Characterization of the peripheral retinopathy in X-linked and autosomal recessive Alport syndrome

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Abstract

Background. Alport syndrome is an inherited disease resulting in kidney failure, hearing loss and ocular abnormalities. Alport syndrome is however often unrecognized, and the aim of this study was to characterize the associated but rarely described peripheral retinopathy and determine whether its demonstration was diagnostically helpful.

Methods. Index cases were diagnosed with Alport syndrome on renal biopsy in themselves or a family member. Inheritance and affected status were determined using microsatellite markers at the COL4A5 and COL4A3/COL4A4 loci, respectively. Participants' eyes were dilated, and examined with direct and indirect ophthalmoscopy, and slit lamp biomicroscopy by an expert ophthalmologist who was unaware of the patients' disease status.

Results. Ten males and nine females with X-linked Alport syndrome and seven with autosomal recessive disease were studied. Of the 26 patients, 16 had central retinopathy (62%), and 19 patients had peripheral retinopathy (74%). The peripheral changes occurred in both males and females with X-linked and autosomal recessive Alport syndrome, and were more common when renal failure, hearing loss, lenticonus and the central changes were present, but were also noted in 3 X-linked carriers with normal renal function.

Conclusions. The peripheral retinopathy occurs in X-linked and autosomal recessive Alport syndrome even when the central retinopathy is absent. Careful retinal examination and photography that includes the periphery is a safe and inexpensive method that may help in the diagnosis of Alport syndrome especially in carriers of X-linked disease.

Keywords: Alport syndrome; collagen type IV; glomerular basement membrane; retinopathy

Introduction

Alport syndrome is an inherited kidney disease that affects one in 50,000 live births [1]. It is characterized by haematuria, progressive renal failure, hearing loss, ocular abnormalities and a lamellated glomerular membrane with an abnormal collagen composition [2–4]. Inheritance is X-linked in 80% of the patients and autosomal recessive in most of the others [5], when mutations affect the type IV collagen genes, COL4A5, and COL4A3 and COL4A4, respectively [6,7].

The most common ocular abnormalities in Alport syndrome are anterior lenticonus and a central or perimacular retinopathy that comprises multiple whitish-yellow dots and flecks and spares the macula [8–13]. The central retinopathy is pathognomonic for Alport syndrome, and occurs in 40–70% males and 10% females with X-linked inheritance, and 70% individuals with autosomal recessive disease [11,12]. There is no retinal involvement in the rare autosomal dominant disease. The central retinopathy is often accompanied by hearing loss and lenticonus, and is usually present by the time renal impairment is first noted but progresses until at least middle age. The retinopathy is usually evident on ophthalmoscopy but is best documented photographically. Vision is normal and no treatment is necessary. The variation in reported frequencies of retinal changes is probably partly due to whether patients have renal failure (which is more common in patients with the retinopathy or who are hospital-based anyway) and how carefully their eyes are examined. A mid-peripheral or peripheral retinopathy is recognized less frequently [13].

The aim of this study was to characterize the peripheral retinopathy in X-linked and autosomal...
Peripheral retinopathy in Alport syndrome

recessive Alport syndrome, to examine its relationship to the central retinopathy and other clinical features, and to determine whether inclusion of the periphery increased the sensitivity of the retinal examination for the diagnosis of Alport syndrome.

Patients and methods

Diagnosis of Alport syndrome

Index cases were diagnosed with Alport syndrome when they had haematuria or kidney failure together with a lamellated glomerular basement membrane in a renal biopsy from themselves or a family member. In addition, all family members were invited to participate in the study whether or not they were known to be affected.

Participants were asked about a hearing loss or previous abnormal audiometry, and each provided a urine specimen which was examined by phase contrast microscopy for glomerular haematuria [14], as well as a peripheral blood sample for estimation of serum creatinine and for DNA extraction.

Genetic studies

In each family, the mode of inheritance and disease status were confirmed by the correlation of haematuria or renal failure with haplotypes at the \( \text{COL4A5} \) and \( \text{COL4A3} / \text{COL4A4} \) loci [12]. DNA was extracted from blood or mouth brushings using conventional techniques. Haplotypes were constructed after PCR amplification of microsatellite markers at \( \text{COL4A5} \) (DXS1120, DXS 1105, 2B6, 2B20 and DXS456) and at \( \text{COL4A3} / \text{COL4A4} \) (D2S351, CA11, \( \text{COL4A4}/\text{HaeIII} \), D2S401 and PAX3). Linkage studies in many of these families have been described previously [12].

Ophthalmological examination

All participants were examined by an ophthalmologist with an interest in Alport syndrome (DC) who was not aware of the patients’ disease status. Participants were asked about any abnormalities of night vision, colour vision, visual fields, or a change in spectacle strength. They were then examined for the ‘oil-droplet sign’ of anterior lenticonus using a handheld refractoscope. Their eyes were dilated with tropicamide 1%, and their optic fundi examined for central and peripheral retinal abnormalities by direct ophthalmoscopy, slit lamp biomicroscopy with a 78D lens (in most cases), and by indirect ophthalmoscopy with a 20D lens. The peripheral retina was defined as being beyond the perifovea and thus about 3 mm or 2 optic disc diameters from the foveola [15].

Retinal photography including at least eight retinal views was performed with a digital or Zeiss film camera in 22 cases. Three individuals had ‘red-free’ retinal photographs which filter out the background colour and better demonstrates drusen.

This study had the approval of the Austin Hospital Human Research Ethics Committee and all participants provided signed informed consent.

Results

In this study, 26 individuals from 12 families (80%) with X-linked and 3 families (20%) with autosomal recessive disease were examined (Table 1, Figure 1). Fourteen who had been examined for the central retinopathy were recalled for these examinations, and eight individuals were from six families who had not been studied previously.

X-linked Alport syndrome

Ten males from ten different families (median age 34 years, range 11–54) were examined. Three (30%) had not reached end-stage renal failure, and seven (70%) were on dialysis or had undergone transplantation. Nine had a hearing loss (90%), seven (70%) had lenticonus (or had a lens replacement) and eight (80%) had the typical central dot and fleck retinopathy. Nine (90%) also had a peripheral retinopathy. For example, an 11-year-old male with normal renal function and a hearing loss had both the central and peripheral retinopathy. A 40-year-old male with renal failure, hearing loss and lenticonus, had the peripheral retinopathy but no central changes. In contrast, a 38-year-old male with normal renal function and normal hearing had no central or peripheral retinopathy.

Nine females from nine families (median age 41 years, range 8–68) were studied. (Both males and females were studied in 7 families). All had haematuria, one (11%) had kidney failure, two (22%) had a hearing loss, none had lenticonus and one had the central retinopathy (11%). Three had the peripheral retinopathy (33%). One woman (11%) had both central and peripheral retinal changes, and two (22%) had only the peripheral retinopathy. One of these was the mother of an affected 27-year-old male who had both the central and peripheral retinopathy, and the other was the mother of the 38-year-old affected male who had no retinopathy.

Autosomal recessive Alport syndrome

Seven individuals (six males and one female, median age 32 years, range 26–47) from three different families were examined. Six (86%) already had end-stage kidney failure, five of these had undergone transplantation, and all seven (100%) had a hearing loss, anterior lenticonus and the central retinopathy. All seven (100%) had the peripheral retinopathy.

Unaffected family members

None of the 21 unaffected family members (no haematuria, normal renal function, absence of disease haplotype) had lenticonus, or the central or peripheral retinopathy.
Table 1. Peripheral retinopathy and other clinical features in patients with X-linked and autosomal recessive Alport syndrome

<table>
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<tr>
<th>Patient</th>
<th>Gender</th>
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<th>Renal status</th>
<th>Age at renal failure (years)</th>
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<th>Lenticulosis</th>
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M, male; F, female; H, haematuria; P, proteinuria; RF, renal failure; N/A, not applicable; Y, yes; N, no.

*aThe three patients in whom the peripheral retinopathy occurred without the central retinopathy.

Fig. 1. (A) Central retinopathy demonstrating perimacular dots and flecks. (B) Typical peripheral retinopathy showing confluent white areas. (C) Peripheral retinopathy showing fine dots and flecks in the mid-periphery and periphery but not centrally. This is from a female carrier of X-linked Alport syndrome. (D) Red-free photograph of same patient as in 1c showing fine white stippling in the mid-periphery consistent with retinopathy.
Peripheral Alport retinopathy (Figure 1)

A mid-peripheral or peripheral retinopathy was very common in the males with X-linked Alport syndrome and individuals with autosomal recessive disease (16/17, 94%) who were examined in this study. The peripheral retinopathy occurred in 3 of the 9 X-linked Alport carriers (33%) and was more common than the central retinopathy in female carriers of X-linked Alport syndrome (3/9, 33%). Overall it occurred in 19 of the 26 individuals studied (74%) compared with the central retinopathy which was present in 16 (62%).

The peripheral retinopathy affected the mid-periphery, the periphery or both. In some cases, the changes were localized and sparse but occasionally affected nearly all the periphery. The mid-peripheral retinopathy often comprised dots and flecks (like the central changes) while the peripheral retinopathy often comprised diffuse confluent areas of depigmentation. The extent of involvement and the pattern varied in different family members. Vision was not affected. The youngest patient in whom these changes were noted was an 11-year-old boy with X-linked Alport syndrome. The peripheral retinopathy was more likely to be present when the affected individual had renal failure, hearing loss, lenticonus and the central retinopathy.

Of the 26 individuals examined, 22 (85%) underwent both clinical and photographic examination of the retina. Photography detected peripheral changes in 19 individuals (19/22, 86%) compared with expert clinical fundal examination (18/22, 82%), but the single individual in whom the peripheral retinopathy was overlooked clinically had poorly dilated pupils.

The ‘red-free’ photographs demonstrated the central and peripheral retinopathy more clearly and more extensively than did ordinary retinal photography.

Discussion

This study found a mid-peripheral or peripheral retinopathy was very common in affected individuals and carriers with X-linked Alport syndrome and affected individuals with autosomal recessive disease even when there was no central retinopathy. Alport syndrome is often unrecognized which means many affected individuals and their family members who are at risk of renal failure are not screened and do not receive genetic counselling. The diagnosis of Alport syndrome usually depends on the demonstration of the typical clinical features, a positive family history, a lamellated glomerular basement membrane, abnormal basement membrane collagen composition, or the demonstration of mutations in the \textit{COL4A5}, \textit{COL4A3} or \textit{COL4A4} genes. However all these methods are problematic. The clinical features are often atypical, and there is no family history if the disease has arisen \textit{de novo} or the family is small, comprises only females or young boys, or the affected males have atypical disease [16]. In addition, some patients with Alport syndrome have a glomerular membrane that is thinned rather than lamellated [17], and appears to have a normal composition. Although genetic testing is the gold standard for the diagnosis of Alport syndrome it is not widely available.

However, there are some ocular clues to this diagnosis. The central perimacular dot and fleck retinopathy, when present, is characteristic, and retinal examination is particularly useful in the elderly, where the clinician is reluctant to perform a renal biopsy, where the biopsy has been unhelpful, and in individuals who have already undergone transplantation. Nevertheless, the demonstration of the central retinopathy is also relatively insensitive for Alport syndrome especially in carriers of X-linked disease.

This study found that a peripheral retinopathy may occur even in the absence of the central retinopathy and suggests that including the periphery increases the sensitivity of retinal examination for the diagnosis of Alport disease. We acknowledge though that most patients studied here had renal failure which makes retinal changes more likely. In addition, the importance of fully dilating the pupils, collaborating with an interested ophthalmologist, and using full retinal photography and even ‘red-free’ views cannot be overstated. Furthermore, peripheral changes must be distinguished from other retinal disease including fundus albipunctatus, other causes of generalized drusen and the pigmentary retinopathies that are usually accompanied by night blindness and progressive visual loss.

The central and peripheral retinopathies appear to have an identical pathogenesis in X-linked and autosomal recessive Alport syndrome. Like the central retinopathy, the peripheral retinal changes were first noted in adolescence and worsened until at least middle age. In the patients described here, the peripheral retinopathy was more common when the central retinopathy occurred, and when renal failure, lenticonus and the hearing loss were also present. However, while most affected patients in our series had a more severe phenotype with a younger age of onset of renal failure, the peripheral retinopathy was also present in individuals with normal renal function. The increased likelihood of the peripheral retinopathy may reflect the earlier age at onset of changes or the larger surface area of the periphery compared with the central retina.

The peripheral retinal changes occurred in some affected family members but not in others and were thus not related to the nature of the underlying genetic mutations. For example, in one family, a female carrier had haematuria, normal renal function and a peripheral retinopathy but her 40-year-old affected son with renal failure had no retinal abnormalities.

In conclusion, careful retinal examination and photography are useful clinical tests that may demonstrate the central and peripheral retinopathies diagnostic of Alport syndrome.
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References


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