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EDUCATIONAL REVIEW

Henoch–Schönlein purpura nephritis

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Abstract Henoch–Schönlein purpura (HSP) is the one of most common types of systemic vasculitis in childhood. Glomerulonephritis (HSPN) occurs in 30–50 % of HSP patients, mostly in a mild form but a small percentage of patients present with nephrotic syndrome or renal failure. HSPN is caused by the glomerular deposition of immunoglobulin A1 (IgA1)-containing immune complexes in the mesangium, the subepithelial and the subendothelial space. Formation of the IgA1 immune complex is thought to be the consequence of aberrantly glycosylated IgA1 molecules secreted into the circulation and their subsequent recognition by IgG specific for galactose-deficient IgA1. Mesangial proliferation and renal damage are triggered by the deposited immune complexes, which likely require activation of the complement system. Whereas other organ manifestations of HSP are mostly benign and self-limiting, HSPN might lead to chronic renal disease and end stage renal failure, thereby justifying immunosuppressive treatment. Long-term renal outcome correlates to the severity of the initial clinical presentation and the extent of renal biopsy changes, both of which are used to decide upon a possible treatment. As there are no evidence-based treatment options for severe HSPN, a large variety of therapeutic regimens are used. Prospective randomized controlled treatment studies are needed, but the low incidence of severe HSPN renders such studies difficult.

Keywords IgA nephritis · Galactose-deficient IgA · Immunosuppression · Leucocytoclastic vasculitis · Immune complex nephritis · Nephrotic syndrome

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Introduction

Henoch–Schönlein purpura (HSP) is a small-vessel, leucocytoclastic vasculitis which can cause a large variety of symptoms in different organs [1]. As renal involvement is the main origin of the resulting chronic disease, the kidney should be closely observed and—in case of significant involvement—treated in accordance with the best evidence obtainable. Current treatment options are mainly based on anecdotal evidence and results from studies on immunoglobulin A-nephritis (IgAN) patients. If these current treatments are to be improved, better prognostic markers and a better understanding of the pathophysiology are required. This review summarizes important aspects of the epidemiology and the clinical course of HSP-nephritis (HSPN), including renal biopsy findings and their potential prognostic significance. Prevailing concepts on etiology and pathophysiology as well as different treatment approaches are discussed.

Epidemiology of HSP and HSPN

Henoch–Schönlein purpura is one of most common types of systemic vasculitis in childhood, with a slightly higher incidence in boys than in girls. Between six and 24 per 100,000 children below 17 years of age are affected, depending on the ethnic background of the children [2]. The incidence is highest in children aged 4–7 years (up to 70 cases/100,000 children per year) and in children of Asian descent [2]. The diagnostic criteria for HSP must include a palpable purpura. In addition, either diffuse abdominal pain, acute arthritis, arthralgia, hematuria, proteinuria or a tissue biopsy showing predominant IgA deposition should be present [3]. In most cases the patient presents with symptoms characteristic of the disease, and the diagnosis is readily made. HSP frequently follows a respiratory tract infection, and a large variety of different viral and

bacterial pathogens have been implicated as trigger(s) of the disease. A positive throat culture for group A beta-hemolytic streptococci has been found in 20–30 % of HSP patients [1, 4], and glomerular deposition of a streptococcal antigen may be responsible for some of the cases of HSPN [5]. HSP is generally self-limited in children, although relapses occur in one-third of cases. Renal involvement may become chronic and lead to permanent organ damage [1, 4], determining the long-term prognosis of the disease. A high proportion of HSP patients (30–50 %) either have or develop hematuria and/or proteinuria as a symptom(s) of HSPN, both of which are mostly of minor extent and self-limited [1, 6]. Of all HSP patients with abnormal urinalysis, a minority develop severe glomerulonephritis, which is associated with an increased risk of long-term chronic kidney disease [7, 8]. Children with no urinary pathology during the first 6 months after the onset of HSP do not develop renal impairment during the long term follow-up [6].

Clinical course of HSPN

About 20 % of HSPN patients (7 % of all HSP cases) develop either a nephritic or a nephrotic syndrome. Unfortunately, not all studies use the same definitions. Nephritis has been defined as hematuria plus one or two of the following symptoms: hypertension, renal insufficiency and/or oliguria. Nephrotic syndrome is diagnosed when proteinuria is >40 mg/m^2 h, but some studies additionally require either edema or a serum albumin of <2.5 g/dl [6, 7, 9]. These differences in study definitions contribute to the differences in reported incidence and variable outcome results. In patients presenting with HSP, renal involvement occurs in 85 % within 4 weeks of the initial HSP manifestation, in 91 % within 6 weeks and in 97 % within 6 months [6]. Therefore, repeated urinary investigations are recommended for 6 months after the onset of HSP, even in patients in whom all other symptoms have subsided [6]. Results from a meta-analysis of 1,133 unselected patients with HSP demonstrate that long-term renal impairment, defined as persisting nephritic or nephrotic syndrome, renal insufficiency or hypertension, occurred in 19.5 % of these patients with initial nephrotic or nephritic syndrome [6]. Other studies evaluating patients from tertiary care centers with pediatric nephrology services found long-term renal impairment in 33–44 % of patients following the development of HSPN with nephrotic syndrome or nephritis [7, 8, 10]. The risk of suffering from clinically severe HSPN with a higher risk of long-term renal sequelae seems to increase with age [11], but the prognosis of equally severe HSPN is not different in children and adults [12]. The time course of renal impairment is unpredictable in patients at the individual level, and active renal disease may develop after an initially mild nephritis or many years after stable minor urinary abnormalities [7, 10]. In an analysis of 52 adults who had had HSP during childhood, 18 had initially presented with hematuria and/or proteinuria of <40 mg/m^2/h, of whom two (11 %) suffered from active renal disease after a mean follow up of 24.1 years [10]. The severity of renal histological changes also correlates with the renal long-term outcome and, consequently, influences treatment decisions [7, 11]; therefore, a renal biopsy is recommended in the more severe cases of HSPN [13, 14].

Renal biopsy findings

The dominant or predominant finding of glomerular IgA deposition is the hallmark of renal histology in HSPN. IgA deposition is mainly present in the mesangium, but can also be found in the subepithelial and subendothelial space [15]. In the majority of biopsies, the deposition of IgG, C3 and other complement factors can be found in the glomerulus [16]. In addition, a variable extent of acute inflammation or chronic damage is present [17]. As such, HSPN leads to a similar renal pathology as IgAN and can be regarded as part of the histological spectrum of IgAN. Compared to IgAN, HSPN renal biopsy samples are reported to show increased endocapillary proliferation, epithelial crescents, perivascular glomerular IgA, subendothelial/subepithelial IgA deposits and fibrin deposits [18]. The Oxford Classification, based on the identification of histopathological features of renal biopsies and assessment of associations between candidate histopathological predictors and renal prognosis, has improved the predictive value of renal biopsies for IgAN; however, HSPN patients were excluded from the analysis [19, 20]. The Oxford Classification uses a score of mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis and tubular atrophy/interstitial fibrosis to predict the outcome of the IgAN. Extracapillary crescents are not included in the Classification because of their scarcity in the study population. In subsequent studies, the value of this histological classification has also been shown for pediatric IgAN patients [21], but to date it has not been evaluated in HSPN patients. Since the publication of the International Study of Kidney Disease in Children (ISKDC) classification [22], in HSPN, the percentage of crescents has been used for estimating disease severity and predicting outcome. In this clinical context, the extent of the renal histological pathology appears to correlate with the severity of the clinical presentation and long-term prognosis [7, 23]. In a recent analysis, 58 % of the patients with >50 % crescentic glomeruli had a poor outcome compared to only 17 % of patients with fewer or no crescents; this was a significantly different outcome after a mean follow-up of 23 years [23]. Although no randomized prospective study has been undertaken to prove this assumption, most retrospective studies published to date show a correlation between the percentage of extracapillary crescents and outcome. Other

histological markers have been reported to correlate with the clinical severity of HSPN or IgAN, but these have not yet been introduced into clinical practice [17, 24]. For example, IgAN patients whose renal biopsies show mannose-binding lectin (MBL) deposition have a significantly worse renal function and significantly more proteinuria than IgAN patients without MBL deposition [24]. In future, a more detailed set of activity and chronicity markers may be able to increase the predictive value of renal biopsies in HSPN. Howevever, as renal biopsies suffer from sampling bias and only reflect the pathological process at the time of the biopsy, the prognostic significance of renal histology at the level of the individual patient is limited and is regarded by some authors as being less important than the clinical severity of HSPN [10, 25].

Etiology and pathophysiology

Based on the results of a multitude of clinical and experimental investigations, it is believed that in HSPN glomerular deposition of IgA-containing immune complexes from extrarenal sources leads to the renal inflammatory changes and, therefore, that HSPN can be regarded as an immune complex nephritis. In HSPN, IgA deposition can be found not only in the kidney, but also in other organs, such as the skin. IgA deposition recurs in some patients after renal transplantation [26, 27], and after the transplantation of kidneys with mild forms of IgAN, immune complex deposition and nephritic changes decrease and disappear [28], rendering an extrarenal source of IgA very likely. To date, the pathophysiology of IgAN and HSPN seems to be identical, with only quantitative differences, possibly accounting for the different clinical presentation with more acute signs of nephritis in HSPN and a more insidious onset in IgA nephropathy. Most of the patients biopsied 2–9 years after an episode of HSPN show persisting IgA deposition and mesangial expansion, congruent with the diagnosis of IgAN [29]. In both entities, aberrantly glycosylated IgA1 polymers are found in the plasma, which are deposited as immune complexes, but in HSPN larger immune complexes are found than in IgAN [18, 30]. The hinge region of each heavy chain of the human IgA1 molecule carries up to six *O*-glycosylation sites, where a Gal–GalNAc disaccharide is attached. IgA1 from patients with IgAN or HSPN lack galactose residues at these sites (Fig. 1). These aberrantly glycosylated IgA molecules have been shown to form immune complexes with IgG-antibodies specific for galactose-deficient IgA1, thereby inhibiting the binding of the IgA molecules to hepatic receptors and avoiding their internalization and degradation by hepatic cells [31, 32]. In addition, the complexes might be too large to pass through the endothelium to come into contact with hepatic cell surface receptors. In vitro experiments have demonstrated the activation and proliferation of cultured mesangial cells stimulated by large immune complexes containing galactose-deficient IgA1 (Gd-IgA1). For the in vitro stimulatory activity, the size of the immune complexes needs to exceed 800 kDa [33, 34]. The binding of IgG to Gd-IgA1 has been found to correlate with the level of proteinuria and also shown to be a specific test for the diagnosis of IgAN [35]. The authors hypothesized that the occurrence of IgG antibodies directed against the Gd-IgA1 is necessary for the development of IgA nephritis, although in renal biopsies IgG deposition is not always found

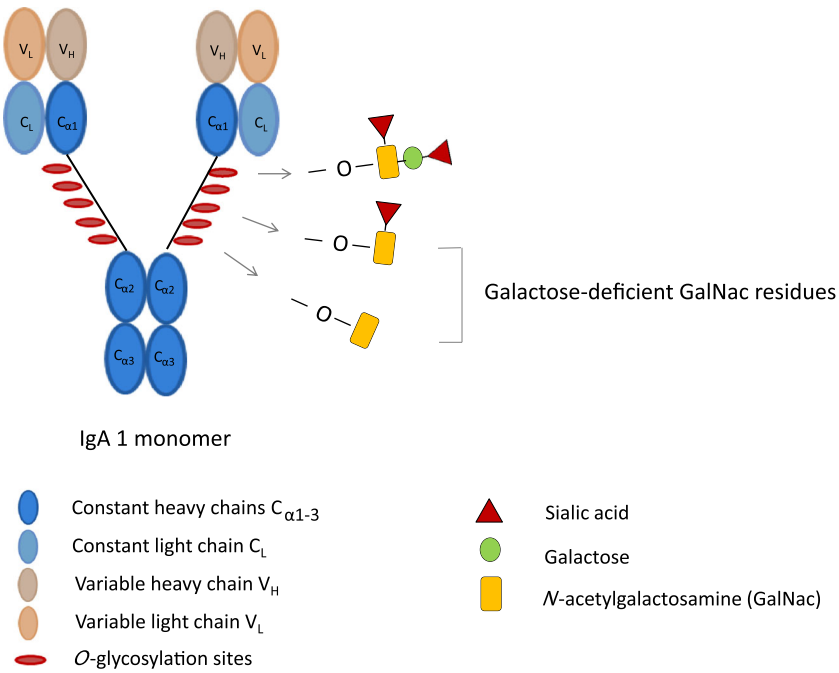

Fig. 1 The immunoglobulin A1 (*IgA1*) monomer is composed of two heavy chains ($C_{\alpha 1-3}$ and V_H) and two light chains (V_L and C_L). Each of the light and heavy chains contains a constant and a variable domain (V_H and V_L). Two of the constant domains of the heavy chains ($C_{\alpha 1}$, $C_{\alpha 2}$) are linked by the hinge region, which carries up to six *O*-glycosylation sites. Attached to the *O*-glycosylation site is an *N*-acetylgalactosamine residue (*GalNac*), to which galactose is bound. Polymeric IgA1 molecules with a reduced content of galactose-carrying GalNac residues (*Gd-IgA1*) are found in Henoch–Schönlein purpura nephritis and IgA-nephritis patients

[35]. The finding of IgA antibodies directed against Gd-IgA1 could explain the lack of IgG deposition, but in a different study although the serum levels of IgA and IgG antibodies against Gd-IgA1 correlated with the clinical progression of IgAN, not all patients had increased levels compared to controls and none showed renal IgG deposition [36]. Therefore, it remains to be proven whether serum antibodies against Gd-IgA1 are a specific requirement for the formation of the renal IgA1-containing immune complexes found in IgAN. The deposition of the IgA1-containing immune complexes appears to be mediated by binding to the mesangial transferrin receptor 1 (CD71) and CD89 [37, 38]. In transgenic mice expressing human IgA1 and CD89, IgA and CD89 deposition occurs in the mesangium, and IgA nephropathy develops. In this model, soluble CD 89 binds to IgA1, induces mesangial expression of the transferrin receptor 1 and acts together with cell surface transglutaminase 2, leading to the binding of IgA–CD89 to the transferrin receptor 1 on the mesangial cell surface. CD89 deposition has also been found in renal biopsies from patients with IgAN. Thus, the interaction between IgA1, soluble CD89, transglutaminase 2 and transferrin receptor 1 may contribute to the development of IgA nephropathy [37], but it remains to be shown whether this interaction is an important part of the pathophysiology and whether it is also involved in the development of HSPN.

After deposition, the activation of the complement system appears to play a major role in the pathophysiology. In a mouse model for IgA nephritis, mice lacking either C3 or IgG did not develop the IgAN phenotype [39]. Also, glomerular MBL deposition has been found to be associated with a severe clinical presentation, and initial C4d deposition has been shown to be a risk factor for a worse clinical outcome [24, 40]. The deposition of Gd-IgA1-containing immune complexes stimulates mesangial cells to secrete chemokines, such as transforming growth factor beta or tumor necrosis factor alpha, which alter podocyte function [41].

A genetic disposition for developing IgAN or HSPN is highly likely to be part of the etiology. The incidence of both diseases varies between different ethnic groups. IgAN and HSPN have been described to run in families, and in a pair of identical twins, one sibling developed IgAN and the other developed HSPN [42, 43]. Genome-wide association studies have identified several susceptibility genes for IgAN [44–46]. In addition to risk alleles in the major histocompatibility complex, the deletion of CFHR1 and CFHR3 was found to be protective against the development of IgAN, again pointing towards a role of the complement system in IgAN. Variations in the identified risk loci are distributed at different frequencies in different populations, thereby explaining the wide range in the incidence of IgAN among different ethnic groups [47]. No genome-wide association study has yet been performed in patients with HSPN, but it has been shown that Gd-IgA1 serum levels are inherited in both IgAN and HSPN, suggesting that the genetic predisposition for developing HSPN is the same as that for developing IgAN [48]. In summary, acute and chronic glomerular damage in HSPN is thought to be the result of mesangial Gd-IgA1-containing immune complex deposition, potentially mediated by mesangial receptors, and the ensuing complement-mediated stimulation of the mesangial cells, leading to their proliferation and cytokine secretion (Fig. 2).

Treatment

Treatment decisions in HSPN are difficult due to the large proportion of patients with a favorable prognosis and the unpredictable clinical course in individual patients. In addition, no evidence-based treatment is as yet available, even for the severe cases. In the past, this has led to a large diversity of treatment approaches and an extensive literature comprising reports on treatment effects in small, uncontrolled and mainly

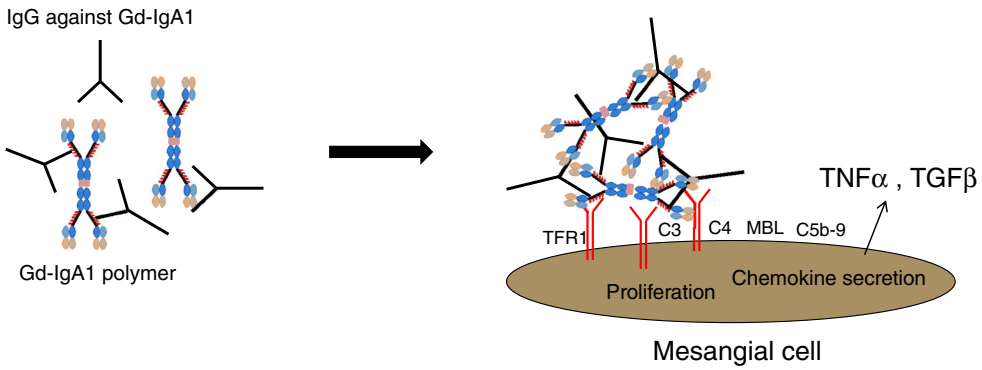

Fig. 2 Galactose-deficient IgA1 (*Gd-IgA1*) polymers are recognized by immunoglobulin G (IgG) antibodies forming circulating large IgG-IgA1 immune complexes. The immune complexes (>800 kDa) bind to renal mesangial cells, probably at least partially mediated by the transferrin receptor 1 (*TFR1*), leading to mesangial deposition of complement factors [C3, mannose-binding lectin (*MBL*), C4, C5b-9], mesangial cell proliferation and chemokine secretion. *TNFα* Tumor necrosis factor alpha, *TGFβ* Transforming growth factor beta

retrospective studies. As the long-term prognosis appears to be clouded in patients with renal failure, nephrotic syndrome and/or a high percentage of histopathological extracapillary lesions, most pediatric nephrologists treat those patients with immunosuppressive therapy. In several retrospective studies, a late initiation of therapy was linked to a worse outcome [49–52]. Therefore, despite the possibility of a spontaneous remission, it might be advisable to treat severely affected patients as early as possible, even though the value of an early treatment regimen has not yet been proven. The current therapeutic approach is based on the assumed pathophysiology and published case series of HSPN. As the pathophysiology of HSPN appears to be similar or identical to that of IgAN, results from studies with IgAN patients are also a valuable source of information for the development of potential treatment options. Therapy with angiotensin-converting enzyme inhibitors (ACEIs) is based on evidence from a prospective study in pediatric IgAN patients [53]. A variety of other immunosuppressive therapies have also been assessed. Either intravenous or oral corticosteroids are part of most treatment regimens, and there is some evidence of their beneficial effect on the long-term outcome of adult IgAN patients, who had significantly less renal failure and proteinuria 10 years after an initial steroid treatment than control patients [54]. In analogy to patients with rapidly progressive glomerulonephritis of different etiology, cyclophosphamide has been used for the most severe manifestations of HSPN [52]. Other immunosuppressive therapies, such as azathioprine, mycophenolate mofetil, cyclosporine A or rituximab, have been reported to be efficacious in individual cases or small patient series [17, 55–57]. Interestingly, early-onset plasmapheresis was found to be beneficial in some patients even without additional immunosuppression [50, 58]. Based on data reported in the literature, different treatment regimens are justifiable. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend an approach as in IgAN patients, but do not take into account the more acute onset of HSPN with more aggressive lesions in renal histology. Unless crescentic glomerulonephritis (>50 % crescents) with deteriorating renal function and/or nephrotic syndrome is present, an initial therapy with ACEI or angiotensin receptor blocker for only for 3–6 months is recommended by these guidelines [59]. In the opinion of other experts, this approach may lead to undertreatment mainly because an acute and potentially aggressive glomerular inflammation is either not treated or its immunosuppressive treatment is delayed for several months [60]. The German Society of Pediatric Nephrology has recently proposed an early treatment approach for patients with major renal involvement based on the available experience from HSPN and IgAN treatment studies, stratified according to the clinical and histological presentation of the disease [13]. Following this treatment proposal, HSPN patients with nephritic syndrome, nephrotic syndrome or cellular glomerular crescents will be placed on a standardized 2-month initial corticosteroid therapeutic regimen, followed by additional immunosuppression in patients with insufficient response 3–6 months after treatment initiation. Due to the rarity of severe HSPN, standardization of the diagnostic and therapeutic approach on at least a national scale, but preferably on a multinational level, is necessary to gain more experience and move towards an evidence-based treatment. Future treatment strategies need to be evaluated in large multicenter studies. As the incidence of HSPN is highest in children and given that most children with active glomerulonephritis present to tertiary care centers, such studies might be best undertaken in children, but the results of such studies might also influence the treatment considerations for adult HSPN and IgAN patients.

Key summary points

- HSPN may develop up to 6 months after HSP, and repeat urinary investigations are required for 6 months after onset in all HSP patients
- HSPN is mostly mild and self-limited but may lead to chronic kidney disease
- Genetic susceptibility increases the risk of developing HSPN
- Deposition of Gd-deficient IgA1 in the mesangium, subepithelial and subendothelial space triggers glomerular damage
- Different immunosuppressive therapies or plasmapheresis are used in severe cases

Key research points

- Origin of galactose-deficient IgA1
- Elucidation of the role of complement
- Definition of a genetic and/or histological marker set that correlates to renal prognosis
- Search for a therapeutic agent which interferes with the immune complex formation or deposition
- Initiation of prospective randomized therapy trials

Multiple choice questions (answers are provided following the reference list)

1) For how long should the urine be tested for hematuria and albuminuria in patients with HSP?

   A) 4 weeks
   B) 3 months
   C) 6 months

D) 12 months
E) Continuously every 6 months

2) In which histological compartment is IgA mainly deposited in a renal biopsy sample of HSPN patients?

A) Endothelial surface
B) Glomerular basal membrane
C) Peritubular interstitium
D) Bowman's space
E) Mesangium

3) The deposited immune complexes in HSPN typically contain:

A) IgA2, C3 and IgG
B) Galactose-deficient IgA1
C) IgM–IgA2 immune complexes
D) IgA1–IgA2 immune complexes
E) Fibrin

4) In HSPN, aberrant glycosylation is found where?

A) In the variable part of the light IgA1 chain
B) In the constant part of the heavy IgA2 chain
C) In the hinge region of the heavy IgA1 chain
D) In the constant part of the light IgA1 chain
E) In the junction protein of both IgA1 and IgA2 polymers

5) The estimated risk of chronic kidney disease in pediatric HSPN patients with nephritic or nephrotic syndrome is

A) 5 %
B) 10 %
C) 20 %
D) 50 %
E) 75 %

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Answers to the multiple choice questions

1) C
2) E
3) B
4) C
5) C