THE TURKISH JOURNAL OF
PEDIATRICS
A HACETTEPE BULLETIN VOLUME 14 / NUMBER 4 / OCTOBER 1972

Hereditary Renal Diseases

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Hereditary renal diseases can be divided from the practical point of view into three groups: *macroanatomical*, *microanatomical* and the *biochemical disorders*. From the genetical viewpoint, the macroanatomical group is confused and even distant. The microanatomical group consists of those that the clinician usually considers as renal diseases. Their common characteristic is the leakage of the basement membrane and as result of this: proteinuria. In the biological group there need not even be any detectable electronmicroscopical changes, only some specific functions of the renal tubules are defective.

In many hereditary "renal diseases" the renal disorder is only a feature of the disease, however, it is often the major cause of the morbidity and mortality. One cannot overemphasize the thorough careful general examination and eliciting of certain symptoms and signs. One has also to bear in mind the limitation of the microscope as a diagnostic tool in hereditary renal disease. In virtually all these diseases the histology rather reflects the stage of the disease and there are very few diagnostic features to be found. A given pathologist rarely sees all the types of renal disease. Diagnostic pitfalls seem to be particularly frequent when interpreting cystic changes. Diagnosis of biochemical errors is more pronounced. This article deals only with a selected group of diseases important in practice.

As useful reviews, I would like to mention the chapter on the urogenital system in Becker's Handbook of Human Genetics[5] and Perkoff's articles.[10] Review articles (in list form) and other articles dealing with genetics of renal disease (e. g., the cystic diseases) are to be found in Birth Defects, Original Article Series number 3/1970[11,12] "The Metabolic Basis of Inherited Diseases" edited by Stanbury et al.[14] is clinically and genetically an excellent source of information on biochemical diseases.

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Macroanatomical disorders

Macroanatomical renal anomalies are found in many malformation syndromes, which are rarely inherited. For instance, the unilateral multicystic kidney found by palpation in the newborn is not inherited. The only group of disorders worth mentioning here are the cystic disorders of the kidneys and often simultaneously also of the liver. The classification of these disorders is, however, often very obscure.

The benign polycystic disease of the kidneys frequently expresses itself at a mature age and is called the adult type. In these cases, cysts may also be found in the liver and basal arteries of the brain. It has a *dominant inheritance.* (Table I)

The very large *cystic kidneys*, seen in the newborn, are functionally inadequate from birth, and are called the infantile type. Cysts of the liver and pancreas are often also found, as well as other abnormalities. This group is *recessively inherited.*

TABLE I

MACROANATOMICAL INHERITED KIDNEY DISEASES

Polycystic disease
– Adult type (D)
– Infantile type (Rec)
Medullary cysts (D)
Medullary spongious kidney (Rec)
Cystic dysplasia (Rec)

Together with the liver fibrosis of Banti's syndrome, appearing in the first decade of life, cystic changes resembling medullar "mushroom kidneys" are also found, without any kidney symptoms. The syndrome seems to be *recessively inherited.*

Microanatomical renal diseases

This group presents itself to the physician in three different ways. Possible genetic etiology should be borne in mind when examining any unclear renal involvements especially of the younger age group. The detection of proteinuria by routine examination of apparently healthy patients exposes renal disease of which some are of genetic etiology. The third group is present in those patients who complain of completely unrelated symptoms, e. g., poor hearing, dislocation of the patellae or skin diseases. Thus specialists in other fields should consider renal disease from a certain combination of symptoms and signs.

Congenital nephrosis (nephrosis congenita, congenital nephrotic syndrome) is a rare disease but well-known in Finland. It manifests itself within the first weeks of life. Clinical signs are proteinuria, edema, hypoproteinemia and hyperlipemia. It is assocated with a large placenta, low birthweight, failure to thrive, frequent infections and death in a few years. Treatment is symptomatic. Neither steroids nor immunosuppressive drugs bring relief. In Helsinki five patients have had bilateral nephrectomy and renal transplantation, however, without success to date. Veriner (personal communication) has reported the suceess of a renal transplant in a five year-old child. One infers from this that the disease affects only the kidneys. (Table II)

TABLE II

MICROANATOMICAL INHERITED KIDNEY DISEASES

Congenital nephrotic syndrome (Rec)
Nephrotic syndrome of older children ?
Alport's syndrome (D)
"Chronic benign nephritis" (D)
Juvenile nephronophthisis (Rec)
Nail patella syndrome (D)
Fabry's disease, glycolipid lipidosis (Incompl. Rec., X-linked)

The inheritance of the disease is *autosomal recessive.* About ten new cases (1: 8.000) are born in Finland every year. The large placenta is of diagnostic significance. All cases would be diagnosed if congenital nephrosis was suspected in all cases where the placenta weighs more than a quarter of the baby's weight.

Other nephrosis. There are reports of families in which an early nephrotic syndrome appears that is apparently recessively inherited, this differs from the Finnish type in having a milder course. Proteinuria is detectable in the first weeks of life. Development is near normal and the children learn to walk and reach even school age. (Table III)

There are reasons to believe that the so-called *idiopathic lipoid nephrosis* is associated with a *polygenetic inheritance.*[9] This has no practical importance. It is worth while to know, however, that without exception both pairs of monozygotic twins reported in the literature have the nephrotic syndrome.

Alport's syndrome (hereditary hematuria and deafness) is characterized by hematuria but this can disappear for a time. Most com-

TABLE III

INHERITED TUBULAR DISEASES

Renal glucosuria
Renal aminoaciduria
– Cystinuria (Rec)
– Hartnup's disease (Rec)
– Familial iminoaciduria
Renal phosphatemia - hypophosph.
D. -vit. resistent rachitis (D)
Renal tubular acidosis (D)
– Proximal
– Distal
Nephrogenic diabetes insipidus (Rec)

monly it is microscopic and is aggravated by even mild infections. Because of this, acute nephritis is sometimes diagnosed. The deafness, seen often, is of neurogenic origin. In Alport's families, there are also cases of deafness without renal involvement. Both renal disorders and deafness are worse in men and that is why they frequently die of uremia before the reproductive age. In women, the disease does not usually threaten life, but they have an increased frequency of toxemia during pregnancy. A clinically healthy woman can be a carrier. There is nothing diagnostic in the renal histology. Macrophages filled with lipids, i. e., foam cells, are seen in some cases but they are not pathognomanic.

Alport's syndrome is *dominantly inherited*, with some exceptions: in siblings more than 50 % will be affected and the majority are female. The most plausible explanation is the so-called preferential segregation theory: the dominant gene responsible for the disease is located on the autosomal chromosome which in meiosis goes with the X chromosome into that part that becomes the active "sex gene rather than barr body".[1] In practice, it is sufficient to remember that the disease is inherited in an atypical dominant fashion.

Benign chronic nephritis. This is to be remembered in the differential diagnosis of Alport's syndrome, as a milder proteinuria hematuria disease without deafness. The men suffering from it may live to a ripe old age. It is inherited *dominantly.*

Nephronophthisis (familial juvenile nephronophthisis, medullary cystic disease?) is both typical and a specific disease.[3] Its first and consistent symptoms are polyuria and polydipsia of unknown etiology,

starting before school age. These symptoms are not as severe as in diabetes insipidus, but nevertheless clearly noticeable. The children have a compulsive need for water, and they may even empty a flower vase if denied of other sources. The specific gravity of the urine is respectively low. Both anemia and stunted growth are common. Other renal symptoms and signs are, however, almost absent. There is no hypertension, edema or abnormal urine sediments, even proteinuria may be absent or minimal. The terminal stage appears at school age with the sudden appearance of uremia although the proteinuria may still be scanty. The autopsy shows contracted kidneys with a severe destruction of the nephrons, interstitial and especially periglomerular fibrosis and medullary cysts. The children may die suddenly. Renal transplantation is the only possible cure. Inheritance is *recessive.*

Cases of nephronophthisis were unknown until recently in the USA.[6] A similar disease was, however, described there under the name of "*medullary cystic disease*". It is a milder disease and seems to be *dominantly* inherited. Clinical differentiation of the two is often difficult. Some hold the view that the two are the same disease[8] and the recessive inheritance of nephronophthisis has been questioned.[15] At this moment, it is difficult to decide whether these two diseases are different manifestations of the same gene. The severe *juvenile form* being *recessively inherited*, is a disease of the homozygotes. The same gene appearing in a heterozygous form produces a milder disease in adults, often without polydipsia but leading slowly to uremia.

Nail patella syndrome (osteo-onychodysplasia hereditaria) is easy to diagnose if one only remembers it. The following are typical findings, though not all are present in any given patient: the nails are hypoplastic; there is limited extension of the elbow joint due to proximal radial head abnormalities and subluxation; the patellae are missing or are small and luxate easily; iliac bones have horn-like processis, which are seen for instance in intravenous pyelograms and may produce prominences in the gluteal region. The renal involvement varies.

The renal involvement is significant to the patient though the disease is known as an orthopaedic condition. The degree of renal involvement can vary from a lifelong proteinuria of no consequence to chronic nephritis leading to uremia at a young age. There is no characteristic renal histology, but the diagnosis is made from the other characteristic findings. Every proteinuria patient's examination should include looking at the nails, extension of the elbow joint and palpation for the patellae. The disease is inherited *dominantly*. Thus other cases will

be found in close relatives. The gene is found in the same chromosome as the ABO blood group genes.

Angiokeratoma corporis diffusum (Fabry's disease, glycolipid lipidosis) belongs to the sphingolipidosis group. There are bifrigent sudanophilic lipid deposits in the body which are found e. g., in the media of blood vessels, in smooth and cardiac muscle, in ganglion cells and in all parts of the nephron.

The disease derives its name from the drawing pin head size dark red haemangectasia which first appear mainly between the umbilicus and the knees. Some granular and round opacities appear in the cornea which hardly interfere with sight and are best detected with a split light and corneal microscope. Dilated and tortuous blood vessels are seen in the conjunctiva and in the retina. The patients suffer from varying degrees of intermittent pains in extremities, joint symptoms (e. g. inter-phalangeal joint nodes), pyrexia, hypohidrosis, neurological symptoms and different vascular complications. If the patient does not die from the latter the most common cause of death will be from the renal insufficiency due to renal lipid deposits. The possible enzyme defect is not known although many characteristics of the deposited lipid are known.[14]

The disease is inherited as *incompletely recessive bound on the X chromosome.* Thus, only men suffer from the disease in its severe form. Heterozygote women may have mild manifestations of it, especially corneal opacity. Because of the telangectasia it should be easily distinguished in the group of multi-symptom uremic patients.

Other inherited proteinurias: I shall limit myself to mention a group, e. g., rare renal and systemic diseases that have proteinuria as one of the signs. These are Lowe's syndrome, selective B_{12} vitamin malabsorption, nephropathy + hyperprolinemia, nephropathy + polyneuropathy, retinorenal dysplasia, "periodic illness" + amyloidosis, gout, cystinosis, alkaptonuria, hemochromatosis and glycogenosis. This list shows that when presented with an unexplained proteinuria one should always make a complete examination of the body and not to limit oneself to the kidneys. It is possible, that at least some of the so-called benign proteinurias, often labelled for instance as orthostatic, present a manifestation of a rare inherited kidney disease or even a disease at present unknown.

Biochemical renal disturbances

In this group the defect lies in the tubular function, which controls the glomerular filtrate concentration according to the needs of the

homeostasis in the body. This happens by a selective and active reabsorption of the components with small molecular weight from the filtrate, e. g., glucose, amino acid and electrolytes. In addition, the tubules regulate the body water content and acid base balance by altering the volume and hydrogen-ion concentration of the urine. Any of these processes may be impaired because of an inherited metabolic defect.

Renal glycosturia. This is the condition when glucose is detected in the urine in spite of the normal blood level. It is mostly associated with renal aminoaciduria, phosphaturia and acidosis caused by proximal tubular deficiences or damages. True renal glucosuria as a single finding is a *dominantly inherited* condition. As patients who afterwards have developed diabetes mellitus have been diagnosed as renal glycosurias, the real frequency of the latter is unknown. Thus in practice, when faced with a case of renal glycosuria one should exclude other possible metabolic diseases that damage the tubules, e. g., by measuring the urinary amino acids, and bear in mind the possibility of diabetes mellitus.

Renal aminoacidurias: The amino acids of the glomerular filtrate are reabsorbed by four different "amino acid pumps". These are the pump for cationic amino acids and cystine, the pump for neutral amino acids, the proline pump (which also pumps hydroxyproline and glycine), and the pump for anionic amino acids. Inborn disorders have been detected in the first three instances. These confirm the "pump-model" that has been proposed from experimental data.

Cystinuria: This is the best known and most frequent of the amino acid transport defects. It is one of the classical "inborn errors of metabolism" that was shown by Sir Archibald Garrod. The defect lies in the cationic pump and large amounts of cystine, lysine, arginine and ornithine are found in the urine. A similar transport deficiency has been shown to be present in the intestinal mucosa.

The name cystine was given because it was "found" in renal calculi. The formation of renal calculi is to our knowledge the only clinical symptom. The diagnosis is easily made by means of amino acid analysis of the urine. The cystine test (nitroprusside reaction) is a useful preliminary test. To prevent calculi formation alkalization of urine, increased diuresis and even the administration of penicillamine are used. The results have been satisfactory.[2]

The inheritance of the defect is *autosomal recessive*. Genetically it is not completely consistent. Some heterozygotes excrete more cystine and lysine, in some other families urinary amino acids of the hetero-

zygotes are on normal level. The frequency of cystinuria is higher among the mentally deficient.[13]

Hartnup's disease. The disturbance of the neutral amino acid pump is known as Hartnup's disease, after the family in which it was first detected. Some 20 cases have been described to date. Clinical symptoms include a pellagra type dermatitis which is cured by nicotinamide. Patients present also neurological symptoms: cerebellar ataxia, attacks of unconsciousness, headache as well as muscle pains and weakness. Laboratory examination reveals strong generalized aminoaciduria with the largest increase in the neutral amino acid group, with the exception of proline. In addition, there is an increase of indole metabolites in urine due to gastrointestinal absorption deficiency of tryptophan. The condition is *autosomally recessively* inherited.

Familial Iminoaciduria: A defect in the proline pump causing iminoaciduria is a very rare condition. Only a few patients have been reported.[4] The urinary amino acid finding is the same as in hyperprolinemia, but examination of the plasma amino acids differentiates the two conditions. The clinical symptomatology of this disease is not clear and uniform.

Renal phosphaturia is better known as *hypophosphatemic vitamin D resistant rickets.* A prominent phosphaturia is present. Some consider this the primary deficit, others a secondary manifestation. It is among the most commonly inherited metabolic disorders.

The disease appears clinically as late rickets. The first signs occur not before the end of the second year of life. The commonly noted symptoms are bone deformities, usually bowed legs. The children are also stunted in growth which is not entirely attributed to the bowed legs. The X-ray pictures show typical rachitic changes in the epi-physeal lines. Serum calcium is normal, alkaline phosphatase usually high and characteristically the inorganic phosphate level of the serum is very low. One should remember that the normal serum phosphate level decreases with age. A normal phosphate level in the adult would be considered pathologic in the childhood. No aminoaciduria nor urinary acidosis is, however, present. The symptoms vary, some suffer from a full blown rachitic disease, others have no more than a detectable hypotholphatemia. Hypophosphatemia is inherited dominantly *on the X chromosome* but, it is unknown why the active rachitic disease appears only in some patients.

In differential diagnosis other causes of renal rickets such as renal acidosis and the Fanconi syndrome have to be considered. In practice,

the most important to exclude is the late onset of rickets in malabsorption syndrome caused by deficient vitamin D absorption. An important rule of thumb is that every late onset of rickets must be referred to a specialist for examination.

As the name implies the disease is resistant to vitamin D therapy. However, with very large doses the rachitic changes can be cured. This does not however, completely arrest the phosphate loss and so no great improvement of growth is seen with this therapy. Thus in more recent therapies phosphate is administered with vitamin D.[7]

Renal tubular acidosis: Typical to these disorders is either inability of the tubules to reabsorb bicarbonate normally (proximal renal tubular acidosis) or inability to acidify the urine (distal tubular acidosis). In the former case, the urine does not become acidic until the bicarbonate level of the extracellular compartment is below 20 mmol/l, in other words, only during a definite metabolic acidosis. In the latter condition the urine pH does not drop below six even then. Renal acidosis is generally seen as a secondary manifestation as well in acquired renal diseases as in inherited metabolic disorders with generalized tubular functional deficiencies (e. g. fructose intolerance cystinuria). It is also seen as a single and transient phenomenon, above all in young infants. On the other hand, the permanent and apparently inherited metabolic disorder, tubular acidosis also called Albright's disease, is a very rare disease.

Typical symptoms for this disease are: skeletal manifestations, late onset of rickets, pathological fractures etc.. The patients are liable to severe fluid balance crises. Laboratory findings show hyperchloreemic acidosis, neutral or slightly acid urine, hypopotassemia and typical renal calcifications. Therapy includes correction of acidosis with citrates and the treatment of rickets with calcium and vitamin D. It is inherited *dominantly*.

Nephrogenic diabetes insipidus: is a metabolic disorder that is *inherited recessively on the X chromosome.* Thus, it is seen mainly in men, though heterozygote women may display varying degrees of symptoms. It is not a great rarity. The defect lies in the inability of the tubules to react to antiuretic hormone. Thus, the clinical picture resembles the diabetes insipidus but with symptoms starting from birth. The disease may remain harmless if the parents allow the child to drink freely. But because there are parents who feed their child with rigrous measures of food, a dehydration state requiring hospitalization may develop. These run a risk of permanent brain damage from hypertonic dehy-

dration. If the child is given adequate fluid, the prognosis is generally, good. Diagnosis is confirmed by lacking response to administered antidiuretic hormone. Reduction of urine volume by administering thiadiazides has been lately recommended.

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