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Pregnancy in Alport syndrome: A report of two differently-evolving cases

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Introduction

Alport syndrome (AS) is a familial progressive nephritis caused by defects in type-IV collagen, a major component of the basement membrane. In approximately 80% of patients, this disease is inherited as an X-linked trait arising from mutations in the COL4A5 gene on the X chromosome, encoding the α5 chain of type-IV collagen (Matsubara et al. 2009). Clinically, the disease presents as a progressive nephropathy, characterised by the association of progressive haematuric nephritis, with ultrastructural changes in the glomerular basement membrane (irregular thinning, thickening and splitting), high-tone sensorineural hearing loss and ocular lesions (anterior lenticonus, macular flecks, corneal endothelial vesicles, recurrent corneal erosion and cataract) (Artuso et al. 2012). X-linked Alport syndrome (XLAS) is clinically and genetically heterogeneous. Its allelic heterogeneity is clear from the large number of mutations in the COL4A5 gene and the associated phenotypic variability. Clinically, the natural history of XLAS nephropathy is also rather varied. Age at end-stage renal disease (ESRD) differs between families and generally ranges in males between the 2nd and 3rd decades, though in milder cases, it may be delayed until the 5th or 6th decade (Bekheirnia et al. 2010). While progression to renal failure is constant in boys and men, heterozygous females have widely variable disease outcomes; some affected females exhibiting normal urinalysis and kidney function, while others develop ESRD, probably caused by X-chromosome inactivation (Rheault 2012). Although women of reproductive age can be affected by this syndrome, few studies have focussed on the effect of pregnancy on AS. A recent report indicated, however, that pregnancy may prompt a deterioration in renal function (Matsuo et al. 2007).

Here, we report on two patients with AS, who were followed up during their pregnancy and for 22 months afterwards.

Case reports

Case 1

A 38-year-old nulliparous female with a biopsy-confirmed diagnosis of Alport syndrome since her childhood (given her family history), was referred to our unit at 30 weeks' gestation. Clinically, she had proteinuria (3.4 g/24 h), with a creatinine clearance rate of 86.3 ml/min and normal blood pressure; she was started on ASA therapy 100 mg/day. In the following weeks, her proteinuria increased to 7 g/24 h, with hyperuricaemia (6.1 g/dl), while her blood pressure remained normal. Due to her worsening renal function, caesarean section was programmed after administering antenatal steroids. The patient delivered a male weighing 2,165 g (with a 5-min Apgar score of 9), at 34 weeks' gestation. During the subsequent follow-up, her proteinuria gradually improved (0.99 g/24 h after 22 months) and so did her uricaemia (4.2 mg/7 dl), with no deterioration in renal function (serum creatinine concentration 0.9 mg/dl, creatinine clearance 81.7 ml/min), judging from ultrasound and renal scintigraphy.

Case 2

A 26-year-old nulliparous female with a biopsy-confirmed diagnosis of Alport syndrome since childhood (given her family history), was referred to our unit at 7 weeks' gestation. She presented with proteinuria (3.26 g/24 h), normal renal function and normal blood pressure. In the weeks that followed, her proteinuria became worse, reaching 5.98 g/24 h, and she developed gestational hypertension. Therapy was recommended with ASA 100 mg/day, low-doses of methyldopa and nifedipine, which proved difficult to manage due to the patient's poor compliance. Due to the onset of pre-eclampsia (inability to control blood pressure, heavy proteinuria >7 g/24 h, hyperuricemia), she delivered a male infant weighing 2,400 g (with a 5-min Apgar score of 9) at 33 weeks' gestation, after antenatal steroids administration. During the follow-up, the patient's clearance creatinine rate dropped (to 42 ml/min at 22 months), with serum creatinine concentration of 1.48 mg/dl and proteinuria returned to 3.21 g/24 h, while her blood pressure was normal. Ultrasound confirmed chronic renal failure.

Both patients had a normal audiogram and ophthalmological evaluation.

The patients gave their informed consent to molecular analysis for AS, and the study was performed on the two patients and their children.

For Case 1, DNA analysis revealed a heterozygous point mutation 3120G$>$T in exon 34 (p.Gly973Val) of the COL4A5 gene, that was transmitted to her child, who was entrusted to a paediatric nephrologist.

In Case 2, DNA analysis identified a heterozygous point mutation 3710 G$>$A in exon 39 (p.Gly1170Ser) of the COL4A5 gene, that was not found in her son. We consulted the Alport database in ARUP Scientific Resource for Research and Education (a disease-specific database with updated and curated entries for all mutations and polymorphisms reported in the literature, previous online resources and laboratory findings).

Discussion

Renal disease used to be considered a contraindication to pregnancy, but now many women with chronic renal disease (CKD) have successful outcomes. The key pre-pregnancy factors predicting outcome include the degree of renal impairment, control of hypertension before pregnancy and the degree of proteinuria. Most women with mild renal impairment (serum creatinine concentration <1.5 mg/dl) and controlled hypertension have a successful pregnancy outcome. Pre-existing hypertension is probably the main predictor of pregnancy outcome in women with mild renal impairment. In contrast, those with moderate (serum creatinine concentration of 1.5–2.5 mg/dl) to severe (>2.5 mg/dl) renal impairment, particularly when it is accompanied by hypertension and heavy proteinuria, have a lower chance of having a live baby and a greater risk for maternal complications, including progression of renal disease.

Little is known about the effect of pregnancy on women with AS. There are reports in the literature of different outcomes of pregnancy and maternal nephropathy. Matsuo et al. (2007) described a rapid progression of renal disease, coupled with severe, early-onset placental disease, in the form of pre-eclampsia and fetal growth restriction, and long-lasting effects on renal function. On the other hand, Matsubara et al. (2009) reported on a patient with AS who delivered at term with a good pregnancy/postpartum course.

We looked into our patients' renal conditions prior to their becoming pregnant: in Case 1, the renal symptoms of AS were microhaematuria, low level of proteinuria <1 g/24 h, normal serum creatinine and normal blood pressure. Case 2 had microhaematuria, proteinuria 3.26 g/24 h and normal serum creatinine and blood pressure. The clinical course of these two cases seems to be consistent with the literature, emphasising the importance of a patient's renal condition (i.e. proteinuria) prior to pregnancy, which seems to also have influenced the evolution of our patients' nephropathy.

Our AS patients' nephropathy took a different course after their pregnancy. In both women, close patient monitoring enabled a good fetal outcome, and the newborns were of adequate weight. The subsequent follow-up (22 months) showed a normal renal function in Case 1, with a low level of proteinuria, while there was a decline in renal function in Case 2, whose creatinine clearance rate was 42 ml/min with a proteinuria of 3.21 g/24 h. It is hard to say whether this was due to the patient's previous renal involvement or to her poor compliance.

Both of our patients have missense mutations. The mutation found in Case 2 (p.Gly1170Ser) had already been described by Inoue et al. (1999) and is considered 'moderate', leading to ESRD at over 30 years of age. The mutation found in our first case (p.Gly973Val) had not been described before. It could also be a 'moderate' mutation, given its position and type. A strong relationship was recently demonstrated between the position of a mutation and the age of onset of ESRD; more severe renal and extrarenal symptoms of AS being associated with mutations located at the 5′ end of the gene. Missense mutations result in less severe phenotypes than splice-site mutations, large deletions or nonsense and frameshift mutations (Bekheirnia et al. 2010).

Identifying AS gene mutations will improve our understanding of the evolution of the disease, based on genotype–phenotype correlations. Genetic analyses provide us with prognostic indicators regarding the disease evolution in the offspring of mothers with AS, who will probably have late-onset ESRD and no extrarenal manifestations.

In accordance with previous data, we recommend careful monitoring of urinary protein levels, renal function and blood pressure in pregnant women with AS. Close cooperation between the nephrologist, obstetrician and neonatologist is also important.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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