

A syndrome of immune complex glomerulonephritis and ophthalmic abnormalities

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Abstract

Two sibs (one male and one female) suffering from a combination of immune complex glomerulonephritis and various ophthalmologic disorders are presented. The two cases belong to a family in which the parents are not related and seven sibs are affected, three females and a male with the combination, and three males with severe ophthalmological changes and proteinuria. Clinically, case 2 had only ophthalmological manifestations but renal biopsy findings were similar to those of case 1, which could mean that all the others with eye abnormalities also had renal disease. Although there are several reports of combinations of eye and renal disorders, the sibs reported here do not fit into any of the known syndromes.

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Association of glomerular diseases with other systemic manifestations and a genetic basis have been described previously.¹⁻⁷ The glomerular lesions in these are immune complex glomerulonephritis,⁷ extensive deposition of type III collagen,^{1,2} and irregular widening and splitting of the basement membrane.³ In Lowe syndrome the renal abnormality is described as a proximal renal tubular defect⁸ and glomerular sclerosis.⁴ Other abnormalities include renal dysplasia⁵ and nephronophthisis.⁶ We report two sibs with a previously unde-

scribed inherited disease involving the eyes and the kidneys with immune complex glomerulonephritis.

Case reports

CASE 1

A five year old Pakistani girl presented with shortness of breath for four days and was noted to have total blindness which had been present since one month before presentation at the clinic. She was transferred from a peripheral clinic because of severe anaemia (Hb 5 mg/dl), low urine output which had reduced to a trickle since one month before referral, and loss of vision which was noted first at the age of 2 years; vision had gradually diminished until one month previously when she became totally blind. The father has two wives. The first wife, this patient's mother and not related to the father, has 14 children, seven of whom are blind. Four of these also have end stage renal disease and three are on peritoneal dialysis. The second wife, who is her husband's distant relative, has seven children, all of whom are healthy. There is no history of blindness or kidney disorder in the family. The family pedigree is shown in fig 1. The three blind boys including case 2 described below had 3+ proteinuria. Urine analysis was also done on one of the male sibs, who was not blind and did not have renal failure, and showed 1+ proteinuria, and on the parents who did not have proteinuria.

On physical examination she was tachypnoeic, dyspnoeic, and febrile. Respiratory rate was 42/min, heart beat rate was 122/min, BP was 140/90 mm Hg, and weight was 14.5 kg.

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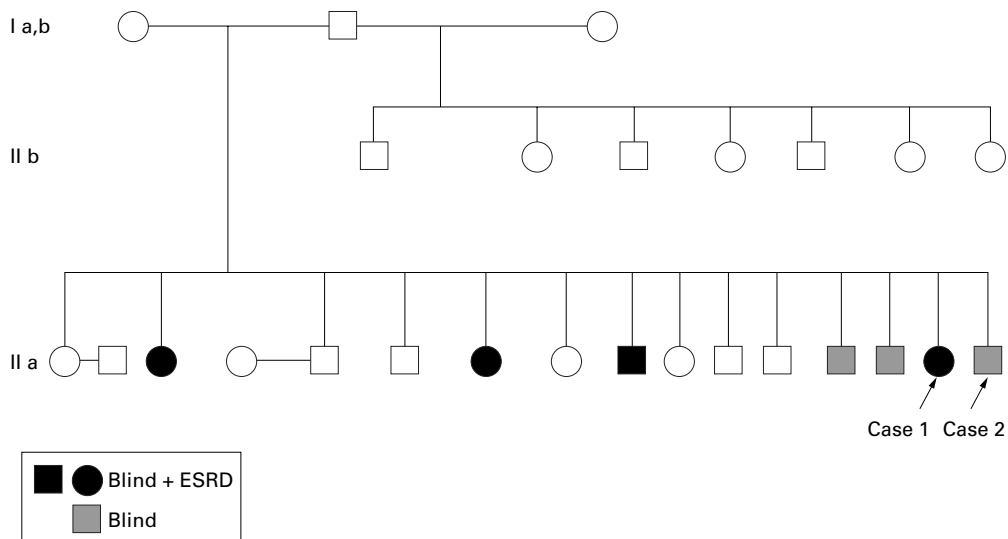


Figure 1 Pedigree of the family with seven children of non-consanguineous parents affected either by both end stage renal disease and ophthalmic abnormalities (four children) or only ophthalmic abnormalities (three children).

Ophthalmological examination by an ophthalmologist showed questionable light perception in both eyes and wandering eye movement. The right eye had a shallow anterior chamber, occlusio pupillae, and cataract. The fundus could not be seen. The left eye had posterior synechiae, mild posterior subcapsular cataract, and vitreous opacities. There was questionable total retinal detachment (fig 2). The parents were also seen by an ophthalmologist and their eyes were found to be normal.

The results of the laboratory investigations performed were: blood urea nitrogen 48 mmol/l, creatinine 1060 μ mol/l, P 3.7 mmol/l, Ca 1.88 mmol/l, fasting glucose 6 mmol/l, Na 142 mmol/l, K 3.6 mmol/l, HCO₃ 2.5 mmol/l, Hb 4.7 g/dl, MCV 78.4, MCH 26.6, RDW 14.4%, blood group O+, PO₂ 10.2 kPa (77 mm Hg), PCO₂ 1.5 kPa (10.9 mm Hg), BE -26.9 mmol/l, pH 6.996, ESR 103 mm/in the first hour. HIV was non-reactive. Urine analysis showed protein, glucose, and ketone. Serum amino acids and urinary amino acid excretion were normal in this patient and in both her parents. ANA and anti-DNA antibodies were negative. C3 and C4 levels were normal.

The parents refused dialysis at first but later accepted it. By then the child had Kussmaul respiration, corneal clouding, and slight disorientation. Ultrasound of the abdomen showed fluid in the abdominal cavity and the kidneys, which were of normal size and shape, showed grade III parenchymal density. The patient was treated with sodium bicarbonate, blood transfusion, and peritoneal dialysis. Other studies

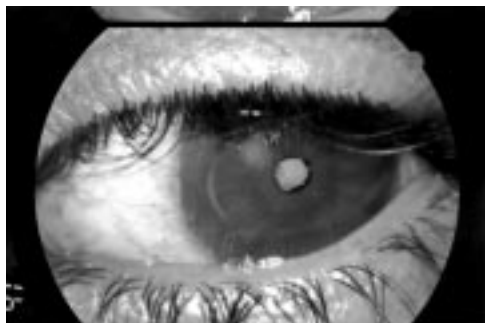


Figure 2 Case 1. Photograph of the left eye showing cataract.

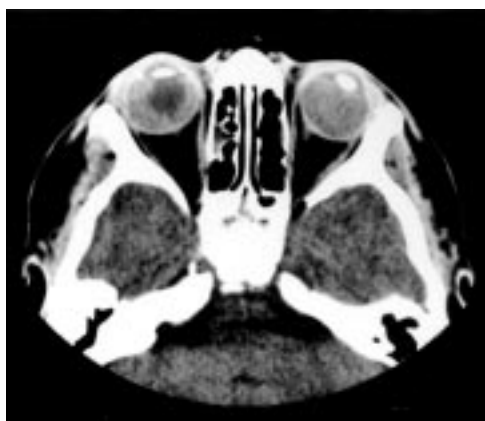


Figure 3 Case 1. CT scan of the orbits showing increased density of both lenses and questionable cataract. The density of the eyeball was increased on the left side.

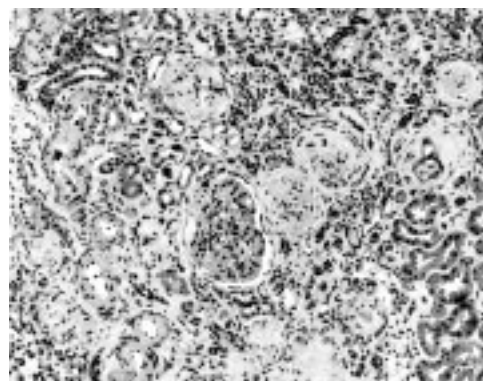


Figure 4 Case 1. Most glomeruli are sclerosed. The viable glomerulus shows increase in mesangial matrix and cells. Chronic tubulointerstitial changes and vascular sclerosis are evident. (Light microscopy, H&E.)

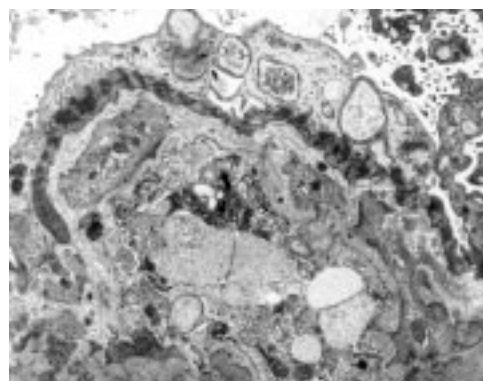


Figure 5 Case 1. The capillary basement membrane has an irregular epithelial surface and the lamina densa is reticulated. (Electron microscopy.)

performed were amino acid chromatography, which was normal, and CT scan of the brain and orbits. There was no brain abnormality, but the orbits showed increased density of both lenses and questionable cataract. The density of the eyeball was increased on the left (fig 3).

A kidney biopsy was performed. In the light microscopy sections more than 50 glomeruli were present of which 75% were completely sclerosed. The viable glomeruli showed increase in mesangial matrix and minimal increase in cells (fig 4). There were extensive chronic tubulointerstitial changes and foam cells were noted. On electron microscopy, the capillary basement membranes were found to be either thin or of normal thickness and in some the lamina densa was reticulated and fibrillar (fig 5). Along occasional capillaries intramembranous and rare mesangial deposits (immune complex type) were present. There was focal effacement of foot processes (fig 6). On immunofluorescence microscopy, focal, granular deposits of moderate intensity (2+) of C3 were present in the mesangia. Immunoglobulins, C1q, fibrinogen, light chains, and albumin (control) were negative.

CASE 2

A 4½ year old Pakistani boy was admitted for investigation because his sister (case 1) was blind and had end stage renal disease. His perinatal history was unremarkable. He was well up to the age of 2 years when he was noted

to have decreased vision and gradually became blind. There were no other symptoms.

On physical examination the child was noted to be well built with wandering eye movements and puffy eyelids. BP was 90/60 mm Hg. The right eye was noted to have microphthalmia, corneal opacification, phthisis bulbi, deep anterior chamber, posterior synechiae, partially absorbed cataract, atrophic iris, and occlusio pupillae. The left eye had corneal opacification, wandering nystagmus, deep anterior chamber, posterior synechiae, and partially absorbed cataract. CT of the orbit showed increased density of the lens on both sides. There was also an abnormal thickening of the posterior chamber on the left side which looked like retinal detachment with reaction. The optic nerves on both sides showed abnormalities which suggested demyelination (fig 7). Various stages of retinal detachment were also seen.

Results of laboratory investigations were as follows: blood urea nitrogen 3.93 mmol/l, electrolytes were all normal, creatinine 44 μ mol/l, creatinine clearance 113 ml/min/1.73 m², Ca 2.15 mmol/l, PO₄ 1.68 mmol/l, total protein 4 g/dl, albumin 2.5 g/dl, IgA 93 mg/dl, IgG 514 mg/dl, IgM 93.8 mg/dl, ESR 16 mm/h, Hb 8.59 g/dl, Hct 25.3, MCV 56.3, MCH 18.8, MCHC 33.5 g/dl, RDW 19.2%, platelets 633 \times 10³/ml, HIV negative. ANA antibodies and

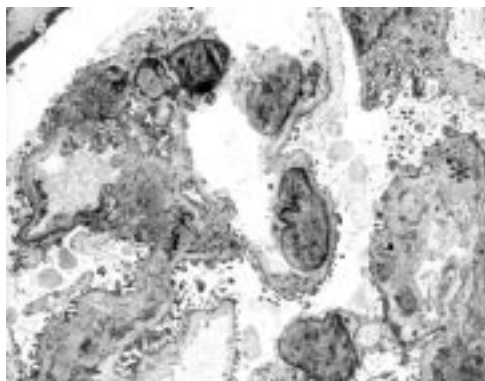


Figure 6 Case 1. Intramembranous and mesangial deposits are present. The mesangium shows increase in matrix and there is patchy foot process fusion. (Electron microscopy.)



Figure 7 Case 2. CT of the orbit showing increased density of the lens on both sides. There is also an abnormal thickening of the posterior chamber on the left side. The optic nerves on both sides show abnormalities which suggested demyelination.

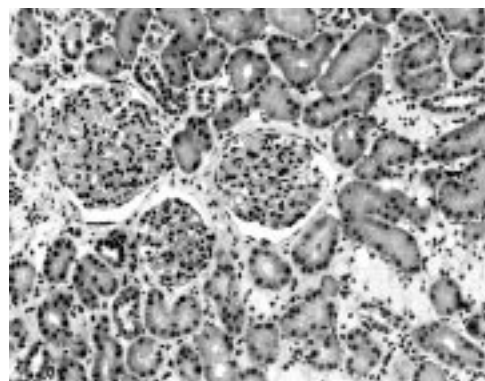


Figure 8 Case 2. Glomeruli show mild increase in cells and mesangial matrix. There is interstitial oedema and foam cells are present. (Light microscopy, H&E.)

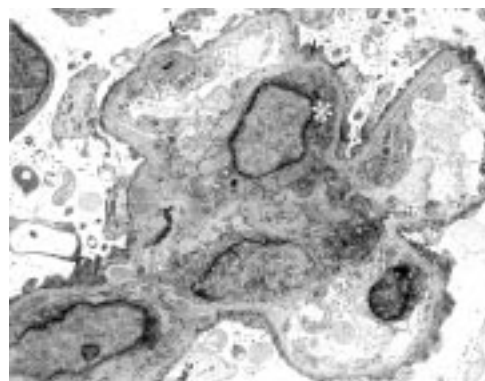


Figure 9 Case 2. Subepithelial deposits (arrows) are present. The mesangial area is widened and contains deposits (*). (Electron microscopy.)

anti-DNA antibodies were negative. C3 and C4 levels were normal.

A kidney biopsy was performed. In the light microscopy sections more than 50 glomeruli were present. They showed moderate variable increase in cells and mesangial matrix. Except for small scars and interstitial oedema, the tubules, interstitium, and vessels were within normal limits. Foam cells were present (fig 8). On electron microscopy, the capillary basement membranes were found to be of normal size, but in places appeared thickened owing to rare intramembranous and subepithelial deposits. The mesangia showed increase in matrix and also contained deposits (fig 9). On immunofluorescence microscopy, all glomeruli showed diffuse, granular deposits of moderate intensity of IgG and C3 along capillary walls with a membranous pattern. Focal deposits of low intensity (1+) of IgM were also present along capillary walls. IgA, C1q, fibrinogen, light chains, and albumin were negative.

Discussion

We describe two patients who presented with a combination of renal and ocular symptoms. The association of renal and eye disorders is described in oculocerebrorenal syndrome (Lowe syndrome),⁸ oculorenal-cerebellar syndrome (ORC syndrome or Hunter Jurenko syndrome),⁴ renal dysplasia-cataracts-blindness,⁵ Senior-Loken syndrome,⁶ and Alport syndrome. All these syndromes have many other features. Lowe

syndrome includes wasting, poor muscle development, thin build, fine, sparse hair, frontal bossing, osteoporosis, osteopenia, joint contractures, arthritis, cerebral cortex atrophy, mental retardation, seizures, and psychosis, along with renal tubular defect and eye abnormalities such as megalocornea, glaucoma, and buphthalmos among many more. ORC syndrome includes microcephaly, cerebellar agenesis, mental retardation, paraplegia, optic nerve atrophy and paresis of ocular muscles, malocclusion of teeth, and a sclerosing glomerulopathy with immune complex deposition in some. In renal dysplasia-cataract-blindness syndrome there is glaucoma, microcornea, seizures, spasticity, and dysplastic polycystic kidneys. Alport syndrome was excluded by electron microscopy findings. Although the two cases described have a combination of renal and ocular findings, they did not conform to any specific syndrome.

In these two patients immune deposits containing IgG, IgM, and C3 were noted with a membranous pattern in case 2. Common immune complex associated glomerulonephritis (GN) in children include streptococcal infection⁹ and viral infections such as hepatitis,^{10,11} human immunodeficiency virus, Coxsackie B4 virus, *Haemophilus parainfluenza*, herpes simplex type I and II, and parvovirus B19. These and other possible causes, such as systemic lupus erythematosus¹² and interferon induced GN,¹³ were excluded in these two patients. Although there are a variety of nephropathies associated with IgA deposition including diet,¹⁴ immune complex associated,¹⁵ viral infections,^{16,17} bacterial antigens,¹⁸ experimental cirrhosis,¹⁹ and lysinuric protein intolerance,¹⁶ none of these diseases shows ocular abnormalities, and in our two patients deposits containing IgA were absent. In these conditions, the glomeruli are hypercellular with deposition of IgG, IgA, IgM, C3, C1q, light chains, and fibrinogen along capillary walls, show renal calcinosis, and have factor H deficiency.¹

The two cases presented belong to a family of 14 children of whom seven are affected and whose parents are non-consanguineous (fig 1). These seven include four males and three females thus excluding X linked recessive inheritance and suggesting autosomal recessive inheritance of a gene carried by both parents.

In conclusion, the two cases described showed eye and renal manifestations with immune complex deposition. The clinical and pathological findings did not conform to any known renal-ocular syndrome. The occurrence of renal and ocular involvement in seven of 14 sibs has not previously been described.

- 1 Vogt BA, Wyatt RJ, Burke BA, Simonton SC, Kashtan EC. Inherited factor H deficiency and collagen type III glomerulopathy. *Paediatr Nephrol* 1995;9:11-15.
- 2 Thompson R, Winterborn M. Hypocomplementemia due to a genetic deficiency of B₂H globulin. *Clin Exp Immunol* 1981;46:110-19.
- 3 Barten S, Proesmans W. Alport syndrome: clinical experience with 21 paediatric patients. *Eur J Pediatr* 1996;155:49-52.
- 4 Hunter AG, Jurenka S, Thompson D, Evans JA. Absence of the cerebellar granular layer, mental retardation, tapetoretinal degeneration and progressive glomerulopathy: an autosomal recessive oculo-renal-cerebellar syndrome. *Am J Med Genet* 1982;11:383-95.
- 5 Fairley KF, Leighton PW, Kincaid-Smith P. Familial visual defects associated with polycystic kidney and medullary sponge kidney. *BMJ* 1963;i:1060-3.
- 6 Schimke RN. Hereditary renal-retinal dysplasia. *Ann Intern Med* 1969;70:735-44.
- 7 Parto K, Kallajoki M, Aho H, Smell O. Pulmonary alveolar proteinosis and glomerulonephritis in lysinuric protein intolerance: case reports and autopsy finding of four paediatric patients. *Hum Pathol* 1994;25:400-7.
- 8 Kenworthy L, Charnas L. Evidence for a discrete behavioral phenotype in the oculocerebrorenal syndrome of Lowe. *Am J Med Genet* 1995;59:283-90.
- 9 Korbet SM, Schwartz MM. Human immunodeficiency virus infection and nephrotic syndrome. *Am J Kidney Dis* 1992;20:97-103.
- 10 Stokes MB, Chawla H, Brody RL, et al. Immune-complex glomerulonephritis in patients coinfecting with human immunodeficiency virus and hepatitis C virus. *Am J Kidney Dis* 1997;29:514-25.
- 11 Guerra IL, Abraham AA, Kimmel PL, Sabnis SG, Antonovych TT. Nephrotic syndrome associated with chronic persistent hepatitis B in an HIV antibody positive patient. *Am J Kidney Dis* 1987;10:385-8.
- 12 Contreras G, Green DF, Pardo V, Schultz DR, Bourgoignic JJ. Systemic lupus erythematosus in two adults with human immunodeficiency virus infection. *Am J Kidney Dis* 1996;28:292-5.
- 13 Kimmel PL, Abraham AA, Phillips TM. Membrane-proliferative glomerulonephritis in a patient treated with α -interferon for human immunodeficiency virus infection. *Am J Kidney Dis* 1994;24:858-63.
- 14 Coppo R, Mazzucco G, Martina G, et al. Gluten induced experimental IgA glomerulopathy. *Lab Invest* 1989;60:499-506.
- 15 Moninaro V, Esparza AR, Cavallo T, Rifai A. Antigen as mediator of glomerular injury in experimental IgA nephropathy. *Lab Invest* 1991;64:508-18.
- 16 Yoshida K, Suzuki J, Suzuki S, et al. Experimental IgA nephropathy induced by coxsackie B₂ virus in mice. *Am J Nephrol* 1997;17:81-8.
- 17 Suzuki S, Nakatomi Y, Sato H, Tsukada H, Arakawa M. Haemophilus parainfluenzae antigen and antibody in renal biopsy samples and serum of patients with IgA nephropathy. *Lancet* 1994;343:12-20.
- 18 Endo Y, Kanbayashi H, Hara M. Experimental immunoglobulin A nephropathy induced by gram negative bacteria. *Nephron* 1993;65:196-205.
- 19 Gormly AA, Smith PS, Seymour AE, Clarkson AR, Woodroffe AJ. IgA glomerular deposits in experimental cirrhosis. *Am J Pathol* 1986;104:50-4.