Abstract citation ID: gfae069.404

#1468
Alport syndrome family screening and management—experience of a tertiary center

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Background and Aims: Alport syndrome (AS) is the most common cause of inherited chronic kidney disease. This disorder is caused by deleterious variants on COL4A3, COL4A4 or COL4A5 genes. These genes codify the proteins that constitute collagen type IV of the glomerular basement membrane (GBM). Importantly, AS patients can develop chronic kidney disease (CKD) kidney disease that can be delayed or possibly prevented by timely initiation of therapy. The identification of at-risk relatives and their genetic testing allow to identify AS patients and initiate appropriate renal care and avoid unnecessary vigilance if the test is negative. Our aim was to assess the outcomes of Alport Syndrome cascade family screening in a tertiary hospital.

Method: In this study, we retrospectively assessed familial relatives at risk of AS index cases in our Nephrogenetics consult, from January 2018 to November 2023. After referral, routine tests to detect renal disease were done and AS gene panel was performed. Demographic and clinical data were also compiled.

Results: A total of 75 at-risk relatives were assessed, belonging to 26 families with a COL4A variant identified in the index case. Relatives at risk were mostly referred by primary care doctors (n = 52, 69.3%), with other 15 patients (20%) directly scheduled for consultation, and 8 (10.7%) referred by a nephrology clinic.

In this cohort, an AS diagnosis was confirmed in 43 relatives (57.3%), with an additional 13 (17.3%) of the at-risk relatives with ongoing biochemical or molecular analyses. In 19 (25.4%) relatives the molecular study allowed the exclusion of AS.

In the subgroup of patients diagnosed with AS (n = 43): median age at molecular diagnosis was 40.5 years (IQR 20.2-56.5 years) and 26 (60.5%) were female. Thirty-five patients (81.4%) patients had autosomal dominant AS: 32 had a variant in COL4A3 (6 different variants were found: 4 were pathogenic or likely pathogenic and 2 were of uncertain significance) and 3 patients on COL4A4. COL4A5 variants were identified in 8 patients, 5 of them were female. Three (7%) patients presented with intermittent hematuria, 14 (32.6%) patients presented isolated hematuria, 10 (23.2%) patients had urinary protein/creatinine (Up/cr) <0.3g/g, 7 (16.2%) presented Up/cr between 0.3g/g and 1g/g, 3 (7%) patients had Up/cr >1g/g; Six (14%) had CKD. Twenty-two (52.8%) patients were started on a renin angiotensin system inhibitor (RASI) and 5 (11.6%) were already under a RASI. At the last visit in this group of AS patients, the mean epiTFG was 104.2 ml/min (IQ 85.6-120.5 ml/min) and 6 (14%) patients had epiTFG below 60 ml/min; mean Uprot/creat was 0.11g/g (IQR 0.06-0.32), 12 (28%) patients had no proteinuria.

In the subgroup of relatives at risk were AS excluded (n = 19): median age was 38.5 years (IQR 20.2-56.0) and 11 (58%) were female. One patient had CKD, 7 (36.8%) had no signs of renal disease and 8 (42%) patients had intermittent hematuria.

Conclusion: Our retrospective review showed that the systematic screening of relatives at risk in our hospital was met with a high discovery rate of AS patients. Since there is clinical benefit in an early AS diagnosis, namely through improved renal care and prevention of disease progression, timely genetic/biochemical screening of at-risk relatives is advisable. Additionally, by discharging the relatives with a negative test, this is a more cost-effective approach than providing continuous vigilance to all.