ESPN Journal Club

Immune Mediated Renal Disorders Working Group

Papers included in this month's Journal Club are selected current approaches in pediatric hemolytic uremic syndrome and IgA nephropathy topics. First paper demonstrate that systemic complement activation and increased C5-9 levels predicts poor prognosis in EHEC induced HUS . Second paper emphasizes the importance of cobalamine deficiency in differential diagnosis of renal trombotic microangiopathy. Last two papers present new approaches to improve diagnostic markers ,new treatments, prognosis and outcomes of IgA nephropathy

1. Ahlenstiel-Grunow T, Hachmeister S, Bange FC, Wehling C, Kirschfink M, Bergmann C, Pape L. Systemic complement activation and complement gene analysis in enterohaemorrhagic Escherichia coli-associated paediatric haemolytic uraemic syndrome. Nephrol Dial Transplant. 2016 Jul;31(7):1114-21

BACKGROUND:

In contrast to atypical haemolytic uraemic syndrome (aHUS), only single case reports and limited data have been published on systemic activation of the complement system and mutations in complement genes in paediatric enterohaemorrhagic Escherichia coli-inducedHUS (EHEC-HUS).

METHODS:

Complement activation (CH50, APH50, C3d, sC5b-9) was analysed at four timepoints (Week 1, Week 2, Month 3 and Month 6 after primary diagnosis of HUS) in 25 children with EHEC-HUS. Seven patients received the complement C5 inhibitor eculizumab. Targeted next generation sequencing for a total of 89 genes involved in complement regulation and coagulation and haemostasis was performed in all patients.

RESULTS:

Activity of classical (CH50) and alternative (APH50) complement pathways was normal or even elevated throughout the observation time, except for patients under eculizumab treatment. In contrast, the mean concentration of the soluble terminal complement complex (sC5b-9) was significantly elevated at the first timepoint (mean 498 ng/mL), dropping to normal values after 2 weeks. Initially elevated (42 mU/L) median C3d concentration reached normal levels from Week 2. Levels of sC5b-9 >320 ng/mL at the time of HUS diagnosis were associated with arterial hypertension, oedema and lower platelet counts, but not with the duration of dialysis. Genetic analysis revealed various changes that may have had a modifying impact on the clinical course.

CONCLUSIONS:

Complement activation at the acute phase of EHEC-HUS, indicated by increased levels of sC5b-9, predicts a poor outcome. Complement alterations appear to be more frequent in patients with EHEC-HUS than previously thought and are suspected to have a role in the severity of the disease.

2. Beck BB, van Spronsen F, Diepstra A, Berger RM, Kömhoff M. Renal thrombotic microangiopathy in patients with cblC defect: review of an under-recognized entity. **Pediatr Nephrol.** 2016 Jun 11

Abstract

Methylmalonic aciduria and homocystinuria, cobalamin C (cblC) type, is the most common genetic type of functional cobalamin (vitamin B_{12}) deficiency. This metabolic disease is characterized by marked heterogeneity of neurocognitive disease (microcephaly, seizures, developmental delay, ataxia, hypotonia) and variable extracentral nervous system involvement (failure to thrive, cardiovascular, renal, ocular) manifesting predominantly early in life, sometimes during gestation. To enhance awareness and understanding of renal disease associated with cblC defect, we studied biochemical, genetic, clinical, and histopathological data from 36 patients. Consistent clinical chemistry features of renal disease were intravascular hemolysis, hematuria, and proteinuria in all patients, with nephrotic-range proteinuria observed in three. Renal function ranged from normal to renal failure, with eight patients requiring (intermittent) dialysis. Two thirds were diagnosed with atypical (diarrhea-negative) hemolytic uremic syndrome (HUS). Renal histopathology analyses of biopsy samples from 16 patients revealed glomerular lesions typical of thrombotic microangiopathy (TMA). Treatment with hydroxycobalamin improved renal function in the majority, including three in whom dialysis could be withdrawn. Neurological sequelae were observed in 44 % and cardiopulmonary involvement in 39 % of patients, with half of the latter group demonstrating pulmonary hypertension. Mortality reached 100 % in untreated patients and 79 and 56 % in those with cardiopulmonary or neurological involvement, respectively. In all patients presenting with unclear intravascular hemolysis, hematuria, and proteinuria, cblC defect should be ruled out by determination of blood/plasma homocysteine levels and/or genetic testing, irrespective of actual renal function and neurological status, to ensure timely diagnosis and treatment.

3. Coppo R. Biomarkers and targeted new therapies for IgA nephropathy **Pediatr Nephrol.** 2016 Jun 20. [Epub ahead of print]

Abstract

IgA nephropathy (IgAN) has variable clinical presentation and outcome. There is a need to identify children who have the potential to progress to end stage renal disease (ESRD). Biomarkers related to the pathogenetic process of IgAN can detect risk factors and identify targets for new therapies. Galactose-deficient IgA1 (Gd-IgA1) is a specific biomarker of IgAN and could be the first treatment target. In experimental mice, reduction of IgA1 deposits and hematuria was observed after treatment with a bacterial protease that selectively cleaves human IgA1. Glycan-targeted drugs that may act to neutralize Gd-IgA1 inhibit abnormal enzymatic glycosylation of IgA1 or deplete cells producing Gd-IgA1. The autoimmune response to Gd-IgA1 produces autoantibodies that are sensitive and specific biomarkers of IgAN development and progression and suggests the possible benefits of anti-B cell therapies directed against CD20, B-cell activating factor (BAFF), or B cell receptor, and also proteasome inhibitors. The activation of complement in IgAN offers new biomarkers and the rationale for using complement inhibitors, including eculizumab. Renal pathological features represent sensitive biomarkers of added value over clinical data and may drive steroid therapy in selected cases. Finally, the hypothesis of the involvement of intestinal mucosal immunity in the pathogenesis of IgAN suggests the possibility of avoiding the systemic effect of steroid. Enteric budesonide targeting Peyer's patches at the ileocecal junction is an interesting option that has provided some preliminary favorable results in IgAN. In conclusion, the identification of new biomarkers is a promising area for therapies targeting IgAN in patients at risk of progression.

4. Inker LA, Mondal H, Greene T, Masaschi T, Locatelli F, Schena FP, Katafuchi R, Appel GB, Maes BD, Li PK, Praga M, Del Vecchio L, Andrulli S, Manno C, Gutierrez E, Mercer A, Carroll KJ, Schmid CH,Levey AS. Early Change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis **Am J Kidney Dis.** 2016 Mar 29. pii: S0272-6386(16)00214-6.

Abstract

BACKGROUND:

The role of change in proteinuria as a surrogate end point for randomized trials in immunoglobulin A nephropathy (IgAN) has previously not been thoroughly evaluated.

STUDY DESIGN:

Individual patient-level meta-analysis.

SETTING & POPULATION:

Individual-patient data for 830 patients from 11 randomized trials evaluating 4 intervention types (renin-angiotensin system [RAS] blockade, fish oil, immunosuppression, and steroids) examining associations between changes in urine protein and clinical end points at the individual and trial levels.

SELECTION CRITERIA FOR STUDIES:

Randomized controlled trials of IgAN with measurements of proteinuria at baseline and a median of 9 (range, 5-12) months follow-up, with at least 1 further year of follow-up for the clinical outcome.

PREDICTOR:

9-month change in proteinuria.

OUTCOME:

Doubling of serum creatinine level, end-stage renal disease, or death.

RESULTS:

Early decline in proteinuria at 9 months was associated with lower risk for the clinical outcome (HR per 50% reduction in proteinuria, 0.40; 95% CI, 0.32-0.48) and was consistent across studies. Proportions of treatment effect on the clinical outcome explained by early decline in proteinuria were estimated at 11% (95% CI, -19% to 41%) for RAS blockade and 29% (95% CI, 6% to 53%) for steroid therapy. The direction of the pooled treatment effect on early change in proteinuria was in accord with the direction of the treatment effect on the clinical outcome for steroids and RAS blockade. Trial-level analyses estimated that the slope for the regression line for the association of treatment effects on the clinical end points and for the treatment effect on proteinuria was 2.15 (95% Bayesian credible interval, 0.10-4.32).

LIMITATIONS:

Study population restricted to 11 trials, all having fewer than 200 patients each with a limited number of clinical events.

CONCLUSIONS:

Results of this analysis offer novel evidence supporting the use of an early reduction in proteinuria as a surrogate end point for clinical end points in IgAN in selected settings.