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PERSPECTIVES IN RENAL MEDICINE

What is the difference between IgA nephropathy and Henoch-Schönlein purpura nephritis?

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What is the difference between IgA nephropathy and Henoch-Schönlein purpura nephritis? Henoch-Schönlein purpura nephritis (HSPN) and IgA nephropathy (IgAN) are considered to be related diseases since both can be encountered consecutively in the same patient, they have been described in twins, and bear identical pathological and biological abnormalities. Apart from the presence of extrarenal clinical signs found only in HSPN, other differences are noticed between the two diseases. The peak age ranges between 15 and 30 years for a diagnosis of IgAN, whereas HSPN is mainly seen in childhood. Nephritic and/or nephrotic syndromes are more often seen at presentation in HSPN. In contrast to IgAN, HSPN has been described in association with hypersensitivity. Endocapillary and extracapillary inflammations as well as fibrin deposits in the glomerulus are more frequent in HSPN. No major biological differences have been found between the two illnesses, except for a larger size of circulating IgA-containing complexes (IgA-CC) and a greater incidence of increased plasma IgE levels in HSPN. As tissue infiltration by leukocytes is a major feature of HSPN vasculitis, a possible role of a more potent activation of the latter cells by IgA-CC and/or circulating chemokines in HSPN should be considered. Further studies are required to elucidate this possible mechanism as well as the role of hypersensitivity in HSPN.

Heberden was probably the first to report a case of Henoch-Schönlein purpura [1]. He described a five-year-old boy presenting with generalized edema, macroscopic hematuria associated with a purpuric rash, colicky pain, bloody stools, and arthralgia. The association between an erythematous or purpuric rash and joint pain was reported again by Schönlein [2]. Schönlein's former pupil, Henoch, described four children with a combination of rash, colic, bloody diarrhea, and joint pain [3] and, in a later report added hemorrhagic nephritis to the list of components of the syndrome [4], thus completing the modern definition of the disease. The latter has been recently formulated by the International Consensus Conference on Nomenclature of Systemic Vasculitides as "a vasculitis with IgA-dominant immune deposits affecting small vessels and typically involving skin, gut, and glomeruli and associated with arthralgias or arthritis" [5].

In 1968, Berger and Hinglais reported for the first time a form of glomerulonephritis characterized by mesangial accumulation of IgA associated with less intense deposits of IgG and/or C3 [6]. Light microscopy revealed mainly focal and segmental mesangial proliferation and matrix expansion, whereas electron-dense deposits were demonstrated by electron microscopy between the glomerular basement membrane and mesangial cells (MCs). The finding of glomerular IgA deposits led later on to the denomination of IgA nephropathy (IgAN). At the same time, Urizar et al showed similar pathological findings in renal biopsies of patients with Henoch-Schönlein purpura nephritis (HSPN) [7].

Henoch-Schönlein purpura nephritis and IgAN currently are considered to be related diseases since both can be encountered consecutively in the same patient [8], have been described in identical twins [9], and bear identical pathological and biological abnormalities [10, 11]. The present review points out the similarities and differences between the two diseases in order to propose pathogenetic mechanisms that may explain the occurrence of systemic vasculitis in HSPN only (Tables 1 and 2).

PREVALENCE, DISTRIBUTION, AGE, AND SEX

IgA nephropathy represents 1.6% of all new cases of end-stage renal failure (ESRF) recorded in the European Dialysis and Transplantation Association registry for the year 1988 [12]. In a large series of children with ESRF recorded in France [13], 1.3% had IgAN. The overall prevalence of IgAN is not known. However, the overall frequency of IgAN in renal biopsies has been reported in several series as reviewed by Emancipator [14]. The frequency varies from 4 to 44% of all renal

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Table 1. Similarities of IgAN and HSPN

Clinical features
More frequent in male
Gross hematuria simultaneous to a respiratory infection
Frequent evolution to chronic renal insufficiency
Relapse after transplantation
Histology
Predominant mesangial IgA1 deposits
Electron dense deposits in the mesangium
Mesangial proliferation
Cutaneous IgA deposits
IgA immunological abnormalities
Abnormal IgA1 glycosylation pattern
Increased IgA plasma levels
Increased IgA1 plasma levels
Increased polymeric IgA plasma levels
Circulating IgA-containing complexes
Increased IgA synthesis by B lymphocytes
Other immunological abnormalities
Reduced function of the reticuloendothelial system
Low grade complement activation
High IgE plasma levels
High incidence of C4B null phenotype
Increased TNF-α and IL-1 urinary excretion
Abnormalities of mucosal barriers
Increased intestinal permeability to ^{51}Cr EDTA
Increased long carbon monoxide diffusion
Coagulation abnormalities
Intact cross-linked fibrin (XFb)
Increased von Willebrand factor plasma levels

Abbreviations are: TNF-α, tumor necrosis factor-α; IL-1, interleukin-1.

Table 2. Differences between IgAN and HSPN

	IgAN	HSPN
Clinical features		
Extra-renal symptoms	−	+
Age at onset	>15 y	<15 y
Nephritic/nephrotic syndrome	+/−	+++
Risk of chronic renal failure (CRF)	+	++
Hypersensitivity	−	+
Secondary forms	++	+/−
Histology		
Endocapillary proliferation	+/−	++
Epithelial crescents	+/−	++
Perivascular glomerular IgA	+/−	++
Subepithelial/subendothelial dense deposits	+/−	++
Increased lambda/kappa ratio	+	−
Fibrin deposits	+/−	++
Circulatory IgA abnormalities		
IgA-containing complexes size	7S-19S	>19S
Other blood immunologic abnormalities		
High IgE plasma levels	+	++
High eosinophil cationic protein (ECP) plasma levels	−	+

biopsies. This wide range depends on criterion for performing a biopsy, but also on racial features [14]. IgAN seems to be a relative rarity in blacks, in both the United States and Africa. American Indians, on the other hand, have a higher incidence of IgAN than the world population at large.

The peak age at the time of the first clinical manifestations of primary IgAN ranges between 15 and 30 years [15]. Affected children do not present symptoms before the age of three years; thereafter, they are evenly spread through childhood [16]. Worldwide, the male-to-female sex ratio is 2:1 [14].

The proportion of HSPN as cause of ESRF in adults is minimal [17], whereas it can reach up to 5.1% in children [13]. The prevalence of HSP is difficult to assess from previously reported studies. Epidemiological studies on HSP performed to date have not taken into account the presence of IgA deposits in tissue as a diagnostic criterium. This is important since the latter is the gold standard of distinguishing HSP from other vasculitides such as hypersensitivity vasculitis [5]. However, it is generally agreed that the incidence of HSP decreases with age [17]. The lack of using appropriate diagnostic criteria possibly explains why the proportion of patients presenting with renal involvement varies considerably among the different reports (20 to 100%) according to a review from White and Yoshikawa [18]. Another explanation might reside in the use of different criteria for diagnosing HSPN, since many of the earlier studies did not utilize serial routine urinalysis, and transient microscopic hematuria was probably missed [18]. Finally, an underestimation could result from the existence of renal lesions without any clinical signs and the delay that can occur between the initial signs and renal symptoms. Indeed, the incidence of renal involvement increases with time after HSP diagnosis in children [19]. Kaku, Nohara, and Honda have shown that the latter percentage increased progressively to reach 35.4% after one year and continued to increase thereafter [19]. In contrast to studies in children, the incidence of renal involvement in HSP in adults has been more precisely assessed in one study using a cohort of patients in whom the diagnosis was made by showing the characteristic leukocytoklastic skin vasculitis accompanied by IgA deposits [20]. This study demonstrated that 49% of patients presented with abnormal urinary signs. In HSPN also, the sex ratio (male:female ratio 1.5) shows an increased frequency in males [21].

CLINICAL FEATURES

The most prominent clinical feature of IgAN is synpharyngitic macroscopic hematuria. Less often, macroscopic hematuria in IgAN is accompanied by other infections (pulmonary, intestinal, or urinary) [22]. In Western countries, macroscopic hematuria is the most frequent initial presentation in children (76 to 100%) [23], followed by the fortuitous finding of microscopic hematuria accompanied or not by proteinuria (0 to 19%). In contrast to children, microscopic hematuria and/or proteinuria are the most frequent initial presentations in adults (28 to 61% vs. 12 to 43% for macroscopic hematuria) [24]. Renal insufficiency and hypertension are less often encountered as initial signs, but are more frequent at

first presentation in adults (15 to 36% and 31 to 43%, respectively) [24] than in children (4 to 12% and 0 to 18%, respectively) [23]. In a few cases, a nephrotic or a nephritic syndrome can be the first sign in adults (4 to 13%) [24] but also in children (4 to 8%) [23]. Finally, in some adult patients, the diagnosis is made when ESRF is already present [25].

A history of a recent or simultaneous infection is also common in HSP. Indeed, the latter is reported in one third to two thirds according to the studies [17]. Although any of the four major components of the syndrome (rash, joint pain, abdominal symptoms, and renal disease) may be present before the other, it is rare for the renal disease to do so [17]. According to a single series from a tertiary center [25], initial signs of HSPN are hematuria and proteinuria in 50% of patients, acute nephritic syndrome in 8%, nephrotic syndrome in 13%, and an association of nephritic and nephrotic syndrome in 29% of patients [25]. As expected, the incidence of mild symptoms is higher in unselected series [26, 27]. Unfortunately, none of the latter studies used cutaneous IgA deposits as a diagnostic criterion, and therefore, their results must be considered with caution.

PROGNOSTIC FACTORS

At 10 years after diagnosis, 15% of adult patients with IgAN reach ESRF, rising to 25 to 34% at 20 years after diagnosis [24, 28]. Studies about the prognosis of IgAN in children are contradictory. Yoshikawa, Ito, and Nakamura have shown that 10% of children with IgAN display chronic renal failure after 20 years of follow-up [29]. In contrast, Wyatt et al have shown a similar prognosis in children and in adults [30]. In children as well as in adults, the intensity of proteinuria and hypertension and the severity of histologic findings are related with evolution to chronic renal failure [14, 22, 23]. Recurrence in the transplanted kidney is observed in about two thirds of patients and leads to graft failure in 25% of them [31].

According to a national multicentric Italian study, the risk of ESRF in adults with HSPN 10 years after diagnosis is about 15% and therefore does not differ from that of IgAN [32]. In childhood, the prognosis of HSPN seems to be worse than that of IgAN. HSPN leads to chronic renal failure in 20% of children 20 years after the diagnosis [18] compared with 10% of children with IgAN after the same follow-up period [29]. The risk of chronic renal failure is related to the initial clinical presentation (Fig. 1) [18, 25]. Chronic renal failure will be encountered in less than 5% when clinical signs at presentation are hematuria and/or minimal proteinuria, 15% when proteinuria is heavy but not nephrotic or in case of acute nephritic syndrome, 40% in case of nephrotic syndrome, and more than 50% when nephritic and nephrotic syndromes are associated. Of interest, even minimal urinary

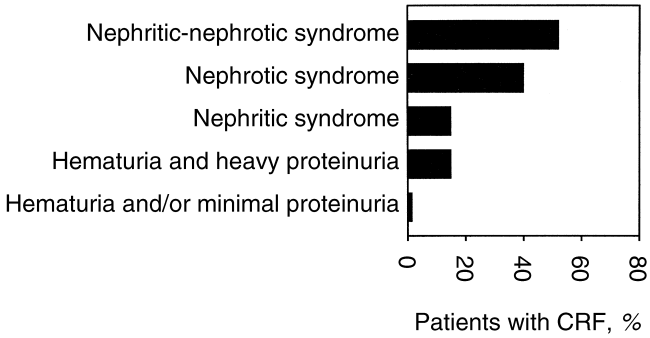

Fig. 1. Relationship between initial clinical signs and risk of chronic renal failure in Henoch-Schönlein purpura nephritis (HSPN) [25].

abnormalities can lead to chronic renal failure after decades [25]. The general opinion is that HSP has a worse prognosis in adults than in children [reviewed in 33]. However, in their study of patients with a clinical presentation that warranted renal biopsy, Coppo et al showed that HSPN had a similar prognosis in children and adults [32]. Several risk factors for renal involvement have been reported in children [19]: older age, abdominal symptoms, low factor XIII activity, and persisting purpura. In adults—unlike children—the patients with renal involvement do not seem to differ from those without, according to any clinical parameter such as sex, prevalence of bullous or necrotic lesions of the skin, or gastrointestinal and joint involvement [20].

Interestingly, remissions of Henoch-Schönlein purpura have been reported during pregnancy or sex-hormone therapy [34]. The latter observation as well as the mean sex ratio (male:female 1.5) is in favor of a pathogenic role of male hormones. As in IgAN, recurrence can affect the transplanted kidney and lead to graft loss in 11 to 35% of patients five years after transplantation [reviewed in 35].

SECONDARY FORMS OF IgAN AND OF HSP

Secondary forms of IgAN have been extensively reviewed by Emancipator [14] and Mustonen and Pasternak [36].

A high proportion of patients presenting with diseases involving the liver (for example, alcoholic cirrhosis and biliary ectasy) or secretory mucosae (celiac and Crohn's disease, chronic infection or cancer) have mesangial deposits of IgA indistinguishable from those with primary IgAN. Secondary forms of IgAN can also be observed in lymphoproliferative disorders (for example, IgA gammopathies and non-Hodgkin lymphomas). Finally, autoimmune and hypersensitivity diseases such as dermatitis herpetiformis, ankylosing spondylitis, scleritis, and sundry collagen-vascular diseases are also seen in association with mesangial IgAN. In the secondary forms, however,

the association of complement with IgA deposits is much less frequent than in IgAN, and thus, pathological and clinical signs of inflammatory disease are usually absent. Most patients with secondary IgAN have been recognized at autopsy and had never been observed to have had urinary or renal functional abnormalities. Episodic macroscopic hematuria and/or renal insufficiency or proteinuria are rarely reported but do occur.

In contrast to IgAN, HSPN has been described in association with hypersensitivity. Indeed, several drugs such as ciprofloxacin, acetylsalicylic acid, vancomycin, carbidopa/levodopa, cocaine, angiotensin-converting enzyme inhibitors, carbamazepine, and streptokinase have been implicated in HSP induction [37–45].

Henoch-Schönlein purpura is much less frequently associated with other diseases than IgAN. Cancer [46], blunt trauma [47], monoclonal IgA gammopathy [48], Wiskott-Aldrich syndrome carrier status [49], and chronic alcoholic liver disease [50] have been reported as possible causes of HSPN.

Henoch-Schönlein purpura has been reported in association with α_1-antitrypsin deficiency in two patients [51]. A case of rapidly progressive glomerulonephritis associated with IgG and IgA ANCAs has been described recently in a patient with IgAN [52].

RENAL PATHOLOGY

Immunofluorescence

Per definition, predominant IgA deposits are observed in the mesangium of all glomeruli in IgAN (Fig. 2) [6]. In HSPN, mesangial IgA also is an almost constant finding [7]. In the latter disease, however, capillary wall staining for IgA is more frequently found and may even predominate on mesangial IgA, which might be absent in some rare cases (Fig. 3) [reviewed in 14]. Extensive capillary deposits are associated with more severe diffuse endocapillary proliferation and/or extensive crescent formation in both diseases [reviewed in 14].

Glomerular deposits of IgG and IgM are also found in variable proportions in IgAN and HSPN [6, 7, 14, 23]. In both diseases, C3 and alternative complement pathway components are also frequently found, but complement factors of the classic pathway are rarely demonstrated [6, 7, 14, 23]. In IgAN, mesangial IgA deposits are almost exclusively composed of IgA1, with a larger proportion of polymeric form and of lambda chains than in normal circulating IgA [53–55]. In HSPN, polymeric IgA1 mesangial deposits are also found, but the ratio of lambda chains remains normal [reviewed in 14]. Interestingly, glomerular fibrin deposits are much more frequently present in HSPN than in IgAN [14].

Light microscopy

At light microscopy, glomerular lesions of IgAN have been classified mainly according to the presence and extent of mesangial proliferation and sclerosis (Fig. 4) [14]. The classification of pathologic glomerular changes in HSPN is based on endocapillary and extracapillary inflammation of the glomerulus (Fig. 5) [14] and bears a strong similarity to the glomerular lesions observed in systemic vasculitis. Glomeruli show crescents in more than 50% of patients [14]. There is an obvious correlation between neutrophil glomerular infiltration, endocapillary proliferation, and crescent formation [14, 56, 57].

Ultrastructural microscopy

By ultrastructural microscopy, the finding of electron-dense deposits in the mesangium confirms the accumulation of IgA and C3 and is the rule in IgAN and HSPN [6, 14]. Capillary wall deposits, especially large subepithelial deposits, are frequently associated with the crescents and synechiae [57]. Subepithelial and subendothelial deposits are more frequently seen in HSPN than in IgAN, and their size is directly related with the severity of histology [14].

OTHER ORGAN INVOLVEMENT

Histologically, cutaneous HSP is a leukocytoclastic form of vasculitis, with vessel wall necrosis and perivascular accumulation of inflammatory cells, mostly polymorphonuclear leukocytes (PMNLs) and mononuclear cells, surrounding the capillaries and postcapillary venules of the dermis [57, 58]. Immunofluorescence staining reveals the presence of IgA, C3c, a complex of C4+C3c+C3d, fibrin/fibrinogen, rarely C4, and no C1Q in vessels and connective tissue of clinically involved and uninvolved skin [59], which suggests an activation of the complement system by the alternative pathway.

Baart de la Faille-Kuyper et al also have shown IgA deposits constantly accompanied by C3c and the complex of C4+C3c+C3d in the cutaneous capillary walls of 33 out of 36 patients with IgAN [59]. IgM deposits were found in half of the patients and IgG only in a few (5 of 33). Several other groups have confirmed these findings in approximately 50% of patients with IgAN [14].

Also in the digestive tract, a leukocytoclastic vasculitis accompanying IgA deposits has been reported in HSP [60].

The clinical association of respiratory tract infections with acute episodes of HSP and macroscopic hematuria episodes in IgAN suggests a triggering role for infectious agents in the pathogenesis of both diseases. Secretory IgA in the mucosal lining plays a major role in the defense against exogenous antigens. In the circulation, the antigens can be captured by circulating IgA1. Thus, formed IgA-containing complexes (IgA-CCs) are cleared by the asialoglycoprotein receptor of hepatocytes, which binds the oligosaccharidic chains of the IgA1 Fc frag-

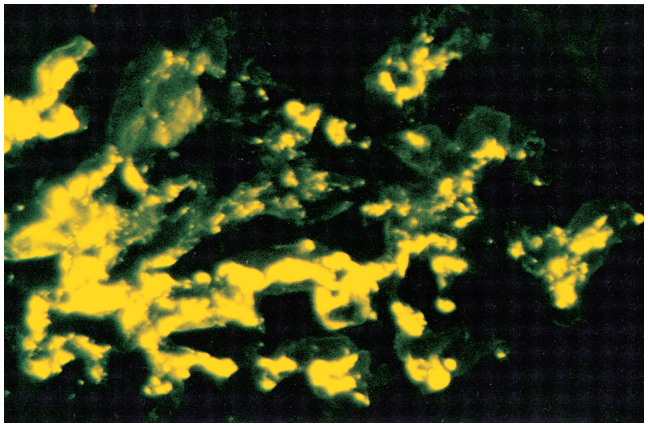

Fig. 2. Immunofluorescence micrograph of a glomerulus from a patient with IgA nephropathy (IgAN) stained for the presence of IgA. A coarsely granular, mesangial staining pattern can be observed (×250).

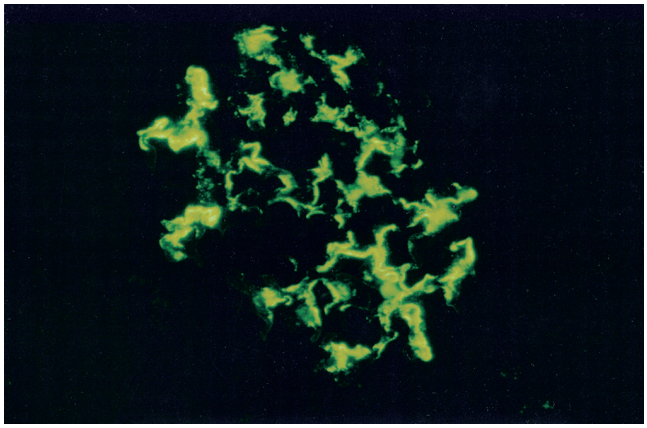

Fig. 3. Immunofluorescence micrograph of a glomerulus from a patient with HSP nephropathy stained for the presence of IgA. A granular, partial capillary, partial mesangial staining pattern can be observed (×200).

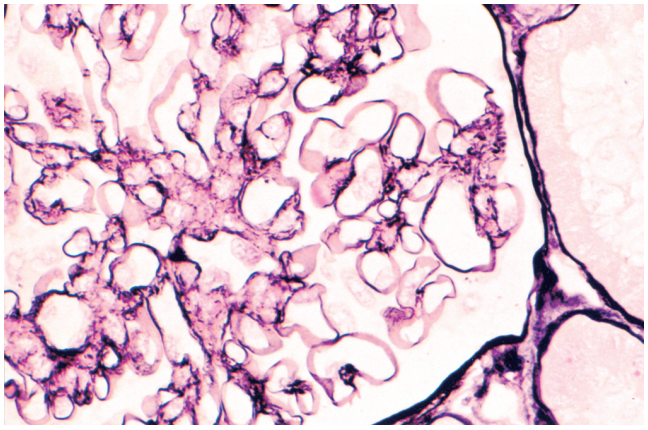

Fig. 4. Light micrograph of a glomerulus from the same patient with IgAN as in Figure 2 showing mesangial expansion caused by accumulation of extracellular matrix and hypercellularity. Methenamine silver (×250).

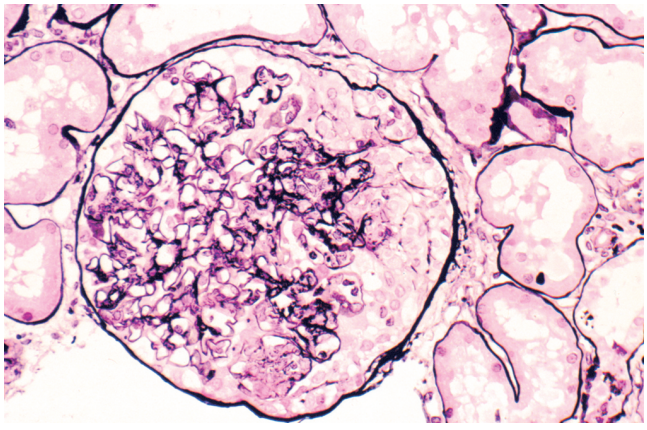

Fig. 5. Light micrograph of a glomerulus from the same patient with HSP nephropathy as in Figure 3 with influx of neutrophils, fibrinoid necrosis, and intracapillary and extracapillary proliferation, a pattern typical for systemic vasculitis. Methenamine silver (×200).

ment. Other clearance mechanisms involve the recognition of other components of IgA-CC [reviewed in 11]. The finding of IgA1 deposits in glomeruli and the relationship between their localization pattern and the type of histologic lesions strongly suggest their pathogenetic role as well as a dysfunction of the IgA system. The latter theoretically might concern the control of IgA1 synthesis, IgA1 specificity for antigens that should favor the formation of IgA-CC, the penetration of antigens inside of the organism, IgA-CC clearance, and finally physiochemical and biological properties of IgA and IgA-CC, which allow their accumulation in the mesangium and in perivascular sites and provoke tissue lesions.

The following section explores the data in the literature on the IgA system in IgAN and HSPN. We also focus on the differences between the two diseases and propose pathogenetic mechanisms.

IMMUNOLOGICAL ABNORMALITIES

Plasma IgA

Increased IgA plasma concentrations have been found in various percentages of patients in IgAN and HSPN [reviewed in 10, 11, 24]. In both diseases, the increase mainly involves polymeric IgA1. Qualitative abnormalities of IgA molecules might favor IgA-CC formation or their binding to MCs or extracellular matrix. IgAN—but not HSPN—is characterized by raised plasma lamda-IgA1, which preferentially binds to mesangial cells [55, 61]. IgA antibody specificities to endogenous (for example, IgG Fc and Fab fragments, IgA, endothelial cells, albumin, simple-strand DNA) or exogenous antigens (for example, pneumococcus polysaccharides, *Haemophilus influenzae*, lactalbumin, ovalbumin, gliadin, anti-α galactosyl antibodies) were reported in IgAN. Some of them, such as IgA rheumatoid factor and anti-α galactosyl antibodies,

have also been found in HSPN [reviewed in 11, 24]. Early reports of plasma anti-neutrophil cytoplasmic antibody (ANCA) in IgAN and HSPN could not be confirmed, and have been attributed to technical artifacts and to aspecific binding based on lectin-like or electrostatic interactions [32, 62–64].

In both diseases, increased binding of IgA to fibronectin (FN) leads to IgA-FN complex formation [65, 66], whereas incomplete glycosylation of IgA [24, 67–69] favors the formation of IgA-lectin complexes, IgA1-IgG, or IgA1-IgA1 aggregates [24, 70–73]. Abnormally glycosylated IgA1 was demonstrated in HSPN, but not in patients presenting with HSP without renal involvement [74]. The latter observation may explain why not all patients with HSP present with renal involvement.

IgA synthesis

Increased synthesis of IgA has been demonstrated in both diseases [75, 76]. In IgAN, increased IgA production is at least partly related to a dysregulation of B-cell control by T lymphocytes, with increased proportions of activated T helper cell subpopulations and decreased proportions of activated T-suppressor cells [77, 78]. Moreover, coculture experiments displayed enhanced T helper and decreased T suppressive functions [79]. Increased production of T cells cytokines [interleukin (IL)-2, interferon-γ, IL-4, IL-5, and IL-6) can also be involved in this stimulation in IgAN [77, 80, 81]. The regulation of B cells by T lymphocytes in HSPN has not been studied so far.

IgA complexes

Glomerular deposition of circulating IgA-CC is thought to play a crucial role in the development of mesangial proliferation and extracellular matrix production leading to glomerular sclerosis in IgAN and HSPN. This hypothesis results partly from the analysis of glomeruli and serum of patients. Besides, the pathogenic role of IgA-CC is also suggested in various experimental models of IgAN resulting from glomerular deposition of circulating IgA-CC either preformed and injected intravenously or endogenously synthesized [82]. Glomerular IgA is at least partly polymeric (pIgA) and belongs to the IgA1 isotype in both diseases [14, 53, 83]. The dissociation of high molecular weight IgA eluted from glomeruli by acidic pH also strongly suggests the presence IgA-CCs in glomeruli [54]. High levels of circulating IgA-CC have been demonstrated by various methods in IgAN [reviewed in 24] and HSPN [reviewed in 10]. These complexes contain IgA1 and also IgA2, IgG, and FN. The correlation between their detection and the presence and intensity of hematuria in IgAN was reported in several studies [reviewed in 24]. Likewise, IgA-CCs are generally found during acute phases of HSPN and are also correlated with hematuric episodes [65, 76, 84]. No major differences concerning IgA-CC were noted between the two diseases except for the size of complexes and their IgG content. Indeed, using sucrose density gradient ultracentrifugation and polyethylene glycol precipitation of circulating IgA-CC, Levinsky and Barratt [85] and thereafter Kauffman, van Es, and Daha [86] have reported that circulating IgA-CCs were concentrated entirely in the 7S-19S peak in IgAN, whereas those from HSPN were also found in a peak greater than 19S. Additionally, Levinsky and Barratt [85] and Cederholm et al [65] have shown higher amount of IgG in IgA-CC from patients with HSPN than in those with IgAN. In experimental models of IgAN, some features of IgA-CC such as the type of antigen used and their content in polymeric IgA and in IgG seem crucial for induction of glomerular lesions [reviewed in 82].

Clearance of IgA complexes

The formation of circulating IgA-CC is a normal process involved in the clearance of mucosal antigens that escape the mucosal barrier protective mechanisms and enter the organism. IgA-CCs are mainly cleared by the liver after binding of IgA to hepatocyte receptors for asialoglycoproteins [87, 88]. Thereby, hepatic clearance of IgA-CC prevents accumulation in the circulation and deposition in other organs such as the kidney. High plasma levels of IgA-CC may theoretically result from an increase production or a reduced clearance or both.

IgA-containing compounds' clearance depends also on the mononuclear phagocyte system function. Apart from IgA, IgA-CCs also may contain IgG, IgM, FN, and complement components [24, 65, 89–91]. Although Fcα receptors on blood cells are down-regulated in IgAN [92], liver clearance of aggregates prepared from normal IgA is normal in IgAN [93]. However, abnormally glycosylated IgAs found in IgAN and in HSPN [24, 68, 74, 79] are possibly less efficiently cleared by the hepatocyte receptor for asialoglycoproteins than normal IgA. In contrast to normal IgA clearance mechanisms, a reduction of Fcγ, C3b, and FN receptor function of mononuclear phagocytes was reported in IgAN and HSPN [94, 95]. These abnormalities were mostly not correlated with clinical signs and transient, and therefore are more probably secondary to saturation of receptors rather than a primary event.

Antigen penetration

Increased formation of circulating IgA-CC in IgAN can be the consequence of transmucosal penetration of exogenous antigens. The intestinal permeability to ^{51}Cr EDTA is increased in IgAN and HSPN [96, 97]. This increase is correlated with circulating IgA-CC plasma levels and with hematuria as well as with systemic symptoms in HSPN [96, 97]. Transiently increased lung transfer for carbon monoxide (TCLO) has been reported in

acute phases of IgAN and HSPN [98, 99]. The reason for this increased mucosal permeability remains unknown. Its reversibility suggests that it is most probably secondary to alterations of the mucosal capillaries caused by deposition of IgA containing immune complexes. Increased penetration of antigens inside of the human organism may also result from a lack of specific mucosal IgA production, as demonstrated recently by de Fijter et al using intranasal immunization with cholera toxin subunit B as a novel antigen in patients with IgAN [100]. Many studies have implicated viral agents such as cytomegalovirus, Epstein-Barr, and hepatitis B virus as etiologic factors in IgAN [101–104]. Hemophilus parainfluenzae antigens are found in the glomeruli of all patients with IgAN but not in those with other glomerular diseases [105]. Alimentary antigens such as soy, rice, and cow milk proteins have been detected in a variable percentage of cases, reaching 75% for soy [106, 107]. These data indicate that several different antigens are probably involved in the pathogenesis of IgAN. Some authors suggest that undergalactosylated IgA1 itself may play the role of antigen [74].

Allergy

Several studies have documented the association of HSP with hypersensitivity type 1 [37–45]. Early studies reported high IgE plasma levels in HSP [95, 108]. Studies of IgE plasma levels in IgAN are conflicting [109–112]. High IgE plasma levels have been preferentially found in patients with mild histologic changes and proteinuria responding to steroids [112]. Davin et al have found that the incidence of increased plasma IgE levels according to age-matched normal values were significantly higher in HSPN than in IgAN [109]. Moreover, IgE deposits were demonstrated on cutaneous Langerhans and mast cells in four out of six patients with HSPN. Recently, Namgoong, Lim, and Kim have shown that serum eosinophil cationic protein (ECP) levels were elevated in HSP, but not in IgAN, as compared with normal controls [113]. Furthermore, these levels were higher in HSP with than in HSP without renal involvement.

Complement

The plasma concentrations of the different components of the complement system are generally normal in IgAN and HSPN [95, 114]. However, an activation of the complement cascade does occur since degradation products in plasma and glomeruli have been shown in both diseases [95, 115, 116]. The role of this activation remains unclear. Results of studies trying to correlate the level of complement-split products in the blood with clinical signs [95, 117, 118] or the glomerular deposition of various complement factors and histologic lesions are contradictory [95, 115, 116].

Immunogenetic factors

Several lines of evidence have revealed that immunogenetic factors are involved in the pathogenesis of IgAN. First, a number of familial cases have been reported [119]. Furthermore, IgAN is rare in black people [14]. An increased production of IgA by lymphocytes in vitro has been described in healthy relatives of patients [120]. The unusual polymorphism of the heavy chain switch region and the abnormally high frequency of homozygote phenotypes C4B nul, C3FF and BfFF are also in favor of the intervention of immunogenetic factors in IgAN [121, 122]. Immunogenetic studies in HSPN have also demonstrated a strong link with homozygous C4A or C4B null phenotype [123].

COAGULATION

The coagulation system is possibly involved in the pathogenesis of IgAN and HSPN, as suggested by quantitative and functional deficit of plasminogen in IgAN [124], the presence of a circulating factor able to inhibit PGI_2 synthesis in IgAN and HSPN [125], the depletion of fibrin-stabilizing factor (factor XIII) in acute HSP, the increased von Willebrand factor plasma levels found in HSPN and IgAN [126–128], and the intact cross-linked fibrin (XFb) intraglomerular deposits in IgAN and HSPN [129]. As already mentioned, glomerular fibrin deposits are more abundant in HSPN than in IgAN. Although most of those coagulation abnormalities are probably secondary to a previous damage of the endothelium, they may contribute to further deterioration of glomerular structures and particularly to the formation of glomerular crescents.

PATHOGENESIS OF GLOMERULAR LESIONS

The deposition of IgA-CC in glomeruli is favored by their high plasma concentration in IgAN and HSPN. Their preferential accumulation in the mesangial area is at least partly related to their relative large size [54, 130, 131]. Once in the mesangium, different components of IgA-CC (for example, Fcα and Fcγ fragments, FN, C3b, lectins) can bind to their specific receptors on the surface of mesangial cells (MCs) [reviewed in 132]. Moreover, the physicochemical properties of plasma IgA in IgAN and HSPN favor their binding to MCs and their stimulation. Indeed, the binding capacity to MCs of polymeric IgA and lambda IgA1 is higher than monomeric IgA and κ IgA1, respectively [61, 133]. Besides, aggregated forms of IgA1, but not monomeric IgA1, are able to stimulate MCs after binding to a receptor different from FcαR1 [134]. Interactions of IgA with MC in vitro induces the expression and synthesis of chemokines monocyte chemoattractant protein-1 (MCP-1) and IL-8 [135, 136], which are overexpressed in glomeruli in IgAN [137]

Table 3. Mesangial cell receptors and products

Receptors	Products
Angiotensin II	IL-1
Adenosine	IL-6
Endothelin	TNF-α
Prostaglandin	PDGF
Putative IgA receptor	TGF-β
Fcγ R	ECM components
C3b	Metalloproteinases
Lectins	
ECM components	
IL-1	
IL-6	
IL-8	
TNF-α	
PDGF	
TGF-β	

Abbreviations are: ECM, extracellular matrix; IL, interleukin; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-β; PDGF, platelet-derived growth factor.

and can account for the attraction of PMNLs and monocytes found in patients biopsies. MCs may also be stimulated by cytokines of the acute phase [IL-1, tumor necrosis factor-α (TNF-α), IL-6] and of the chronic phase [platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β)] produced by themselves (Table 3) [reviewed in 132] and/or by infiltrating cells. The detection of those cytokines in glomeruli of patients with IgAN suggests their role in MC proliferation and extracellular matrix overproduction [138–141].

PATHOGENESIS OF EPITHELIAL CRESCENTS

As already mentioned, capillary necrosis and glomerular crescents are much more numerous in HSPN than in IgAN, and their number is closely related to the severity of clinical signs and to the prognosis in both entities. Their presence is related to capillary wall destruction and is generally associated with endothelial proliferation as well as with subendothelial deposits [14], as further discussed later in this article. The role of fibrin deposition in crescent formation is suggested by the almost constant presence of glomerular fibrin in HSPN in contrast to IgAN [14], and is supported by the experimental work of Vassalli and McCluskey [142]. They reported that the anticoagulant warfarin entirely prevented crescent formation in nephrotoxic serum nephritis in rabbits. Fibrin is a chemoattractant for macrophages that should play a major role in crescent formation [143].

All together, those observations suggest that the following succession of events are involved in the crescent formation in HSPN and IgAN: subendothelial deposition of IgA-CC, stimulation of endothelial cells to express von Willebrand factor, initiation of the coagulation cascade leading to glomerular fibrin deposition, macrophages attraction, and cytokine-induced epithelial cells proliferation. Whether massive mesangial immune deposits may also induce crescent formation by disruption of the overlying glomerular basement membrane and subsequent podocyte injury is unclear.

PATHOGENESIS OF LEUKOCYTOCLASTIC VASCULITIS

Invasion of leukocytes involves a three-step process of rolling, sticking, and firm adhesion to endothelial cells followed by leukocyte migration into the tissues. This process is regulated by a network of cytokines and chemokines leading to expression of adhesion molecules on endothelial and inflammatory cells. The primary event is probably damage of endothelial cells, which can be induced by subendothelial immune-complex deposition (for example, in serum sickness), binding of cytotoxic antibodies (for example, in Kawasaki disease), or interaction with activated circulating cells (possibly in Wegener's disease) [reviewed in 144]. The involvement of these in HSPN is suggested by the presence of IgA-CC in plasma and tissues. Why this leads to a systemic vasculitis in HSPN and not in IgAN remains unknown.

A possible role of a more potent activation of PMNL by IgA-CC and/or circulating chemokines in HSPN should be considered in this respect. The intensity of the cellular response to the binding of extracellular factors depends on the specificity of the receptor-ligand pair, on the amount of ligand bound, and on the simultaneous binding of other types of ligands. A great number of neutrophils surface receptors have been described so far [reviewed in 144]. Among these, FcαR, FcγR, CR1, CR2, and CR3 are able to bind to components of IgA-CC such as IgA and IgG Fc fragments and C3bi [10, 24, 65, 85, 86, 89]. It can therefore be postulated that a greater diversity and a higher amount of ligand present in IgA-CC in HSPN might result in a higher degree of leukocyte stimulation. The finding of large-sized IgA-CC with a higher IgG content in HSPN pleads for this hypothesis [65, 85].

Chemokines such as IL-8 could also be involved in the neutrophil recruitment in HSPN. Indeed, IL-8 is a potent neutrophil attractant secreted by circulating cells such as monocytes, eosinophils, and neutrophils as well as by resident cells such as endothelial cells and mast cells. The monocyte cytokine response is stimulated after binding with IgA and IgG in vitro [145, 146]. In HSPN, stimulation of eosinophils is suggested by an increased eosinophil cationic protein (ECP) plasma concentration [113]. High plasma levels of von Willebrand factor during the acute phase of HSPN imply stimulation of endothelial cells [128]. The latter is also suggested by the glomerular endothelial proliferation observed in HSPN [14]. Mast cells are also a potential source of IL-8 in HSPN. Their close apposition to the vasculature places them in

an ideal position to influence leukocyte recruitment. They have recently been shown to be involved in the development of an experimental adjuvant-induced vasculitis [147]. In HSPN, they might be stimulated by the IgE deposits demonstrated in perivascular sites in the skin of most patients [109].

We have reviewed the main differences between IgAN and HSPN in order to propose pathogenic mechanisms that may explain the occurrence of a multiorganic vasculitis only in HSPN. Apart from the typical systemic signs of HSPN, two main clinical differences are observed. First, the peak age is lower in HSPN. Second, the initial presentation with acute renal failure and/or massive proteinuria is much more common in HSPN. Of interest, HSPN is more often described in association with drug hypersensitivity. Histologically, necrotizing glomerular lesions, diffuse endocapillary proliferation, and fibrin deposits are more typically encountered in HSPN. Biological findings are similar in both diseases. However, the frequency of high IgE plasma levels is higher in HSPN. Further studies may elucidate the role of hypersensitivity in explaining the differences between HSPN and IgAN, thus allowing for a rational treatment.

Finally, recent developments in the knowledge of mechanisms leading to the formation and the glomerular deposition of IgA-CC, such as the deficiency of uteroglobins involved in an experimental model of IgAN in mice [148], open new fields of clinical investigation that may contribute to a better understanding of common links and differences in the pathogenesis of IgAN and HSPN.

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REFERENCES

1. Heberden W: *Commentaries on the History and Cure of Diseases.* London, T. Payne, 1801, p 395
2. Schönlein JL: *Allgemeine Und Specielle Pathologie Und Therapie* (vol 1, 3rd ed), 1847, p 48
3. Henoch E: Über eine eigentümliche Form von Purpura. *Berl Klin Wochenschr* 11:641, 1874
4. Henoch E: *Vorlesungen über Kinderkrankheiten* (vol 10). Berlin, A. Hoischwald, 1989, p 839
5. Jennette JC, Falk RJ, Andrassy K, *et al*: Nomenclature of systemic vasculitides: Proposal of an International Consensur Conference. *Arthritis Rheumatol* 37:187–192, 1994
6. Berger J, Hinglais N: Les dépôts intercapillaires d'IgA-IgG. *J Urol Nephrol* 74:694–695, 1968
7. Urizar RE, Michael A, Sisson S, *et al*: Anaphylactoid purpura. II. Immunofluorescent and electron microscopy studies of the glomerular lesions. *Lab Invest* 19:437–440, 1968
8. Ravelli A, Carnevale-Maffe G, Ruperto N, *et al*: IgA nephropathy and Henoch-Schönlein syndrome occurring in the same patient. *Nephron* 72:111–112, 1996
9. Meadow SR, Scott DG: Berger disease: Henoch-Schönlein without the rash. *J Pediatr* 106:27–32, 1985
10. Knight JF: The rheumatic poison: A survey of some published investigations of the immunopathogenesis of Henoch-Schönlein purpura. *Pediatr Nephrol* 4:533–541, 1990
11. Davin JC, Weening JJ: Berger disease: Thirty years later. *Eur J Pediatr* 158:437–443, 1999
12. Fassbinder W, Brunner FP, Brynger H, *et al*: Combined report on regular dialysis and transplantation in Europe, XX, 1989. *Nephrol Dial Transplant* 6(Suppl 1):5–35, 1991
13. Broyer M: Fréquence et cause de l'-insuffisance rénale chez l'enfant, in *Néphrologie Pédiatrique*, edited by Royer P, Habib R, Matthieu H, *et al*, Paris, Flammarion Médecine-Sciences, 1983, pp 425–433
14. Emancipator SN: Primary and secondary forms of IgA nephritis and Schönlein–Henoch syndrome, in *Pathology of the Kidney*, edited by Heptinstall RH, Toronto, London, Little, Brown, 1993, pp 389–476
15. Schena FP: IgA nephropathies, in *Oxford Textbook of Clinical Nephrology*, edited by Cameron S, Davison AM, Grünfeld JP, *et al*, Oxford, Oxford University Press, 1992, pp 339–369
16. Levy M, Gonzales-Burchard G, Broyer M, *et al*: Berger's disease in children: Natural history and outcome. *Medicine (Baltimore)* 64:157–180, 1985
17. Haycock GB: The nephritis of Henoch-Schönlein purpura, in *Oxford Textbook of Clinical Nephrology*, edited by Cameron S, Davison AM, Grünfeld J-P, *et al*, Oxford, New York, Tokyo, Oxford University Press, 1992, pp 595–612
18. White RHR, Yoshikawa N: Henoch-Schönlein nephritis, in *Pediatric Nephrology*, edited by Barratt TM, Holiday M, Baltimore, Williams & Wilkins, 1993, pp 729–738
19. Kaku Y, Nohara K, Honda S: Renal involvement in Henoch-Schönlein purpura: A multivariate analysis of prognostic factors. *Kidney Int* 53:1755–1759, 1998
20. Tancrede-Bohin E, Ochonisky S, Vignon-Pennamen MD, *et al*: Schönlein-Henoch purpura in adult patients: Predictive factors for IgA glomerulonephritis in a retrospective of 57 cases. *Arch Dermatol* 133:438–442, 1997
21. Habib R, Cameron JS: Schönlein-Henoch purpura, in *The Kidney: Rheumatic Disease*, edited by Bacon PA, Hadler NM, London, Butterworth Scientific, 1982, p 178
22. Clarkson AR: Clinical and laboratory features of IgA nephropathy, in *IgA Nephropathy*, edited by Clarkson AR, Boston, Dordrecht, Lancaster, Martinus Nijhoff, 1987, pp 9–15
23. Hogg RG, Silva FG: IgA nephropathy in children, in *IgA Nephropathy*, edited by Clarkson AR, Boston, Dordrecht, Lancaster, Martinus Nijhoff, 1987, pp 16–38
24. Davin JC: *Contribution à l'étude de la pathogénie des néphropathies à IgA: Thèse d'Aggrégation.* Liège, Université de Liège, 1993
25. Goldstein AR, White RHR, Akuse R, *et al*: Long-term follow-up of childhood Henoch-Schönlein nephritis. *Lancet* 339:280–282, 1992
26. Koskimies O, Rapola J, Savilahti E, *et al*: Renal involvement in Schönlein-Henoch purpura. *Acta Paediatr Scand* 63:357–363, 1974
27. Nielsen HE: Epidemiology of Schönlein-Henoch purpura. *Acta Paediatr Scand* 77:125–131, 1988
28. D'Amico G: Natural history and treatment of idiopathic IgA nephropathy, in *Nephrology*, edited by Robinson RR, New York, Springer, 1984, pp 686–699
29. Yoshikawa N, Ito H, Nakamura H: IgAN in children from Japan. *Child Nephrol Urol* 9:191–199, 1989
30. Wyatt RJ, Kritchevsky SB, Woodford SY, *et al*: IgA nephropathy: Long-term prognosis for pediatric patients. *J Pediatr* 127:913–919, 1995

31. Hartung R, Livingstone B, Excell L, *et al*: Recurrence of IgA deposits/disease in grafts: An Australian Registry Survey 1980-1990. *Contrib Nephrol* 111:13–17, 1995
32. Coppo R, Mazzuco G, Cagnoli L, *et al*: Long-term prognosis of Henoch-Schönlein nephritis in adults and children. *Nephrol Dial Transplant* 12:2277–2283, 1997
33. Lahita RG: Influence of age on Henoch Schönlein purpura. *Lancet* 350:1116–1117, 1997
34. Merrill J, Lahita RG: Henoch-Schönlein purpura remitting in pregnancy and during sex steroid therapy. *Br J Rheumatol* 33:586–588, 1994
35. Meulders Q, Pirson Y, Cosyns JP, *et al*: Course of Henoch-Schönlein nephritis after renal transplantation: Report on ten patients and review of the literature. *Transplantation* 58:1179–1186, 1994
36. Mustonen J, Pasternak A: Associated diseases in IgA nephropathy, in *IgA Nephropathy*, edited by Clarkson AR, Boston, Dordrecht, Lancaster, Martinus Nijhoff, 1987, pp 47–65
37. Moots RJ, Keeling PJ, Morgan SH: Adult Schönlein-Henoch purpura after enalapril. *Lancet* 340:304–305, 1992
38. Disdier P, Harle JR, Verrot D, *et al*: Adult Schönlein-Henoch purpura after lisinopril. *Lancet* 340:985, 1992
39. Drago F, Arditi MR, Rebora R: Henoch-Schönlein induced by fluoroquinolones. *Br J Dermatol* 131:448, 1994
40. Prajapati C, Casson IF: Henoch-Schönlein purpura associated with ranitidine. *Int J Clin Pract* 51:251, 1997
41. Chevalier X, Rostoker G, Larget-Piet B, *et al*: Schönlein-Henoch purpura with necrotizing vasculitis after cocaine snorting. *Clin Nephrol* 43:348–349, 1995
42. Kaneko K, Igarashi J, Suzuki Y, *et al*: Carbamazepine-induced thrombocytopenia and leucopenia complicated by Henoch-Schönlein purpura symptoms. *Eur J Pediatr* 152:769–770, 1993
43. Niedermaier G, Briner V: Henoch–Schönlein syndrome induced by carbidopa/levodopa. *Lancet* 349:1071–1072, 1997
44. Michail S, Vaiopoulos G, Nakopoulou L, *et al*: Henoch-Schönlein purpura and acute interstitial nephritis after intravenous vancomycin administration in a patient with a staphylococcal infection. *Scand J Rheumatol* 27:233–235, 1998
45. Sola Alberich R, Jammoul A, Masana L: Henoch-Schönlein purpura associated with acetyl salicylic acid. *Ann Intern Med* 126:665, 1997
46. Cairns SA, Mallick NP, Lawler W, *et al*: Squamous cell carcinoma of bronchus presenting with Henoch-Schönlein purpura. *Br Med J* 2:474–475, 1978
47. Talbot D, Craig R, Falconer S, *et al*: Henoch-Schönlein purpura secondary to trauma. *Arch Dis Child* 63:1114–1115, 1988
48. Dosa S, Cairns SA, Mallick MP, *et al*: Relapsing Henoch-Schönlein syndrome with renal involvement in a patient with an IgA monoclonal gammopathy. *Nephron* 26:145–148, 1980
49. Lasseur K, Allen AC, Deminière C, *et al*: Henoch-Schönlein purpura with IgA nephropathy and abnormalities of IgA in a Wiskott-Aldrich syndrome carrier. *Am J Kidney Dis* 2:285–287, 1997
50. Feriozzi S, Onetti Muda A, Faraggiana T, *et al*: Henoch-Schönlein disease with IgA nephropathy associated with chronic alcoholic liver disease. *Nephrol Dial Transplant* 10:1231–1233, 1995
51. Elzouki AN, Sterner G, Erikson S: Henoch-Schönlein purpura and α-1-antitrypsin deficiency. *Nephrol Dial Transplant* 10:1454–1457, 1995
52. Ramirez SB, Rosen S, Niles J, *et al*: IgG antineutrophil cytoplasmic antibodies in IgA nephropathy: A clinical variant. *Am J Kidney Dis* 31:341–344, 1998
53. Tomino Y, Endoh M, Nomoto Y, *et al*: Immunoglobulin A1 and IgA nephropathy. *N Engl J Med* 305:1159–1160, 1981
54. Monteiro RC, Albwachs-Mecarelli L, Roque-Barreira MC, *et al*: Charge and size of mesangial IgA in IgA nephropathy. *Kidney Int* 28:666–671, 1985
55. Lai KN, Chui SH, Lai FM, *et al*: Predominant synthesis of IgA with lambda light chain in IgA nephropathy. *Kidney Int* 33:584–589, 1988
56. Kincaid-Smith P, Nicholls K, Birchall I: Polymorphsinfiltrate glomeruli in mesangial IgA glomerulonephritis. *Kidney Int* 36:1108–1111, 1989
57. Emancipator SN: IgA nephropathy: Morphologic expression and pathogenesis. *Am J Kidney Dis* 23:451–462, 1994
58. Vernier RL, Farquhar MG, Brunson JG, *et al*: Anaphylactoid purpura. I. Pathology of the skin and kidney and frequency of streptococcal infections. *Pediatrics* 27:181–187, 1961
59. Faille-Kuyper EH, Kater L, Kuijten RH, *et al*: Occurrence of vascular IgA deposits in clinically normal skin of patients with renal disease. *Kidney Int* 9:424–429, 1976
60. Gunasekaran TS: Henoch-Schönlein purpura: What does the "rash" look like in the gastrointestinal mucosa. *Pediatr Dermatol* 6:437–440, 1997
61. Lai KN, To WY, Li PK, *et al*: Increased binding of polymeric lambda-IgA to cultured human mesangial cells in IgA nephropathy. *Kidney Int* 49:839–845, 1996
62. Ronda N, Esnault VLM, Layward L, *et al*: Anti-neutrophil cytoplasm antibodies (ANCA) of IgA isotype in adult Henoch-Schönlein purpura. *Clin Exp Immunol* 95:49–55, 1994
63. Saulsbury FT, Kirkpatrick PR, Bolton WK: IgA antineutrophil cytoplasmic antibody in Henoch-Schönlein purpura. *Am J Nephrol* 11:295–300, 1991
64. Sinico RA, Tadros M, Radice A, *et al*: Lack of IgA anti-neutrophil cytoplasmic antibodies in Henoch-Schönlein purpura and IgA nephropathy. *Clin Immunol Immunopathol* 73:19–26, 1994
65. Cederholm B, Linne T, Wieslander J, *et al*: Fibronectin-immunoglobulin complexes in the early course of IgA and Henoch-Schönlein nephritis. *Pediatr Nephrol* 5:200–204, 1991
66. Davin JC, Li Vecchi M, Nagy J, *et al*: Evidence that the interaction between circulating IgA and fibronectin is a normal process enhanced in IgA nephropathy. *J Clin Immunol* 11:78–94, 1991
67. Mestecky J, Tomana M, Crowley-Nowick PA, *et al*: Defective galactosylation and clearance of IgA1 molecules as a possible etiopathogenic factor in IgA nephropathy. *Contrib Nephrol* 104:172–182, 1993
68. Saulsbury FT: Alteration in the O-linked glycosylation of IgA1 in children with Henoch-Schönlein purpura. *J Rheumatol* 24: 2246–2249, 1997
69. Allen AC, Harper SJ, Feehally J: Galactosylation of N- and O-linked carbohydrate moities of IgA1 and IgG in IgA nephropathy. *Clin Exp Immunol* 100:470–474, 1995
70. Davin JC, Dechenne C, Lombet J, *et al*: Acute experimental glomerulonephritis induced by the glomerular deposition of circulating polymeric IgA-concanavalin A complexes. *Virchows Arch A Pathol Anat Histopathol* 415:7–20, 1989
71. Kokubo T, Hiki Y, Iwase H, Horii A, *et al*: Evidence for involvement of IgA1 hinge glycopeptide in the IgA1-IgA1 interaction in IgA nephropathy. *J Am Soc Nephrol* 8:915–919, 1997
72. Libetta C, Rampino T, Palumbo G, *et al*: Circulating serum lectins of patients with IgA nephropathy stimulate IL-6 release from mesangial cells. *J Am Soc Nephrol* 8:208–203, 1997
73. Tomana M, Matousovic K, Julian BA, *et al*: Galactose-deficient IgA1 in sera of IgA nephropathy patients is present in complexes with IgG. *Kidney Int* 52:509–516, 1997
74. Allen AC, Willis FR, Beattie J, *et al*: Abnormal IgA glycosylation in Henoch-Schönlein purpura restricted to patients with clinical nephritis. *Nephrol Dial Transplant* 13:930–934, 1998
75. Beale MG, Nash GS, Bertovich MJ, *et al*: Similar disturbances of B-cell activity and regulatory T-cell function in Henoch-Schönlein purpura and systemic lupus erythematosus. *J Immunol* 128:486–491, 1982
76. Davin JC, Foidart JB, Mahieu PR: Relation between biological IgA abnormalities and mesangial IgA deposits in isolated hematuria of childhood. *Clin Nephrol* 28:73–80, 1987
77. Lai KN, Leung JC, Li PK, *et al*: Cytokine production by peripheral blood mononuclear cells in IgA nephropathy. *Clin Exp Immunol* 85:240–245, 1991
78. Sakai H, Miyazaki M, Endoh M, *et al*: Increase of IgA-specific switch T cells in patients with IgA nephropathy. *Clin Exp Immunol* 78:378–382, 1989
79. Casanueva B, Rodriguez-Valverde V, Farinas MC, *et al*: Autologous mixed lymphocyte reaction and T-cell suppressor activity in patients with Henoch-Schönlein purpura and IgA nephropathy. *Nephron* 54:224–228, 1990

80. Emancipator SN: Immunoregulatory factors in the pathogenesis of IgA nephropathy. *Kidney Int* 38:1216–1229, 1990
81. Ichinose H, Miyasaki M, Koji T, *et al*: Detection of cytokines mRNA-expressing cells in peripheral blood of patients with IgA nephropathy using non-radioactive in situ hybridization. *Clin Exp Immunol* 103:125–132, 1996
82. Scivittaro V, Amore A, Emancipator SN: Animal models as a mean to study IgA nephropathy. *Contrib Nephrol* 104:65–78, 1993
83. Egido J, Sancho J, Mampaso F, *et al*: A possible common pathogenesis of the mesangial IgA glomerulonephritis in patients with Berger's disease and Schönlein-Henoch syndrome. *Proc Eur Dial Transplant Assoc* 17:660–666, 1980
84. Kauffman RH, Herrman W, Meyer CJLM, *et al*: Circulating IgA-immune complexes in Henoch-Schönlein purpura: A longitudinal study of their relationship to disease activity and vascular deposition of IgA. *Am J Med* 69:859–866, 1980
85. Levinsky RJ, Barratt TM: IgA immune complexes in Henoch-Schönlein purpura. *Lancet* 24:1100–1103, 1979
86. Kauffman RH, van Es LA, Daha MR: The specific detection of IgA in immune complexes. *J Immunol Methods* 40:117–129, 1981
87. Stockert RJ, Kressner MS, Collins JC, *et al*: IgA interaction with the asialoglycoprotein receptor. *Proc Natl Acad Sci USA* 79:6229–6231, 1982
88. Delacroix DL: *The Human Immunoglobulin A System: Its Vascular Compartment.* Thesis, European Medical Press, Brugge, 1985
89. Coppo R, Basolo B, Piccoli G: IgA1 and IgA2 immune complexes in primary IgA nephropathy and Henoch-Schönlein nephritis. *Clin Exp Immunol* 57:583–590, 1984
90. Czerkinsky C, Koopman WJ, Jackson S: Circulating immune complexes and immunoglobulin A rheumatoid factor in patients with mesangial immunoglobulin A nephropathies. *J Clin Invest* 77:1931–1938, 1986
91. Schena FP, Pastore A, Ludovico N, *et al*: Increased levels of IgA1-IgG immune complexes and anti F(ab′)2 antibodies in patients with primary IgA nephropathy. *Clin Exp Immunol* 77:15–20, 1989
92. Grossetête B, Launay P, Lehuen A, *et al*: Down-regulation of Fcα receptors on blood cells of IgA nephropathy patients: Evidence for a negative regulatory role of serum IgA. *Kidney Int* 53:1321–1335, 1998
93. Rifai A, Schena FP, Montinaro V, *et al*: Clearance kinetics and fate of macromolecular IgA in patients IgA nephropathy. *Lab Invest* 61:381–388, 1989
94. Nicholls KM, Kincaid-Smith P: Defective in vivo Fc and C3b receptor function in IgA nephropathy. *Am J Kidney Dis* 4:128–134, 1984
95. Davin JC, Vandenbroeck MC, Foidart JB, *et al*: Sequential measurements of the reticulo-endothelial system function in Henoch-Schönlein disease in childhood. Correlation with various immunological parameters. *Acta Paediatr Scand* 74:201–206, 1985
96. Davin JC, Forget P, Mahieu PR: Increased intestinal permeability to (51 Cr) EDTA is correlated with IgA immune complex-plasma levels in children with IgA-associated nephropathies. *Acta Paediatr Scand* 77:118–124, 1988
97. Davin JC, Mahieu PR: Sequential measurements of intestinal permeability to 51 Cr EDTA in children with Henoch-Schönlein purpura nephritis. *Nephron* 60:498–499, 1992
98. Chaussain M, de Boissieu D, Kalifa G, *et al*: Impairment of lung diffusion capacity in Schönlein-Henoch purpura. *J Pediatr* 121:12–16, 1992
99. Ravilly S, Chaussain M, Iniguez JL, *et al*: Alteration of lung diffusion capacity in IgA nephropathy. *Arch Dis Child* 74:236–238, 1996
100. de Fijter JW, Eijgeraam JW, Braam CA, *et al*: Deficient IgA1 immune response to nasal cholera toxin subunit B in primary IgA nephropathy. *Kidney Int* 50:952–961, 1996
101. Lai KN, Lai FM, Lo S, *et al*: IgA nephropathy associated with hepatitis B virus antigenemia. *Nephron* 47:141–143, 1987
102. Gregory MC, Hammond ME, Brewer ED: Renal deposition of cytomegalovirus antigen in immunoglobulin-A nephropathy. *Lancet* 1:11–14, 1988
103. Iida H, Izumino K, Asaka M, *et al*: IgA nephropathy and hepatitis B virus: IgA nephropathy unrelated to hepatitis B surface antigenemia. *Nephron* 54:18–20, 1990
104. André PM, Le Pogamp P, Griffais R, *et al*: Is Epstein-Barr virus involved in primary IgA nephropathy? *Nephron* 54:185–186, 1990
105. Suzuki S, Nakatomi Y, Odani S, *et al*: Circulating IgA, IgG and IgM class antibody against Haemophilus parainfluenzae antigens in patients with IgA nephropathy. *Clin Exp Immunol* 104:306–311, 1996
106. Russell MW, Mestecky J, Julian BA, *et al*: IgA-associated renal diseases: Antibodies to environmental antigens in sera and deposition of immunoglobulins and antigens in glomeruli. *J Clin Immunol* 6:74–86, 1986
107. Sato M, Kojima H, Takayama K, *et al*: Glomerular deposition of food antigens in IgA nephropathy. *Clin Exp Immunol* 73:295–299, 1988
108. Urbanek R, Karitzky D, Kunzer W: Serum-IgE bei Hauterkrankungen im Kindersalter. *Deutsche Med Wochenschr* 103:503–508, 1978
109. Davin JC, Pierard G, Dechenne C, *et al*: Possible pathogenic role of IgE in Henoch-Schönlein purpura. *Pediatr Nephrol* 8:169–171, 1994
110. Davin JC, Nagy J, Mahieu PR: Incidence of atopy in IgAN. *Nephron* 59:528, 1992
111. Yano N, Endoh M, Miyazaki M, *et al*: Altered production of IgE and IgA induced by IL-4 in peripheral blood mononuclear cells from patients with IgA nephropathy. *Clin Exp Immunol* 88:295–300, 1992
112. Shu KH, Lu YS, Chen CH, *et al*: Serum immunoglobulin E in IgA nephropathy. *Clin Nephrol* 44:86–90, 1995
113. Namgoong MK, Lim BK, Kim JS: Eosinophil cationic protein in Henoch-Schönlein purpura and in IgA nephropathy. *Pediatr Nephrol* 11:703–706, 1997
114. Julian BA, Wyatt RJ, McMorrow RG, *et al*: Serum complement proteins in IgA nephropathy. *Clin Nephrol* 20:251–258, 1983
115. Wyatt RJ, Julian BA: Activation of complement in IgA nephropathy. *Am J Kidney Dis* 12:437–438, 1988
116. Miyamoto H, Yoshioka K, Takemura T, *et al*: Immunohistochemical study of the membrane attack complex of complement in IgA nephropathy. *Virchows Arch A Pathol Anat* 413:77–86, 1988
117. Zwirner J, Burg M, Schulze M, *et al*: Activated complement C3: A potential novel predictor of progressive IgA nephropathy. *Kidney Int* 51:1257–1264, 1997
118. Smith GC, Joyce ED, Hughes DA, *et al*: Complement activation in Henoch-Schönlein purpura. *Pediatr Nephrol* 11:477–480, 1997
119. Egido J, Julian B, Wyatt RJ: Genetic factors in IgA nephropathy. *Nephrol Dial Transplant* 2:134–142, 1987
120. Sakai H, Nomoto Y, Tomino Y, *et al*: Increase of in vivo and in vitro production of polyclonal IgA in patients and their family members with IgA nephropathy. *Adv Exp Med Biol* 216B:1507–1514, 1987
121. Welch TR, Berry A, Beischel LS: C4 isotype deficiency in IgA nephropathy. *Pediatr Nephrol* 1:136–139, 1987
122. Demaine AG, Rambausek M, Knight JF, *et al*: Relation of mesangial IgA glomerulonephritis to polymorphism of immunoglobulin heavy chain switch region. *J Clin Invest* 81:611–614, 1988
123. McLean RH, Wyatt RJ, Julian BA: Complement phenotypes in glomerulonephritis: Increased frequency of homozygous null C4 phenotypes in IgA nephropathy and Henoch-Schönlein purpura. *Kidney Int* 26:855–860, 1984
124. Kitamoto Y, Nakayama M, Sakata Y, *et al*: IgA nephritis associated with plasminogen abnormalities. *Clin Nephrol* 33:61–65, 1990
125. Turi S, Nagy J, Haszon I, *et al*: Plasma factors influencing PGI_2-like activity in patients with IgA nephropathy and Henoch-Schönlein purpura. *Pediatr Nephrol* 3:61–67, 1989
126. Hernandez E, Toledo T, Alamo C, *et al*: Elevation of von Willebrand factor levels in patients with IgA nephropathy: Effect of ACE inhibition. *Am J Kidney Dis* 30:397–403, 1997
127. De Mattia D, Penza R, Giordano P, *et al*: Von Willebrand factor and factor XIII in children with Henoch-Schönlein purpura. *Pediatr Nephrol* 9:603–605, 1995
128. Soylemezoglu O, Sultan N, Gursel T, *et al*: Circulating adhesion molecules ICAM-1, E-selectin and von Willebrand factor in Henoch-Schönlein purpura. *Arch Dis Child* 75:507–511, 1996

129. Ono T, Muso E, Suyama K, *et al*: Intraglomerular deposition of intact cross-linked fibrin in IgA nephropathy and Henoch-Schönlein nephritis. *Nephron* 74:522–528, 1996
130. Germuth FG, Rodriguez E: *Immunopathology of the Renal Glomerulus.* Boston, Little, Brown, 1973, p 15
131. Batsford SR, Weghaupt R, Takamiya H, *et al*: Studies on the mesangial handling of protein antigens: Influence of size, charge and biologic activity. *Nephron* 41:146–151, 1985
132. Davies M: The mesangial cell: A tissue culture view. *Kidney Int* 45:320–327, 1994
133. Gommez-Guerrero C, Gonzalez E, Egido J: Evidence for a specific IgA receptor in rat and human mesangial cells. *J Immunol* 151:7172–7181, 1993
134. Diven CS, Caflish CR, Hammond DK, *et al*: IgA induced activation of human mesangial cells: independent of FcαR1 (CD 89). *Kidney Int* 54:837–847, 1998
135. Duque N, Gomez-Guerrero C, Egido J: Interaction of IgA with Fc alpha receptors of human mesangial cells activates transcription factor nuclear factor-kappa B and induces expression and synthesis of monocyte chemoattractant protein-1, IL-8, and IFN-inducible protein 10. *J Immunol* 159:3474–3482, 1997
136. Westerhuis R, van Zandbergen G, Verhagen NAM, *et al*: Human mesangial cells in culture and in kidney sections fail to express Fc Alpha receptor (CD89). *J Am Soc Nephrol* 10:770–778, 1999
137. Yokohama H, Wada T, Furuichi K, *et al*: Urinary levels of chemokines (MCAF/MCP-1, IL-8) reflect distinct disease activities and phases of human IgA nephropathy. *J Leukoc Biol* 63:493–499, 1998
138. Horii Y, Muraguchi A, Iwano M, *et al*: Involvement of IL-6 in mesangial proliferative glomerulonephritis. *J Immunol* 143:3949–3955, 1989
139. Kashem A, Endoh M, Yano N, *et al*: Glomerular FcaR expression and disease activity in IgA nephropathy. *Am J Kidney Dis* 30:389–396, 1997
140. Terada Y, Yamada T, Nakashima O, *et al*: Expression of PDGF and PDGF receptor mRNA in glomeruli in IgA nephropathy. *J Am Soc Nephrol* 8:817–819, 1997
141. Niemir ZI, Stein H, Noronha IL, *et al*: PDGF and TGF-β contribute to the natural course of human IgA glomerulonephritis. *Kidney Int* 48:1530–1541, 1995
142. Vassalli P, McCluskey RT: The pathogenetic role of the coagulation process in rabbit Masugi nephritis. *Am J Pathol* 45:653–661, 1964
143. Mathieson PW: The ins and outs of glomerular crescent formation. *Clin Exp Immunol* 110:155–157, 1997
144. Cohen Tervaert JW, Kallenberg CGM: Vasculitis, in *Klinische Immunologie*, edited by The TH, de Kallenberg CGM, Leij L, Houten/Antwerpen, Bohn Stafleu Van Loghum, 1991, pp 216–233
145. Roitt I, Brostoff J, Male D: *Immunology.* London, Philadelphia, St. Louis, Sydney, Tokyo, Mosby, 1998
146. Foreback JL, Remick DG, Crockett-Torabi E, *et al*: Cytokines responses of human blood monocytes stimulated with Igs. *Inflammation* 21:501–517, 1997
147. Johnston B, Burns AR, Kubes P: A role for mast cells in the development of adjuvant- induced vasculitis and arthritis. *Am J Pathol* 152:2, 1998
148. Zheng F, Kundu GC, Zhang Z, *et al*: Uteroglobin is essential in preventing immunoglobulin A nephropathy in mice. *Nat Med* 5:1018–1025, 1999