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Alport's syndrome (hereditary nephritis)

Report of six cases and review of the literature

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UP to 1958, more than 50 families with Alport's syndrome had been reported.[1] This syndrome consists of a high incidence of renal disease that occurs in several generations of a family, associated with perceptive nerve deafness and occasional ocular abnormalities. According to Alport[2] early mention of a possible hereditary factor in nephritis was made by Dickinson in 1875. Reports then began to be published, describing families with a tendency toward the development of hematuria and progressive renal failure. Hurst in 1915 described such a family, and 12 years later this family was examined by Alport,[2] for whom the syndrome is named.

Alport's[2] original description was of a clan of 25 persons in seven family groups. There were 10 males and 15 females; of the 10 males, seven were apparently affected and died in childhood. Although almost all the females described were either deaf or had recurrent hematuria, apparently none died with nephritis. Many of his patients had a history of hematuria that was related to eating certain berries, a phenomenon of interest, of undetermined significance, but not commented upon in recent reviews.

Report of cases

Case 1. A boy aged six years, was first examined at the Cleveland Clinic in 1959. He had three attacks of pneumonia during the first year of life. Throughout early childhood he had had frequent "bronchial infections" and episodes of otalgia. Over the years he had also had urgency and nocturia, and episodes of asthma, followed by hematuria. The family history revealed that his mother had had "kidney infections" and that his father was diabetic.

On examination of the patient, the only abnormal findings were diffuse sibilant rales heard over both lung fields, and bilateral costovertebral tenderness. Laboratory studies revealed hematuria; the blood urea value was normal. A renal biopsy was performed and the tissue was reported as showing "slight focal membranous glomerulopathy." The patient was treated for asthma; subsequent urinalyses after the boy was discharged from the hospital showed persistent microhematuria.

The patient was next examined in 1965, when he was 12 years old, because his brother (case 2) was being seen here for renal evaluation. Over the years, the patient had become progressively deaf. Urinalysis showed 1.64 g of protein excreted per 24 hours, and more than 50,000,000 eyrthrocytes on Addis count. Another renal biopsy was performed and the tissue was reported as showing "proliferative glomerulonephritis with many interstitial lipid-laden foam cells." Otologic evaluation revealed a high-frequency hearing loss. Despite treatment with prednisone, 30 mg per day, there has been no apparent change in the renal lesion as evidenced by continued abnormal urinalyses.

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At the present time the boy is 15 years old and is asymptomatic aside from some fatigability. The blood urea is 29 mg per 100 ml and he continues to have mild hematuria and proteinuria.

Case 2. The patient (a brother, case 1) was first examined at the Cleveland Clinic when he was seven years old, in 1965. At the age of three years he was found to have "albumin in the urine." At the age of seven years, albuminuria was again found; he was hospitalized and treated with nitrofurantoin. His history included frequent upper respiratory tract infections and otalgia. He had an allergy to penicillin. According to the family history, the father of the two brothers (cases 1 and 2) died from renal failure and diabetes. Three sisters, aged 17, 14, and 10 years were alive and well.

The patient's blood hemoglobin content was 11.8 g per 100 ml. Urinalysis revealed from 2 to 6 g of protein per 24 hours, and more than 50,000,000 erythrocytes. The blood urea content was 54 mg per 100 ml, creatinine clearance 38 ml per minute, and the serum cholesterol content 385 mg per 100 ml. A single urine culture was sterile. A percutaneous renal biopsy was performed; the specimen showed "proliferative glomerular changes with focal tubular atrophy." Otologic evaluation showed bilateral high-frequency hearing loss. The patient was given a course of prednisone; the proteinuria decreased to a mildly abnormal level.

During the next 20 months his status deteriorated. Another renal biopsy specimen disclosed "mild glomerular changes, marked interstitial fibrosis, and inflammatory infiltrates with tubular atrophy." Progressive renal failure ensued and the patient died at the age of 10 years.

Case 3. The patient, a 24-year-old man, was first admitted to the Cleveland Clinic Hospital in 1966 because of a six-week history of fatigue. He had been hospitalized and had received several blood transfusions, to which he responded well. His weakness recurred rapidly, though, and he became dyspneic and convulsions developed. He underwent peritoneal dialysis, after which he was transferred to the Cleveland Clinic Hospital in a comatose condition. The family history available was the statement that his "mother's family had nephritis and deafness."

When examined, the patient was in a coma and hypertensive with Cheyne-Stokes respiration. A grade 2/6 systolic murmur was heard at the cardiac apex. After several hemodialyses were administered to the patient, he underwent bilateral nephrectomy. Histologic examination of the kidneys revealed "end stage kidneys, suggestive of chronic glomerulonephritis." On subsequent otologic examination the patient was found to have a high-frequency hearing loss. Six months later a renal transplant was performed; he died shortly after from gram-negative septicemia.

Case 4. The patient, a 22-year-old man, was first examined at the Cleveland Clinic in 1968 because of severe cramping and abdominal pains. In childhood he had progressive deafness diagnosed as "cochlear," and an episode of hematuria when he was six years of age; severe otitis occurred frequently. The patient has one brother and two maternal uncles who have "nephritis."

At the time of admission to the hospital, the blood urea nitrogen was 37 mg per 100 ml and continuous hematuria was found. A gastrointestinal series of roentgenograms was diagnostic of Crohn's disease of the small bowel, for which he is receiving appropriate treatment.

Case 5. The patient, a young man 18 years old, an identical twin, was first examined at the Cleveland Clinic in 1964, along with his twin brother (case 6), because of a history dating back to the age of seven years, when in each a "strep throat" developed and they were found to have hematuria and albuminuria. One year later the patient was given a sulfonamide for a "possible kidney infection." At the age of nine years, a course of "cortisone" was given for five days, with no effect on the continued abnormal urinalyses. One year before examination at the Cleveland Clinic, the patient began to have headaches, general weakness, fatigability, and burning sensations in his feet and hands. After being admitted to a hospital, he was given blood transfusions and a diet of rice and fruit. Convulsions ensued, and he began to have nausea with vomiting, and fatigue. Peritoneal dialysis was performed, after which he was transferred to the Cleveland Clinic Hospital.

The family history was notable for renal disease. A maternal great aunt died from "renal disease" at the age of 60 years. One aunt has diabetes, "renal disease," and "heart trouble." A maternal grandmother, 61 years old, was known to have albuminuria. Two second cousins have "nephritis." A cousin of the patient's mother died at the age of 23 years from "renal disease," as did another cousin with "renal disease" and leukemia, at the age of 27 years.

On examination the patient was hypertensive, with a diastolic pressure of 120 mm Hg. A grade 3/6 systolic murmur was noted in the second left intercostal space. The blood hemoglobin content was 9.2 g per 100 ml, the blood urea 104 mg per 100 ml, and the serum creatinine 9.0 mg per 100 ml. One month after admission to the hospital and after several hemodialyses, a cadaver renal transplant was performed. Postoperatively, therapy with azathioprine and prednisone was initiated; his course was complicated by recurrent fever with bronchitis and pneumonia.

Four months after transplantation, the patient underwent bilateral nephrectomy, thymectomy, and appendectomy. His kidneys were noted to be granular and small with an increase in peripelvic fat. Histologically, the kidneys revealed "chronic atrophic pyelonephritis." He has continued to have recurrent fever and infections.

Case 6. The patient is the identical twin brother to the young man in case 5. He also was first examined at the Cleveland Clinic at the age of 18 years, in 1964. His history, too, dated back to the age of seven years, when he was noted to have blood in the urine, one week before his brother's illness. He was hospitalized for five weeks; urinalysis revealed albuminuria, casts, and erythrocytes. A question of "strep throat" preceding this illness was raised and he was treated with antibiotics. One year later a course of a sulfanomide was given for persistent urinary abnormalities, and, at the age of nine years he was also given several days' treatment with "cortisone" without effect. Headaches, fatigue, dyspnea on exertion, and hypertension developed one year before being seen at our institution. He, too, had burning sensations in his hands and feet. Along with his brother he began to have convulsions and was diagnosed as having uremia. He was given a rice diet with fruit, and underwent dialysis.

Examination disclosed a grade 2/6 systolic murmur at the cardiac apex and left sternal border, and blood studies revealed anemia and azotemia. A cadaver renal transplant was performed on him the same day as on his brother, from the same donor. Postoperatively he did poorly, with leakage of the ureter anastomosis. Another transplant was performed two months later, followed by thymectomy, splenectomy, and nephrectomy. The patient's own kidneys were small and granular. Microscopic examination revealed "chronic atrophic pyelonephritis with multiple cysts."

After transplantation melena and gross hematuria occasionally occurred. Fifteen months after the second transplant, the patient noted weakness in the left side of the face and the left arm. A spinal fluid examination revealed increased protein, and he was thought to have a cerebral infarction. After further deterioration of his neurologic status, another spinal tap was performed and was diagnostic for meningitis. A slow, progressive, downhill course followed, and he died from monilial septicemia and a brain abscess superimposed on a large cerebral infarction.

Etiology

A number of causes have been postulated in regard to Alport's syndrome. An inherent weakness or varicosity of the blood vessel walls was questioned, and terms such as renal hemophilia were used.[3] The question of a relation to streptococcal infection was raised by Alport,[2] and later by other authors.[4] Genetically controlled enzyme defects,[5] and structural changes[6] have also been considered.

Pathology

When Alport's syndrome is first diagnosed in early childhood, no changes may be present other than a few erythrocyte casts in the tubules.[5] In adult-

hood, the kidneys in the terminal stage are indistinguishable from those seen in other end-stage disease. The absence of a specific pathologic pattern for all cases has been perhaps the most confusing part of this syndrome. On gross examination at postmortem, the kidneys are usually small, shrunken, granular, and atrophic. Linear yellow streaks or yellow flecks may be present on the cut surfaces.[7]

The glomeruli may show increased cellularity, occasional crescent formation, capsular adhesions, and thickened basement membranes; some early fibrosis may also be present.[5] Slight focal endothelial or mesangial hypercellularity has been noted.[8] It should be emphasized that, unlike typical acute poststreptococcal glomerulonephritis, the involvement of the glomeruli is patchy. Electron microscopy has shown a knobby swelling of the lamina densa of the glomerular tuft. Numerous single-membrane limited inclusions containing an electron-dense material have been found in the cytoplasm of visceral cells; these are thought to be a lipid substance. The foot processes have been noted to be blunted. The cortical tubules typically show atrophy alternately with areas of tubular dilatation, hypertrophy, and regeneration. Proteinaceous casts, mild arteriolosclerosis, and nephrocalcinosis may be present.[5]

Foam cells, once thought to be the typical lesion of Alport's syndrome, are found in rows and nests in the interstitium. However, foam cells have been associated with many diseases in addition to Alport's syndrome.[7] These cells are usually found in parallel rows lining the tubular cells and are 50 to 80μ in diameter.[7] Histochemical technics have shown that neutral fats, phospholipids, and cholesterol are present in these cells.[9, 10] Their origin has long been disputed and many theories have been presented. One of the most enlightening studies was an electron microscopic study in which many proximal and distal tubular cells had single-membrane limited inclusions containing homogeneous material that was suggestive of lipids.[8] From this it could be assumed that the origin of these controversial cells is tubular; their significance, though, is not known.

A prominent feature in many instances is interstitial inflammation. Characteristically, interstitial fibrosis is present with increased numbers of fibroblasts; round cell infiltrates may be present, but polymorphonuclear leukocytes are rare.[5, 8]

In one case at autopsy, the seventh and eighth cranial nerves were examined microscopically. The nuclei of those nerves were found to have fatty infiltration and slight chromatolysis.[7]

Clinical manifestations

Typical of Alport's syndrome are the episodes of hematuria which occur in childhood; these may develop at any age, and hematuria has been reported to occur in infancy. The frequency of these episodes may vary from a single bout to attacks recurring once a week to once a year; periods of apparent

normalcy may intervene. Pain in the flank associated with chills, fever, and symptoms of urinary tract infection may dominate the early clinical picture.[11] Nocturia, weight loss, headaches, general weakness, and fatigability may be prominent signs.

Many precipitating factors have been described in case reports. The early publications tell of numerous instances of certain foods causing exacerbations.[3] Most students[7] of this syndrome, including Alport[2] himself, agree that respiratory infections play a large role in precipitating symptoms. Infections caused by β-hemolytic *Streptococcus* seem particularly likely to do so. Pregnancy also causes exacerbations; Alport again reported this and many authors have since confirmed it.

Characteristically, in affected males, episodes of hematuria in childhood precede the development of progressive renal failure, and death ensues in the early or late teens;[7] whereas, affected females, although they may have hematuria, live a normal life span.

Some authors[12] have attempted to classify the disease into two symptom types: (1) the symptoms similar to those described above, and (2) the symptoms primarily of pyelonephritis. In surveys of affected members of families, an increased incidence of bacteriuria has been found, whether the symptoms are mainly glomerulonephritic or pyelonephritic.

Associated defects

Associated defects include deafness, a most prominent symptom. It is a characteristic, bilateral, high-frequency hearing loss, with decreased speech discrimination.[13] This may be first noted in early childhood, but usually becomes apparent around the age of 10 years. It occurs in both males and females, and may be found as an isolated abnormality in patients with or without evidence of renal disease. Investigation of one large family revealed an incidence of deafness in more than 50 percent of males and 30 percent of females.[14] A distinct tendency toward the development of otitis media is also present in these patients.[14] Most often it is a severe, recurrent infection with β-hemolytic *Streptococcus*.

Ocular changes constitute a less common finding. The most frequently discussed abnormality is spherophakia,[15] a condition in which the round, infantile lens fails to assume its flattened, adult form; myopia results, along with glaucoma. Cataracts of various types have been described, including anterior and posterior;[15] lens rupture,[16] posterior vitreous detachments,[8] myopia without spherophakia,[15] and retinal detachment[14] have also been reported. Recently other changes including retinitis pigmentosa have been reported.[17]

Other associated conditions include a nonspecific aminoaciduria in two families.[18, 19] Erythromelalgia, arachnodactyly, chronic bronchitis,[18] growth retardation, and retarded eruptions of permanent teeth have also been reported.[14] One isolated report is of a symmetric, progressive, severe,

peripheral neuropathy, occurring in a patient with Alport's syndrome.[20] A high incidence of allergy in this disease has been emphasized.[4]

Perkoff,[21] in his large study, noted that of 134 patients 19 had some deformity of the mitral valve; 15 had mitral stenosis, and four had mitral insufficiency.

Hypertension is a feature that is not consistent. In a large series of patients from the National Institutes of Health, one third of the affected males and one fourth of the affected females were hypertensive.[14] It is not unusual for patients to remain normotensive until they reach the uremic stage.

Inheritance

Over the years the following mechanisms have been proposed as the mode of inheritance: (1) simple dominance, (2) simple dominance with early intrauterine mortality of the male, and (3) partial sex-linked dominance with 15 percent crossover. Shaw and Glover[22] reviewed the records of a large family reported by Perkoff,[21] and postulated nonrandom dysjunction and preferential segregation of the gene and the X-chromosome. The female, by this mechanism, is thought to produce ova with the gene that carries the abnormality going to the ovum during oogenesis, instead of randomly to the polar body or ovum.[23] A further study[4] of pedigree in another series has confirmed that hypothesis. The sparsity of affected males is thought to be due to early intrauterine death. A recent study of an affected family has been most revealing in the finding of chromosomal abnormalities.[15] Since the deafness does not correlate completely with manifestations of renal disease, it has been questioned whether this deafness trait is inherited in a separate manner.[11]

Laboratory evaluation

The urinalysis remains the most important test available in the laboratory evaluation of these patients.[14] Typically, hematuria ranges between gross and microscopic, and there is pyuria in cases of superimposed infection. Proteinuria and cylindruria are other major abnormalities noted in patients whose progress has been followed for long periods.[1] Evaluation of the urine is also the most accurate means of predicting the extent of renal impairment. The most sensitive, early index of renal impairment is the Addis count, and the extent of renal impairment most closely correlates with the inability to conserve water in the state of dehydration.[14] The results of urine cultures are not consistent. Those patients whose major manifestations are those of pyelonephritis have a much higher incidence of positive urine cultures.[12] Urography has not demonstrated any consistent abnormality, and in most cases, is normal.[10, 13] Several instances of abnormalities, such as duplication of ureters, have been reported. The kidneys may be large, normal sized, or small in the end stages of the disease.

Other laboratory tests have been evaluated including normal and abnormal serum proteins, and variations in blood lipids.[14, 24]

Diagnosis

Acute poststreptococcal glomerulonephritis, glomerulitis of other etiology, hemorrhagic cystitis, Schönlein-Henoch purpura, hemophilia, crystalluria, tuberculosis, tumors, angiomas, and cystic diseases are to be considered along with collagen diseases and abnormalities of the urogenital system causing obstruction.[25, 26] Also, idiopathic hematuria, angiokeratoma corpora diffusum, and oculo-cerebral-renal dystrophy can be included in the differential diagnosis. Recurrent or persistent macroscopic hematuria may also be due to familial benign hematuria.[25]

Differentiating acute poststreptococcal glomerulonephritis from Alport's syndrome seems to present the greatest challenge. In the absence of the typical or suggestive family history, there are several clues that can be of assistance. Hypertension and edema are usually absent in Alport's syndrome, and the antistreptolysin-O titer is not elevated, unless the episode of hematuria was precipitated by a streptococcal infection. A serum complement level may be diagnostically helpful, the activity being normal in Alport's syndrome.[26, 27]

Treatment

Another problem in regard to the patients with Alport's syndrome which remains unresolved, is what modern medicine can offer them. Little has been done in a controlled manner in regard to treatment, although several clinicians have suggested that penicillin be given in a manner similar to prophylaxis for rheumatic fever, based on the supposition that there is increased sensitivity to streptococcal infections. Most certainly, if a urinary tract infection is present, this should be treated specifically. Prednisone has been found to be of no value. As renal failure ensues, appropriate treatment of this state should be given.

Summary

Six cases of Alport's syndrome are reported and a review of the literature is presented. The criteria for the diagnosis of this disorder include: (1) evidence of renal dysfunction, (2) high-tone hearing defect, (3) a positive family history of renal disease, and (4) a frequent association with recurrent otitis media. Most important in the diagnosis is a careful analysis of a fresh, concentrated urine specimen for microhematuria, and a detailed, painstaking, family history.

References

1. Perkoff, G. T., and others: A follow-up study of hereditary chronic nephritis. A.M.A. Arch. Intern. Med. **102**: 733–746, 1958.

2. Alport, A. C.: Hereditary familial congenital haemorrhagic nephritis. Brit. Med. J. **1**: 504–506, 1927.

3. Guthrie, L. G.: "Idiopathic," or congenital hereditary and familial hematuria. Lancet **1**: 1243–1246, 1902.

4. Mulrow, P. J., and others: Hereditary nephritis; report of a kindred. Amer. J. Med. **35:** 737–748, 1963.

5. Krickstein, H. I.; Gloor, F. J., and Balogh, K., Jr.: Renal pathology in hereditary nephritis with nerve deafness. Arch. Path. **82:** 506–517, 1966.

6. Metcoff, J.: Hereditary, Developmental, and Immunologic Aspects of Kidney Disease. Northwestern University Press, 1962, 175 p.; p. 11.

7. Whalen, R. E., and others: Hereditary nephropathy, deafness and renal foam cells. Amer. J. Med. **31:** 171–186, 1961.

8. Rome, L.; Cuppage, F. E., and Vertes, V.: Familial hematuric nephritis. Pediatrics **38:** 808–818, 1966.

9. Evans, D. M. D., and Sanerkin, N. G.: Foam cells in renal cortical adenomata. J. Path. Bact. **88:** 533–536, 1964.

10. Rosen, S.; Pirani, C. L., and Muehrcke, R. C.: Renal interstitial foam cells; a light and electron microscopic study. Amer. J. Clin. Path. **45:** 32–41, 1966.

11. Perkoff, G. T., and others: A clinical study of hereditary interstitial pyelonephritis. A.M.A. Arch. Intern. Med. **88:** 191–200, 1951.

12. Goldman, R., and Haberfelde, G. C.: Hereditary nephritis; report of a kindred. New Eng. J. Med. **261:** 734–738, 1959.

13. Johnson, W. J., and Hagan, P. J.: Hereditary nephropathy and loss of hearing. Arch. Otolaryng. **82:** 166–172, 1965.

14. Cassady, G., and others: Hereditary renal dysfunction and deafness. Pediatrics **35:** 967–979, 1965.

15. Sohar, E.: Renal disease, inner ear deafness, and ocular changes; a new heredofamilial syndrome. A.M.A. Arch. Intern. Med. **97:** 627–630, 1956.

16. Gregg, J. B., and Becker, S. F.: Concomitant progressive deafness, chronic nephritis, and ocular lens disease. Arch. Ophthal. **69:** 293–299, 1963.

17. Sarles, H. E., and others: Hereditary nephritis, retinitis pigmentosa and chromosomal abnormalities. Amer. J. Med. **45:** 312–321, 1968.

18. Cross, E. G.: The familial occurrence of erythromelalgia and nephritis. Canad. Med. Assn. J. **87:** 1–4, 1962.

19. Wallace, I. R., and Jones, J. H.: Familial glomerulonephritis and aminoaciduria. Lancet **1:** 941–944, 1960.

20. Marin, O. S. M., and Tyler, H. R.: Hereditary interstitial nephritis associated with polyneuropathy. Neurology **11:** 999–1005, 1961.

21. Perkoff, G. T.: The hereditary renal diseases. New Eng. J. Med. **277:** 79–85, and 129–138, 1967.

22. Shaw, R. F., and Glover, R. A.: Abnormal segregation in hereditary renal disease with deafness. Amer. J. Hum. Genet. **13:** 89–97, 1961.

23. Cohen, M. M.; Cassady, G., and Hanna, B. L.: A genetic study of hereditary renal dysfunction with associated nerve deafness. Amer. J. Hum. Genet. **13:** 379–389, 1961.

24. Chappell, J. A., and Kelsey, W. M.: Hereditary nephritis. A.M.A. J. Dis. Child. **99:** 401–407, 1960.

25. McConville, J. M.; West, C. D., and McAdams, A. J.: Familial and nonfamilial benign hematuria. J. Pediat. **69:** 207–214, 1966.

26. West, C. D.; Northway, J. D., and Davis, N. C.: Serum levels of beta-1C globulin, a complement component, in the nephritides, lipoid nephrosis, and other conditions. J. Clin. Invest. **43:** 1507–1517, 1964.

27. Wasserman, E., and others: Diagnostic value of serum complement determination in hereditary glomerulonephritis. J. Lab. Clin. Med. **65:** 589–599, 1965.