GSD-I) is a group of autosomal recessive disorders with an incidence of 1 in 100,000. There are two major subtypes. Glycogen storage disease type Ia (GSD-Ia, von Gierke disease) is common and is caused by s deficiency in glucose-6-phosphatase-alpha (G6Pase-alpha), a key enzyme in glucose homeostasis that catalyzes the hydrolysis of glucose-6-phosphate (G6P) to glucose and phosphate in the terminal step of gluconeogenesis and glycogenolysis (140). G6Pase-alpha is a hydrophobic endoplasmic reticulum-associated transmembrane protein. Glycogen storage disease type Ib (GSD-Ib) is caused by a deficiency of microsomal glucose-6-phosphatase transporter (G6PT). G6PT translocates G6P from cytoplasm to the lumen of the endoplasmic reticulum. Therefore, G6PT and G6Pase-alpha work in concert to maintain glucose homeostasis. Whereas G6Pase is exclusively expressed in gluconeogenic cells, G6PT is ubiquitously expressed and its deficiency generally causes a more severe phenotype.

Patients with GSD-Ia manifest a phenotype of disturbed glucose homeostasis characterized by fast life-threatening hypoglycemia, hepatomegaly, nephromegaly, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, lactic acidemia, neutrophilia, and growth retardation (141, 142). Infants with GSD-Ia typically present with

seizures and hepatomegaly at 6–8 months of age. Approximately 75% of adolescent and adult patients develop hepatocellular adenoma (HCA), which can lead to considerable morbidity and mortality (143). The incidence of HCA to hepatocellular carcinoma is recently increasing because the patients can live longer than before (144). The presence of GSD-Ia and GSD-Ib are associated with reduced quality of life, independent functioning, and elevated levels of internalizing distress, and parental stress relative to healthy peers.

Renal complications include renal enlargement, gout nephropathy, renal stones, nephrocalcinosis, Fanconi-like syndrome, and chronic renal disease leading to renal insufficiency (145). Hepatomegaly is a common finding in GSD-Ia. Hyperuricemia and uric acid stone in GSD-Ia are explained by a combination of increased synthesis of purine and a competitive inhibition of renal tubular excretion of uric acid (urate) by lactate (146). Proximal tubular dysfunction has been observed in patients with GSD-Ia. Patients manifest proximal renal tubular acidosis due to loss of bicarbonate in the urine, hyperphosphaturia, generalized aminoaciduria and increased excretion of beta 2-microglobulin which are ameliorated by intensive diet therapy (147, 148). This finding suggests that good metabolic control can prevent proximal tubular dysfunction. Chronic renal disease is a long-term complication. Renal biopsies reveal interstitial fibrosis, tubular atrophy, and focal segmental glomerulosclerosis with marked glomerular basement membrane (GBM) thickening and lamellation in patients with GSD-Ia (149–151). Glycogen granules are present in the areas of abnormal GBM. The glycogen content in the mesangium and in the epithelial, mesangial and endothelial cells is increased. Recent treatment has significantly alleviated the metabolic abnormalities and delayed the clinical manifestation of chronic renal disease and renal insufficiency in patients with GSD-Ia. However, glomerular hyperfiltration, hypercalciuria, hypocitraturia that worsens with age, and urinary albumin excretion still occur in metabolically compensated patients with GSD-Ia (152, 153). Although the molecular mechanism responsible for chronic renal disease is still poorly understood, activation of the angiotensin system is suggested to have an important role for the disease progression (154). The expression of TGF-beta 1 in kidney tissue is increased in a patient with GSD-Ia manifesting proteinuria, interstitial fibrosis, and tubular atrophy (155).

The objective of treatment is to maintain normoglycemia to avoid metabolic complications and lactic acidosis. Normoglycemia is accomplished at night with nasogastric feeding of glucose or with orally administered uncooked cornstarch (156). A single dose (1.75–2.5 g kg^{-1} of body weight) of uncooked cornstarch will maintain serum glucose concentration higher than 3.9 mmol L^{-1} for 7 h in most young adults (157, 158).

Liver transplantation is indicated in the patients when medical treatment fails to control the metabolic problems or when HCA or hepatocellular carcinoma develops. Living-donor liver transplantation is a viable option to restore normal metabolic balance and keeping normal renal function (159). Hepatocyte transplantation can be a potential therapeutic intervention to prevent hypoglycemia despite the discontinuation of cornstarch meals (160).

Fanconi-Bickel Syndrome

Fanconi-Bickel syndrome (FBS) is an autosomal recessive disorder characterized by failure to thrive, "doll-like" face, hepatomegaly, nephromegaly, and severe rickets. Patients with FBS manifest glycogen accumulation in hepatocytes and proximal tubular cells, fasting hypoglycemia, galactose intolerance, and FS including glucosuria, aminoaciduria, hyperuricosuria, hyperphosphaturia, proteinuria, and sodium and potassium wastage (161, 162). Some patients manifest cataracts in neonatal period (163). Overall prognosis of FGS is considered as favorable (164). However, some patients manifest neonatal diabetes mellitus and galactosemia and die of hepatic failure during infancy (165).

FBS is caused by the mutations in facilitative glucose transporter gene (*SLC2A2*, also referred to as *GLUT2*) expressed in liver, kidney, intestine, and pancreatic islet cells (166). Over 60 mutations in *SLC2A2* were reported (167). This facilitative glucose transporter is expressed in hepatocytes, pancreatic beta cells, and renal and intestinal epithelial cells and is important for the exchange of glucose between these cell types and the bloodstream (168). Renal histology reveals an increase in mesangial cellularity, glomerulosclerosia, and patchy swelling of epithelial foot process and irregularly thickened lamina rara interna in the glumeruli, and vacuolization of epithelial nuclei in the proximal tubule cells suggesting the presence of glycogen in a 7 year-old patient with FBS (169).

The therapy for FBS is directed at the renal solute losses including sodium bicarbonate and potassium-sodium phosphate; treatment of rickets including active vitamin D3; and frequent feeding including night-time supplementation to prevent ketosis. Uncooked cornstarch has been shown to lessen hypoglycemia and improved growth (170). Galactose–free milk is also used for infant patients (165, 171).

Tyrosinemia I

Hereditary tyrosinemia type I (TI) is an autosomal recessive disorder of an amino acid metabolism. TI is due to the defect in the fumarylacetoacetate hydrolase (FAH) gene (172, 173). FAH is the last enzyme in the tyrosine catabolic pathway.

Patients with TI display a variety of clinical symptoms, such as liver damage from infancy that advances to cirrhosis, reduced coagulation factors, hypoglycemia, high plasma concentrations of methionine, phenylalanine, and aminolevulinic acid, high risk of hepatocellular carcinoma, and tubular and glomerular renal dysfunction (174).

Progressive renal damage begins from early infancy in severe form. Chronic liver damage with a high incidence of hepatoma (hepatocellular carcinoma) is characteristic in milder form (175). Even a patient without clinical manifestations of TI can manifest hepatoma during childhood (176). Accumulated fumarylacetoacetate in the patients with TI is pathogenic for hepatoma. Patients with milder form of TI are at risk for acute exacerbation of liver dysfunction. A common presentation mode is the "acute hepatic crisis" in which ascites, jaundice, and gastrointestinal bleeding are precipitated by an acute event such as an infection. Acute hepatic crises usually resolve spontaneously but on occasion progress to complete liver failure and encephalopathy. Acute, painful peripheral neuropathy may appear and can lead to transient paralysis. Autonomic dysfunction with hypertension and tachycardia can be associated with this acute neuropathy (177). Plasma tyrosine and methionine levels usually are elevated in untreated patients. The presence of succinylacetone in plasma and urine is diagnostic of TI. A rapid ultra performance liquid chromatography tandem mass spectrometric method is used for mass screening of tyrosinemia (178).

FS and developmental hypophosphatemic rickets are features of the kidney involvement. Generalized aminoaciduria, renal tubular acidosis, and mild proteinuria are also often seen, whereas glucosuria is less common because plasma glucose levels are low. Kidney enlargement is common, and nephrocalcinosis can be seen (179). FS leads to carnitine deficiency (180). Glomerulosclerosis and impaired GFR may be seen with time.

Disturbances in tyrosine metabolism lead to increased levels of succinylacetone and succinylacetoacetate. However, the mechanisms causing liver failure, cirrhosis, renal tubular dysfunction, and hepatocarcinoma are still unknown. Apoptosis of hepatocytes and renal tubular epithelial cells are characteristic features of this disease and the apoptotic signal in this disease seems to be initiated by fumarylacetoacetate (181, 182). Accumulated maleylacetoacetate and fumarylacetoacetate in affected tissues can react with free sulfhydryl groups and reduce intracellular levels of glutathione. They may be capable of acting as alkylating agents. Maleylacetoacetate and fumarylacetoacetate are not detectable in plasma or urine but are converted to succinylacetoacetate. Succinylacetone, a metabolite of succinylacetoacetate, is structurally similar to maleic acid, which is known to induce FS and may be the cause of tubular dysfunction of HI. Experimentally, succinylacetone administration to rats leads to FS (183, 184).

Treatment with a low-phenylalanine and low-tyrosine diet dramatically improves the renal tubular dysfunction (185). However, this treatment cannot necessarily improve the hepatic involvement. Moreover, there is a risk of inducing deficiencies of phenylalanine or tyrosine. The formation of pathogenic fumarylacetoacetae is prevented by 2- (2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC). NTBC is used for the patients with TI during the first 6 months of life in addition to a diet low in tyrosine and phenylalanine. NTPC clearly improves the vital prognosis and quality of life in the patients (186). However, some patients with NTBC treatment develop hepatoma. A rise of alpha-fetoprotein (AFP), a slow AFP decrease, and never normalizing levels of AFP are important predictors of hepatoma development (187). Liver transplantation has been used for patients with liver failure and to prevent the development of hepatoma (174). Liver transplantation leads to rapid correction of FS (188).

Wilson Disease

Wilson disease (WD, progressive hepatolenticular degeneration) is an autosomal recessive inborn error of copper (Cu) metabolism that affects numerous organ systems (189). Biliary excretion of Cu and incorporation into ceruloplasmin is impaired, leading to liver damage, neuronal degeneration, and impairment of other organs from accumulation of Cu in patients with WD.

The majority of patients with WD presents with either predominantly hepatic or neuropsychiatric symptoms, and with either clinically asymptomatic or symptomatic liver involvement. Approximately 40% of patients presents with liver disease, 40% with extrapyramidal symptoms, and 20% with psychiatric or behavioral abnormalities. Symptoms rarely occur before 6 years of age. Hepatic involvement includes acute hepatitis, fulminant hepatic failure, or progressive chronic liver disease in the form of either chronic

active hepatitis or cirrhosis of the macronodular type. Neuropsychiatric involvements are variable. The most common initial presentation is bulbar symptoms characterized by difficulties with speech and swallowing, and drooling. They frequently manifest dysarthria and coordination defects of voluntary movements accompanied by involuntary movements. One third of the patients with WD manifest psychiatric disturbances. The remaining patients with WD may present with symptoms including hemolytic anemia, bone fracture, arrhythmias, FS, hyperpigmentation, Kayser-Fleisher ring, cataract, and gynecological problems that are attributable to the involvement of the organs.

WD is caused by a mutation in the gene *ATP7B* that encodes a P-type Cu transporting ATPase beta polypeptide enzyme (ATP7B) (190). This ATPase is targeted to the mitochondria, suggesting that its role in Cu dependent processes takes place in this organelle. The disease frequency is estimated to be between 1 in 5,000 and 1 in 30,000, and the carrier frequency is approximately 1 in 90 (191).

Cu is absorbed by the intestinal cells and stored with metallothionein in a non-toxic form. The Cu is later delivered into the circulation by a Cu transporter 15,000 amino acid protein, Cu-transporting P-type ATPase 1 (ATP7A), which is located on the membrane of enterocytes (▶ *Fig. 42-7*) (192). It is then transported to the liver tagged with albumin, from where it is accepted by hepatocytes. The ATOX1 chaperone protein directs Cu to its binding targets in the hepatocytes. Some of Cu bounds to metallothionein for storage, and the remainders are excreted into ATP7B-regulated biliary canaliculi. ATP7B also mediates the transfer of Cu to apoceruloplasmin to form a six-Cu binding protein, ceruloplasmin (193). Ceruloplasmin is released into the blood, carries 90% of the Cu present in the plasma, and acts as a source for peripheral organs. Mutations of the *ATP7A* gene result in the storage of Cu in enterocytes, preventing entry of Cu into the circulation and thus causing a complete Cu deficiency (Menkes kinky hair disease) (192).

Mutations in *ATP7B* gene lead to a reduction in the conversion of apoceruloplasmin into ceruloplasmin, which is usually present at low levels in the patients of WD. A failure to excrete Cu into the biliary canaliculi leads to toxic effect to hepatocytes. Excess Cu damages mitochondria, which produce oxidative damage to the cells and allows spillage of Cu into the blood, thereby overloading other tissues including the brain, kidney, and red blood cells, initiating toxic effects.

Excessive accumulation of Cu in the kidney leads to renal tubular dysfunction in patients with WD. Patients show most features of FS before the onset of hepatic failure and is characterized by intermittent glucosuria, aminoaciduria, hyperphosphaturia, hyperuricosuria, and proteinuria (194–196). Patients can manifest rickets or osteomalacia. hypercalciuria, urolithiasis, nephrocalcinosis, decreased urine concentrating ability and distal renal tubular acidosis are reported (197). Glomerular function decreases as the disease progresses, but death from extrarenal causes occurs before the onset of renal failure.

Histological analysis of the patients with WD revealed no alteration on light microscopy or only flattened proximal tubule cells without recognizable brush border (198). Electron microscopy disclosed loss of the brush borders, electron dense deposit in the subapical region of tubular cytoplasm probably representing metalloproteins, and cavitation of the mitochondria with disruption of the normal cristae pattern (199).

All subjects presenting with symptomatic or asymptomatic liver disease with no apparent causes or with extrapyramidal features along with a past or family history of similar hepatic or neurological illnesses in other siblings should be screened for WD (200). Measurement of the serum ceruloplasmin is valuable for diagnosis. Any value below 200 mg L^{-1} is abnormal, and reduced levels are seen in up to 95% of the patients with WD. An estimation of 24 h urinary Cu excretion is another reliable test for the diagnosis of WD. Normal excretion is between 20 and 50 µg a day, and Cu excretion is increased to in excess of 100 µg a day in patients with WD. Serum free Cu is a measure of nonceruloplasmin toxic Cu in the blood, and normal value range from 1.3 to 1.9 µmol L^{-1} (8–12 µg dL^{-1}) in parallel with the increased urinary Cu excretion, because of saturation of the hepatic storage of Cu. A hepatic biopsy and a measurement of its Cu content are helpful for diagnosis. 80% of the patients manifest increased hepatic Cu (>250 µg/g of dry tissue weight). Genetic analysis of *ATP7B* gene is a helpful confirmation of WD. Brain MRI is a very sensitive method for revealing abnormalities in patients with WD. Generalized brain atrophy and hyper-intensity in the basal ganglia, white matter, thalamus, or brainstem are common findings in the patients. Patients exhibit characteristic features on MRI; "face of the giant panda" is seen in the midbrain and "face of the miniature panda" is seen in the tegmentum region of the pons in T2-weighted images (201, 202).

WD has a fatal outcome if not treated appropriately and in a timely manner. The aim of treatment for WD is to remove the toxic deposit of Cu from the body to produce a negative Cu balance, and to prevent its reaccumulation (190, 203). Successful therapy is measured in terms of a restoration of normal levels of free serum Cu and its excretion in the urine. The average daily diet
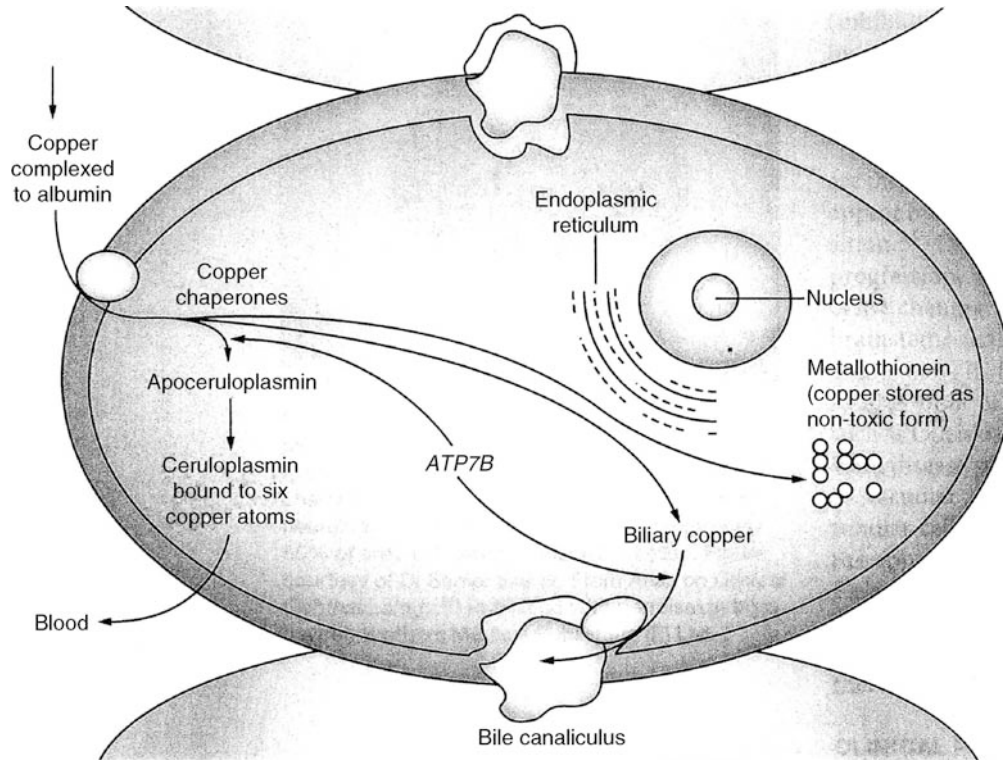
contains 2–4 mg of Cu, and 0.8 mg is normally lost into the feces. Patients should avoid Cu-rich foods including chocolate, nuts, shellfish, mushrooms, and liver. D-penicillamine therapy (20 mg kg^{-1} of body weight a day) has been the most commonly used chelating agent that may reverses multiple tissue dysfunction including FS. However, use of D-penicillamine has been questioned, because of reported side effects. The side effects from D-penicillamine can occur both early and late in the treatment period. Early side effects include a hypersensitivity reaction characterized by fever, skin rash, and lymphadenopathy. Delayed side effects including Goodpasture's syndrome, polymyositis, systemic lupus erythematosus, and bone marrow suppression are caused by immunological reactions. Trientine is another effective chelating agent (750–2,000 mg a day for adults). Ammonium tetrathiomolybdate (2–3 mg kg^{-1} of body weight a day in six doses along with meals and in the interval between meals) is a potent agent in removing Cu from the body and may be the drug of choice for patients with neurologic disease to prevent the immediate worsening of

symptoms that can occur with D-penicillamine therapy. Zinc acetate or sulfate induces intestinal metallothionein and helps in the prevention of Cu absorption from the gut (3–5 mg kg^{-1} of body weight a day in three divided doses before meals). D-penicillamine should be taken 2 h after meals to avoid any interaction with the zinc. Zinc acetate or zinc sulfate has been used successfully in asymptomatic or presymptomatic affected family with WD, and is equally as effective as D-penicillamine in a group of patients predominantly with neurological disease (204, 205). The use of trientine, tetrathiomolybdate, and zinc has been advocated, although results of long-term trials are awaited. The best therapeutic approach remains controversial and there is no universally accepted regimen. Liver transplantation is effective for the patients with progressive live failure or acute liver failure. Liver transplantation is also indicated for patients with WD in whom medical therapy is ineffective. Symptomatic patients with WD require lifelong treatment, because an interruption to therapy or inadequate treatment can lead to fatalities within 9 months to 3 years (189, 203).

Idiopathic Fanconi Syndrome

Although the significant numbers of genetic causes for the disorders leading to FS are identified, there exist patients with idiopathic FS. Idiopathic FS should be diagnosed when all other known causes have been excludes. Idiopathic FS can be inherited as an autosomal dominant (206–211), autosomal recessive (212, 213), and X-linked form (214). However, most of the familial forms are autosomal dominant inheritance.

Children with idiopathic FS manifest failure to thrive, frequent bouts of dehydration, and rickets. They often have other features of FS, including polyuria, polydipsia, hypokalemia, hypophosphatemia, proximal renal tubular acidosis, aminoaciduria, glucosuria, and proteinuria. Glomerular filtration rate is usually normal during childhood. However, some develop chronic renal insufficiency or chronic renal failure 10–30 years after the onset of symptoms (208, 209, 213). Nephrocalcinosis and *genu vulgum* (knock knee) are seen in some patients (213). Bone pain, bone fracture, and scoliosis due to osteomalacia can become serious complications in adult patients with idiopathic FS (❯ *Fig. 42-8*).

Renal histology reveals chronic tubulointerstitial fibrosis. The interstitium demonstrates patchy fibrosis associated wit tubular atrophy and focal collections of mononuclear inflammatory cells. Occasional cystically dilated tubules are seen containing eosinophilic proteinaceous material that stains positive for PAS (213).

Treatment for idiopathic FS remains symptomatic. Careful follow-up of these patients is necessary to prevent recurrent bouts of dehydration, electrolyte imbalance, and metabolic bone diseases. Glomerular function and nephrocalcinosis must be checked regularly. Renal transplantation has been done in a few patients who had end-stage renal failure (209).

Acquired Fanconi Syndrome

Nephrotic syndrome is associated with FS (215). The renal pathology is focal segmental glomerulosclerosis. Although the true pathogenesis is not clarified, mitochondriopathies can manifest FS, focal segmental glomerulosclerosis leading to nephrotic syndrome, and both (79–84).

Immunological or hematological disorders are associated with dysproteinuria leading to FS. They are multiple myeloma, Sjögren syndrome, and amyloidosis. Almost all of the patients with theses diseases are adults. In early stages of myeloma, light chain nephrotoxicity often presents with proximal tubular functional abnormalities leading to FS. Proximal tubule dysfunction is the most common mode of renal involvement and it can manifest in a variety of ways. Endocytosis in the proximal tubules is overloaded and cell stress responses that include phosphorylation of MAPKs, prominently, p38 MAPK, and nuclear transcription factors NF-kappa B, AP-1 are activated resulting in production of inflammatory and proinflammatory cytokines, TNF-alpha, interleukin-6, 8 and monocyte chemo-attractant protein-1 (216). These proximal tubule alterations often progress to a severe tubulointerstitial nephritis and end stage renal failure.

Sjögren syndrome is an autoimmune connective tissue disorder that affects exocrine glands. Renal involvement of Sjögren syndrome is mainly manifested as tubular disorders; 70% of the patients manifest distal renal tubular acidosis (217). Urinary concentration defect, proteinuria and LMW proteinuria are often seen in the patients. Only 4% of the patients manifest FS (217). Patients with FS and Sjögren syndrome manifest osteomalacia including bony deformities of rib cage, bilateral humeral shaft fractures, and marked cortical bone thinning (218). Characteristic histological feature of Sjögren syndrome is chronic interstitial nephritis, with diffuse or focal plasmacytoid lymphocytic infiltration. In the late stage of the disease, tubulointerstitial fibrosis is severe. Corticosteroid or/and immunosuppressant therapy can improve the prognosis.

❒ **Figure 42-8**
Plain X-ray showing scoliosis and osteopenia in a 35-year-old female with idiopathic Fanconi syndrome.

FS has appeared rarely after renal transplantation (219). Acute tubular necrosis, chronic rejection reaction, and nephrotoxic drugs can induce the progression of FS in the patients.

Acute tubulointerstitial nephritis with uveitis (TINU) syndrome is an immunological disease that leads to tubulointerstitital nephritis and anterior uveitis (220). Patients with TINU syndrome manifest asthenia, malaise, weight loss, nocturia, and thirst. Patients also manifest incomplete or complete FS including proteinuria, LMW proteinuria, glucosuria, aminoaciduria, bicarbonaturia, phosphaturia, and uricosuria due to proximal tubule dysfunction and acute renal failure (221). Urine concentration is decreased in the patients. Corticosteroid therapy can improve renal and eye manifestations.

Autoimmune interstitial nephritis and membranous nephropathy is a distinct disorder. The patients manifest failure to thrive, multiple renal tubular disorders including FS and proteinuria (222, 223). Renal biopsy revealed interstitial nephritis with lymphocytic infiltration and fibrosis, and membranous nephropathy. In advanced stage, focal segmental glomerulosclerosis and tubular atrophy develop. Immunofluorescence analysis shows linear staining of IgG along the glomerular capillaries and the tubular basement membrane. These renal lesions result from an autoimmune response to the 58-kD tubular basement membrane autoantibody (224). This disorder is genetically related to HLA B7 serotype (224).

A patient with anorexia nervosa is described to manifest reversible FS like condition including glucosuria, phophaturia, and uricosuria, although the precise pathogenesis is not known (225). These manifestations subside with nutritional recovery.

Untreated patients with distal renal tubular acidosis manifest LMW proteinuria, generalized aminoaciduria, phosphaturia, uricosuria, and hypercalciuria (226, 227). These proximal tubular abnormalities are transient and disappear by the alkali and potassium therapy. Although the precise pathogenic mechanisms underling the development of proximal tubular dysfunction remains unclear, decreased pH in the cytoplasm of the proximal tubule cells resulting from the intracytoplasmic accumulation of H^+ due to luminal membrane H^+-ATPase dysfunction can disturb trafficking of endosome.

Exogenous Factors

Drugs

Numerous drugs and herbs are implicated in the pathogenesis of FS. Drugs and herbs are usually filtered from the glomerulus and reabsorbed in the proximal tubules. They include outdated tetracycline (228), aminoglycosides (229, 230), salicylate (231), valproic acid (232, 233), and Chinese herbs (234, 235). Aminoglycoside antibiotics reduce glucose reabsorption in kidney tissue by reducing mRNA, protein expression, and function of the Na^+-dependent glucose transporter, which is located in the luminal membrane of the proximal tubule (236). Covalent binding of salicylate or its metabolites to mitochondria in proximal tubule cells alters the function of mitochondria (231). Valproic acid produces the defects of mitochondrial respiratory chain and lysosomal enzyme activity in the proximal tubule cells leading to multiple renal transport abnormalities (13, 237). Chinese herbs containing aristolochic acids cause proximal tubular injury, and this is called as aristolochic acid-related nephropathy.

A number of cancer chemotherapy agents are associated with renal glomerular and tubular dysfunctions including FS. The nephrotoxicity of cancer chemotherapy agents is dose dependent and often irreversible. Ifosfamide is an alkylating agent widely used in the treatment of various solid tumors. Chloroacetaldehyde (CAA), one of the main metabolites of ifosfamide, contributes to inhibit endocytosis in the proximal tubule cells (238). CAA decreases total glutathione and ATP levels in the proximal tubule cells. CAA also inhibits endosomal H^+-ATPase activity, which disturbs intracellular vesicle trafficking (239). Patients receiving ifosfamide who have received prior cisplatin are at significantly higher risk of developing FS than are those who have received no prior nephrotoxic therapy (240). When the patients manifest FS, renal sonography reveals hyperechogenicity of the parenchyma with good corticomedullar differentiation (241). Taurine can protect against ifosfamide-induced renal dysfunction without compromising its anti-tumor activity (242). Cisplatin also reduces glucose reabsorption in kidney tissue by reducing mRNA, protein expression, and function of the Na^+-dependent glucose transporter (243). Cisplatin inhibits various types of amino acid transporters in the proximal tubule cells leading to a generalized aminoaciduria (243).

Imanitib mesylate is a specific tyrosine kinase inhibitor that is the first line therapy for patients with chronic myeloid leukemia. This agent induces partial FS including phosphaturia and uricosuria with mild renal failure. Combined blockade of both platelet-derived growth factor receptor and c-Kit receptor tyrosine kinase in proximal tubules causes partial FS (244).

Nucleotide reverse transcriptase inhibitors that are used as anti-human immunodeficiency virus (HIV) agents including adefovir, cidofovir, and tenofovir induce

FS, nephrogenic diabetes insipidus, and acute renal failure (245–248). Adefovir and cidofovir interact with organic anion transporters (OAT); these drugs enter into proximal tubule cells by activated OAT located in the basolateral membrane. However, their efflux into the tubular lumen is decreased by inactivated multidrug-resistance-protein 2 (MRP 2) located in the luminal membrane. Thus, these drugs are accumulated in the proximal tubule cells leading to mitochondrial damage and tubular toxicity. Cytotoxicity of adefovir and cidofovir is proportional to cellular OAT expression (246). Histologic and ultra-structural examination reveals tubular degenerative changes of proximal tubules with swollen and dysmorphic mitochondria. In tubular cells, respiratory chain components encoded by mitochondrial DNA (cytochrome oxidase subunit I) are selectively deficient in renal tubular cells, and mitochondrial DNA is quantitatively reduced (249). In contrast to adefovir and cidofovir, renal toxicity of tenofovir is much less frequent. Tenofovir has little mitochondrial toxicity and it does not interact with OAT (250). Therefore, the precise mechanisms of nephrotoxicity by tenofovir remain unknown.

Chemical Compounds

Paraquat, a non-selective herbicide, and colloidal bismus subcitrate cause FS (251, 252). Large amount of these compounds are usually ingested in a suicide attempt. Patients manifest FS and acute renal failure. Treatment with the chelating agent sodium-2,3-dimercapto-1-propanesulfonate in combination with hemodialysis is highly effective in reducing the serum bismus level. Methyl-3-chromone (diachrome) (253), 6-mercaptopurine (254), and toluene also lead to FS (255).

Heavy Metals

Heavy metals such as lead, cadmium, mercury, chromium, and platinum are a major environmental and occupational hazard. They are very toxic at very low doses. The kidney is the first target organ of heavy metal toxicity. The extent of renal damage by heavy metals depends on the nature, dose, route, and duration of exposure. Both acute and chronic intoxication have been demonstrated to cause nephropathies, with various levels of severity ranging from tubular dysfunctions like acquired FS to severe renal failure (256). Lead poisoning leads to FS, predominantly in children (257). As lead is non-biodegradable with a very long biological half-life, aminoaciduria and

glycosuria persist up to 13 years after childhood severe lead poisoning (258).

Cadmium intoxication leads to FS after a long exposure (259). The industrial waste contaminating cadmium in the Jinzu River basin in Toyama prefecture in Japan produced a lot of patients with *Itai-Itai* (*ouch-ouch*) disease that is compatible to FS with severe osteomalacia. Patients complained severe bone pains that are derived from advanced non-traumatic multiple bone fractures. Cadmium produces free radicals that alter mitochondrial activity or induce mitochondrial gene deletion in the proximal tubules (260, 261). Cadmium inhibits H^+-ATPase, which results in a Fanconi-like syndrome (6).

Therapy

Identification of the underling cause for FS is a first step and is critical to direct specific therapy. Avoidance of offending nutrients in galactosemia, HFI, and tyrosinemia and avoidance of Cu-rich foods in WD are therapeutically critical. Specific treatments with Cu-chelating agents including D-penicillamine, trientine, and ammonium tetrathiomolybdate, and zinc are effective for WD. Imuunosuppressive drugs are used for immunologically induced disorders including Sjögren syndrome, TINU syndrome and autoimmune interstitial nephritis and membranous nephropathy. These treatments can completely resolve FS.

When specific therapy does not exist, therapy is directed at the biochemical abnormalities secondary to renal solute and fluid losses and the metabolic bone diseases. Proximal renal tubular acidosis usually requires large amount of alkali (2–15 mEq kg^{-1} of body weight a day) divided into four to six daily doses. High dose of alkali can produce volume expansion, further bicarbonate wasting and potassium loss in the patients with FS. 1–3 mg kg^{-1} of body weight a day of hydrochlorothiazide can reduce the dose of alkali by preventing the volume expansion. Administration of potassium salt of citrate, bicarbonate, or acetate fulfills the dual purpose of treating acidosis and preventing hypokalemia. Sodium wasting and dehydration are treated with combination of sodium bicarbonate, citrate, and chloride, depending on the degree of acidosis. Ensuring adequate fluid and electrolyte intake is essential, especially in the case of infants or gastrointestinal diseases. Early intervention with intravenous replacement therapy is required for the patients with FS who manifest vomiting and diarrhea.

Hypophosphatemia and impaired renal vitamin D3 metabolism in patients with FS lead to rickets and other metabolic bone diseases. 1–3 g of phosphate supplementation

is necessary as neutral phosphate (the mixture of sodium phosphate dibasic 1.94 g and potassium phosphate monobasic 0.34 g contains 0.5 g of phosphate) divided into four to six daily doses. Supplementation of 1,25-dihydroxyvitamin D3 or dihydrotachysterol is effective to treat or prevent rickets and osteomalacia. Vitamin D3 therapy improves the hypophosphatemia and lessens the risk of hyperparathyroidism. Hypercalcemia and hypercalciuria are toxic side effects of vitamin D3 therapy. An adequate amount of physical activity, as well as appropriate diet with calcium, phosphate, and vitamin D3, is necessary to prevent bone deformations, non-traumatic fractures leading to bone pain, deterioration of motor development and disability (262).

Aminoaciduria, glucosuria, proteinuria, LMW proteinuria, and uricosuria usually do not induce clinical symptoms and do not require specific treatments.

Growth failure is a major complication in FS. Despite correction of electrolyte abnormalities, some patients manifest severe growth retardation, especially those with cystinosis and Fanconi-Bickel syndrome. A patient with FS was reported to have growth hormone deficiency (263). Supplemental growth hormone has been used successfully in a few patients with FS.

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