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Chronic hereditary nephritis with nerve deafness : a Nebraska kindred

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CHRONIC HEREDITARY NEPHRITIS WITH NERVE DEAFNESS

A NEBRASKA KINDRED

By

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Chronic Hereditary Nephritis With Nerve Deafness

A Nebraska Kindred

Introduction

The intention of this paper is to report a kindred with the now classic syndrome of chronic hereditary nephritis associated with nerve deafness. A new genetic influence will be proposed, adding to the already perplexing problem of determining the mechanism of inheritance of this entity.

History

One of the first narratives suggesting that renal disease might be hereditary was written by Kidd[20] in 1882. Guthrie,[14] Kendall,[19] and Hurst[18] followed the same family that was eventually reported by Alport[1] in 1927, to be perpetuating a definitely hereditary nephritis associated with nerve deafness. Males are more severely afflicted than females and usually die in uremia before the fourth decade. The female life span is usually not limited, but pregnancy appears to aggravate the condition with a tendency toward toxemia. The disease may present from the first to third decade as intermittent hematuria, cylinduria, pyuria, and proteinuria and be variably progressive. The existence of this entity has been verified by many others,[6,7,8,11,33,36,37] and by 1966 over 60 familes

had been reported.[15] The pathology is nonspecific and has shown elements of glomerulonephritis and pyelonephritis in the same family.[2,16,17,24] Interstitial foam cells have been noted,[10,11,21] but their value in diagnosis of this syndrome is only suggestive.[3,16,17,38] Most cytogenetic studies have been normal[24,25] except for a family reported recently with hereditary nephritis, ocular deformities, and a tendency toward nondysjunction.[32] Spherophakia and cortical cataracts[35] as well as other ophthalmic pathology[7,8,10,22,29,32] have also been associated with hereditary nephritis and nerve deafness. In some families, the typically high frequency nerve deafness is absent.[30,31] Perkoff has done extensive work in the field of hereditary nephritis and reviewed the literature in 1964[26] and 1967.[27] The debated hereditary mechanism will be discussed later. The diagnosis can be made only on clinical grounds and its differentiation from other causes of hematuria is important. The rarity of the disease may in part be due to general unfamiliarity with it.[5]

Materials and Methods

The proband (IV-50)* was admitted to Bishop Clarkson Hospital (hospital #184492), Omaha, Nebraska, on September 10, 1967, for renal evaluation after a routine urinalysis

*IV-50 indicates pedigree number in figure 2.

revealed significant microhematuria and albuminuria. He had been in excellent health except for an acute episode of nephritis at age 12 and the recent onset of high frequency hearing deficit. He had served in the armed forces. Physical examination revealed an essentially normal 37-year old white male. Complete blood count, erythrocyte sedimentation rate, fasting blood sugar, Lee-White coagulation time, platelet count, partial thromboplastin time, serum calcium, pH, CO_2 content, chloride, sodium, cholesterol, urea-nitrogen, creatinine, serology, total serum protein by electrophoresis, creatinine clearance, urine sodium, potassium, lupus erythematosis preparation, and urine culture determinations were all normal as were an intravenous and retrograde pyelogram. The serum uric acid was 11.8 mg. percent and the total uric acid excretion in a 24 hour urine sample was 991.3 mg. The 24-hour urinary protein was 1.9 grams. A urinalysis revealed microhematuria and proteinuria. A percutaneous needle biopsy of the left kidney disclosed minimal patchy interstitial nephritis, glomerulosclerosis, and foam cells. (Figure 1.) The patient was discharged on allopurinol and by December of 1968, with a serum uric acid of 7.2 mg. percent, he continued to have microhematuria and proteinuria (on one occasion totaling 4.2 grams per 24 hours) and showed evidence of hyposthenuria.

A project was undertaken to obtain the proband's pedigree and family medical history. (Figure 2). Most family members or household heads were interviewed by the author and specifically questioned about a history of kidney disease, hearing deficit, and ocular deformity. All family members were offered routine urinalysis and serum urea nitrogen determinations as screening procedures at the University of Nebraska Hospital laboratory. Medical technologists performed the urinalyses on fresh urine specimans with Labstix,* the sulfosalicylic acid method for protein, and microscopic, spun sediment examinations. These screening procedures were used to confirm family history or initiate further studies and were not to be criteria of a "kidney dysfunction" (figure 2) with the exception of cases that will be discussed. Cases II-1, II-7, and III-2 by reliable family history were determined to have died of nephritis. On this basis alone they were considered to have "kidney dysfunction". Cases III-14, V-114, V-116, V-129, and V-131 had solitary urinalyses which showed at least greater than five red blood cells per high power field (Only one other person in the 117 urinalyses done on asymptomatic individuals showed greater than two red blood cells per high power field.) and were therefore also considered to have a "kidney dysfunction". All others classified in

*Ames Company, Indianapolis, Indiana

this category had had extensive hospital and laboratory work-ups with evidence of chronic nephritis. IV-43, IV-48, and V-8 had recently had kidney biopsies and III-3 had an autopsy.

Audiograms were obtained on patients with abnormal urine findings and on those suspected of being carriers. The term "deafness", associated classically with the syndrome is not intended to be taken literally. It is used in this paper to mean hearing impairment of greater than 25 decibels in either or both ears between the 4000-8000 cycle per second range. Several family members including a few with nephritis produced testimonial evidence of hearing deficit, but this was considered equivocal and they are not indicated to be so afflicted in figure 2.

Medical records and/or urinalyses and serum urea nitrogen determinations were obtained on 132 of the approximately 244 persons in the kindred and these individuals are indicated as "examined" in figure 2. IV-48 and IV-50 had normal chromosome analyses. Physical examinations were not done routinely. No history of unusual eye pathology was elicited from the family.

I-1 and I-2, pioneers of the Scribner, Nebraska, area, immigrated from Germany in about 1860. Time and geographical limitations precluded more extensive evaluation of the kindred. Three young members of generation VI were omitted from figure 2 to save space.

Discussion

The part of the family most amenable to genetic analysis at the time of this writing is that descendent to II-4 since all members had been examined. The chance of any pattern of occurrence of an autosomal dominant trait in a given generation is 2^n where n equals the number of offspring of affected individuals in that generation. Therefore, in generation V the chance of any pattern of distribution of an autosomal dominant trait in descendents of II-4 is 1 in 2^9 or 1 in 512. If the mechanism of inheritance is sex-linked dominant with the trait absent in all sons and present in all daughters of affected fathers, the chance of distribution of the trait as it is is 1 to 1. Bias of ascertainment may have affected these results, but obviously, sex-linked dominance is more likely than autosomal dominance in this small group (descendents of II-4). In critiscism of this analysis several persons were considered afflicted on the basis of only one abnormal urinalysis. Also, microscopic urinary findings may be present intermittently, and therefore, some affected individuals may have been omitted. In addition, this group of individuals is not as large as some that have shown occasional male to male transmittance.[28,36] Further inaccuracy could be due to coincidental renal disease from other causes.

The mode of transmission of hereditary nephritis has escaped clarification. Perkoff and others[28] studied a large Utah kindred and felt that sex-linked dominance with occasional crossing-over between homologous portions of the X- and Y-chromosomes to explain male to male transmission was the answer. However, crossing-over between the X- and Y-chromosomes has not been proven, and this theory has therefore been questioned. Graham[13] reanalysed the Utah data and concluded that a sex influenced autosome was more likely. Shaw[34] hypothesized autosomal nonrandom segregation in the female and preferential association with the X-chromosome in the male, and others have concurred.[9,24] Dr. ten Bokkel Huinink[27] proposed that male to male transmission may be due to the mechanism of Kleinfelter's syndrome. Unfortunately, this present report adds little toward resolving the controversy.

One theory that has not previously been connected with hereditary nephritis is sex-limitation as well as sex-linkage. Sex hormones are responsible for expression of a genotype in a sex-limited trait, and one common example is androgen influence in hereditary male pattern baldness, being more extensive in males than females. In individuals with a familial tendency towards baldness, eunichs do not become bald, yet females with masculinizing tumors may.[23] In hereditary nephritis it has been long observed that males are more severely affected than females, suggesting sex-limitation. Also, female carriers

of hereditary nephritis tend to exacerbate during pregnancy which, if this condition is sex-limited, could be due to the fact that female plasma androgen levels increase in the third trimester.[39] If androgens are in part responsible for progressive renal failure, orchiectomy might be palliative in the male patient. Alternatively, and more likely, if the responsible gene is sex-linked dominant, females would be afforded protection from the deleterious gene as explained by the Lyon hypothesis. Should a carrier female develop a coincidental masculinizing tumor, a study of such a patient before and after therapy might add to the credibility of sex-limitation influence in hereditary nephritis.

Unfortunately, little has been done toward determining the basic defect in hereditary nephritis, and therapy is nonspecific. An anatomic defect[10] and an increased susceptibility to beta-hemolytic Streptococcus[2] have been proposed. Krickstein and others[21] have pointed out that neither of these theories account for normal biopsies when the disease is clinically evident early in childhood. They have proposed that there is an enzymatic or protein synthesis defect common to both auditory and renal physiology. That dihydrostreptomycin and kanamycin sulfate are toxic to both the ear and kidney has been integrated into support of this last theory with the idea that these drugs and hereditary nephritis may have a common avenue of pathology,

being exogenous in the former and heritable in the latter. Interestingly, kanamycin sulfate renal toxicity presents as pyuria, hematuria, cylinduria, and proteinuria[12] as does hereditary nephritis.

Summary

A kindred with hereditary nephritis associated with nerve deafness has been presented. The trait appears to be sex-linked dominant in this kindred with variable, less severe manifestation in the female explainable by the Lyon hypothesis; or, males may be more severely affected because of sex limitation.

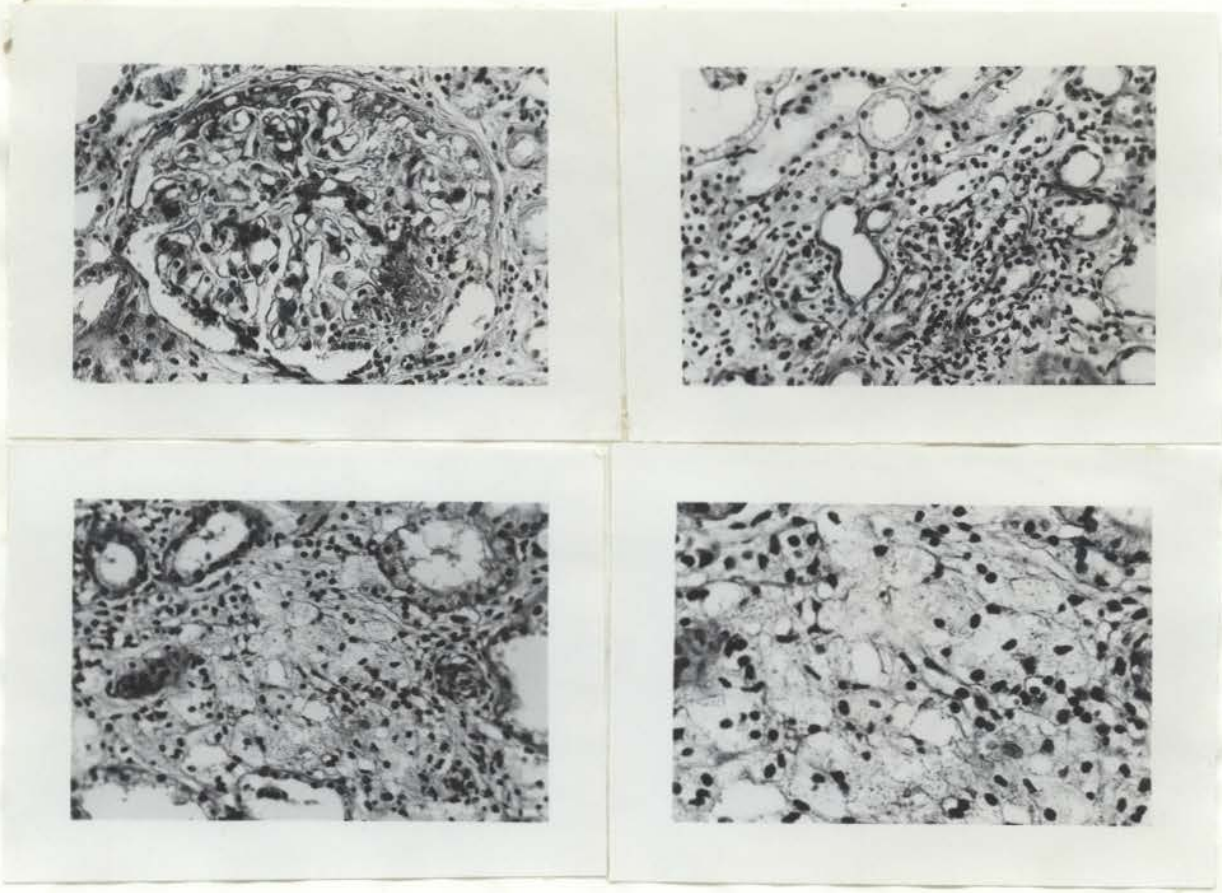

Figure 1. Upper left: Glomerulus showing focal deposition of collagen; Mallory's triple stain, X250. Upper right: Lymphocytic interstitial infiltrate; periodic acid-Schiff (PAS) stain, X250. Lower left: Interstial foam cells; PAS, X250. Lower right: Interstitial foam cells; PAS, X400.

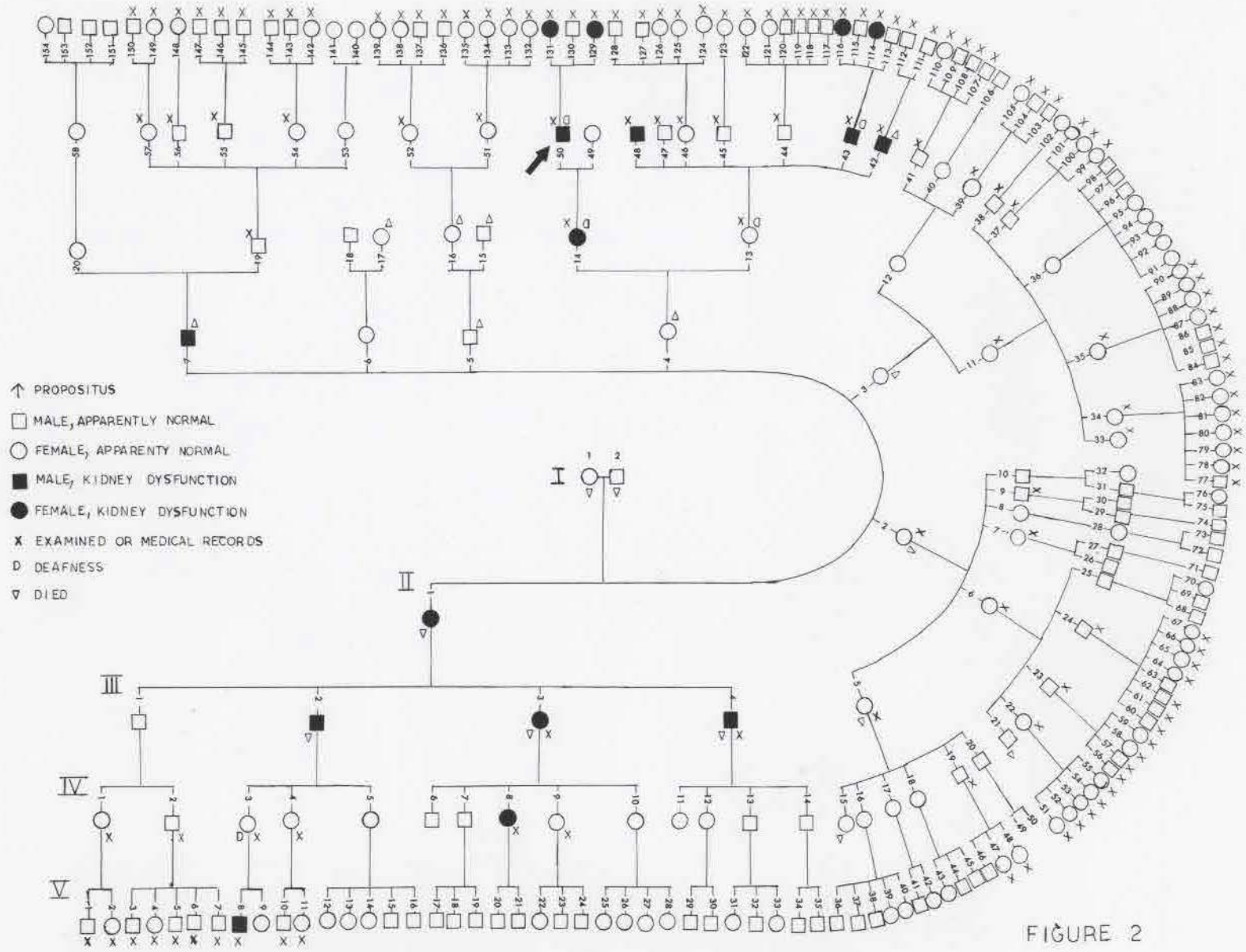
↑ PROPOSITUS
□ MALE, APPARENTLY NORMAL
○ FEMALE, APPARENTY NORMAL
■ MALE, KIDNEY DYSFUNCTION
● FEMALE, KIDNEY DYSFUNCTION
X EXAMINED OR MEDICAL RECORDS
D DEAFNESS
▽ DIED
I
II
III
IV
V

FIGURE 2

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