Drooping Upper Eyelids and Polycystic Kidney Disease¹

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ABSTRACT

Over the last 26 yr, 33 cases and/or families of patients with autosomal dominant polycystic kidney disease (ADPKD) and a particular appearance of the eyes have been observed. ADPKD was unremarkable and in most cases had led to the usual slow development of end-stage renal failure. The facial feature concerned the upper eyelid, which drooped obliquely over the eyeball with a fold hiding the upper segment of the iris (blepharochalasis). The aspect was so typical that the diagnosis of ADPKD was suggested on first contact with new renal patients. All affected patients were white, of various origins, including French, Polish, Scandinavian, Italian, and Spanish. In retrospect, drooping eyelids had been present in the parents and/or grandparents who had died of renal failure, with or without an established diagnosis of ADPKD. In order to disclose the cosegregation of blepharochalasis with ADPKD, the screening of its prevalence in a well-circumscribed region with a catchment population of 410,000 was undertaken. The facial feature was found in 24 (32%) of 75 ADPKD families. Family transmission was confirmed in those kindreds, because at least two members suffered from ADPKD. Cosegregation was sought by analyzing family group photographs taken over several generations, the oldest member of which was born in 1873. All members with blepharochalasis had died of renal failure or are presently being followed up for ADPKD. Cosegregation was sought by analyzing family group photographs taken over several generations, the oldest member of which was born in 1873. All members with blepharochalasis had died of renal failure or are presently being followed up for ADPKD. A bibliographic search showed that the association of ocular and/or eyelid deformities and various inborn renal diseases is far from rare, suggesting a simultaneous event in the embryonic timetable. It was concluded that, for some still undetermined reason, there is an unusually high association of blepharochalasis and ADPKD and that blepharochalasis should be included among the extrarenal abnormalities possibly associated with ADPKD.

Key Words: Polycystic kidney disease, oculorenal syndrome, blepharochalasis, autosomal dominant polycystic kidney disease epidemiology

The hereditary nature of autosomal dominant polycystic kidney disease (ADPKD) has long been recognized and has now been substantiated by the discovery of a gene abnormality in chromosome 16 (1). ADPKD is not a disease restricted to the presence of cysts in the kidney and the liver, but may be associated with various, noncystic abnormalities in different organs (2-4). No distinctive physical appearance has so far been described, however, in ADPKD. Over the last 26 yr, one of us (A. Meynier) observed 33 cases and/or families of patients with ADPKD who were remarkable by a particular, hitherto unreported, facial appearance that we felt should be added to the extrarenal manifestations of ADPKD (5,6). These observations prompted one of us (P. Simon) to undertake an epidemiologic study in a well-circumscribed catchment population in northern Brittany, France. This study was based on an inquiry among all patients dialyzed for end-stage renal failure because of documented ADPKD or followed up for ADPKD. Then, patients' families were screened to determine the incidence of upper eyelid folds and their relationship to ADPKD. We came to the conclusion that blepharochalasis is strongly associated with ADPKD.

DESCRIPTION

The upper eyelid droops obliquely over the eyeball with a fold, generally hiding the upper segment of the iris. The drooping (blepharochalasis) is so pronounced that the eyelashes emerge from beneath the eyelid and a sizeable portion of the lashes is hidden (Figure 1). The iris is frequently (but not exclusively) blue. The drooping eyelid gives the facies such a typical appearance that the diagnosis of ADPKD is suggested at first contact with new renal outpatients. In retrospect, blepharochalasis had often been present in forebears who had died of chronic renal failure, with or without an established diagnosis of ADPKD. Interestingly, in some of the Breton families, this feature had been noticed and the patients referred to it as "Toeil en patte d'oeie" (literally, "goose-palmed eyelid"). All patients were white, originating from various European countries, including France, Poland, Scandinavia, Italy, and Spain. The renal polycystic disease was unremarkable.
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ADPKD families. ADPKD was invariably associated with ADPKD. Members with ADPKD were summoned to the Nephrology Unit and examined in order to evaluate the prevalence of ADPKD in this area was 254. The prevalence of ADPKD in this region was calculated to be 0.81 in 1,000 (48%). Thus, the number of persons affected by ADPKD under 25 yr of age supports our hypothesis of a transmission linkage between the renal disease and the eye deformity. This was intended to determine the incidence of such drooping eyelids in the general population, information that is unavailable in the ophthalmologic literature.

RESULTS

Families With ADPKD

In 24 (32%) of 75 families, at least one member had both ADPKD and blepharochalasis. In 12 of these families, there were at least two members with both the renal and eyelid abnormalities. Questioning of the patients did not reveal any family cases of drooping eyelids without renal disease, but for understandable practical reasons, this indication of an obligatory linkage between the two abnormalities could not be confirmed by systematic ultrasound examination of all other family members. The approach of studying family group photographs was especially rewarding in one large family, where wedding photos showed 34 members spanning four generations, with the eldest member born in 1873 (Figure 2). Fifteen had ADPKD, and 13 of 15 had blepharochalasis. Some children pictured on these photographs taken about 50 yr ago clearly had such upper eyelid folds. When retrieved at the time of this inquiry, they proved to have ADPKD. Taken together, these findings were considered strongly suggestive of a transmission linkage between the eye features and ADPKD.

To avoid a bias in our interpretation of blepharochalasis, patients with ADPKD as well as family photographs were shown to two ophthalmologists who were unaware of the renal diagnosis. In each patient where they confirmed that the eye deformity was blepharochalasis, the patient had renal cysts.

General Population

The results of an inquiry of 200 patients seen in two different hospital eye clinics (50% in Brittany and 50% in Bobigny) are shown in Table 1. The incidence of blepharochalasis was nil before age 25 and increased with aging. This eyelid feature of the aging skin is well known. Thus, blepharochalasis is not specific of ADPKD, but its unusual frequency in patients with ADPKD under 25 yr of age supports our hypothesis of a relationship between the renal disease and the eye deformity.

COMMENTS

ADPKD is the most frequent genetic disorder leading to chronic renal insufficiency. Its prevalence has been estimated in several epidemiologic studies. The frequency of symptomatic ADPKD in 4 million inhabitants in Western France was evaluated to be 1 in 2,165 (P. Simon et al., unpublished observation). Interestingly, these results in a population of Celtic origin are similar to those observed by Davies et al. in Wales (8), which was 1 in 2,459 among 2.1 million inhabitants. However, when systematic ultrasound examination was carried out in kindreds of our refer-

Figure 1. Marked blepharochalasis in a patient with renal polycystic disease. Note that the upper eyelid fold is so pronounced that the eyelashes emerge from beneath the eyelid.

EPIDEMIOLOGICAL SURVEY

Background

St. Brieuc General Hospital is located in northern Brittany, France. Its catchment population is 410,000, with 99.5% whites. The population is very stable, and the physicians in this area refer virtually all of their renal patients to the St. Brieuc Nephrology Unit. This reference region is a reliable epidemiologic source in all aspects of renal disease. In 1989, we retrieved 71 families comprising 211 members with symptomatic ADPKD aged 32 to 80 yr. Three hundred fourteen living members were at risk of developing ADPKD. Renal ultrasound examination was undertaken in 85, aged over 21 yr. ADPKD was diagnosed in 44 (46%). Thus, the number of persons affected by ADPKD in this area was 254. The prevalence of ADPKD in this region was calculated to be 0.81 in 1,000 (1 in 1,220). These results are comparable to those reported in 1957 by Dalgaard in Copenhagen (7). Genotypic screening was carried out in kindreds of our refer-

Patients and Methods

In 1992, an inquiry on the frequency of blepharochalasis was carried out among 75 families with known cases of ADPKD. Members with ADPKD were summoned to the Nephrology Unit and examined in order to evaluate the prevalence of upper eyelid folds. They were questioned as to the existence of such appearance in other family members. Also, the patients were requested to provide family group photographs, traditional at the time of marriages, in order to retrieve other living members with the eye features and to determine whether they had renal cysts.

A parallel inquiry consisted of requesting one ophthalmology unit in Brittany and one in Bobigny (the suburban borough of the Paris area where the Avicenne University Hospital is located) to examine the eyes of 100 consecutive outpatients with no known personal or family history of renal disease and to note the presence or absence of blepharochalasis. This was intended to determine the incidence of such drooping eyelids in the general population, information that is unavailable in the ophthalmologic literature.
Figure 2. Two wedding photos spanning four generations of a family with ADPKD. On this montage, the inserts show blepharochalasis in some members with ADPKD. The gentleman with a moustache (upper left) was born in 1873. He died of renal failure due to ADPKD. The young girl in the lower left was aged 5 when this photograph was taken. She is now 50 and dialyzed for end-stage renal failure due to ADPKD. The subjects in the righthand inserts, whose blepharochalasis is evident, also suffered from ADPKD.
It is now established that ADPKD may be trans-

TABLE 1  Prevalence of blepharochalasis in a population of 200 consecutive outpatients without known familial renal disease examined in the Eye Departments of St. Brieuc General Hospital and Bobigny University Hospital

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<th>Parameter</th>
<th>Age Range (yr)</th>
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<td>5-14</td>
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<tr>
<td>N</td>
<td>15</td>
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<tr>
<td>Females/Males</td>
<td>6/9</td>
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<tr>
<td>Blepharochalasis</td>
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<td>N</td>
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ence region, we found that the prevalence of symptomatic + asymptomatic ADPKD was much higher, about 1 in 1,000.

ADPKD may be associated with extrarenal manifestations, comprising cerebral artery aneurysms, colon diverticulosis, hialtal hernia, and heart valve abnormalities (2-4). The rare, X-linked orofaciodigital syndrome (9,10) may be accompanied by renal cysts, but it only affects females, its features are peculiar, and it does not comprise an eye component. Careful search of the nephrologic literature concerning extrarenal dysmorphism in ADPKD did not reveal any mention of eyelid abnormalities. Conversely, the nephrologist screening the book entitled Diseases Affecting the Eye and the Kidney (11) is struck by the number of rare syndromes associating simultaneous renal and ocular deformities, several of the latter comprising epicanthal folds, eyelid abnormalities, and even complete cryptophthalmos. Such associations include Potter syndrome (Reference 12, p. 29), Zellweger syndrome (p. 337), Apert syndrome (p. 436), Beckwith-Wiedeman syndrome, Cri-du-Chat syndrome (p. 436), Ehlers-Danlos syndrome, Riley-Day syndrome (p. 437), Jadassohn syndrome (p. 438), Joubert syndrome, Leber amaurosis, Meckel-Gruber syndrome, Steinert disease (p. 439), Neu-Laxova syndrome (p. 440), Smith-Lemli-Opitz syndrome, and Edwards syndrome (p. 441). Nine of these inborn errors of eye and kidney development include renal cysts, and eight include epicanthal folds or even absent eyelids.

It has been determined that the embryogenetic stages of the eye and kidney development occur simultaneously from the second half of the fourth week up to the end of the sixth week. From the 7th to the 10th weeks, the development of the ocular architecture progresses parallel to the differentiation of the kidney tubules (12,13). It is known that ADPKD may be occasionally diagnosed in the fetus (14). It is conceivable that the unknown factor leading to the development of renal tubular cysts in utero (15) might simultaneously affect the eye and the kidney.

The most important breakthrough in the understanding of the hereditary nature of ADPKD was the demonstration by Reeder et al. (16) of a linkage between the renal disease and chromosome 16 markers. It is now established that ADPKD may be transmitted with this gene abnormality in more than 90% of kindreds. In 10%, the transmission is not linked to chromosome 16 (the so-called "ADPKD2" form of renal polycystic disease). However, the ADPKD1 gene awaits identification, and routine genetic studies based on molecular biology cannot be envisaged in large-scale inquiries until the gene has been cloned (4). In this respect, the finding of a heretofore overlooked clinical feature linked to ADPKD may have a clinical interest for evoking the possibility of ADPKD before ultrasound evidence of cysts, which can become apparent as late as age 25 (17). Although our findings substantiate a clearcut association between blepharochalasis and ADPKD, several issues call for more detailed studies. One is the precise percentage of patients under 30 yr of age with both polycystic disease and blepharochalasis, a study requiring the screening of a much larger population of patients with polycystic renal disease. Another is to determine why blepharochalasis affects subjects with ADPKD inconsistently. A third point would be to understand the embryologic basis of the coincidence between renal cysts and ocular deformities.

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