ESPN Journal Club

Immune Mediated Renal Disorders Working Group

From Dr Esra Baskin

Papers included in this month's Journal Club are selected current approaches in pediatric atypical hemolytic uremic syndrome, HSPnephritis and SLE nephritis topics. First paper demonstrate that influenza B strain as a trigger for aHUS in children with primary hereditary forms . Second paper emphasizes STEC-induced HUS and aHUS patients, complement is activated in the acute phase of the disease but not during remission. The C3d/C3 ratio displayed the best discrepancy between acute and convalescent phase and between STEC-HUS and aHUS and might therefore be used as a biomarker in disease diagnosis and monitoring.

Third paper demonstrate that inducible nitric oxide synthase gene polymorphisms are associated with a risk of nephritis in Henoch-Schönlein purpura. Fourth paper suggests mycophenolate mofetil and low-dose prednisone combined therapy in the treatment of severe HSPnephritis.

Last three papers present new approaches in the diagnosis, treatments and prognosis of SLE nephritis in children

Atypical HUS

1.van Hoeve K, Vandermeulen C, Van Ranst M, Levtchenko E, van den Heuvel L, Mekahli D. **Occurrence of atypical HUS associated with influenza B**. Eur J Pediatr. 2017 Apr;176(4):449-454.

Abstract

Hemolytic uremic syndrome (HUS) is a disease characterized by thrombotic microangiopathy with a triad of non-immune hemolytic anemia, thrombocytopenia, and renal impairment. Approximately 10% of cases of HUS are classified as atypical (aHUS). While today many genetically forms of aHUS pathology are known, only about 50% of carriers precipitate the disease. The reason remains unclear, and triggering events like

intercurrent infections have been postulated. In rare cases, influenza A is the known trigger of aHUS; however, no cases of influenza B have been reported.

CONCLUSION:

We describe for the first time that influenza B strain as a trigger for aHUS in children with primary hereditary forms. We also showed in our three cases that immunization appears to be safe; however, this needs to be confirmed in a larger cohort. What is Known: • Known triggers of aHUS are infectious specimen. • Influenza A-associated aHUS cases are rarely published. What is New: • aHUS can be triggered by influenza B virus infection. • Influenza vaccination of patients with aHUS appears safe.

2.Westra D[1], Volokhina EB[2], van der Molen RG[3], van der Velden TJ[2], Jeronimus-Klaasen A[2], Goertz J[3], Gracchi V[4], Dorresteijn EM[5], Bouts AH[6], Keijzer-Veen MG[7], van Wijk JA[8], Bakker JA[9], Roos A[10], van den Heuvel LP[2,11], van de Kar NC[2]. **Serological and genetic complement alterations in infection-induced and complement-mediated hemolytic uremic syndrome. Pediatr Nephrol. 2017 Feb;32(2):297-309.**

Abstract

BACKGROUND:

The role of complement in the atypical form of hemolytic uremic syndrome (aHUS) has been investigated extensively in recent years. As the HUS-associated bacteria Shiga-toxin-producing Escherichia coli (STEC) can evade the complement system, we hypothesized that complement dysregulation is also important in infection-induced HUS.

METHODS:

Serological profiles (C3, FH, FI, AP activity, C3d, C3bBbP, C3b/c, TCC, αFH) and genetic profiles (CFH, CFI, CD46, CFB, C3) of the alternative complement pathway were prospectively determined in the acute and convalescent phase of disease in children newly diagnosed with STEC-HUS or aHUS. Serological profiles were compared with those of 90 age-matched controls.

RESULTS:

Thirty-seven patients were studied (26 STEC-HUS, 11 aHUS). In 39 % of them, including 28 % of STEC-HUS patients, we identified a genetic and/or acquired complement abnormality. In all patient groups, the levels of investigated alternative pathway (AP) activation markers were elevated in the acute phase and normalized in remission. The levels were significantly higher in aHUS than in STEC-HUS patients.

CONCLUSIONS:

In both infection-induced HUS and aHUS patients, complement is activated in the acute phase of the disease but not during remission. The C3d/C3 ratio displayed the best discrepancy between acute and convalescent phase and between STEC-HUS and aHUS and might therefore be used as a biomarker in disease diagnosis and monitoring. The presence of aberrations in the alternative complement pathway in STEC-HUS patients was remarkable, as well.

Henoch-Schönlein Purpura Nephritis.

3.Jiang J, Duan W, Shang X, Wang H, Gao Y, Tian P, Zhou Q. **Inducible nitric oxide synthase gene polymorphisms are associated with a risk of nephritis in Henoch-Schönlein purpura children.** Eur J Pediatr. 2017 Jun 8. doi: 10.1007/s00431-017-2945-5. [Epub ahead of print]

Abstract

Henoch-Schönlein purpura (HSP) is the most common form of systemic small-vessel vasculitis in children, and HSP nephritis (HSPN) is a major complication of HSP and is the primary cause of morbidity and mortality. Previous studies have suggested that inducible nitric oxide synthase (iNOS) may play an important role in the pathogenesis of HSP. In this study, we performed a detailed analysis to investigate the potential association between iNOS polymorphisms and the risk of HSP and the tendency for children with HSP to develop HSPN in a Chinese Han population. A promoter pentanucleotide repeat (CCTTT)n and 10 functional single-nucleotide polymorphisms (SNPs) from 532 healthy controls and 513 children with HSP were genotyped using the MassARRAY system and GeneScan. The results suggested that the allelic and genotypic frequencies of the rs3729508 polymorphism were nominally associated with susceptibility to HSP. In addition, there was a significant difference in the allelic distribution of the (CCTTT)12 repeats and rs2297518 between the HSP children with and without nephritis; the HSP children with nephritis exhibited a significantly higher frequency of the (CCTTT)12 repeats and A allele of rs2297518 than the HSP children without nephritis (P_{FDR} = 0.033, OR = 1.624, 95% CI = 1.177-2.241 and P_{FDR} = 0.030, OR = 1.660, 95% CI = 1.187-2.321, respectively).

CONCLUSION:

Our results support that iNOS polymorphisms are associated with the risk of HSP and may strongly contribute to the genetic basis of individual differences in the progression to nephritis among children with HSP in the Chinese Han population. What is Known: • The etiology of HSP is unknown, but the genetic factors may play an important role in the pathogenesis of HSP. • iNOS could contribute to the development and clinical manifestations of HSP, and this has not been studied extensively so far. What is New: • Our results support that iNOS polymorphisms not only are associated with HSP risk but also strongly contribute to the genetic basis of individual differences in the progression of HSP to nephritis among Chinese Han children.

4.Lu Z, Song J, Mao J, Xia Y, Wang C. **Evaluation of Mycophenolate Mofetil and Low-Dose Steroid Combined Therapy in Moderately Severe Henoch-Schönlein Purpura Nephritis.** Med Sci Monit. 2017 May 18;23:2333-2339.

Abstract

BACKGROUND The most appropriate management of Henoch-Schönlein Purpura (HSP) nephritis with nephrotic-range proteinuria remains uncertain. The aim of this study was to evaluate the clinical therapeutic effects of mycophenolate mofetil and low-dose steroid in Henoch-Schönlein purpura nephritis (HSPN) with nephrotic-range proteinuria and pathological classification less than IV in children. MATERIAL AND METHODS The clinical effects of MMF and low-dose steroid therapy were studied in children with Henoch-Schönlein purpura nephritis manifested with nephrotic-range proteinuria, normal kidney function, and <50% crescents or sclerosing lesions on renal biopsy. We enrolled 32 boys and 29 girls with nephrotic-range proteinuria, normal kidney function, and pathological classification less than IV on renal biopsy. We treated 41 cases (67.2%) with mycophenolate mofetil and low-dose prednisone combined therapy and 20 cases (32.8%) were treated with full-dose prednisone alone. RESULTS Short-term response was significantly different between 2 groups (χ^2=4.371, P=0.037), while no significant difference was found in long-term prognosis (χ^2=0.419, P=0.522) after follow-up. The ROC curve showed that the most appropriate cutoff value was 30.67 μg·h/ml for MPA-AUC and the area under the ROC curve was 0.731, with 85.2% sensitivity and 64.3% specificity. CONCLUSIONS Mycophenolate mofetil and low-dose prednisone combined therapy is a reasonable treatment choice which can promote the remission of proteinuria without increasing obvious adverse reactions in pediatric HSPN with nephrotic state and pathological classification less than grade IV. MPA-AUC more than 30 μg·h/ml was an

appropriate value for MMF in the combined therapy with MMF and steroid for treating children with HSPN.

SLE nephritis

5.Basu B, Roy B, Babu BG. **Efficacy and safety of rituximab in comparison with common induction therapies in pediatric active lupus nephritis.** Pediatr Nephrol. 2017 Jun;32(6):1013-1021. doi: 10.1007/s00467-017-3583-x. Epub 2017 Feb 12.

Abstract

BACKGROUND:

Childhood-onset lupus nephritis (LN) is one of the most severe manifestations of systemic lupus erythematosus (SLE). Despite treatment-related toxicities, cyclophosphamide (CYC) and glucocorticoid-based treatment protocols are still considered standard therapy in managing this multisystem disorder. An effective and safe alternative induction regimen is needed.

METHODS:

Forty-four pediatric patients with active LN aged 3.5-13.8 (median 8.4) years, of whom 32 entered the study at diagnosis of SLE, were followed over 36 months. Induction therapy consisted of methylprednisolone pulses followed by either rituximab (RTX) (n = 17), mycophenolate mofetil (MMF) (n = 12) or pulse-CYC (n = 15), with tapering dose of prednisolone orally. MMF was added as maintenance immunosuppressant (800 mg/m^2 daily) in all children from the third month onward.

RESULTS:

Flare-free survival was significantly higher at 36 months with RTX compared with MMF and CYC (100% for RTX vs. 83% for MMF. and 53% for CYC, p = 0·006). Twelve patients (76.5%) achieved complete remission with RTX compared with five (41.7%) and seven (46.7%) with MMF and CYC, respectively, at last follow-up. Requirement of mean daily dosage of prednisone was significantly lower in RTX group [p = 0.005 (RTX vs MMF); 0.0001 (RTX vs CYC) at 36 months] compared with other groups after the 3-month follow-up. In comparison with few minor adverse events in the other two cohorts, several serious adverse events occurred in the CYC group.

CONCLUSIONS:

Efficacy and medium-term safety of RTX induction followed by MMF maintenance therapy in inducing and maintaining remission among children with LN were evident in this study.

6.Wright TB, Punaro M. **Paediatric systemic lupus erythematosus: insights from translational research** Rheumatology(Oxford). 2017 Apr 1;56(suppl_1):i24-i31. doi: 10.1093/rheumatology/kew447.

Abstract

Investigations in paediatric SLE contributed significantly to the discovery of the association of type I IFNs with lupus and underscored the potential application of this knowledge by informing the use of glucocorticoid therapy. Recent, promising research reveals biomarkers that may yield more focused clinical monitoring and assessment of response to treatment. This article reviews unique features of paediatric SLE and details important developments in paediatric lupus research.

7. Tian SY, Silverman ED, Pullenayegum E, Brown PE, Beyene J, Feldman BM. **Comparative effectiveness of mycophenolate mofetil for the treatment of childhood-onset proliferative lupus nephritis.** Arthritis Care Res (Hoboken). 2017 Feb 9. doi: 10.1002/acr.23215. [Epub ahead of print]

Abstract

OBJECTIVES:

Although childhood-onset proliferative lupus nephritis (cPLN) leads to significant morbidity and mortality, there is no trial evidence to support the treatment effectiveness of any therapy for cPLN. Marginal structural models (MSMs) enable us to estimate treatment effectiveness using observational data while accounting for confounding by indication.

METHODS:

We used prospectively collected data to examine the effect of mycophenolate mofetil (MMF), compared to the use of other therapies, on the long-term outcome of our cPLN cohort (age at onset of PLN < 18 years). The major outcome variable was the estimated glomerular filtration rate (eGFR) using the revised Schwartz formula. Confounding by indication was corrected for using an MSM model.

RESULTS:

A total of 172 subjects with cPLN were included with a mean followup duration of approximately 4 years. Overall MMF was superior to other therapies with a relative effect estimate for MMF of 1.06, i.e., 6% better eGFR on average (95% confidence interval: 0.7%, 11.3%), corrected for potential confounding by indication. We found that beginning in year 4 there was a significant improvement in eGFR in the patients who were treated with MMF versus other therapies. This improvement was maintained until the end of the study.

CONCLUSION:

MMF was more beneficial than other therapies in improving/maintaining long-term renal function in patients with cPLN up to a maximum followup of 7 years. This finding is consistent with trial evidence for adult PLN