

Not just a carrier: severe X-linked Alport Syndrome causing childhood kidney failure in a female patient

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Abstract

Background

Alport Syndrome, a defect in Type IV collagen in the basement membrane, cochlea and eye, is commonly known to be a cause of kidney failure in males, due to X-linked inheritance of pathogenic variants. There is a paucity in the literature describing the natural history of this disease in female children with X-linked associated Alport Syndrome. We aim to describe the case of a female child with early-onset rapid progression to kidney failure the first decade.

Case

An eighteen-month-old female was referred to paediatric nephrology for review of microscopic haematuria on the background of a paternal family history of Alport Syndrome. Despite early ACE inhibition and nephroprotective care she progressed to kidney failure at nine years of age requiring renal replacement therapy.

Conclusion

XLAS can manifest as kidney failure in early life in females and as such, early nephroprotection with ACE inhibition and appropriate genetic counselling should be given careful consideration in females, as well as males with XLAS.

What is new?

This case demonstrates a rare phenotype of early-onset rapid progression to kidney failure in a female child with Alport Syndrome, challenging the natural history known of this disease in females and carrying implications as such for genetic counselling, surveillance and threshold for commencing nephroprotective measures in female paediatric patients.

Introduction

First described in 1927 by Cecil Alport as a 'familial haemorrhagic nephritis' [1], noted primarily in male patients, Alport syndrome has since been recognised as the second most common cause of monogenic chronic kidney disease [2]. Pathogenic variants in genes encoding for collagen type IV (COL4A3, COL4A4, COL4A5) affect the collagen production in the basement membrane of the kidney, cochlea and retina, leading to a spectrum of clinical manifestations comprising haematuria, sensorineural deafness and ocular abnormalities.

Alport Syndrome exhibits three main patterns of inheritance and a more recently recognized digenic form of the disease [3]. The most common form of inheritance is the X-linked pattern, accounting for

approximately eighty percent of cases [4]. In an X-Linked pattern of inheritance, males are noted to progress to end stage kidney disease commonly, however in female carriers, due to random X-chromosome inactivation, there is highly variable clinical courses documented. To our knowledge, no reports have been published of paediatric female patients with end stage kidney disease secondary to X-linked Alport Syndrome (XLAS). [3–9]

Case Presentation

An eighteen-month-old female was referred to paediatric nephrology for investigation of persistent microscopic haematuria and nephrotic-range proteinuria detected following an admission to hospital for pyelonephritis. The child had been previously well, was developmentally appropriate and was growing well. Her family history was significant for Alport Syndrome diagnosed in her father, paternal aunt, uncle and paternal grandmother. Both her father and grandmother had reached ESKD and were being managed with intermittent haemodialysis at that time. The child's mother was well with no haematuria and no relevant family history of kidney disease. The child's initial serum creatinine was normal (36 $\mu\text{mol/L}$), with urinalysis revealing microscopic haematuria. She was normotensive. Considering these findings, she underwent genetic testing for Alport Syndrome.

Genetic investigations yielded a positive result for a hemizygous COL4A5 pathogenic sequence variant [COL4A5 c.3773G > A p.(Gly1258Asp)], not previously described but deemed to be pathogenic given cases of missense variants within this region previously being described in Alport Syndrome patients. Variants of COL4A3 and COL4A4 were excluded in testing. This result was deemed consistent with X-Linked AS. A female first-degree cousin was also diagnosed in childhood secondary to this patient's diagnosis. Rarely, presentations of Alport Syndrome may mimic focal segmental glomerulosclerosis and although this patient's albumin level was normal, she had persistent nephrotic range proteinuria and thus underwent kidney biopsy to rule out dual pathology. Kidney biopsy revealed marked foot process effacement and the glomerular basement membrane (GBM) was noted to have loops of scalloping and thickening with suggestion of splitting in some loops visualised on biopsy. Occasional loops of GBM showed evidence of reduplication. No immune complex deposition was noted, in keeping with the genetic diagnosis of AS. At this point, ACE inhibition (Enalapril) was commenced due to nephrotic range proteinuria (598mg/mmol) for nephroprotection.

The patient's condition remained stable throughout early childhood, with normal kidney function, normal serum albumin and diminishing proteinuria with ACE inhibition at maximum tolerated dose (urine PCR 100-150mg/g). However, at age eight years of age, our patient's kidney function began to decline (Creatinine 87 $\mu\text{mol/L}$, urine PCR 1000mg/g) and enalapril was discontinued with a trial of Losartan (Angiotensin II Receptor Blocker) to determine if this would be better tolerated. Despite this, the child's chronic kidney disease progressed to stage V and losartan was discontinued.

Further genetic analysis was undertaken to assess x-inactivation skew for this patient, perhaps explaining this patient's severe phenotype of XLAS in childhood. This demonstrated a ratio of 69:31 of

the x-mutation found in this patient, a skew which is considered random inactivation, a normal embryonic process. A limitation of this testing is that it only represents peripheral blood sampling, and the possibility of random tissue inactivation of higher skew cannot be estimated in this sampling. A skewed sample (considered to be a ratio of more than 80:20) would be associated with one X-chromosome being inactivated more than the other, often seen in x-linked recessive disorders which manifest in females and may represent disease severity in X-linked dominant conditions [5]

Over the course of twelve months, our patient's eGFR fell rapidly and the patient progressed to CKD Stage V and prepared for commencement of peritoneal dialysis with elective catheter insertion at age nine years. Pre-emptive transplantation was not possible for this patient who had no suitable living donor available.

By ten years of age, our patient was transitioned to haemodialysis for ineffective solute clearance despite adequate fluid removal on peritoneal dialysis. She underwent thrice weekly in-centre haemodialysis for ten months until she received deceased donor transplant at age 11 years. Her immediate post-transplant course was uneventful, and she was discharged home with close outpatient follow-up in keeping with local protocols.

Discussion

Advances in genetic testing and histopathology have enhanced our knowledge of Alport Syndrome in the recent past and with increasing awareness of the illness, comes increased opportunity to slow progression to ESKD. This case demonstrated the importance of early referral of those with persistent microscopic haematuria in expediting diagnosis and appropriate monitoring for disease progression, particularly given this patient's significant family history. In aiming to prevent progression to ESKD, genomic sequencing of children with persistent microscopic haematuria was shown to have a 67% diagnostic yield in one study conducted at the Kidney Genetics Clinic at the Royal Children's Hospital, Melbourne [6]. Early diagnosis allows for appropriate early intervention to slow progression with ACE inhibition where appropriate and cascade genetic testing as required for family members. As per recent guidelines issued by ERKNet (European Rare Kidney Disease Reference Network), children and young adults with isolated persistent glomerular haematuria should be tested for Alport Syndrome [7]. ERKNet report an approximate 20% risk of kidney failure by 60 years in female patients of XLAS.

ERKNet guidelines have considered the variable modes of inheritance and the patterns of disease known in patients with AS from a multi-system perspective. Aside from nephroprotection with ACE/ARB medications, female patients with XLAS should have hearing evaluation at diagnosis and every five years thereafter. Similarly, ophthalmology assessment should be completed at the time of diagnosis. Our patient demonstrated no audiology or ophthalmology manifestations at this stage of her disease.

Therapeutic interventions for children with Alport Syndrome are currently limited. Although, clinical trials assessing the utility of SGLT2- inhibitors in paediatric patients with Alport Syndrome are in progress, having demonstrated meaningful benefit in reduction in proteinuria in adult patients with Alport

Syndrome [9]. The results of phase-three clinical trials in paediatric populations are expected in the coming months.

Our patient, despite early initiation of ACE inhibition to reduce proteinuria and slow progression of disease developed ESKD in the first decade, not previously reported in the literature for female XLAS patients. One study reported two familial cases of females with ESKD requiring RRT by twenty years of age [8] although none to date have been demonstrated in early childhood. It is important to consider that it is reported that up to 95% of females with XLAS have microscopic haematuria that can be noted in early childhood, with median age of proteinuria onset being seven years [10]. This shifts the paradigm that this is a disease affecting females only later in life. Heterogeneity in the female XLAS spectrum of disease has been widely appreciated but the natural history of disease progression should be considered similarly variable, as exhibited in our case.

Conclusion

It is increasingly recognised that females with Alport Syndrome can develop early-onset chronic kidney disease. Children and adolescents of both genders warrant surveillance with urinalysis, blood pressure and ophthalmological and audiological review. Nephroprotection with ACE inhibition should be considered in accordance with international guidelines. Appropriate respect should be given to the diagnosis of XLAS in both sexes and the potential kidney outcomes discussed. The ongoing call for the inclusion of children in clinical trials for therapeutic interventions for glomerular disease is pertinent to improving outcomes of this cohort.

Declarations

Conflict of Interest Statement:

The authors of this manuscript declare that they have no conflicts of interest of a financial nature or otherwise.

Contribution Statement:

SC wrote the first manuscript draft. DW sought patient consent for publication of case and was involved in the editing of the manuscript. CS and BD contributed figures and comment from histopathology department re: patient biopsy. MS and CQ oversaw the editing of the manuscript. All authors critically reviewed and appraised the manuscript prior to submission for publication.

Patient Consent:

The parents of this patient have kindly consented for use of their child's information in this case.

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Figures

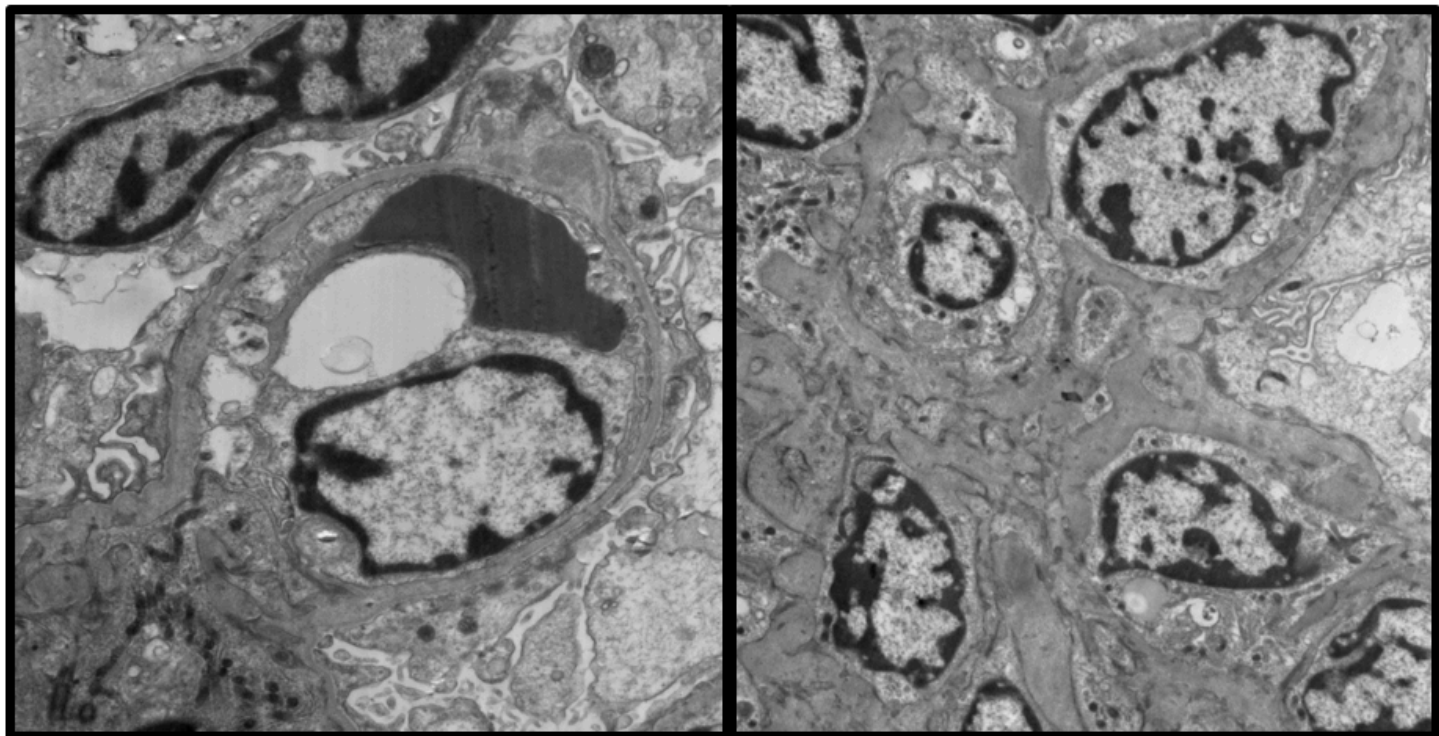


Figure 1

Electron microscopy slides at time of diagnosis demonstrating alternating thickening and thinning of the basement membrane, with 'basket-weave appearance' of the lamina densa. Findings are in keeping with diagnosis of Alport Syndrome.