CLINICAL VIGNETTE

Delayed Presentation of Alport Syndrome

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A 43-year-old male presented for a general checkup. He denied any new symptoms but noted that he had hearing loss in both ears and started using hearing aids in his early 30s. He had worked on a farm with loud equipment and had assumed the noise exposure was the cause of his early hearing loss. He was also diagnosed with microscopic hematuria and mild factor XI and XII deficiencies during childhood. However, he denied a history of easy bleeding or bruising. During a prior surgery on his right leg, he did not have excess bleeding.

His family history revealed that his older brother had hematuria during childhood. His brother was going to have a renal biopsy, but on preoperative evaluation, he was found to have a prolonged PTT. He had further workup, which revealed a factor XI and XII deficiency. Our patient was tested after this finding and was also found to have mild factor XI and XII deficiency. Because of the factor deficiencies, his brother's physician decided not to proceed with a renal biopsy. Our patient's brother also developed early hearing loss by his 30s. His father never developed hearing loss, and his mother did not start losing her hearing until she was in her 70s. Our patient's 3-year-old daughter was recently found to have microscopic hematuria.

On physical exam, he was well-nourished and in no apparent distress. Vital signs were within normal limits. His pupils were equal, round, and reactive to light and accommodation. His extraocular movements were intact. On ENT exam, his tympanic membranes and external ear canals were normal in appearance. He was wearing bilateral hearing aids. On cardiac exam, he had a regular rate and rhythm without murmurs or gallops. His lungs were clear to auscultation bilaterally and no wheezing, rales, or rhonchi were appreciated on exam. His abdomen was soft and nontender without hepatosplenomegaly. He did not have costovertebral angle tenderness. No bruising, purpura, or petechiae were noted. He had no palpable cervical, supraclavicular, axillary, or inguinal lymphadenopathy on exam.

Labs and Studies

His labs showed a normal white blood cell count, hemoglobin, hematocrit, platelet count, PT, PTT, INR, and liver function tests. His creatinine was in a normal range at 0.9mg/dL with a GFR>89. His total CO2 was elevated at 33mmol/L, but his sodium was normal at 137mmol/L with a normal potassium at 4.4mmol/L and normal chloride at 99mmol/L. He had microscopic blood in the urine with 14 red blood cells/uL (normal range 0-11 cells/uL). His nephrologist examined the urine sediment, which revealed a few dysmorphic red blood cells. His albumin/creatinine ratio was high at 1484.7mcg/mg (normal range <30mcg/mg). His factor XI activity was low at 45% (normal range is >50% activity). His factor XII activity was low at 30% (normal range is >50%). His factor VIII and IX activity were in a normal range. A doppler ultrasound of both kidneys showed mild increased echogenicity in the parenchyma but normal perfusion. The right kidney measured 11.2cm in length and the left kidney was 12.1cm in length. No mass, stone, or hydronephrosis was noted.

Since his factor XI and XII levels were only mildly low, his hematologist felt that it would be safe to proceed with a renal biopsy. The renal biopsy confirmed Alport syndrome with thickening and lamellation of the glomerular basement membrane on electron microscopy. The biopsy also showed focal segmental glomerulosclerosis as well as mild interstitial fibrosis with tubular atrophy.

Initial Treatment Course

The patient was placed on losartan to help with the proteinuria. He was instructed to avoid nephrotoxic medications. He was referred to a geneticist, ENT specialist, and ophthalmologist. However, he had not completed these evaluations yet at the time this article was written.

Discussion

Alport syndrome (AS) is a progressive hereditary nephritis caused by mutations in type IV collagen that alter basement membranes.[1] Mutations in the alpha-3, alpha-4, or alpha-5 chains of type IV collagen primarily affect the kidneys, eyes, and cochlea.[2] Common manifestations of the disease include hematuria, proteinuria, renal failure, sensorineural hearing loss, hypertension, myopia, pigmentary changes around the fovea, and anterior lenticonus.[1] Anterior lenticonus, which is pathognomonic for AS, occurs when the lens protrudes into the anterior chamber.[1] Our patient was already exhibiting signs of sensorineural hearing loss, hematuria, and proteinuria at the time of his initial presentation.

AS has three modes of inheritance including X-linked, autosomal recessive, and autosomal dominant.[1] The mode of inheritance plays a role in disease severity. The most common mode of inheritance is X-linked inheritance due to mutations in the alpha-5 chain of type IV collagen (COL4A5).[2] X-linked inheritance leads to 85% of cases of AS.[3] Females with X-linked AS are less likely to develop proteinuria, renal failure,

and hypertension than affected males with the X-linked form of the disease.[1] They have a longer life span than men with X-linked AS.[1] On the other hand, the autosomal recessive form of the disease does not show significant gender differences in terms of the progression of symptoms.[1] Both males and females with the autosomal recessive form of AS often progress to end stage renal disease in their 20s-30s.[1]

The diagnosis of AS can be confirmed by renal biopsy, skin biopsy, or genetic testing. Genetic testing can be done to assess for a pathogenic mutation in the COL4A5 gene or two mutations in the COL4A3 or COL4A4 genes.[2] Genetic testing is 90% sensitive for X-linked disease.[2] Our patient has not pursued genetic testing, but his renal biopsy did show characteristic changes to the glomerular basement membrane (GBM). Electron microscopy of the biopsy specimen in an individual with AS shows thickening and splitting (lamellation) of the GBM and can show a "basket-weave" appearance.[3] Obtaining a skin biopsy is also an alternative option. The diagnosis of AS can be made if the alpha-5 chain of type IV collagen is absent on staining of the epidermal basement membrane.[4] However, skin biopsy using immunohistochemical analysis varies in its sensitivity for diagnosis with studies ranging from 50-85%.[4] So a negative skin biopsy should not rule out the diagnosis.[4]

It is also important to monitor patients with AS for the development of a number of medical conditions that they are at higher risk for developing than the general population. X-linked AS can be associated with the development of leiomyomas of the esophagus, airways, and female reproductive tract.[5] These benign smooth muscle tumors can present with symptoms such as cough, dysphagia, vomiting, and retrosternal pain.[5] AS also leads to chronic kidney disease, which increases the risk of cardiovascular events.[6] There are also cases of aortic abnormalities including aortic aneurysms and dissections with earlier onset than the general population.[7]

Though overall there has been progress in managing the complications of AS, we still have a long way to go before individuals with this disease have a normal life expectancy. Renin-angiotensin-aldosterone system (RAAS) blockade does not stop the thickening and the splitting of the glomerular basement membrane that is seen with AS, but it can slow down the progression of tubulointerstitial fibrosis.[8] Angiotensin-converting enzyme (ACE) inhibitors delay renal failure and improve life expectancy for individuals with AS.[6] Unfortunately, the majority of males with AS develop ESRD before age forty.[3] Early initiation of ACE inhibitors, even prior to the onset of proteinuria, has been shown to delay the need for dialysis.[6] In regards to ocular complications such as anterior lenticonus, improvement has been seen with clear lens phacoemulsification and foldable intraocular lens implantation.[9] Sensorineural hearing loss is generally adequately managed with hearing aids.[1]

The diagnosis of AS is not only a challenge for the patient, but it also poses hurdles for their offspring. Unfortunately, our patient has already seen some manifestations in his 3-year-old daughter who has developed microscopic hematuria. For a male with X-linked disease, none of his sons will inherit the genetic mutation, but all of his daughters will inherit the mutation.[2] For a female with X-linked disease, her male and female offspring have a 50% chance of developing Alport syndrome.[2] So his daughter has a high chance of passing on to her offspring the genetic mutations that lead to AS. We hope that further research will provide more treatment options, and a longer life expectancy for the families afflicted with this debilitating genetic condition.

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