Nephrologie + Rheumatologie

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POTENTIAL OF RAAS-BLOCKADE TO HALT RENAL DISEASE IN HETEROZYGOUS CARRIERS OF ALPORT-MUTATIONS: A 4-YEAR PROSPECTIVE STUDY

Johanna Stock, Johannes Künanz, Niklas Glonke, Oliver Gross

Clinic for Nephrology and Rheumatology, University Medicine Göttingen, Germany

Background and Objectives

Heterozygous carriers of mutations in the autosomal (COL4A3, COL4A4) or X-chromosomal (COL4A5) Alport-genes have a one to 20% lifetime risk of developing end stage renal failure. Therefore, the present study evaluated the long-term renal outcome of heterozygous carriers of Alport-mutations "at risk" of progressive disease (chronic kidney disease stages 1 to 4) with and without nephroprotective therapy.

Design, setting, participants, and measurements

The study used a prospective, non-interventional, observational design including a 4-year follow-up of Alport-carriers arriving from the retrospective 2010 dataset of the European Alport registry. Using Kaplan-Meier-estimates and logrank-tests, 52 prospectively updated datasets and 13 new datasets were analyzed. The study evaluated the effect of therapy, extrarenal symptoms and inheritance pattern on renal outcome, including data about time from first symptom to diagnosis.

ClinicalTrials.gov NCT02378805; EudraCT 2014-003533-25

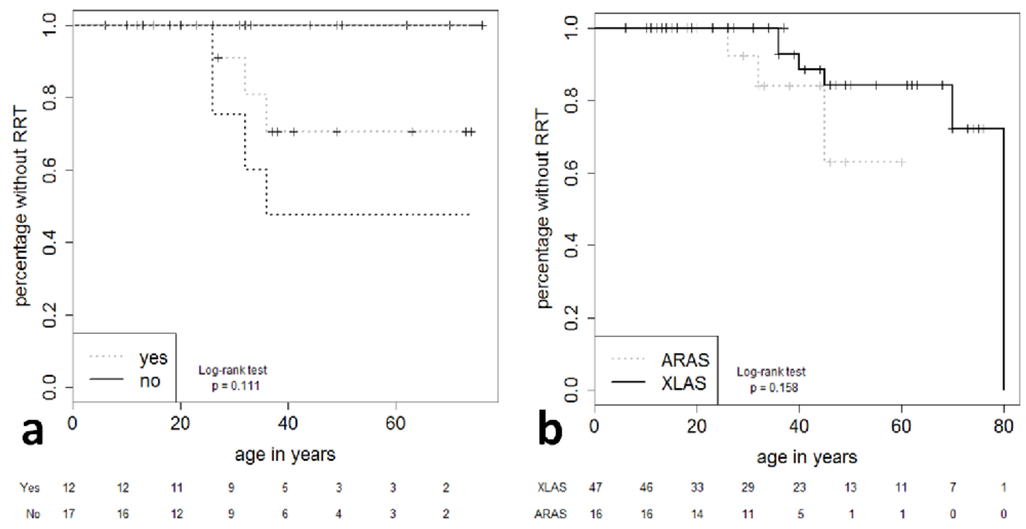

Figure 1 Genotype-Phenotype Correlation

a Hearing loss is a negative predictor of the severity of kidney disease

b The mode of inheritance is not a significant predictor of the severity of Alport kidney disease (dots: 95% confidence-interval)

Results

The mean prospective follow-up was 46+/-10 months with a mean time on therapy of 8.4+/-4.4 years (range 2 to 18, median 7). Mean time from first symptom to diagnosis was 8.1 years. 5.4% started therapy with GFR below 60 ml/min, 67.6% with proteinuria and 27.0% with microalbuminuria. Therapy included ACE-inhibitors in 97.1%, angiotensin-receptor-antagonists in one patient, dual therapy in 11.8%, and statins in 8.8%.

Therapy prevented dialysis in the prospective dataset and the dataset including new patients:

after 4 years follow-up, none of the patients at risk for renal failure progressed to the next stage of disease. Three patients even regressed to a lower stage of disease during therapy.

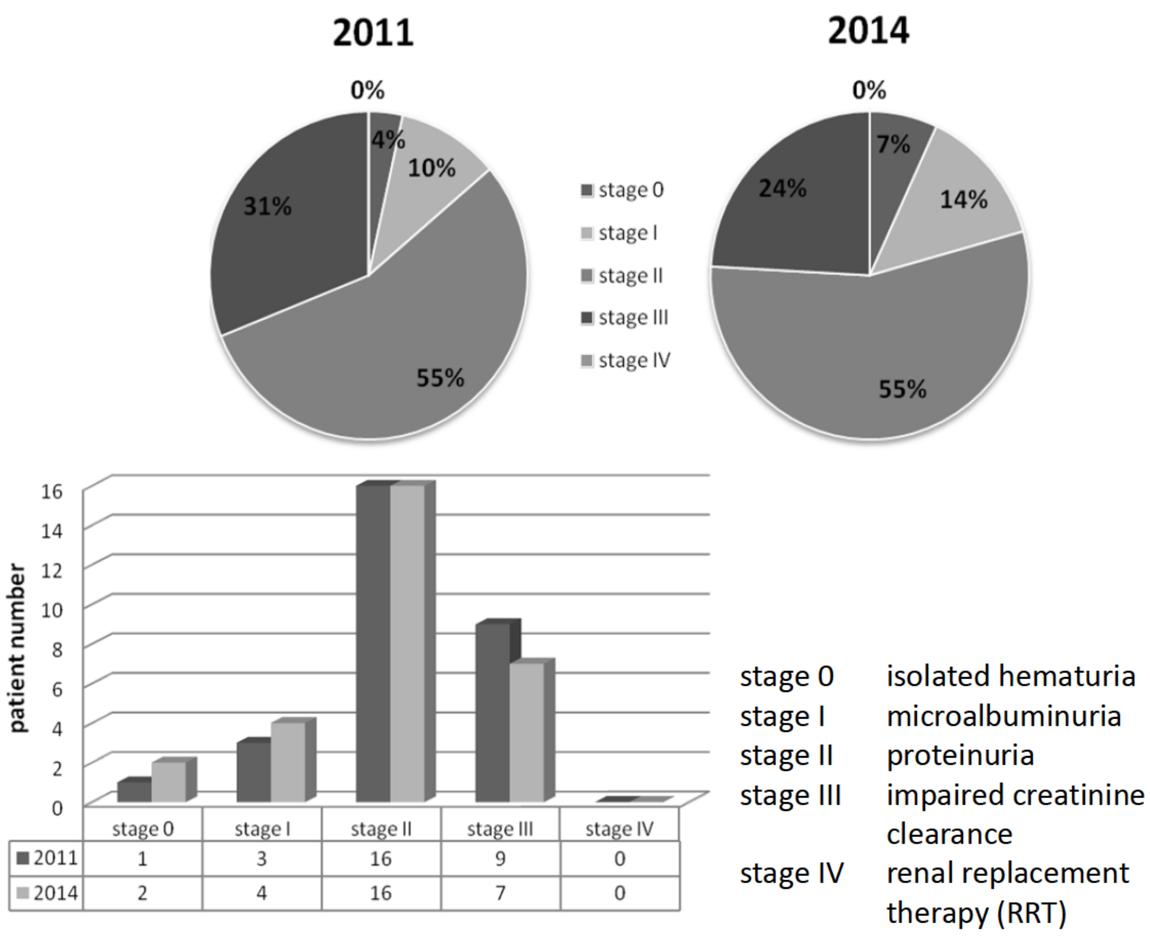

Figure 3 RAAS-Blockade preserves kidney function

upper row: treated patients at different stages of CKD 2011 and 2014

lower row: patient number at different stages of CKD 2011 vs. 2014

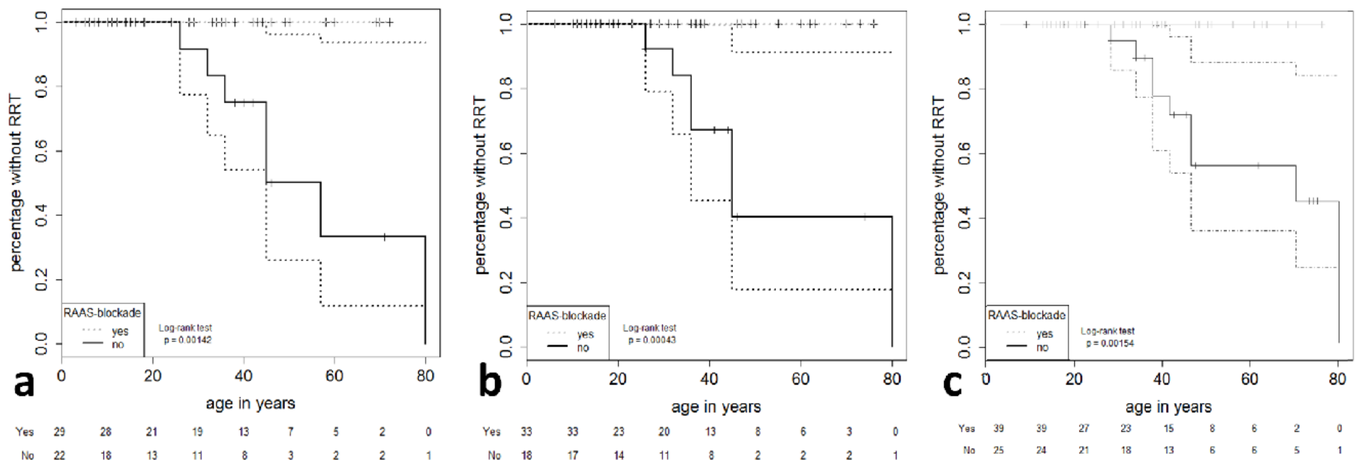

Figure 2 Nephroprotection by RAAS-Blockade

a Patients on renal replacement therapy (RRT) with vs. without RAAS-blockade (retrospective data 2011)

b Patients on renal replacement therapy (RRT) with vs. without RAAS-blockade (prospective data 2014)

c Patients on renal replacement therapy (RRT) with vs. without RAAS-blockade (prospective data 2014 plus new patients 2014)

Conclusions

Awareness of a – in many cases - not benign condition and timely, appropriate therapy can prevent progressive renal failure in most, if not all heterozygous carriers of Alport-mutations. A very considerable number of elderly patients on dialysis might have heterozygous Alport-mutations as underlying disease (1% of the total population have heterozygous Alport-mutations). This condition should lead to a greater alertness towards timely diagnosis and therapy.

Please contact

Prof. Dr. O. Gross gross.oliver@med.uni-goettingen.de

University Medicine Goettingen, Clinic for Nephrology&Rheumatology

Robert-Koch Str. 40, 37075 Goettingen, Germany

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