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Alport Syndrome: A Review

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Abstract

Alport syndrome is a rare genetic disorder of specialized basement membranes in the kidney, ear, and eye. People with Alport syndrome experience progressive loss of kidney function. Almost all affected individuals have blood in their urine, which indicates abnormal functioning of the kidneys. People with Alport syndrome frequently develop sensorineural hearing loss, which is caused by abnormalities of the inner ear, during late childhood or early adolescence. Affected individuals may also have misshapen lenses in the eyes and abnormal coloration of the light-sensitive tissue at the back of the eye.

Keywords: Alport syndrome, genetic disorder, childhood, eye.

Introduction

Alport syndrome is a rare genetic disorder of specialized basement membranes in the kidney, ear, and eye.

Alport syndrome is a genetic condition characterized by kidney disease, hearing loss, and eye abnormalities (Merchant *et al.*, 2004).

People with Alport syndrome experience progressive loss of kidney function. Almost all affected individuals have blood in their urine, which indicates abnormal functioning of the kidneys. Many people with Alport syndrome also develop high levels of protein in their urine. The kidneys become less able to function as this condition progresses, resulting in end-stage renal disease (ESRD) (Merchant *et al.*, 2004).

People with Alport syndrome frequently develop sensorineural hearing loss, which is caused by abnormalities of the inner ear, during late childhood or early adolescence. Affected individuals may also have misshapen lenses in the eyes (anterior lenticonus) and abnormal coloration of the light-sensitive tissue at the back of the eye (retina). These eye abnormalities seldom lead to vision loss.

Significant hearing loss, eye abnormalities, and progressive kidney disease are more common in males with Alport syndrome than in affected females. Alport syndrome occurs in approximately 1 in 50,000 newborns (Merchant *et al*., 2004).

Alport syndrome is genetically heterogeneous

Alport syndrome is genetically heterogeneous, arising from mutations that impair the production, deposition, or function of the collagen IV α345 network, the major collagenous constituent of mature basement membranes in the glomerulus, cochlea, cornea, lens, and retina. The X-linked form of Alport syndrome results from mutations in COL4A5, which encodes the collagen IV α5 chain. Autosomal forms of Alport syndrome are caused by mutations in COL4A3 and COL4A4, which are located on chromosome 2 and encode the collagen IV α3 and α4 chains, respectively. Mutations in both alleles of COL4A3 or COL4A4 are associated with autosomal recessive transmission, while heterozygous mutations cause autosomal dominant disease. Recently, several families transmitting mutations in two of the three genes have been described (Mencarelli *et al*., 2015). In these families with "digenic" inheritance, transmission may not conform to Mendelian expectations.

Results of pedigree analyses and Sanger sequencing suggested relative frequencies for the X-linked, autosomal recessive, and autosomal dominant forms of approximately 80%, 15%, and 5%, respectively. However, recent studies using next-generation sequencing indicate that autosomal dominant disease accounts for a significantly greater proportion of Alport syndrome patients than was previously recognized (Fallerini and Moriniere, 2014). This finding has important implications for genetic counseling and prediction of prognosis, since in autosomal dominant disease gender does not influence the risk of inheritance or the clinical phenotype. Furthermore, patients with autosomal dominant Alport syndrome generally have slower progression to end-stage renal disease (ESRD) than do patients with X-linked disease and are much less likely to have extra-renal manifestations.

Genotype-phenotype correlations in X-linked Alport syndrome were described over 15 years ago. The biochemical basis for these correlations has been elucidated recently and also helps explain the difference in phenotype between X-linked and autosomal dominant disease. Monoclonal antibodies directed against the collagen IV α3, α4, and α5 chains allow expression studies using kidney and skin biopsy specimens. COL4A5 mutations that allow expression of the collagen IV α345 network in glomerular basement membranes (GBMs), such as missense variants and small mutations that do not produce frameshifts, are associated with a slower rate of renal functional loss than are mutations that prevent expression of the network, such as major rearrangements and nonsense mutations. This finding predicts that heterozygous mutations in the COL4A3 or COL4A4 genes, which rarely prevent GBM expression of the collagen IV α345 network, would also be associated with slower progression of Alport renal disease (Fallerini and Moriniere, 2014).

The earliest clinical manifestation of the absence of the collagen IV α345 network from basement membranes is hematuria. Deficiency of this network is associated with GBM attenuation in both animals and humans with Alport syndrome and appears to regularly allow the passage of erythrocytes through microruptures of the glomerular capillary wall, a rare event under normal conditions (Liapis, 2002). The lens capsule of Alport patients, especially males, is also attenuated and lacks the mechanical integrity to maintain normal lens shape, resulting over the course of years in anterior lenticonus, or bulging of the central portion of the lens into the anterior chamber. Normal expression of the collagen IV α345 network in basement membranes of the cochleae is prevented in Alport syndrome, although the mechanism through which this abnormality leads to hearing loss in Alport patients remains uncertain. Findings in Alport mice suggest that the hearing loss may arise from dysfunction of the stria vascularis mediated through endothelin-1, but there are no corresponding human data. On the other hand, studies of human Alport cochleae suggest that the absence of the collagen IV α345 network may disturb cochlear micromechanics but there are no supportive animal data. The pathophysiology of deafness in Alport syndrome thus remains unsettled, at least in my opinion. Inclusion of audiologic outcomes in clinical trials may provide at least empirical information about mechanisms of hearing loss in Alport syndrome (Liapis, 2002).

In Alport GBM, the collagen IV α345 network is replaced by the collagen IV α112 network, which spreads from its normal sub endothelial location to occupy the entire width of the GBM. This change is accompanied by the ectopic appearance of laminin-2, collagen V, and collagen VI in the GBM. Invasion of mesangial filopodia may be responsible for deposition of these extracellular molecules in Alport GBM. The Alport GBM matrix is less highly cross-linked and more susceptible to proteolytic injury than is normal GBM, Altered signaling through collagen and laminin receptors results in complex cellular events, including

activation of focal adhesion kinase in podocytes, endothelin-A receptor activation in mesangial cells, and glomerular inflammation. Eventually, TGFβ1-mediated pathways promote glomerular and tubule-interstitial fibrosis, leading to ESRD. Albuminuria appears to be an important contributor to tubular epithelial cell injury and fibrosis (Mencarelli *et al*., 2015).

These recent findings in animal models of Alport syndrome suggest a number of potential targets for therapeutic intervention to delay renal disease progression. Attention has focused on early initiation of angiotensin blockade, which is remarkably effective in murine Alport syndrome and, according to retrospective analyses, can delay the onset of ESRD in human Alport syndrome. Starting angiotensin blockade while renal function is still normal appears to be associated with the greatest impact on timing of ESRD (Mencarelli *et al*., 2015).

History

It has been recognised for more than a century that renal disease can be inherited' and the family which Alport described in 1972 had already been reported several times during the previous 25 years. By 1927 three generations of this particular pedigree were affected, and Alport was the first author to comment that the occurrence of "nerve" deafness in most of the patients with haematuria probably represented a specific clinical syndrome, rather than being purely coincidental. He also noted that macroscopic haematuria was the commonest presenting symptom and that males were affected more severely than females. Subsequently many more families were described and the eponym was adopted in 1961. The term Alport's syndrome has been used extensively for patients with a variety of clinically heterogeneous hereditary nephritides, including some without deafness, and even benign familial haematuria. Only a few authors used strict diagnostic criteria to define a clinically homogeneous subgroup of families with "classical" Alport syndrome (Flinter and Rambausek, 1987).

Modes of inheritance of Alport syndrome

Once Alport syndrome has been diagnosed, it is important to distinguish between X-linked and autosomal recessive inheritance because of the different implications, including the risk of renal failure, for family members. X-linked Alport syndrome is five times more common than recessive disease. The mode of inheritance is sometimes suspected from the pedigree. With X-linked inheritance, disease appears to skip a generation, where there is an affected female with hematuria and no other features. With recessive inheritance, disease typically occurs in a single generation, males and females are affected equally often and equally severely, and the father of an affected individual may have hematuria. Recessive inheritance is also suspected where a young female has renal failure, hearing loss, and ocular abnormalities. Inheritance is usually confirmed with genetic testing. Sometimes the GBM collagen IV composition is used; however, this test is not widely available, and interpretation of the results may be difficult in females with X-linked disease (Pohl, 2013).

X-Linked Alport syndrome

Most patients with X-linked Alport syndrome have another family member with haematuria because only 15% mutations occur de novo and penetrance is 95%. Other X-linked causes of haematuria and renal failure are very uncommon. Males with X-linked Alport syndrome who develop end-stage renal failure before age 30 years usually have extrarenal manifestations, but those with late-onset renal failure may have only hearing loss. The high-tone sensorineural hearing loss occurs in 70% and lenticonus in up to 30% of affected males by the fourth decade, when renal failure, hearing loss, and retinopathy are already present. The central fleck (50%) and peripheral coalescing (60%) retinopathies are common. Females have variable clinical features depending on X chromosome inactivation in individual tissues, and their features are described separately. GBM lamellation is usually widespread in men. The GBM is initially thinned in boys, but there is focal lamellation that becomes more extensive with time. The GBM collagen IV composition is typically abnormal and lacks the a3a4a5 network. The epidermal membrane also has no a5 chain, and examination of a skin biopsy specimen is less invasive and the results may be available sooner than assessment of a renal biopsy sample. Genetic Testing Genetic testing is useful when Alport syndrome is suspected but cannot be confirmed with other techniques and when TBMN is suspected but X-linked Alport syndrome must be excluded. Most ethical concerns related to testing children for Alport syndrome are outweighed by the potential treatment to delay end-stage renal failure (Kashtan *et al.*, 2013).

The mutation detection rate in X-linked Alport syndrome is at least 90% with a combined approach of sequencing genomic DNA or hair-root or skin cDNA, followed by multiplex ligation-dependent probe amplification to detect large deletions, insertions, or duplications. Current techniques identify mainly coding region variants. Mutations are more likely to be identified in individuals with early-onset renal failure and extrarenal features, because the diagnosis of Alport syndrome is more likely to be accurate. Mutations are different in each family with X-linked Alport syndrome, and more than 700 variants have been described. Clinical features depend mainly on the mutation's location and genotype. About 50% result in a stop codon either directly or downstream, and 40% of mutations are missense. Large deletions and rearrangements, nonsense mutations, and carboxyl terminal missense mutations typically result in early-onset renal failure, hearing loss, and ocular abnormalities, whereas amino terminal missense mutations are often associated with late-onset renal failure without the extrarenal features. The likelihood of early-onset renal failure in affected males can also be predicted from the effect of the mutation in other affected male relatives. Genetic linkage studies are used rarely to exclude a mode of inheritance in families where no mutation has been demonstrated, and, sometimes, in prenatal or preimplantation genetic diagnosis where the mutation is not known. Individuals with suspected Alport syndrome but no COL4A5 mutation may have a deletion, splice site, or a deep intronic variant in COL4A5, autosomal recessive Alport syndrome, or, indeed, another inherited nephropathy (Kashtan, 2007).

Screening Members of a Family with X-Linked Alport Syndrome

All affected members of a family with X-linked Alport syndrome, including females, should be identified because of their own risk, and their offspring's risk, of renal failure. For any female with X-linked disease, each of her sons has a 50% risk of being affected and developing renal failure, and each of her daughters has a 50% risk of being affected. In contrast, a male with X-linked disease can be reassured that none of his sons will inherit the mutation, but all of his daughters, and half of her sons and daughters, will be affected. Thus, overall, the immediate risks are greater for the offspring of an affected female than for a male with X-linked disease. In any family with X-linked Alport syndrome, individuals with haematuria are highly likely to be affected, but other coincidental causes of haematuria must be excluded. When the mutation in any family is known, genetic testing can be used to confirm the affected status (Gomez, 2015).

X-linked Alport Syndrome in Females

Almost all (95%) females with X-linked Alport syndrome have hematuria, and many eventually develop other clinical features, especially proteinuria (75%), end-stage renal failure (8%–30%, overall 15%, by the age of 60), hearing loss (40%), or peripheral retinopathy (40%). Lenticonus may not occur, and central retinopathy is rare. It is therefore debatable whether females should be considered affected or carriers. Those who prefer the term "affected" maintain that it conveys the risks for any female and the need for ongoing monitoring and treatment. Most (85%) mothers of affected boys also have the mutation, but many are asymptomatic, and 80% are diagnosed only after their son or another male relative has presented. The GBM in affected females is typically thinned with focal areas of lamellation that become more extensive with time. The collagen IV a3a4a5 network is patchily present depending on X chromosome inactivation. Renin-angiotensin system antagonists are nephron protective in females with X-linked Alport syndrome and should be used to treat those with hypertension, proteinuria, and other risk factors for renal failure progression. Again preliminary support, but no evidence, suggests a beneficial effect for the initiation of ACE inhibitor treatment even before the onset of proteinuria. Poor prognostic markers in females include episodes of macroscopic hematuria in childhood and proteinuria. A renal biopsy is warranted if there is significant proteinuria (for example, .1 g/d in adults) or renal impairment. However, changes in the renal biopsy specimen and GBM may be patchy, sampling variation is common, and interpretation may be difficult. Sometimes females with X-linked Alport syndrome themselves require a transplant for renal failure, but they do not subsequently develop anti-GBM disease. A female family member commonly considers donating one of her kidneys to an affected son or brother. The low de novo mutation rate means that most mothers (85%) of affected males also have the mutation. A sister's risk of having the mutation is 50% if her mother is a carrier. Carrier family members who proceed with donation have an increased risk of renal failure in later life, although the extent of this increase is not known. Affected donors also have an increased risk of hypertension and microalbuminuria/ proteinuria compared with other donors (Massella, 2013). A

kidney biopsy is mandatory in a mutation-carrying potential donor, even in those with normal renal function and normal levels of proteinuria, to assess renal damage resulting from the effects of random X inactivation. Female carriers should only be kidney donors of last resort. Conversely, 15% of the mothers of affected boys are not carriers and may donate a kidney to their son without an increased risk of renal failure. They should still undergo renal biopsy to assess damage and, preferably, genetic testing to formally exclude the diagnosis of X-linked Alport syndrome. The risk of preeclampsia is increased in affected females with hypertension, proteinuria, or renal impairment, and pregnancy may accelerate any decline in renal function already present. Preexisting hypertension and renal impairment predict an increased risk of obstetric complications, and proteinuria, hypertension, and renal impairment are all associated with preterm delivery (Delimont *et al*., 2014).

Autosomal recessive Alport syndrome

Clinical features in autosomal recessive Alport syndrome are the same as for males with X-linked Alport syndrome. Autosomal recessive inheritance is suspected where disease is sporadic and occurs in a single generation or a consanguineous family, where males and females in a family are affected with equal frequency and severity, where the father also has hematuria, or where a female has renal failure, hearing loss, or ocular abnormalities. Autosomal recessive inheritance is confirmed when there are two COL4A3 or two COL4A4 pathogenic mutations or the GBM lacks the collagen IV a3, a4, and a5 chains but the a5 chain persists in the Bowman capsule and the distal tubular and the epidermal membrane. Genetic Testing Genetic testing is useful to confirm the diagnosis of autosomal recessive Alport syndrome when it is suspected on the basis of clinical features, family history, or renal immunohistochemistry. Fewer mutations have been described for recessive than for X-linked disease, and too few are known for genotype-phenotype correlations. Usually both the COL4A3 and the COL4A4 genes are examined. Two mutations will be present in one of these genes, and, where possible, the laboratory should confirm that they affect different chromosomes by testing both parents of the affected individual. Sometimes only one mutation is identified and the other is presumed present but undetectable, consistent with autosomal recessive, rather than the very rare autosomal dominant, inheritance. Genetic Counseling Individuals with autosomal recessive Alport syndrome are typically from a single generation within a family, but the situation is more complicated where the family includes multiple examples of consanguinity. The risk of the sibling of an individual with autosomal recessive Alport syndrome also being affected is, on average, one in four. In general, each parent of an individual with autosomal recessive Alport syndrome is an obligate carrier and will be heterozygous for one of the causative mutations. Likewise, each offspring of an individual with autosomal recessive disease will also inherit one of the causative mutations. The parents and offspring have the same phenotype as TBMN with a low risk of renal failure (Pergola *et al*., 2011).

Monitoring and Treatment

Evidence from a small retrospective registry analysis suggests that renin-angiotensin system blockade, for example with ACE inhibitors, delays renal failure and improves life expectancy in individuals with autosomal recessive Alport syndrome and may improve the outlook in carriers (Heidt *et al*., 2001).

TBMN

TBMN affects 1% of the population and is characterized by haematuria, proteinuria (#200 mg/L), normal BP, normal renal function, and a thinned GBM (Savige, 2003). TBMN usually represents the carrier state for autosomal recessive Alport syndrome, and inheritance is autosomal dominant. Typically the prognosis is good, but there is also an increased risk of hypertension, proteinuria, and renal impairment. The risk of renal failure is increased if there is coincidental renal disease or diabetes. It remains important to exclude X-linked Alport syndrome in these patients (Savige, 2003).

Diagnosis

TBMN is suspected clinically and a renal biopsy is required only where features are atypical. The most commonly used method for the diagnosis of TBMN is the demonstration of a thinned GBM with a width, less than 250 nm or a measurement specific to a laboratory and adjusted for age and sex (Haas, 2009). This thinning involves at least 50% of the GBM, without the lamellation found in Alport syndrome. However, the Alport lamellation may be patchy, Anson,1990). Heterozygous COL4A3 and COL4A4 mutations also cause autosomal dominant Alport syndrome (Jefferson, 1997). The diagnosis of autosomal

dominant Alport syndrome is reserved for individuals with a lamellated GBM and autosomal dominant inheritance. Some reports of autosomal dominant Alport syndrome are likely to represent TBMN with a coincidental renal disease, such as IgA GN. Errors in which the diagnosis is actually TBMN mean that family members will be misinformed about their likelihood of renal failure (Jais *et al*., 2000).

Genetic Testing

TBMN is caused by a heterozygous mutation in the COL4A3 or COL4A4 gene. Mutations are typically different in each family, and testing both the COL4A3 and the COL4A4 genes is usually required. This is labor-intensive and expensive, and it is usually more important in an individual with hematuria only to exclude a COL4A5 mutation and hence X-linked Alport syndrome, rather than to make a positive molecular diagnosis of TBMN (Savige, 2003).

Monitoring and Treatment

The prognosis of TBMN is usually good (Savige, 2003). However, some individuals develop hypertension, proteinuria, or renal impairment, which are all risk factors for progression to end-stage renal failure. Again, there is preliminary support from a single retrospective study in humans, a murine model of TBMN, and experience in other forms of diabetic and nondiabetic renal disease that renin angiotensin blockade delays progression to end-stage renal failure in at-risk individual (Savige, 2003).

Genetic Counseling

TBMN is inherited, but the penetrance of hematuria is only 70%. The de novo mutation rate is low, and almost all affected individuals have another family member with the causative mutation, but not necessarily haematuria. On average, half the children of an individual with TBMN inherit the causative mutation but, because hematuria is incompletely penetrant, fewer have haematuria. The offspring of two parents with TBMN have a 25% risk of autosomal recessive Alport syndrome if both parents have a mutation in the same COL4A3 or COL4A4 gene (Savige, 2003).

Pregnancy

Risks are not usually increased during pregnancy in women with TBMN if hypertension, proteinuria, and renal impairment are not present. Preeclampsia is not more common.

Classification of genetic disorders of the collagen IV α345 Network

Compared to patients with hemizygous mutations in COL4A5 (males with X-linked Alport syndrome) and patients with mutations in both alleles of COL4A3 or COL4A4 (autosomal recessive Alport syndrome), patients with heterozygous mutations in these genes tend to have milder renal involvement, with ESRD occurring relatively late in life (or not at all), and are less likely to have extrarenal manifestations such as hearing loss and ocular changes. Nevertheless, heterozygous patients have a higher lifetime risk of ESRD than does the general population and appear to benefit from angiotensin blockade, raising the question of how best to ensure that these patients receive appropriate monitoring and intervention. Although this is a complex issue, it can for the sake of discussion be reduced to two questions:

(1) is there a true carrier state for Alport syndrome, and
(2) is thin basement membrane nephropathy (TBMN) an accurate and useful diagnostic entity?

For many years, female members of Alport families who had hematuria were considered to be carriers who were not at risk for ESRD, despite reports of ESRD in female Alport patients. Thinking began to change in the early 2000s with a report by Jais and colleagues describing clinical outcomes in nearly 300 girls and women with confirmed heterozygous COL4A5 mutations40. In their cohort, the probability of developing ESRD before the age of 40 years was 12% and reached 30% by age 60. Proteinuria developed in 75% of subjects and increased the risk of developing ESRD. An additional finding was that 95% of heterozygous females had haematuria. While ascertainment bias could have inflated some of these percentages, there is no question that girls and women who have heterozygous mutations in COL4A5 have a substantial lifetime risk of ESRD (Jais *et al*., 2003).

If one uses the conventional definition of “carrier” (“an individual that carries, but does not express, a gene for a particular recessive trait”, from Stedman’s Medical Dictionary, Houghton Mifflin Company, 2001), then only about 5% of women with heterozygous mutations in COL4A5 are truly carriers and 95% are affected with X-linked Alport syndrome.

The designation of a woman with a COL4A5 mutation as a carrier creates an expectation of a benign outcome and a potential impediment to regular monitoring and early therapeutic intervention. The authors of an excellent recent review of Alport syndrome in women and girls made note of differences of opinion regarding the use of "carrier" or "affected" for X-linked Alport syndrome heterozygotes and then chose to use the term "affected" to describe these female (Kashtan, 2005)

A similar issue arises for people with heterozygous mutations of COL4A3 or COL4A4. Approximately 40–50% of these individuals are asymptomatic with normal urinalyses and are accurately designated as carriers of autosomal recessive Alport syndrome. Clinical outcomes among heterozygous individuals with haematuria are variable, ranging from normal renal function throughout life to chronic kidney disease to ESRD (Longo, 2002). As with COL4A5 heterozygotes, proteinuria appears to be a risk factor for chronic kidney disease and ESRD (Voskarides, 2007). How should we classify these individuals so as to promote regular monitoring and early therapeutic intervention? My proposal is that we describe them as having autosomal Alport syndrome. This would require the education of patients, physicians, and payers and recognition that progression to ESRD in Alport syndrome is not inevitable (Kashtan, 2005).

This leads us to the topic of so-called TBMN. Patients with hematuria may be classified as having TBMN if thinning of the GBM is the predominant pathological finding on renal biopsy. Although many patients with hematuria and thin GBM follow a benign course, others exhibit progressive renal disease (Tiebosch, 1989). GBM thinning may be found in young males with X-linked Alport syndrome, females of any age with X-linked Alport syndrome, males and females with autosomal recessive Alport syndrome, and males and females with heterozygous mutations in COL4A3 and COL4A4 (Heidt, 2009). GBM thinning may also be found in patients with haematuria who have no detectable pathological alterations in COL4A3, COL4A4, or COL4A5 (Gale, 2016). Other genetic loci for haematuria associated with GBM thinning have yet to be identified, although a recent report described a COL4A1 frameshift mutation in a family with autosomal dominant haematuria, GBM thinning, kidney cysts, and progressive kidney disease (Gale, 2016). Thus, TBMN is a pathological description that does not, in and of itself, allow accurate prediction of prognosis or inheritance in an individual patient. Assigning this diagnosis may lead to deficient follow-up and inaccurate genetic counseling. For these reasons, I think that TBMN has become an obsolete diagnosis. My proposal is that patients with haematuria, thin GBM, and a mutation in COL4A3, COL4A4, or COL4A5 have a form of Alport syndrome and that patients without such mutations have "haematuria with thin GBM". Patients given a diagnosis of "haematuria with thin GBM" would need regular (e.g. annual) monitoring of blood pressure and urine protein excretion to identify those who may benefit from treatment (Kashtan *et al.*, 2013).

Evolving changes in diagnostic evaluation

Sanger sequencing of the COL4A3, COL4A4, and COL4A5 genes progressed from a research procedure with indefinite turn-around times in the 1990s to commercial testing with predictable results reporting in the 2000s. More recently, next-generation sequencing of these genes has been adopted by commercial and hospital-based laboratories, accelerating mutation identification while lowering the cost of sequencing (Fallenrini and Mariniere, 2014). These innovations are modifying the diagnostic evaluation of patients and families with suspected Alport syndrome (Flinter *et al.*, 1998). Prior to the advent of easily available sequencing, the diagnosis of Alport syndrome relied on clinical diagnostic criteria supplemented with pedigree data and tissue studies (Flinter and Mazzucco, 1998). Clinical criteria include haematuria, hearing loss, and ocular changes. Pedigree data consist of family history of haematuria, deafness, and ESRD. Tissue studies include electron microscopy of kidney biopsy specimens supplemented by immuno histochemical assessment of the expression of collagen IV α chains in the kidney (or in skin biopsy material). Informed application of these tools provided reliable but not perfectly accurate diagnosis of X-linked and autosomal recessive Alport syndrome. Where sequencing is readily available, clinical and pedigree data can be used to select patients and families for genetic testing, potentially obviating the need for diagnostic tissue studies. Next-generation sequencing of COL4A3, COL4A4, and COL4A5 before tissue biopsy would be reasonable when suspicion of Alport syndrome is high, e.g. when the patient is a male with haematuria who has an extensive family history of haematuria, deafness, and ESRD. However, nephrologists, especially those caring for children, are often confronted with patients who have haematuria but no extra-renal abnormalities or positive family history. In this patient group, a diagnosis such as IgA nephropathy, which can be made only by

kidney biopsy, is at least as likely as Alport syndrome, if not more so. Collagen IV gene sequencing in this setting may unnecessarily delay diagnosis and appropriate intervention while adding unneeded expense. If renal biopsy is suggestive or diagnostic of Alport syndrome, gene sequencing can then be used to confirm the diagnosis, establish inheritance, and predict prognosis based on genotype. I would argue that this approach is reasonable under present circumstances of access to sensitive genetic testing in the United States. The use of next-generation sequencing or whole exome sequencing in the initial evaluation of mono symptomatic and oligo symptomatic glomerular hematuria, prior to tissue biopsy, may become more widespread as access to these methods spreads and costs decrease, as is already occurring in the United Kingdom and Europe. Identification of sensitive and specific biomarkers for Alport syndrome could contribute to targeted application of genetic analysis (Muckova, 2015).

Novel treatment approaches

The current standard of care for patients with Alport syndrome is angiotensin blockade in those with overt proteinuria (Kashtan and Savige, 2013). Treatment at an earlier stage (microalbuminuria) should be considered in males with X-linked Alport syndrome who have a COL4A5 genotype associated with early progression to ESRD or family history of ESRD before age 30, and in males and females with autosomal recessive Alport syndrome (Kashtan, 2013). Data showing that initiation of angiotensin blockade while renal function is still normal delays the onset of ESRD have not been broken down by genotype, so we do not yet know if certain genotypes are associated with better response to treatment (Kashtan, 2013).

It is possible that early angiotensin blockade could be sufficient to prevent ESRD in Alport males with missense mutations in COL4A5 and in people with heterozygous mutations in COL4A3, COL4A4, and COL4A5. In many patients, angiotensin blockade is likely to provide only an incremental benefit, and additional interventions will be required to attain the goal of preventing ESRD. Studies in transgenic Alport mice have demonstrated beneficial effects of a variety of therapeutic interventions, although none have been as effective in prolonging survival as angiotensin-converting enzyme inhibition. Interventions can be generally grouped as attempts to reverse the genetic defect, normalize altered glomerular cell signaling and behavior (Dufek, 2016; Ninichuk, 2005). or impede TGFβ1- mediated fibrosis (Sayers, 1999).

Pharmaceutical companies have become interested in Alport syndrome in the past several years, a long-awaited and very welcome development. A phase II study of anti-microRNA-21 treatment of Alport syndrome will begin enrolling patients 18 years of age or older with glomerular filtration rates (GFRs) of 45–90 ml/ min/1.73 m2, with a primary outcome of change in the rate of decline in GFR (ClinicalTrials.gov Identifier NCT02855268). In transgenic Alport mice, anti-microRNA-21 treatment reduced glomerular inflammation and impaired renal fibrotic pathways (Gomez, 2015). A phase II/III study of bardoxolone (Pergola, 2011). therapy for Alport syndrome patients with chronic kidney disease has been announced but was not listed on Clinical Trials at the time this review was submitted (Pergola, 2011).

Among the most attractive features of angiotensin blockade therapy for Alport syndrome are the safety and accessibility of these agents (Wuhl, 2004). They are inexpensive, widely available, and *effective* through oral administration, so barriers to treatment should in theory be minimal. While I am an enthusiastic supporter of the development of novel treatments for Alport syndrome (just see my Competing Interests), I am concerned that pricing issues may limit the availability of the next generation of Alport syndrome treatments. Pharmaceutical companies must recoup development costs, investors deserve returns on their investments, and financial profit is expected. At the same time, the primary goal of innovative therapy should be to achieve the maximal benefit for patients, and realizing this goal may be impeded if access is limited by costs (Dufek *et al.*, 2016).

Causes of Alport syndrome

Alport syndrome is caused by mutations in the COL4A3, COL4A4, and COL4A5 genes. These genes are responsible for the formation of a part of type IV collagen. Collagen is the major protein in your body that's responsible for giving strength and support to your connective tissues.

This type IV collagen is really crucial to the work of your glomeruli, and the mutations in these genes make it so that the collagen found in the glomeruli is abnormal. This, in turn, damages your kidneys and makes them unable to clean out your blood properly.

This collagen is found in your inner ears, and abnormalities in it can lead to sensorineural hearing

loss. Type IV collagen is also important in keeping the shape of your eye lens and the normal color of your retina, and it's the abnormalities with it that cause the eye complications associated with Alport syndrome.

Males only have one X chromosome, one mutation of the gene on that chromosome is enough to cause kidney disease and other severe symptoms of the condition in them (Gross *et al.*, 2012).

Females, on the other hand, have two X chromosomes and, accordingly, two copies of the gene, so the mutation of the gene in just one of the chromosomes is usually unable to cause the serious complications of Alport syndrome. Because of this, females that have X-linked Alport syndrome usually only experience blood in their urine and they are sometimes referred to as just carriers. It is uncommon for them to develop the other serious complications of the disease, and even when they do it is milder than in their male counterparts.

With X-linked pattern of inheritance, fathers cannot pass the condition to their sons because biologically, men don't pass down their X chromosomes to their male children. On the other hand, every child has a 50 percent chance of inheriting the gene if the mother has the defective gene on one of her X chromosomes. Boys who inherit the defective gene will typically develop Alport Syndrome during his lifetime (Gale *et al*., 2016).

Autosomal Dominant Pattern

This is a rare form of inheritance, and it's found in only about 5 percent of cases of Alport syndrome. People with this form have one mutation in either the COL4A3 or COL4A4 genes, meaning only one parent has the abnormal gene and passed it on. With this form of Alport syndrome, males and females experience similar symptoms at similar levels of severity.

Autosomal Recessive Pattern

This form of inheritance is found in about 15 percent of cases of Alport syndrome. A child inherits this way when both parents are carriers and each have a copy of the abnormal COL4A3 or COL4A4 gene. With this, too, males and females are affected similarly (Gale *et al*., 2016).

Symptoms of alport syndrome

The major symptoms of Alport syndrome are also its major complications, which are kidney disease, eye abnormalities, and hearing loss/problems. These symptoms also tend to manifest early in life, prior to an official diagnosis of Alport syndrome. The symptoms include:

- Blood in urine (haematuria). This is the first symptom a person with Alport syndrome will have.
- Protein in urine (proteinuria)
- High blood pressure
- Swelling in the feet, ankles and eye area. Swelling is also called edema.
- Smooth muscle tumors (leiomyomatosis)
- Occasional aneurysms (Bekheirnia, 2010).

Diagnosis of Alport syndrome

Your doctor may first suspect that you have Alport syndrome based on your family history. The symptoms you report will also indicate the likelihood of you having this disease. To confirm, your doctor may use these two types of diagnostic tests which are:

A. **Kidney or skin biopsy:** In this test, a very tiny piece of the patient's kidney or skin will be removed and examined with a microscope. A Careful microscopic evaluation of the specimen can show the characteristic findings of Alport's syndrome

B. **Genetic test:** This test is used to confirm whether the patient has the gene that could lead to Alport syndrome. It's also used to determine the particular way one can inherit the gene.

An early diagnosis of Alport syndrome is very imperative. This is because the complications of Alport syndrome usually manifest in childhood/early adulthood and without beginning treatment on time, the kidney disease may become fatal in early adulthood (Hashimura, 2014).

Other types of testing may be important to rule out other diseases on the differential diagnosis list, assess the status of the patient, or develop an initial suspicion of Alport's syndrome. However, these are not diagnostic tests. These include:

Urinalysis: A urinalysis test will be used to check the contents of the patient's urine for the presence of blood or protein.

eGFR test: This is kidney function testing, and it estimates the rate at which the patient's glomeruli are filtering waste. This rate is a strong marker of whether or not the patient has kidney disease. Blood tests such as a blood urea nitrogen (BUN) test and one's creatinine levels help determine the state of one's kidneys.

Hearing test: This test will be used to determine if the patient's hearing has been affected in any way (Meehan, 2016).

Treatment of alport syndrome

There isn't one single treatment for Alport syndrome, because each of the symptoms and complications are treated individually.

Kidney Disease

Managing and slowing down the progression of kidney disease is the first and primary consideration in treating Alport syndrome. In order to do this, a doctor may prescribe:

- Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers to lower the patient's blood pressure, and potentially reduce protein in the patient's urine and slow down the progression of the patient's kidney disease.
- A limited salt intake diet
- Water pills, also known as diuretics.
- A low-protein diet

A doctor will likely recommend that the patient see a dietitian to help him stick to his new limitations while still maintaining a healthy diet.A lot of times, though, the kidney disease will progress to end-stage renal disease, for which one will either have to go on dialysis or alternatively receive a kidney transplant. Dialysis is an artificial process of removing and filtering waste from the body using a machine. The dialysis machine basically functions as a substitute for the kidneys.

Kidney transplant involves surgically replacing the defective kidney with a healthy one from a donor. One doesn't necessarily have to be on dialysis before one can get a kidney transplant and, ultimately, one's doctor will help to decide which option will be better for the patient (Gratton, 2005).

High Blood Pressure

The doctor will prescribe the appropriate pills/medication to help keep the patient's blood pressure under control. Some of these medications are ACE inhibitors, beta blockers, and calcium channel blockers. These help to reduce the patient's chances of developing heart disease and also slow down the progression of the patient's kidney disease.

Eye Problems

The doctor will refer the patient to an ophthalmologist to help solve vision problems, if any, caused by the abnormality in the shape of the patient's lens. This can take the form of changing the prescription of the patient's glasses or the patient undergoing cataract surgery. The white flecks in the eyes do not affect vision in any way, so usually, there's no attention paid to treating it (Gratton, 2005).

Hearing Loss

If one develops hearing loss due to one's Alport syndrome, chances are it'll be permanent. Fortunately, one can get hearing aids that are very effective in helping with this.

In general, the patient may also benefit from lifestyle changes like keeping active, ating well, and maintaining a healthy weight (Sugimoto, 2006).

Conclusion

In conclusion, there are still unresolved issues in the diagnosis and management of patients with Alport syndrome. In the meantime, diagnostic laboratories must improve their methods to ensure detection of both mutations in autosomal recessive disease. Otherwise, TBMN or autosomal dominant Alport syndrome is diagnosed, conditions in which the clinical implications are very different.

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