PERSPECTIVES

Altered glycosylation of circulatory IgA1 involved in Henoch-Schönlein purpura and IgA nephropathy

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Henoch-Schönlein purpura (HSP) is the most common type of systemic small vessel vasculitis in children. HSP most commonly affects children between 2 and 6 years of age. The presence of purpuric rash (100%) is essential to the diagnosis. Other clinical characteristics of HSP include abdominal pain or gastrointestinal bleeding (50–75%), arthralgia and/or arthritis (up to 82%), and hematuria and/or proteinuria (20–60%).1 The disease generally has acute onset, and a benign and self-limiting course that lasts an average of 4 weeks.1 Immunoglobulin A nephropathy (IgAN), however, has an insidious onset and slow progressive nature. IgAN is the most common form of glomerulonephritis in both children and adults. It mostly affects young adults. Renal biopsy findings of IgAN and HSPN are indistinguishable due to the presence of IgA-containing immune complex deposits in the renal mesangium.2 It has been speculated that HSP is a systemic form of IgAN.

The clinical features of children with IgAN are variable, going from asymptomatic microscopic hematuria with/without proteinuria to gross hematuria. A small number of patients present with clinical signs of the nephrotic or nephritic syndrome. About 10–30% of pediatric patients have slow progressive disease, leading to end-stage renal disease in adulthood.3 Poor prognostic factors include older age, heavy proteinuria, renal insufficiency, hypertension and advanced renal histology, such as crescent formation or sclerotic change at diagnosis.2 The Oxford classification of IgAN identified four pathological elements that were of prognostic value in predicting the outcome of renal function: mesangial hypercellularity, endocapillary proliferation, segmental glomerulosclerosis/adhesion, and tubular atrophy/interstitial fibrosis.3 These findings offer the possibility to identify patients who are most likely to progress to renal failure at the time of biopsy.

In IgAN patients with microscopic hematuria and/or low-grade proteinuria, it is not known whether therapy is necessary. If proteinuria is >1 g/1.73 m² body surface area per day, the initiation of treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers is generally accepted. More aggressive treatment with corticosteroids and immunosuppressants should be reserved for children with a poor response to ACEIs/angiotensin receptor blockers or who have hypertension, nephrotic syndrome, reduced renal function or advanced histologic lesions.2 Clinical trials have shown conflicting results for the efficacy of omega-3 polyunsaturated fatty acids in IgAN.5

HSPN is often manifested by microscopic hematuria with/without low-grade proteinuria, mostly within 6 weeks of the initial presentation of HSP. Nephritis or nephrotic syndrome develops in about 20% of children with HSPN (6–7% of children with HSP) at disease onset.1 HSPN is the most serious long-term complication of HSP. Corticosteroids, immunosuppressants such as azathioprine, cyclophosphamide, cyclosporine and mycophenolate mofetil have been used in the treatment of patients with severe HSPN.6 Poor prognostic factors are nephritic/nephrotic syndrome, and advanced renal histology such as crescents

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or sclerosing lesions in >50% of glomeruli at diagnosis. In general, it is estimated that 1–3% of all HSPN patients will ultimately develop chronic kidney disease. Patients presented with nephritic or nephrotic syndrome have a poor prognosis, with a 20–40% risk of chronic kidney disease or end-stage renal disease.6

Although the etiology is unknown, IgAN and HSP are both IgA-containing immune-complex-mediated diseases and are triggered by common viral or bacterial infection. In HSP, IgA anti-endothelial cell antibodies play a role in vascular damage.7 Increased production of underglycosylated IgA1 in the circulation and renal mesangium is characteristic for IgAN and HSPN. Such "nephritogenic" IgA1 is deficient in galactose or prematurely sialylated in the hinge region O-linked glycans. This results in aberrant exposure of N-acetylgalactosamine-containing neoepitopes that are then recognized by naturally occurring IgG or IgA1 antibodies, leading to the formation of immune complexes. Circulating large molecular mass IgA1- and IgG-containing immune-complexes are less efficiently cleared from the circulation by the asialoglycoprotein receptor in the liver and tend to bind to glomerular mesangial cells through CD71 (the transferrin receptor). Mesangial cells undergo proliferation and overproduction of cytokines and growth factors leading to glomerulosclerosis. Complement activation through alternative and lectin pathways, and other immune cells' recruitment and activation also participate in glomerular and tubulointerstitial injury.8 Impaired homing of IgA-producing plasma cells from mucosa to the bone marrow that leads to the overproduction of underglycosylated IgA1 in circulation rather than in the mucosa might also contribute to disease pathogenesis in the animal model of IgAN (ddY mice).9

Our understanding of the genetic susceptibility, pathogenesis and treatment of HSP are less clear than for IgAN. Underglycosylation of IgA1 is assumed to have a pivotal role in the pathogenesis of both IgAN and HSPN. Levels of underglycosylated IgA1 and IgG against underglycosylated IgA1 are elevated in the serum of patients with IgAN and HSPN, compared with HSP patients without nephritis or controls.10 The detection of such antibodies in the serum might offer sensitive and specific, noninvasive diagnostic tests, and they might even be used as disease activity markers in the future. There have been debates about glycosylation defects due to genetic polymorphisms in the glycosylation enzyme or as a consequence of aberrant mucosal immune response. Longitudinal studies to determine whether the glycosylation defects of IgA1 persist following the resolution of clinical symptoms of HSPN should be able to answer this question.

HSP and IgAN might represent different ends of a continuous spectrum of disease. The key factors in deciding the direction of systemic or local involvement have not, however, been identified. Moreover, the research into HSP is greatly limited due to the lack of a suitable animal model. Genome-wide association studies have provided valuable information through the discovery of novel pathogenic pathways in IgAN, and this could be also applied to patients with HSP and HSPN. We hope there will be further studies on the glycosylation of IgA1 molecules and receptors in the immune deposits in the skin, joints or gastrointestinal tract in HSP patients.

The current therapy has not been proven to alter the natural history of either disease. Thus far there is little evidence to indicate the most effective treatment for HSPN and IgAN, especially in children. Large controlled clinical trials with prolonged follow-up are needed to address these concerns.

References