

Pathogenesis of Henoch-Schönlein purpura nephritis

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Abstract The severity of renal involvement is the major factor determining the long-term outcome of children with Henoch-Schönlein purpura (HSP) nephritis (HSPN). Approximately 40% children with HSP develop nephritis, usually within 4 to 6 weeks after the initial onset of the typical purpuric rashes. Although the pathogenetic mechanisms are still not fully delineated, several studies suggest that galactose-deficient IgA1 (Gd-IgA1) is recognized by anti-glycan antibodies, leading to the formation of the circulating immune complexes and their mesangial deposition that induce renal injury in HSPN.

Keywords Henoch-Schönlein purpura nephritis · Children · Galactose-deficient IgA1 · Pathogenesis · Immune complex

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Introduction

Henoch-Schönlein purpura (HSP) is predominantly a childhood vasculitic disease, characterized by the presence of immunoglobulin A1 (IgA1) dominant immune deposits in the small vessels [1, 2]. While HSP is often a self-limited condition, approximately 40% pediatric patients develop nephritis within 4 to 6 weeks of the initial presentation [2]. Some children with HSP nephritis (HSPN) subsequently have an episode or recurrent episodes of macroscopic hematuria, frequently associated with upper respiratory tract infection without the other clinical features of HSP [3, 4]. Thus, these children's clinical phenotype changes to one of IgA nephropathy (IgAN). As the renal histologic and immunofluorescence microscopy findings in HSPN are indistinguishable from those seen in patients with IgAN [5], it has long been speculated that HSPN and IgAN share common pathogenetic mechanisms and may represent different ends of a continuous spectrum of disease [3]. Knowledge acquired from studies of patients with IgAN may also provide important insights into the pathogenesis of HSPN.

The role of IgA in pathogenesis of HSPN

The postulation that HSPN is a systemic immune-complex mediated disease is supported by the clinical or histological recurrences of HSPN in some patients after transplantation [6, 7]. Although detailed pathogenic mechanisms of HSPN have not been fully elucidated, perturbations in the immune system, including elevations in serum levels of IgA1, IgA1-containing circulating immune complexes and IgA-rheumatoid factors have been documented for patients with HSP [8–11]. Elevated serum levels of IgA and IgA-containing immune complexes were observed in patients

with HSPN [12]. Furthermore, it was noted that all HSP patients have IgA1-circulating immune complexes of small molecular mass, but only those with nephritis have additional large-molecular-mass IgA1-IgG-containing circulating immune complexes [13].

The risk for progression of HSPN was associated with increasing mean proteinuria levels during follow-up and was greater in adults and females [14]. IgA1-containing immune complexes are excreted in elevated amounts in the urine in patients with IgAN and HSPN and may provide a specific marker for disease activity and/or severity in these patients [15, 16].

Levels of serum IgA may not be a diagnostic marker of HSPN

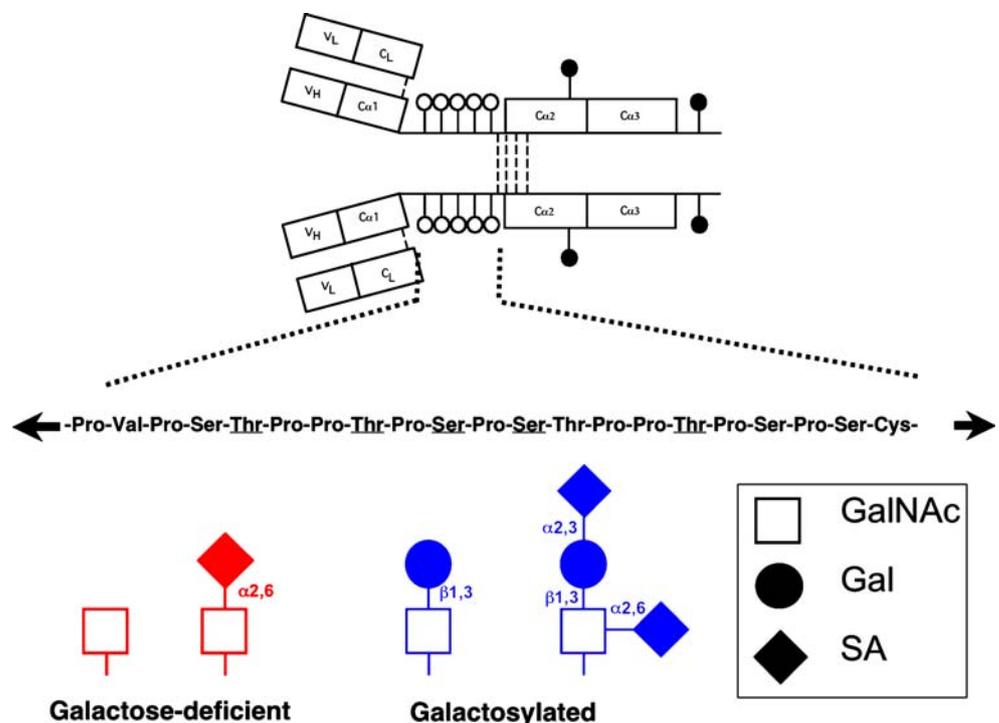
Although serum IgA levels are higher in children with HSP/HSPN than in controls [17], this serum abnormality does not constitute a sensitive diagnostic marker of HSP or HSPN. In a recent retrospective study from Brazil, over 40% children with HSP had elevated serum IgA levels at presentation [18], but the difference in serum IgA levels between patients with and without nephritis was not statistically significant. On the other hand, in spite of high levels of circulating serum IgA in patients with multiple myeloma, HSPN cases have rarely been reported in these patients [19]. These observations argue against the assumption that high serum IgA alone predisposes patients to nephritis.

Abnormal glycosylation of IgA1 and its role in the pathogenesis of HSPN

HSPN is similar to IgAN in that IgA1, but not IgA2, is found in the circulating immune complexes and in mesangial immune deposits [12, 20, 21]. Only humans and higher primates have IgA1 [22]. As depicted in Fig. 1, the human IgA1 molecule has a hinge region containing up to six *O*-linked glycan chains [23, 24] consisting of *N*-acetylgalactosamine (GalNAc), usually with a β 1,3-linked galactose (Gal) attached to it [25, 26]. GalNAc and/or Gal may or may not be sialylated and serum IgA1 from normal healthy subjects predominantly has the Gal-GalNAc disaccharide in its mono- and di-sialylated forms [27, 28].

Similarly as in patients with IgAN, increased galactose-deficient IgA1 (Gd-IgA1) levels have been detected in patients with HSPN [29, 30], but not in subjects with other glomerular diseases. With several lines of evidence, Gd-IgA1 now assumes a pivotal role in the pathogenesis of both IgAN and HSPN. Using GalNAc-specific lectin from *Vicia villosa*, patients with HSPN were shown to have increased lectin binding, indicating elevated levels of Gd-IgA1, while the levels of Gd-IgA1 in patients with HSP without nephritis were similar to healthy controls [29]. We recently reported, using GalNAc-specific lectin from *Helix aspersa*, that the serum levels of Gd-IgA1 were higher in children with IgAN and HSPN compared to healthy controls and patients with C1q nephropathy [30]. Impor-

Fig. 1 IgA1 and its hinge region with *O*-linked glycans (white circles) and *N*-linked glycans (black circles). Underlined amino acids denote usual sites of attachment of as many as five *O*-linked glycans [99]. Examples of galactose-deficient (in red color) and galactosylated (in blue color) *O*-linked glycans in the hinge region of human circulatory IgA1 are shown at the bottom. GalNAc, *N*-acetylgalactosamine; Gal, galactose; SA, sialic acid



tantly, the median levels of serum Gd-IgA1 in children with HSP without nephritis did not significantly differ from those in healthy controls [30]. These data corroborate a potential pathogenic role for Gd-IgA1 in HSPN. Moreover, IgA molecules in the skin immune deposits of patients with HSP regardless of renal involvement are exclusively of IgA1 subclass [31], but there have been no studies on the glycosylation of these IgA1 molecules.

The biosynthetic origin of Gd-IgA1

There are two major sites with IgA1-producing cells: mucosal tissues and bone marrow. Both have been suggested as possible sites of production of the aberrantly glycosylated IgA1 [32–39]. Reduced galactosylation of IgA1 *O*-glycans has been suggested by the results of lectin ELISA [29]; these finding correlated with the observation of reduced activity of β 1,3-galactosyltransferase in the peripheral B cells of patients with IgAN and HSPN [40–42]. The primary defect that leads to the production of such abnormally glycosylated IgA1 is probably heritable [43]. Moreover, Suzuki et al. have recently immortalized and cloned B cells from patients with IgAN that synthesized and secreted an undergalactosylated form of IgA1 [44]. Such glycosylation defects, due to complex changes in expression of specific glycosyltransferases with reduced expression of β 1,3-galactosyltransferase and elevated expression of GalNAc-specific α 2,6-sialyltransferase, were detected in patients with IgAN and HSPN, but not in patients with HSP without nephritis or healthy controls [40, 44, 45]. These data suggest that premature sialylation may contribute to the aberrant IgA1 *O*-glycosylation in IgAN and these cell lines provide a new model for future studies on the mechanisms leading to aberrant IgA1 *O*-glycosylation in IgAN and HSPN.

Interestingly, IgG in the serum and IgG produced by cloned IgG-secreting cells from patients with HSPN had elevated levels of IgG against Gd-IgA1 compared to those from HSP patients without nephritis and controls [40, 46]. The possible origin and role of these anti-glycan antibodies in the pathogenesis of HSPN needs further study. However, they now appear to be the major factor responsible for the formation of the nephritogenic immune complexes, consistent with the previously described large-molecular mass IgA-IgG complexes in the circulation of patients with HSPN [13].

Which sites on IgA1 contain aberrantly glycosylated *O*-glycans?

The assays based on the binding of GalNAc-specific lectins to IgA1 indicated the presence of aberrant glycosylation in

the IgA1 molecules; the assay itself cannot assess whether all the sites contain these anomalies or whether only specific sites are affected. Analysis of the IgA1 molecules from patients with IgAN and HSPN shed some light on the localization of aberrant glycans. Use of bacterial IgA-specific proteases together with lectin western blotting and mass spectrometry suggested presence of Gal-deficient *O*-glycans (terminal GalNAc or sialylated GalNAc - see Fig. 1) at T228/S230 and S232 in the hinge region of IgA1 in patients with IgAN; immune complexes containing such IgA1 bound with IgG specific to Gal-deficient IgA1 were able to stimulate proliferation of cultured human mesangial cells [20, 40, 47–49].

Sialylation of IgA1 molecules in IgAN and HSPN

As sialic acid carries a high negative charge, the degree of sialylation may alter interactions of IgA1 with other molecules and thus affect clearance of IgA1 and IgA1-containing immune complexes. Although removal of sialic acid has been shown to increase the aggregation of IgA1 molecules [50, 51], in a recent study by Leung et al., neuraminidase treatment (removal of sialic acid) significantly reduced the binding capability of polymeric IgA1 from IgAN patients to human mesangial cells in vitro [52]. It is therefore of interest that a portion of IgA1 from patients with IgAN is Gal-deficient and over sialylated [44, 53].

Possible mechanisms involving Gd-IgA1 in the development of HSPN

Figure 2 depicts a proposed mechanism of how aberrantly glycosylated IgA1 may become nephritogenic. Polymeric Gd-IgA1 molecules are recognized by naturally occurring anti-glycan IgA1 or IgG and circulating immune complexes are formed [20, 40, 50, 54–57]. Due to their size, Gd-IgA1-containing immune complexes are less efficiently taken up by the asialoglycoprotein receptor in the liver and catabolized and their amounts increase in the circulation [58, 59]. These complexes may then deposit in the renal mesangium and incite glomerular injury, likely due to the binding to mesangial cells leading to cellular activation. Consequently, mesangial cells start to proliferate and overproduce extracellular matrix components, cytokines and chemokines [29, 60–62]. CD71 (transferrin receptor), was found to be a receptor for polymeric IgA1 on the mesangial cells, and could provide a mechanism for how the Gd-IgA immune complexes bind to the mesangial cells [63]. Expression of CD71 on the mesangial cell surface was increased in pediatric patients with IgAN and HSPN as compared to children with other forms of glomerular disease [63]. The

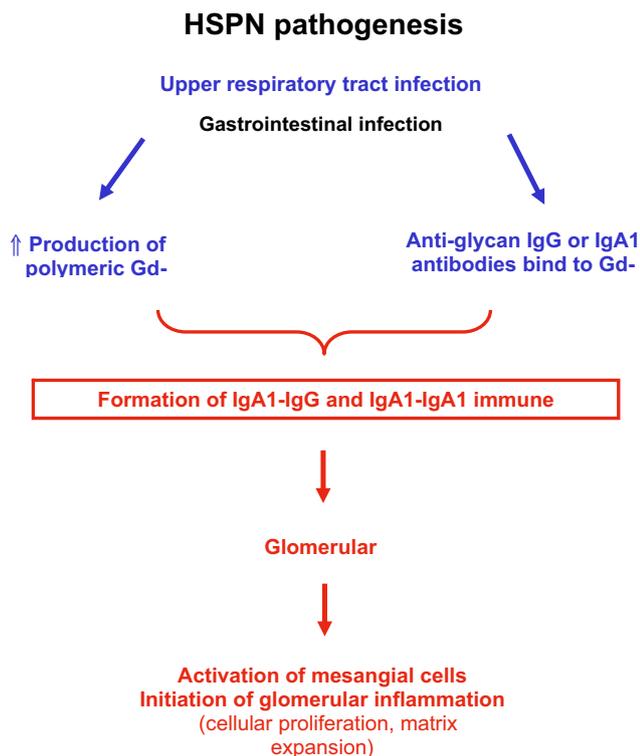


Fig. 2 Possible role of IgA1 and IgA1-containing immune complexes in the pathogenesis of HSPN

intensity of CD71 expression associated with the degree of cellular proliferation rather than the intensity of the IgA staining. Hence, the processes involving IgA1 mesangial deposition, the molecular mechanisms underlying the interaction of IgA1-containing circulating immune complexes and cell receptors that lead to mesangial cell activation and initiation of glomerular inflammatory processes need to be more completely delineated.

Composition of immune deposits in HSPN

While Gd-IgA1-containing immune complexes are increasingly recognized as a major player in the pathogenesis of HSPN [29, 30], other components in these immune complexes have also been examined for their possible pathogenetic roles. Although it has been reported that IgG contents in the IgA-containing circulating immune complexes from patients with HSPN were higher than those with IgAN [64, 65], IgG deposition is not a universal finding in renal biopsies from patients with either disease [13, 66–68]. Likewise, IgM deposits were inconsistently demonstrated in the glomerular deposits of patients with HSPN [67, 68]. Thus, the roles of IgG and IgM in pathogenesis of HSPN still need further elucidation. J-chain has also been demonstrated on renal biopsies from

patients with IgAN, consistent with the presence of polymeric IgA1 [67, 68].

Glomerular depositions of other components, including kappa and lambda light chains, are also variably demonstrated in HSPN. In patients with IgAN, lambda light chains were found predominantly over kappa light chains [69, 70]. However, the ratio of lambda chains to kappa chains in the mesangial deposits remains about equal in patients with HSPN [71]. The discrepancy in synthesis of different types of light chains in patients with IgAN and HSPN, and their implications in pathogenesis, is not clear.

Potential role of complement system in the pathogenesis of HSPN

Complement activation appears to play an important role in the pathogenesis of IgAN and HSPN, as glomerular complement activation may initiate the inflammatory cascade and enhance glomerular injury [72]. Although hypocomplementemia has been reported in some patients with HSPN [73, 74], it is usually transient and not related to the severity of the diseases. Since the first report on higher incidence of either C4A or C4B null variants, or both, in patients with IgAN and HSP [75], C4A and C4B deficiencies had also been described in patients with HSPN [76, 77]. In Iceland, the frequency of C4B null alleles was significantly increased in children with HSP as compared to controls [78]. The role of partial or complete C4 isotype deficiencies in pathogenesis of HSPN may relate to impairment in the ability to solubilize and/or clear immune complexes [79], but the precise mechanisms involved remain speculative.

Although it has long been known that the alternative complement pathway is activated in patients with IgAN and HSPN [80], attention has shifted to the lectin pathway. This third pathway of complement activation is initiated by mannose-binding lectin (MBL). MBL also forms complexes with MBL-associated serine protease-1 (MASP-1), MASP-2 and MASP-3 [81–84]. Recent studies suggested that complement activation occurs through both the alternate and lectin pathways in patients with IgAN [81, 82].

The long pentraxin 3 (PTX3), a complement related protein, has been detected in the renal tissue of patients with glomerulonephritis [85]. In renal biopsies from patients with IgAN, intense staining for PTX3 was observed in the expanded mesangial areas and was localized to the glomerular mesangial and endothelial cells. Normal renal tissue and biopsies from patients with other glomerular nephropathies were negative for PTX3 expression in glomeruli. Cultured human mesangial cells synthesized PTX3 when stimulated with TNF- α and IgA, and exhibited specific binding for recombinant PTX3 [85].

These observations suggest potential role for PTX3 in the modulation of glomerular injury in IgAN and likely also in HSPN. PTX3 appears to be involved in the classical and not the alternative pathway of complement activation [86]. Thus, its role in pathogenesis of HSPN, where the complement activation is alternative and/or lectin pathway mediated [81, 82], will require further clarification.

Possible role of cytokines in the pathogenesis of HSPN

In cell lines isolated from patients with IgAN, but not in those from controls, cytokine stimulation reduced the expression of β 1,3-galactosyltransferase and its molecular chaperone Cosmc, but increased the expression of α 2,6-GalNAc-sialyltransferase II. As a result, the synthesis of sialylated GalNAc was enhanced [87], pointing to a potential role of some cytokines in the pathogenesis of IgAN; these aspects in HSPN require further investigations.

Other possible pathogenic mechanisms of HSPN

Masuda et al. showed that nephritis-associated plasmin receptor (NAPlr), a group A streptococcal antigen, may also have pathogenetic role in a subset of patients with HSPN [88]. Among 33 children with biopsy proven HSPN, 30% had segmental or global mesangial deposition of NAPlr antigen, comparing to 3% in other children with non-HSPN glomerular diseases (half of these children had IgAN). The exact pathophysiologic mechanism, if any, and the relationship between NAPlr and HSPN, needs further investigation.

In a study by Davin et al, 22 children with HSPN were compared to 16 children with IgAN. In their cohort, elevated plasma IgE levels were more commonly found in patients with HSPN (77% versus 44%) [89]. They hypothesized that the IgA containing immune complexes could enhance local IgE production via stimulation the dermal and intestinal mast cells. Deposition of the IgA immune complexes was further enhanced with the subsequent increase in local capillary permeability [89]. Notwithstanding the higher incidence of elevated plasma level of IgE in patients with HSPN, the pathogenetic roles of IgE remains unclear, as the mast cell is not usually found in the mesangium [90, 91].

Eosinophil activation has also been proposed to play a role in the pathogenesis of HSPN [92–94]. Children with HSP, compared to those with IgAN or healthy controls, have higher levels of serum eosinophil cationic protein (ECP) [93]. And the levels were even higher in patients with HSPN. In a recent study from Japan, patients with HSPN were also demonstrated to have higher serum

concentrations of ECP and interleukin-5 [93]. In another study from China, serum levels of ECP were higher only when the patients had active HSPN [94]. These studies suggested that ECP might have a role in the initiation of nephritis in patients with HSP.

Serum IgA anti-cardiolipin and anti-phosphatidylserine-prothrombin complexes were both elevated and associated with the severity of proteinuria in a group of Japanese adult patients with HSP [95]. The role of these IgA antibodies in the pathogenesis in HSP and HSPN is not clear.

Recently, renal expression of alpha-smooth muscle actin (α -SMA) has also been associated with progression of renal injury in patients with HSPN [96]. Thirty five patients in Japan with biopsy proven HSPN were studied in 3 groups: 1) nephritis with histological class (classification system used by the International Study of Kidney Disease in Children [97]) of stage II or less, 2) histological stage III or greater and a good prognosis, and 3) histological stage II or greater and poor prognosis. All patients, except those in group 1, had repeated biopsy during the course of follow-up. The authors found that the mean scores for glomerular and interstitial α -SMA staining at first biopsy were higher in HSPN patients with crescents. And at second biopsy, α -SMA expressions were also higher in patients with poor prognosis. Although α -SMA is the predominant actin isoform within vascular smooth muscle and the mechanism of phenotypic changes of mesangial cells and increased expression of α -SMA in patients with HSPN is unclear, these observations did suggest that increased renal α -SMA expression may be an early histological indicator of progression of HSPN. Similarly, increased expression of α -SMA in the tubulointerstitial area, but not in glomeruli, was associated with poor prognosis of patients with IgAN [98].

Conclusions

HSPN is a common pediatric renal disease with potential long-term morbidity. Co-operative efforts of clinical and basic research scientists have provided valuable information and insights on the pathogenetic mechanisms of HSPN. Although these mechanisms are far from being completely understood, multiple possible players have been identified. Recent data suggest that Gd-IgA1 is likely to play a pivotal role in the formation of nephritogenic immune complexes (Fig. 2) and further investigations as to its role are ongoing.

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Conflict of interest The authors have no conflict of interest to report.

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