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EDITORIAL

Pediatric Alport Syndrome: From Diagnosis to Transitioning Care

Síndrome de Alport na Idade Pediátrica: do diagnóstico até aos cuidados de transição da idade adulta

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Persistent isolated microscopic hematuria is a relatively common occurrence in pediatric practice. It can be caused by multiple disorders including urologic abnormalities, kidney stones, hematologic issues, and glomerular diseases, among others.[1] The cornerstone is to identify cases of hematuria associated with progressive renal disease.[1] Glomerular hematuria occurs when Glomerular Filtration Barrier (GFB) is compromised allowing the leakage of erythrocytes and albumin into the urinary space.[2] A crucial component of GFB is the Glomerular Basement Membrane (GBM), primarily composed of collagen type IV. The collagen type IV is essential for normal function of GBM and its structure is a heterodimer COL4A3A4A5. Any alterations in collagen type IV constituents disrupt the GMB structure, leading to the excretion of erythrocytes and albumin into the urine, ultimately resulting in kidney damage and loss of renal function.[3]

Disorders caused by genetic variants on COL4A3, COL4A4 and COL4A5 genes are classified as Alport syndrome (AS). Data from the Genomics England 100,000 Genomes Project indicate that pathogenic COL4A5 variants occur in approximately 1 in 2320 individuals, while heterozygous COL4A3 or COL4A4 variants affect 1 in 106 individuals and compound heterozygous COL4A3 or COL4A4 variants affect approximately 1 in 88,866 individuals.[4] These data underscore the prevalence of AS as the most common hereditary renal disease.

The spectrum of the kidney damage is broad, ranging from microscopic hematuria, followed by albuminuria, severe proteinuria, and progressive decline in glomerular filtration rate (GFR) to end-stage renal disease (ESRD).[5,6] The loss of GFR can vary from very rapid - requiring kidney replacement therapy in adolescence/early adulthood, to very slow - advanced age patients with normal kidney function.[5] As collagen type IV also exists in the eyes (lens and retinal pigment epithelium) and ears (cochlea), extra-renal manifestations, such as sensorineural deafness and ocular anomalies (perimacular and peripheral coalescing flecks, temporal retinal thinning and lenticonus) can also be detected.[7]

Recently, genetic studies (panel genes and exome studies) conducted in large cohorts of kidney patients, identified Alport syndrome as an important cause of renal failure in patients previously diagnosed with focal segmental glomerulosclerosis (FSGS), IgA familial nephropathy, steroid-resistant nephrotic syndrome (CRNS) and chronic kidney disease (CKD) of unknown cause (uCKD).[8-13]

In AS, genetic inheritance pattern depends in which gene the variant is located and includes X-linked, autosomal recessive (ARAS), autosomal dominant (ADAS) and digenic.[6] The COL4A5 gene is located at chromosome X. Mutations on this gene severely affect male patients, who present with the classic phenotype of AS characterized by the presence of kidney failure, sensorial deafness, and specific ocular lesions at young age. Female patients can also be affected although typically exhibit milder clinical features.[6]

The COL4A3 and COL4A4 genes are located on chromosome 2.[6] ARAS occurs when both alleles of the gene present a genetic variant.

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Usually, these patients have the classical AS phenotype. This pattern of inheritance is suggested when male and female patients are equally affected, when parental consanguinity exists or when the father or both parents of a male patient have microscopic hematuria.[6] ADAS occurs when one allele of COL4A3 or COL4A4 has a genetic variant. Clinical findings can range from no symptoms, isolated hematuria (sometimes intermittent), progressive proteinuria and renal disease to ESRD.[5] Other organs involvement is infrequent. Within the same family, clinical manifestations can be different due to incomplete penetrance and associated risk factors such as smoking, high blood pressure and levels of salt and animal protein intake.[6] ADAS patients progress more slowly to ESRD than XLAS males and ARAS.[14]

Digenic AS occurs when there are inherited pathogenic variants in COL4A5 plus COL4A3 or COL4A4 or in COL4A3 plus COL4A4.[15-17] For digenic variants affecting COL4A5 plus COL4A3 or COL4A4, clinical features depend on sex and the severity of both variants.[18]

In renal biopsy, there are no specific light microscopic findings in AS, and a variety of combined features can be found such as mild glomerular changes, mesangial proliferation and expansion, and interstitial foam cells when long-standing proteinuria occurs, as well as FSGS, tubular atrophy, and interstitial fibrosis. Electronic microscopic (EM) findings can range from thin basement membrane and GBM thickening to lamellation and splitting in lamina densa of GBM.[6,19] Importantly, pathological findings can only be apparent with renal disease progression, even in male XLAS and ARAS patients. In female XLAS and ADAS patients, typical electronic microscopic lesions can be present only at later stages and often only GBM thinning can be found.[7]

Currently, with the recognition of different inheritance patterns and the broad spectrum of renal and extra-renal manifestations, genetic testing has been recommended to confirm the diagnosis of Alport Syndrome. Additionally, genetic testing is more sensitive and specific when compared to kidney biopsy findings and is currently considered as the gold standard to establish the diagnosis.[3] When genetic test allows for the diagnosis of AS, renal biopsy is no longer necessary.

AS patients are at increased risk of development of progressive kidney disease, albeit this risk may be mitigated by timely initiation of therapy.[6,20] Although current treatment does not provide a cure, it can delay the progression of Alport nephropathy, especially if initiated before any reduction in GFR.[5,21,7,22] It is recommended to start angiotensin-converting enzyme inhibitors at the time of diagnosis in males with XLAS and in both males and females with ARAS, at the time of onset of microalbuminuria in females with XLAS and in males and females with ADAS.[23]

Accordingly, in the diagnostic evaluation of a child with hematuria, it is of paramount importance to rule out AS, as the therapeutic intervention can change the natural course of the disease and delay the progression of renal damage. In this scenario, a detailed family history of renal disease – hematuria, proteinuria or kidney failure – is crucial, and it is important to recognize that different phenotypes can be present in AS, depending on the sex, genes affected and type of variants inherited.[24] Additionally, pediatric patients can be diagnosed after family screening. In general, first-degree family members (parents, siblings and offspring) of individuals with AS should undergo cascade testing, regardless of the mode of inheritance.[25]

When diagnosing a pediatric AS patient, screening for non-renal manifestations is important. Audiology evaluations are advised for males with XLAS or males and females with ARAS between the ages of 5 and 6, and anyone with type IV collagen mutations and overt proteinuria or clinical concern for hearing loss should have formal audiology evaluations.[23,24] Hearing loss usually have a good response to amplification with hearing aids.[23] Ophthalmologic manifestations of AS generally develop after adolescence, and screening males with XLAS or males and females with ARAS should begin at age 15-16 years or sooner if symptomatic.[24] In XLAS females and AD patients ophthalmologic should be performed if there is clinical suspicion of abnormal vision.[23]

Pediatric AS patients require regular follow-up to initiate therapy promptly, reinforce the need for a healthy lifestyle and to monitor renal disease. As they grow up, especially during adolescence, it is important to improve their understanding about this condition, to promote the acceptance, disease management and responsibility in the future. This transition process of being care by a caregiver to managing disease themselves must be individualized for each patient, according to their educational, social and psychological characteristics and with the active participation of their parents.[26] Providing appropriate and tailored care during this phase is essential to minimize the likelihood of treatment interruptions.[27]

REFERENCES

1. Kallash M, Rheault MN. Approach to Persistent Microscopic Hematuria in Children. Kidney360. 2020 Jul 10;1(9):1014-1020. doi: https://doi.org/10.34067/KID.0003222020.
2. Kashtan CE. Genetic testing and glomerular hematuria-A nephrologist's perspective. Am J Med Genet C Semin Med Genet. 2022 Sep;190(3):399-403. doi: https://doi.org/10.1002/ajmg.c.31987.
3. Warady BA, Agarwal R, Bangalore S, Chapman A, Levin A, Stenvinkel P, *et al*. Alport Syndrome Classification and Management. Kidney Med. 2020 Aug 7;2(5):639-649. doi: https://doi.org/10.1016/j.xkme.2020.05.014.
4. Gibson J, Fieldhouse R, Chan MMY, Sadeghi-Alavijeh O, Burnett L; Genomics England Research Consortium, *et al*. Prevalence Estimates of Predicted Pathogenic *COL4A3-COL4A5* Variants in

a Population Sequencing Database and Their Implications for Alport Syndrome. J Am Soc Nephrol. 2021 Sep;32(9):2273-2290. doi: https://doi.org/10.1681/ASN.2020071065.

5. Kashtan CE. Alport Syndrome: Achieving Early Diagnosis and Treatment. Am J Kidney Dis. 2021 Feb;77(2):272-279. doi: https://doi.org/10.1053/j.ajkd.2020.03.026.
6. Kashtan CE, Ding J, Garosi G, Heidetet L, Massella L, Nakanishi K, *et al*. Alport syndrome: a unified classification of genetic disorders of collagen IV alpha345: a position paper of the Alport Syndrome Classification Working Group. Kidney Int. 2018;93:1045-1051.
7. Nozu K, Nakanishi K, Abe Y, Udagawa T, Okada S, Okamoto T, *et al*. A review of clinical characteristics and genetic backgrounds in Alport syndrome. Clin Exp Nephrol. 2019 Feb;23(2):158-168. doi: https://doi.org/10.1007/s10157-018-1629-4.
8. Groopman EE, Marasa M, Cameron-Christie S, Petrovski S, Aggarwal VS, Milo-Rasouly H, *et al*. Diagnostic Utility of Exome Sequencing for Kidney Disease. New England Journal of Medicine. 2018;380:142-151.
9. Savige J, Harraka P. Pathogenic Variants in the Genes Affected in Alport Syndrome (COL4A3-COL4A5) and Their Association With Other Kidney Conditions: A Review. Am J Kidney Dis. 2021 Dec;78(6):857-864. doi: https://doi.org/10.1053/j.ajkd.2021.04.017.
10. Gast C, Pengelly RJ, Lyon M, Bunyan DJ, Seaby EG, Graham N, *et al*. Collagen (COL4A) mutations are the most frequent mutations underlying adult focal segmental glomerulosclerosis. Nephrol Dial Transplant. 2016 Jun;31(6):961-70. doi: https://doi.org/10.1093/ndt/gfv325.
11. Li Y, Groopman EE, D'Agati V, Prakash S, Zhang J, Mizerska-Wasiak M, *et al*. Type IV Collagen Mutations in Familial IgA Nephropathy. Kidney Int Rep. 2020 Apr 24;5(7):1075-1078. doi: https://doi.org/10.1016/j.ekir.2020.04.011.
12. Ottlewski I, Münch J, Wagner T, Schönauer R, Bachmann A, Weimann A, *et al*. Value of renal gene panel diagnostics in adults waiting for kidney transplantation due to undetermined end-stage renal disease. Kidney Int. 2019 Jul;96(1):222-230. doi: https://doi.org/10.1016/j.kint.2019.01.038.
13. Leenen E, Erger F, Altmüller J, Wenzel A, Thiele H, Harth A, *et al*. Alport syndrome and autosomal dominant tubulointerstitial kidney disease frequently underlie end-stage renal disease of unknown origin-a single-center analysis. Nephrol Dial Transplant. 2022 Sep 22;37(10):1895-1905. doi: https://doi.org/10.1093/ndt/gfac163.
14. Akihisa T, Sato M, Wakayama Y, Taneda S, Horita S, Hirose O, *et al*. Glomerular Basement Membrane Protein Expression and the Diagnosis and Prognosis of Autosomal Dominant Alport Syndrome. Kidney Med. 2019 Aug 20;1(6):391-396. doi: https://doi.org/10.1016/j.xkme.2019.06.007.
15. Savige J, Renieri A, Ars E, Daga S, Pinto AM, Rothe H, *et al*. Digenic Alport Syndrome. Clin J Am Soc Nephrol. 2022 Nov;17(11):1697-1706. doi: https://doi.org/10.2215/CJN.03120322. Epub 2022 Jun 8. Erratum in: Clin J Am Soc Nephrol. 2023 Apr 1;18(4):511.
16. Mencarelli MA, Heidet L, Storey H, van Geel M, Knebelmann B, Fallerini C, *et al*. Evidence of digenic inheritance in Alport syndrome. J Med Genet. 2015 Mar;52(3):163-74. doi: https://doi.org/10.1136/jmedgenet-2014-102822.
17. Deltas C. Digenic inheritance and genetic modifiers. Clin Genet. 2018 Mar;93(3):429-438. doi: https://doi.org/10.1111/cge.13150.
18. Savige J, Renieri A, Ars E, Daga S, Pinto AM, Rothe H, *et al*. Digenic Alport Syndrome. Clin J Am Soc Nephrol. 2022 Nov;17(11):1697-1706. doi: https://doi.org/10.2215/CJN.03120322. Epub 2022 Jun 8. Erratum in: Clin J Am Soc Nephrol. 2023 Apr 1;18(4):511.
19. Oka M, Nozu K, Kaito H, Fu XJ, Nakanishi K, Hashimura Y, *et al*. Natural history of genetically proven autosomal recessive Alport syndrome. Pediatr Nephrol. 2014 Sep;29(9):1535-44. doi: https://doi.org/10.1007/s00467-014-2797-4.
20. Gross O, Tönshoff B, Weber LT, Pape L, Latta K, Fehrenbach H, *et al*. A multicenter, randomized, placebo-controlled, double-blind phase 3 trial with open-arm comparison indicates safety and efficacy of nephroprotective therapy with ramipril in children with Alport's syndrome. Kidney Int. 2020 Jun;97(6):1275-1286. doi: https://doi.org/10.1016/j.kint.2019.12.015.
21. Gross O, Licht C, Anders HJ, Hoppe B, Beck B, Tönshoff B, *et al*. Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy. Kidney Int. 2012 Mar;81(5):494-501. doi: https://doi.org/10.1038/ki.2011.407.
22. Zeng M, Di H, Liang J, Liu Z. Effectiveness of renin-angiotensin-aldosterone system blockers in patients with Alport syndrome: a systematic review and meta-analysis. Nephrol Dial Transplant. 2023 Oct 31;38(11):2485-2493. doi: https://doi.org/10.1093/ndt/gfad105.
23. Kashtan CE, Gross O. Clinical practice recommendations for the diagnosis and management of Alport syndrome in children, adolescents, and young adults-an update for 2020. Pediatr Nephrol. 2021 Mar;36(3):711-719. doi: https://doi.org/10.1007/s00467-020-04819-6. Epub 2020 Nov 6. Erratum in: Pediatr Nephrol. 2021 Jan 12.
24. Rheault MN, Savige J, Randles MJ, Weinstock A, Stepney M, Turner AN, *et al*. The importance of clinician, patient and researcher collaborations in Alport syndrome. Pediatr Nephrol. 2020 May;35(5):733-742. doi: https://doi.org/10.1007/s00467-019-04241-7.
25. Savige J, Lipska-Zietkiewicz BS, Watson E, Hertz JM, Deltas C, Mari F, *et al*. Guidelines for Genetic Testing and Management of Alport Syndrome. Clin J Am Soc Nephrol. 2022 Jan;17(1):143-154. doi: https://doi.org/10.2215/CJN.04230321. Epub 2021 Dec 20. Erratum in: Clin J Am Soc Nephrol. 2023 Apr 1;18(4):510.
26. Watson AR, Harden PN, Ferris ME, Kerr PG, Mahan JD, Ramzy MF, *et al*. Transition from pediatric to adult renal services: a

consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA). Kidney Int. 2011 Oct;80(7):704-7. doi: https://doi.org/10.1038/ki.2011.209.

27. Scarponi D, Cangini G, Pasini A, La Scola C, Mencarelli F, Bertulli C, *et al*. The process of transition from pediatric to adult healthcare services for nephrological patients: Recommendations vs. reality-A single center experience. Front Pediatr. 2022 Aug 23;10:954641. doi: https://doi.org/10.3389/fped.2022.954641.