Teaching Point
(Section Editor: K. Kühn)

Supported by an educational grant from Fresenius Medical Care

Renal diagnosis without renal biopsy. Nephritis and sensorineural deafness

Donald Richardson, Mike Shires and Alex M. Davison

Department of Renal Medicine, St James’s University Hospital, Leeds, UK.

Abstract
Two examples of hereditary nephropathy within the context of clinical syndromes are described. Emphasis is put on the ability to make a renal diagnosis without renal biopsy and the benefits of screening relatives once a diagnosis is achieved. A variant of Alport’s syndrome with associated macrothrombocytic thrombocytopenia, known as Epstein’s syndrome, is reported. In addition siblings with Alström’s syndrome characterized by pigmentary retinal degeneration (causing blindness in early childhood), progressive sensorineural hearing loss, and progressive renal failure are reported. Both cases had previously presented for non-renal pathology in advance of the onset of symptomatic renal failure and may have benefited from appropriate screening.

Keywords: Alport’s syndrome; Alström’s syndrome; Epstein’s syndrome; hereditary nephropathy; megalakaryocytes; retinitis pigmentosa; sensorineural deafness

Cases
Case 1
A 35-year-old male of middle-eastern origin was admitted to hospital for haemodialysis. He had developed end-stage renal failure 6 weeks previously and had received 13 haemodialysis sessions and multiple transfusions in another country. His past medical history was that of long-standing haematuria from the age of 9 years, which was thought to be secondary to idiopathic thrombocytopenia diagnosed at 7 years of age. A splenectomy was performed to alleviate the thrombocytopenia. No family history of nephropathy was obtained. An ultrasound revealed bilateral small kidneys. A blood film was compatible with previous splenectomy and also demonstrated giant platelets. These large platelets are not recognized as platelets by automated counters because of their large size (Figure 1A and B).

The patient initially commenced haemodialysis and was converted to continuous ambulatory peritoneal dialysis (CAPD) 3 weeks later. The CAPD catheter insertion was complicated by prolonged bleeding that was treated successfully by a platelet transfusion and local injection with adrenaline. Subsequent recurrent bleeding eventually settled without further complication.

Because of the reported association of macrothrombocytic thrombocytopenia and hereditary nephropathy in a variant of Alport’s syndrome, ophthalmic examination was undertaken. There were no signs compatible with Alport’s on either retinal or anterior segment examination. Audiometry was performed in the absence of clinically symptomatic deafness. A high-tone sensorineural hearing deficit was demonstrated (Figure 2). A diagnosis of Epstein’s syndrome was made. Multiple nose bleeds and multiple episodes of bleeding into the CAPD dialysate complicated his treatment. After 3 years he developed CAPD peritonitis, requiring the

Introduction
A number of patients present to nephrologists with end-stage renal failure of unknown cause and many have small kidneys, making renal biopsy inadvisable. A small number of these patients may have clues to the diagnosis of a hereditary nephritis. This may be important not only for the patient but also for any living relatives who could benefit from screening and earlier medical attention. We report two patients in whom diagnoses were reached without renal biopsy.

Correspondence and offprint requests to: Donald Richardson
Department of Renal Medicine, St James’s University Hospital, Leeds LS9 7TF, UK.
removal of the catheter. Attempted reinsertion of a catheter failed secondary to bleeding and he was commenced on haemodialysis. He is well and continues on haemodialysis 7 years after his presentation.

Case 2

A 28-year-old woman was admitted to hospital complaining of increasing anorexia, malaise, nocturia, and nausea. She had retinitis pigmentosa with blindness and bilateral sensorineural deafness requiring bilateral hearing aids. She was of normal intelligence and worked full time. Past medical history included bilateral oophorectomy for giant polycystic ovaries and surgical correction of kyphoscoliosis. Urine dipstick revealed haematoproteinuria. Blood examination on admission showed: Na 137 mmol/l, K 4.8 mmol/l, HCO₃⁻ 13.3 mmol/l, urea 27.5 mmol/l, creatinine 740 µmol/l, albumin 49 g/l, alkaline phosphatase 475 IU/l, alanine transferase 15 IU/l, bilirubin 7 µmol/l, Ca 2.17 mmol/l, PO₄ 2.66 mmol/l, glucose 10.6 mmol/l, Hb 9.6 g/dl, MCV 94 fl, WCC 8.8 × 10⁹/l, platelets 192 × 10⁹/l; clotting screen was normal. Renal ultrasound showed bilaterally small kidneys with bright cortices. The patient was diagnosed as having Alström’s syndrome. Her brother, aged 24 years, also had retinitis pigmentosa (Figure 3) and sensorineural deafness, and was counselled and investigated. Examination revealed testicular atrophy with normal secondary sexual characteristics, frontal balding, hypertension, and glycosuria. Blood test showed impaired renal function with an elevated urea and creatinine, and hyperglycaemia. Renal size was normal and a biopsy showed chronic interstitial nephritis with fibrosis and glomerulosclerosis.

Fig. 1. Electron micrograph of (A) normal platelets, (B) giant platelets (case 1). Bar is 1 µm.

Fig. 2. Audiogram demonstrating bilateral high-tone deafness (decreased air and bone conduction at frequencies ≥2 kHz (A, B) (case 1).
Discussion

Alport’s syndrome is an inherited disorder with nephritis and high-tone sensorineural deafness [1–6]. Alport’s syndrome is predominantly an X-linked dominant disease (85% of families); in 15% it is autosomal recessive; and very rarely an autosomal dominant disease. Alport’s in association with macrothrombocytopenia, is however, autosomally dominant. Histologically, light microscopy is normal in the early stages of Alport’s, but mesangial cell expansion, segmental proliferation, progressive sclerosis, interstitial nephritis, and fibrosis can develop. An irregularly thickened glomerular basement membrane is the most frequent finding on electron microscopy with splitting and splintering of the lamina densa. One of the hallmarks of Alport’s is a defect in glomerular basement membrane antigenicity involving α5, α3, and α4 chains of the type IV collagen. This condition, however, does not correspond to a single clinical syndrome. Epstein described a triad of hereditary nephritis and nerve conduction deafness (indistinguishable from Alport’s syndrome) with macrothrombocytopenic thrombocytopenia [7]. The suggested autosomal dominant nature of this syndrome cannot be tested in our case because of the absence of relatives for testing. The nature of the renal abnormalities in Epstein’s syndrome has not been completely clarified. Fetcher’s syndrome has the additional associations of cataracts and cytoplasmic inclusions in neutrophils and eosinophils [8–10], both absent in the case described here. Platelet defects are characterized by giant forms with abnormal ultrastructure and impaired function in terms of adherence to glass and diminished aggregation in response to ADP, collagen and adrenaline [11,12]. A normal number of megakaryocytes are observed in bone-marrow aspirates. The platelet number is slightly diminished, but Coulter counts dramatically so. The giant platelets appear to be the consequence of defective platelet budding. The megakaryocytes are thought to have a normal life span in the circulation. Donor platelet transfusion corrects the prolonged bleeding time but the bleeding tendency is often mild in these patients. Splenectomy does not increase the platelet count.

The renal natural history of Epstein’s syndrome is indistinguishable from Alport’s syndrome, with frequent progression to end-stage renal failure in the 3rd to 5th decades. Both haemodialysis and peritoneal dialysis can be viable treatment modalities and successful renal transplantation [13] has been described. In our case early recurrent bleeding occurred at the catheter insertion site and peritoneum but CAPD was subsequently successful for 2 years (failure secondary to peritonitis).

Alström’s syndrome [14,15] is a clinical diagnosis with the associated findings of retinitis pigmentosa and sensorineural deafness in childhood, with chronic interstitial nephritis and progressive deterioration of renal function (in the 2nd or 3rd decade). In addition, primary infertility (gonadal atrophy/polycystic ovaries) but with normal development of secondary sexual characteristics and non-insulin-dependent diabetes mellitus (developing in the 2nd or 3rd decade) are associated with this syndrome. The development of diabetes can lead to the correct but delayed diagnosis [16]. The inheritance is autosomal recessive and the siblings described had no identified family history of nephritis, deafness, or blindness. Initially, a misdiagnosis of cone–rod dystrophy, achromatopsia, Leber’s congenital amaurosis, or Bardet–Biedl syndrome may be made. The retinal dystrophy is progressive with the patient’s visual acuity of 6/60 or less by 10 years of age and no light perception by 20 years of age [17]. Alström’s syndrome should be considered, particularly if the weight is above the 90th percentile. Other associations with Alström’s syndrome not described in our cases include; childhood and adult cardiomyopathy, hepatic cirrhosis, hypothyroidism, growth hormone deficiency, asthma, acanthosis nigricans, and hypertriglyceridaemia [18–21].

There are various inherited conditions in which sensorineural deafness is associated with renal disease [22], including the Alport’s variants, Muckle–Wells syndrome, Refsum disease, Cockayne syndrome, renal tubular acidosis, ichthyosis and prolaboria, Charcot–Marie–Tooth syndrome, Alström’s syndrome, ataxia hyperuricaemia, photomyoclonus, diabetes mellitus, familial spastic paraplegia with intellectual retardation, mitochondrial disorders, hypoparathyroidism [23], and hyperparathyroidism. In addition there are various types of inherited thrombocytopenia, which are associated with nephritis including the May–Hegglin anomaly, familial immune thrombocytopenia, and the Wiskott–Aldrich syndrome.

Conclusions

These cases serves to remind us that in those patients presenting late to nephrologists with bilateral small
kidneys, the diagnosis can still be made in some instances through the presence of other clinical signs known to be associated with recognized inherited syndromes. Audiometry can aid the diagnosis in some cases of hereditary nephritis were biopsy is not possible despite the absence of symptomatic deafness as in case 1. This may negate the need for renal biopsy, which remains an invasive test with a measurable (although low) inherent risk even when the kidneys are large enough to biopsy. The importance of making a diagnosis relates not only to the patient’s own prognosis but also to enable screening and counselling of relatives, which avoids the late presentation as occurred in the two patients described. Conditions such as hypertension, anaemia, hyperparathyroidism, and diabetes can be identified and treated earlier, thereby reducing the associated risks independent of the primary diagnosis. Parents can be given genetic counselling if they have not completed their family.

In addition, screening for nephritis should be considered in all cases of hereditary thrombocytopenia, hereditary sensorineural deafness, and retinitis pigmentosa. These conditions usually present to their respective specialties prior to the renal disease becoming symptomatic.

References