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IgA vasculitis with nephritis: update of pathogenesis with clinical implications

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Abstract

IgA vasculitis with nephritis (IgAVN) shares many pathogenetic features with IgA nephropathy (IgAN). The purpose of this review is to describe our current understanding of the pathogenesis of pediatric IgAVN, particularly as it relates to the four-hit hypothesis for IgAN. These individual steps, i.e., hits, in the pathogenesis of IgAN are 1) elevated production of IgA1 glycoforms with some *O*-glycans deficient in galactose (galactose-deficient IgA1; Gd-IgA1), 2) generation of circulating IgG autoantibodies specific for Gd-IgA1, 3) formation of pathogenic circulating Gd-IgA1-containing immune complexes, and 4) kidney deposition of the Gd-IgA1-IgG immune complexes from the circulation and induction of glomerular injury. Evidence supporting the four-hit hypothesis in the pathogenesis of pediatric IgAVN is detailed. The genetics, pediatric

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outcomes, and kidney histopathologic features and the impact of these findings on future treatment and potential biomarkers are discussed. In summary, the evidence points to the critical roles of Gd-IgA1-IgG immune complexes and complement activation in the pathogenesis of IgAVN. Future studies are needed to characterize the features of the immune and autoimmune responses that enable progression of IgA vasculitis to IgAVN.

Keywords

Children; IgA vasculitis; Henoch-Schönlein purpura; progression; IgAVN; IgA1 glycoforms

Introduction

IgA vasculitis (IgAV), formerly known as Henoch-Schönlein purpura (HSP), is a systemic disease affecting multiple organs. The first case of a child with purpuric rash, abdominal colic, bloody stools, arthralgias, and macroscopic hematuria was reported by Heberden in 1806 [1]. In 1837, Schönlein noted the association of purpura and joint pain [2]. Henoch reported four children with purpura, abdominal colic, bloody diarrhea and arthralgia in 1874 and subsequently added nephritis in 1899 [3, 4]. Now it is understood that kidney involvement occurs in approximately 30% of patients with IgAV [5].

The 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides determined that the eponym “Henoch-Schönlein purpura” would be replaced by IgA vasculitis [6]. The conference based this decision upon “the compelling body of literature indicating that abnormal IgA deposits in vessel walls are the defining pathophysiologic feature.” This review follows this recommendation for change in nomenclature; hence Henoch-Schönlein purpura nephritis (HSPN) is referred to as IgA vasculitis with nephritis (IgAVN).

Clinical evidence for shared pathogenesis of IgAN and IgAVN

A connection between IgAV and IgAN was suspected when Jean Berger noted the mesangial deposition of IgA in both conditions in 1969 [7], but IgA deposits in IgAVN had actually been reported prior to the discovery of IgAN [8]. In 1973, the mesangial deposition of IgA, C3, and properdin were shown for “focal nephritis”, i.e., IgAN and IgAVN, indicating involvement of the alternative complement pathway for both conditions [9]. These IgA deposits are of the IgA1 subclass for both IgAN and IgAVN [10]. Wyatt and Julian compared the features of IgAN and IgAV in their review of IgAN in 2013 [11] and more recently, the CureGN Study compared demographic and clinical features of IgAN and IgAV for the children and adults in their cohort [12]. Table 1 compares the characteristics of patients with IgAN and IgAVN.

The change in clinical phenotype from IgAVN to IgAN or vice versa is well documented. The usual example of this is a child with typical IgAVN that resolves, but later develops one or more episodes of macroscopic hematuria during an upper respiratory infection without clinical features of IgAV [13, 14]. Conversely, the development of IgAV after a diagnosis of IgAN occurred in 6 of 53 children at the National Center for Child Health and

Development in Tokyo [15]. Review of these cases and previously reported cases revealed a total of 17 instances in which IgAV developed, sometimes in adulthood, as long as 15 years after diagnosis of IgAN. Eleven cases were from other Japanese centers, while the 6 were single-case reports from centers in Canada and Europe. The incidence of phenotype change is likely underestimated, since new case reports are unlikely to be published.

IgAVN and IgAN have also been described in different members of the same family. Identical twins in the United Kingdom had adenoviral pharyngitis that resulted in isolated macroscopic hematuria in one and IgAVN in the other, and both subjects had mesangial IgA deposits [16]. Similarly, and soon after the description of familial IgAN in Kentucky [17], a survey from the French Society of Nephrology described families with individuals with IgAN or IgAV/IgAVN [18]. Of 58 pedigrees with at least one individual with IgAN, 23 had at least one person with IgAV either with or without nephritis. We have reported a pedigree from southeastern Kentucky including individuals having IgAN or IgAV [19] and have previously followed an unreported family from Memphis in which a mother with IgAN diagnosed in childhood subsequently had two daughters develop IgAV (i.e., without nephritis).

Pathogenesis

Shortly before the publication of the 4-hit hypothesis for the clinical expression of IgAN [20], we reviewed the pathogenesis of IgAVN for this journal [21]. Over the past quarter of a century, there have been several reviews that discussed the similarities in the pathogenesis of IgAN and IgAVN [5, 11, 22, 23]. The purpose of this review is to update the pathogenesis and clinical expression of nephritis associated with IgA vasculitis (i.e., IgAVN) as it relates to the four-hit hypothesis for IgAN (Figure 1).

We will provide a brief overview and then follow with more specific and extended information for each aspect. Hit 1 is related to production of galactose-deficient IgA1 (Gd-IgA1), often presenting with elevated serum levels of Gd-IgA1 [24]. Hit 2 is the generation of circulating IgG autoantibodies specific for Gd-IgA1 [25–28]. Hit 3 is the formation of pathogenic Gd-IgA1-containing immune complexes [25, 29–32]. Hit 4 is the mesangial deposition of Gd-IgA1-containing immune complexes, resulting in mesangial-cell activation, release of inflammatory mediators, and glomerular injury [33–35].

Hit 1: In 1997, Saulsbury [36] used peanut-lectin binding to IgA1 to show that *O*-glycans of IgA1 were deficient with respect to sialic acid in children with IgAV. In 1998, Allen et al. [36] found that children with IgAVN had significantly higher serum levels of Gd-IgA1 than children having IgAV without kidney involvement who had normal levels. This suggested that elevated circulating Gd-IgA1 was important for the development of nephritis in IgAV.

The clustered *O*-linked glycans of the hinge region of IgA1 contain core 1 glycans consisting of *N*-acetylgalactosamine (GalNAc) with β1,3-linked galactose (Gal) wherein either or both sugars may be sialylated. Mass spectrometry studies from adult kidney transplant recipients found that the serum IgA1 *O*-glycosylation profile was similar for recipients with IgAVN as compared to those with IgAN [37]. IgA1 from both types of transplant recipients had fewer *O*-glycans and reduced number of galactose residues

attached to GalNAc as compared to IgA1 from recipients with other kidney diseases and healthy donors [37].

In 2007, we showed that median serum Gd-IgA1 level was significantly higher for children with IgAVN as compared to healthy controls [38]. In that study, 75% of children with IgAN and 52% with IgAVN had elevated serum Gd-IgA1 levels, defined as > 90th percentile for healthy controls. In a larger study of French children, mean serum Gd-IgA1 was significantly higher for IgAVN as compared to IgAV and healthy controls but did not differ between IgAV and healthy controls [39]. Gd-IgA1 could differentiate IgAVN from IgAV with the receiver operator characteristic curve having an area under the curve of 0.73 (P = 0.02). A recent study from Poland confirmed the presence of elevated serum Gd-IgA1 levels in children with IgAVN [40]. For adults in China, serum Gd-IgA1 levels were similarly elevated for patients with IgAN and IgAVN, whereas the levels for patients with IgAV also did not differ from those of healthy controls [41]. We recently reported similar serum Gd-IgA1 levels for children with IgAV as compared to controls and children with inactive IgAVN [42].

Furthermore, using a new tool, IgA1-producing cells derived from Epstein-Barr virus-immortalized B cells from peripheral blood of patients with IgAV and IgAVN, we have assessed degree of *O*-glycan galactose deficiency of the secreted IgA1. IgA1 produced by the cells from patients with IgAVN was deficient in galactose to a similar degree as found for patients with IgAN [42]. In contrast, IgA1 secreted by cell lines from patients with IgAV had normal galactosylation content.

Serum Gd-IgA1 levels appear to be inherited in an autosomal dominant manner for most adult patients with IgAN [43] and two relevant genetic loci were identified in a genome-wide association study (GWAS) [43, 44]. Serum Gd-IgA1 levels are also highly inherited in pediatric patients with IgAN and IgAVN, but in most instances first-degree relatives with elevated serum Gd-IgA1 levels never had clinical features of IgAN or IgAV [42, 45]. *In vitro* experiments suggest that production of Gd-IgA1 in IgAN can be further enhanced by various cytokines, such as interleukin 6 (IL-6), interleukin 4 (IL-4), and leukemia inhibitory factor (LIF) [46–48]. This cytokine-enhanced production of Gd-IgA1 is due to an aberrant signaling that in turn alters expression and activities of key glycosyltransferases, namely the galactosyltransferase C1GalT1 that adds Gal to GalNAc in IgA1 [49–51].

Hit 2: In 2009, Suzuki et al [26] described IgG autoantibodies to Gd-IgA1 in patients with IgAN. These autoantibodies are present in children with IgAVN and their serum levels are significantly higher for patients with active disease than those with resolution of nephritis [42]. In this relatively small study, levels of anti-glycan antibodies were similar for patients with inactive IgAVN as compared to healthy controls. More extensive studies with serial levels are needed to confirm that the IgG autoantibodies may clear after IgAVN has resolved. In IgAN, serum levels of IgG autoantibodies correlate with serum levels of Gd-IgA1 [52]. Furthermore, these IgG autoantibodies are enriched in the glomerular immunodeposits of kidney biopsies from IgAN patients but not those from patients with lupus nephritis or membranous nephropathy [52].

Hit 3: In 1979, Levinsky and Barratt [53] showed that all patients with IgAV had circulating IgA1-containing immune complexes of a relatively small molecular mass, whereas patients with IgAVN had additional large-molecular mass IgA1-IgG immune complexes. Subsequently, circulating immune complexes containing IgA were found in other series of patients with IgAV and IgAVN [39, 40, 54–60]. IgA1-containing immune complexes isolated from the sera of patients with either IgAN or IgAVN stimulate the proliferation of cultured mesangial cells in a similar manner [61].

Glomerular deposits in IgAN contain aberrantly glycosylated IgA1 [62, 63]. Using KM55, a monoclonal antibody that binds to Gd-IgA1, Gd-IgA1 was found in the mesangial deposits for IgAN and IgAVN, but absent in other glomerular diseases such as lupus nephritis and secondary forms of IgAN [64]. Although the initial findings indicated that glomerular Gd-IgA1 deposition was specific for IgAN and IgAVN, a recent publication postulates that KM55 staining may not be specific for primary IgAN [65]. This last study assessed whether immunostaining with KM55 can effectively differentiate primary IgAN from other diseases with IgA deposits. The authors performed double immunostaining using IgA-specific antibody and KM55. Similar patterns of KM55 staining were observed for primary IgAN, IgAVN, and secondary IgAN with hepatitis B virus-antigen deposits. KM55 staining was also observed for patients with lupus nephritis and incidental IgA deposits, but the intensity was lower than that for primary IgAN. The authors thus conclude that immunostaining by KM55 was not specific for primary IgAN [65]. Another recent study did reveal that the glomerular IgG extracted from remnant kidney-biopsy tissue of IgAN cases was specific for Gd-IgA1 [28]. Additionally, confocal microscopy showed co-localization of these autoantibodies with IgA, thus supporting the presence of mesangial immunodeposits consisting of IgG and Gd-IgA1.

Hit 4: Activation of the alternative complement pathway in IgAVN was demonstrated in early reports by presence of properdin in the glomerular deposits [9]. In 2000, Endo et al. [66] also described glomerular deposits of MBL/MASP-1 and plasma C4d, indicating activation of the lectin pathway. Subsequently, the same group found MBL/MASP1 mesangial deposits in 16 of 31 patients with IgAVN [67]. Mesangial deposits containing membrane attack complexes are known to occur in both IgAN and IgAVN [67, 68]. Thus, patterns of glomerular deposition of complement components indicate involvement of the alternative, lectin, and terminal complement pathways in both IgAN and IgAVN [69, 70].

Serum levels of many cytokines are elevated in children with acute IgAV compared to healthy controls [71–77]. These cytokines include tumor necrosis factor α [71–73], IL-2 [73], IL-4 [74], IL-6 [74–76], IL-18 [75], transforming growth factor-β [77], and midkine [74]. The observations of upregulated cytokine/chemokine synthesis may be related to hit 1, 2, or 4, i.e., impacting production of the autoantigen or autoantibody, or altering the local cytokine milieu in the glomerulus.

Genetics

There are three independent lines of support for the role of genetic factors in the pathogenesis of IgAV. First, there are ethnic and geographic differences in the incidence

of IgAV, with a pattern similar to IgAN incidence. IgAV has the highest occurrence in East Asians, intermediate in Europeans, and the lowest in individuals of African ancestry [78, 79]. Second, familial segregation of IgAV has been previously reported, including co-segregation in pedigrees with familial forms of IgAN, suggesting common genetic predisposition between these disorders [18, 19]. Third, genetic association studies suggest involvement of common variants in the pathogenesis of this disorder. However, formal estimates of IgAV heritability are not available, mostly due to the lack of large family-based studies or twin studies of this condition.

The results from multiple candidate gene association studies for IgAV have recently been reviewed in detail by Lopez-Mejias et al. [80]. However, most of these studies were severely underpowered and used outdated methods, falling short of modern standards for genetic association studies. These studies are therefore generally inconclusive.

Although large-scale GWAS have been successfully performed for IgAN in adults [81–86], there are presently no GWAS for pediatric IgAN, and only a single small study for IgAV has been published to date [87]. That study included 285 Spanish patients with IgAV and 1,006 ancestry-matched controls and describes a strong association signal in the MHC class II region. The top single-nucleotide polymorphism (SNP) in the region, rs9275260, maps between *HLA-DQA1* and *DQB1* genes, has relatively large effect size (OR = 1.79, 95% CI = 1.47–2.17), and reaches genome-wide significance despite the small sample size ($P = 3.4\times10^{-9}$). Imputation of classical HLA alleles and the analysis of individual amino-acid residues in MHC class II molecules pointed to the potential role of positions 13 and 11 of *HLA-DRB1* gene, although the small sample size did not allow analysis to further dissect this signal. Moreover, this study is underpowered to detect smaller allelic effects outside of the HLA region. Thus, it is very likely that numerous other non-HLA risk alleles also exist that, because of power issues, escape statistical detection. Lastly, the contributions of rare genetic variants to the risk of IgAV have not yet been studied.

In summary, very little is known presently about the genetic architecture of IgAV with and without nephritis, or its genetic similarity to IgAN. Given the availability of modern genetic tools, such as high-density SNP arrays and next generation sequencing, there is an opportunity to perform high quality large-scale genetic investigations in this area. Such studies should include systematic assessments of common variants (through large-scale high-resolution GWAS) and rare variants (through exome or whole genome sequencing studies), including familial disease. The generation of such data will also facilitate discoveries of specific genetic mechanisms that are either unique to IgAV, or shared with IgAN. The main challenge is the availability of sufficiently large pediatric cohorts to enable adequately powered genetic investigations.

To address this problem, a large multicenter study called GIGA-kids (Genomics of IgA-related disorders in kids, www.gigakids.org) has been established. The study aims to recruit over 1,000 children with early onset IgAN and IgAV with and without nephritis for the purpose of genetic and genomic studies (at 50% recruitment target or ~500 subjects recruited as reported during the annual meeting of the American Society of Nephrology Renal Week 2018 in San Diego, CA). In parallel, similar efforts are ongoing in Europe

under the umbrella name GIGA-Europe Study. We expect that genetic studies of these cohorts will elucidate additional genetic factors underlying IgAV and will help to resolve HLA associations across multiple ethnicities. Moreover, these studies will potentially allow detection of genetic factors that represent specific determinants of kidney involvement in IgAV, enable quantification of SNP-based heritability of IgAV with and without nephritis, and, for the first time, test the genetic correlation between IgAV and IgAN.

Outcome for pediatric IgAVN

The potential for progression to kidney failure in IgAVN was recognized in the earliest case series [13, 88, 89]. Poor outcome, defined as chronic kidney disease without replacement therapy (CKD) or death, was reported for 12 of 88 English pediatric patients with IgAVN in 1977 [89]. The authors concluded that poor outcome correlated with a clinical presentation of combined acute nephritis and nephrotic syndrome and a high proportion of crescents in the kidney biopsy. The following outcome grades were described in that study: A) normal, i.e., no hypertension, hematuria or proteinuria and normal kidney function, B) minor, i.e., same as A) but proteinuria < 1 g/day or 40 mg/m^2/h, C) active kidney disease with proteinuria > 1 g/day or > 40 mg/m^2/h and/or hypertension, but estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73 m^2, and D) CKD with eGFR < 60 ml/min/1.73 m^2 or death. These outcome grades, often with modifications in the definitions for proteinuria and CKD, have been used for many studies up until the present time [90–102]. However, this classification incorporates surrogate markers for the outcome of eventual progression to kidney failure and is clearly outdated. In many studies, definitions for markers in grades C and D are modified or changed, so there has been a lack of uniformity in the definition of outcomes across studies. There has been a tendency to include all of those classified in grades C and D as having a “poor” outcome [89, 93, 94, 98]. Thus, a subject could be classified in the poor outcome category on the basis of a weak surrogate outcome measure such as hypertension or relatively low-grade proteinuria. Such subjects may actually have a relatively low probability of eventual progression to kidney failure.

Relatively few studies have examined kidney failure as the primary outcome measure for IgAVN [103–107]. For these studies, 10-year kidney survival was 78% to 90% [102–105]. In a German study with a primary outcome of kidney failure, eGFR < 40 ml/min/1.73 m^2, CKD at presentation, and nephrotic syndrome, were independent significant predictors of poor outcome. A Swedish study showed eGFR < 90 ml/min/1.73 m^2, hypertension, and presence of proteinuria at time of biopsy were significantly associated with the outcome of kidney failure or eGFR < 90 ml/min/1.73 m^2 [107]. Conversely, in an Italian cohort of 83 pediatric and 136 adult patients, no clinical feature at diagnosis (including CKD, proteinuria, hypertension) was significantly related to decline in eGFR by multivariate analysis [106]. However, degree of proteinuria after diagnosis, age (adult vs. pediatric), and female sex were significant independent predictors for loss of kidney function, defined as doubling of serum creatinine.

Pathological features

A critical need at this time is a widely validated and accepted pathological scoring system that fits with our current understanding of the pathogenesis of IgAVN. The

histological lesions of kidney involvement in pediatric IgAV were initially categorized by the International Study of Kidney Disease in Children (ISKDC) classification [88]. The ISKDC system was widely used for almost three decades [89–91, 99, 100, 102–104, 108] but fell out of favor after the development of the Oxford MEST classification for IgAN (Table 2) [109]. The Oxford MEST classification is widely accepted for IgAN but still under evaluation for IgAVN.

Biopsy grades in the ISKDC system are I (normal light microscopy), II (mesangial proliferation only), and III (focal or diffuse proliferation or sclerosis with < 50% of glomeruli with crescents), IV and V (50–75% and > 75% with crescents, respectively). In addition, Grade VI is used for lesions with membranoproliferative features. This system has its limitations, as it focuses on the degree of crescentic involvement; in more recent series, grades IV and V account for an extremely small percentage of the cases.

Additionally, grade III, which includes biopsies with < 50% of glomeruli with crescents, includes cases without crescents, making it difficult to determine the precise incidence of crescentic involvement in series using this pathologic classification. In addition, the ISKDC system does not grade the chronic changes of segmental glomerular sclerosis, tubulointerstitial injury, or vascular changes.

The presence of glomerular crescents is a common finding in kidney biopsies from pediatric IgAVN [95, 103, 110–112]. However, the percentage of patients with crescents varies greatly in these series from about 30% [95, 103, 112] to about 70% [110, 112]. A recent multicenter study from Germany found one or more crescents of any type in 69% of 202 biopsies [111]. In that study, patients with cellular crescents were biopsied significantly earlier than those without crescents [111]. An Italian study found that crescents occurred in equal frequency in children and adults and about two-thirds of those with crescents also had endocapillary proliferation [103]. Davin and Coppo [5] noted that the paradox of patients without crescents having a worse outcome than those with crescents [93] was most likely due to early treatment of crescentic IgAVN with corticosteroids and/or immunosuppressive agents.

The Oxford classification for IgAN was updated in 2017 to include an assessment of crescents and is now termed MEST-C (Table 2) [113]. In this system C0 denotes no glomerular crescents, C1 denotes < 25% of glomeruli with crescents, and C2 denotes > 25% with crescents. The cutoffs employed for percentage of glomeruli are much more clinically relevant than those in the ISKDC classification.

The acute feature of endocapillary proliferation, a component of the IgAN Oxford classification, is not independently assessed in the ISKDC system. Mesangial proliferation, a component of ISKDC grades II and III, is not defined as rigorously in that system as it is in the Oxford IgAN classification [109]. The chronic features of sclerosis and tubulointerstitial fibrosis are included in the Oxford classification, but not independently assessed in the ISKDC system. Thus, the ISKDC system is inadequate by present standards with respect to assessing both acute and chronic injury. Other systems have been proposed, but they tend to be very complex and lack validation in different clinical cohorts [102, 112]. The

recent review in this journal by Davin and Coppo [114] states “It is now obvious that the ISKDC classification that grades severity according to the amount of crescents only has become obsolete and should be replaced by a new detailed histological classification similar to that recently published for IgAN. This latter classification takes into account not only the crescents but also the following parameters that have been shown to be independent predictors of kidney functional decline and/or response to therapy: mesangial hypercellularity, endocapillary hypercellularity, segmental and global glomerulosclerosis, arterio- and arteriolosclerosis, interstitial inflammation and tubular atrophy and interstitial fibrosis.” The Oxford MEST-C classification’s rigorous assessment of the acute changes of C, M, and E fits our present understanding of the four-hit hypothesis for IgAN, particularly with regards to the earliest mediators of glomerular injury in hit 4.

The Oxford MEST-C classification was utilized in a study of 104 biopsied Chinese children with IgAV having ≥ 12 months follow-up [115]. M1 strongly associated with the degree of proteinuria at time of biopsy. T1, T2 and C2 were significantly associated with reduced estimated GFR at biopsy. S1 significantly associated with the primary outcome of impaired kidney function (≥ 50% reduction in initial eGFR or eGFR below 90 ml/min/1.73 m^2). T1 and T2 were negatively associated with both clinical remission and remission of proteinuria.

A Turkish study of 75 children with IgAVN who were biopsied prior to initiation of treatment with corticosteroids and/or other immunosuppressive agents found that S1 and T1 and T2 were significantly associated with reduced eGFR at time of biopsy [116]. In this study, T1 and T2, S1, and C1 and C2 associated with the outcome of kidney dysfunction defined by eGFR < 90 ml/min/1.73 m^2. A small study in the United States that utilized a “composite” outcome measure of very weak surrogate markers, such as hypertension or any degree of proteinuria, failed to find a significant association with C1 [117]. In a study of 26 children having repeat biopsies, the frequencies of E1, C1, and C2 were significantly less in the second biopsy compared to the first, but the frequency of S1 significantly increased (from 38 to 79%; P = 0.006) [118]. However, this study also indicated that follow-up biopsies (performed at a median of 2.1 years after diagnostic biopsy) provide only limited additional information for IgAVN outcome prediction.

Overall, it appears that the Oxford MEST-C classification may be useful for IgAVN. Results will soon be available from a large multi-national study from the Oxford group on the use of MEST-C score in the assessment of kidney biopsies from children and adults with IgAVN.

Glomerular leukocytic infiltration is a major feature of IgAVN, associating with both endocapillary proliferation and crescent formation [23]. Davin and Coppo [5] observed that the glomerular lesions in the initial biopsy were often more severe for children with IgAVN as compared to those with IgAN. They suggested that this finding may be due to more intense subendothelial deposition of IgA-containing circulating immune complexes. Thus, IgAVN is often associated with acute episodes of glomerular inflammation with the constellation of endocapillary and mesangial proliferation, fibrin deposits, and epithelial crescents that can either heal (spontaneously or in response to treatment) or lead to chronic lesions [5]. By contrast, IgAN may have slowly progressive mesangial lesions resulting from continuous low-grade deposition of IgA1 immunocomplexes [5]. These observations were

supported and extended by the recent study of German children by Hennies et al. [111] in which younger children had a more acute presentation while those over 10 years of age had more insidious onset of non-nephrotic proteinuria, impaired kidney function, longer delay to biopsy, and more chronic histologic lesions. These authors also advocated for earlier biopsy that might lead to effective therapeutic intervention for the older children [111].

Treatment

Treatment of IgAVN remains problematic, as little has changed since evidence-based guidelines for treatment were summarized by Wyatt and Hogg [119] in 2001. Well-designed randomized clinical treatment trials are lacking due to inconsistent screening for kidney involvement in IgAV and due to the self-limited nature of IgAVN in most cases [120]. Two major guidelines based largely on expert opinion have been published to date in an attempt to standardize diagnostic and treatment approaches to IgAVN. The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for Glomerulonephritis for IgAVN, which was based upon very-low-quality evidence, suggested renin-angiotensin system (RAS) blockade with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) for children with urine protein excretion 0.5 to 1 g/1.73 m^2/day [121]. KDIGO also recommended six months of oral corticosteroids for those with proteinuria > 1 g/1.73 m^2/day after a trial of ACEi or ARB [121]. These guidelines for RAS blockade and oral corticosteroids appear to address treatment of chronic disease associated with MEST-C scores of S1 and T1/2. KDIGO further recommended corticosteroids and cyclophosphamide for children with crescentic rapidly progressive disease. Davin and Coppo disagree with KDIGO recommendations, particularly regarding early treatment for acute changes [5, 114]. They emphasized treatment targeted at the MEST-C acute lesions of E1 and C1/2. They contend that early diagnosis and prompt treatment is of paramount importance in determining the final outcome and that both over- and under-treatment are important concerns.

More recently, European consensus-based recommendations for the treatment of IgAV (with and without nephritis) were published in which treatment guidelines were based on severity of IgAVN [120]. These recommendations supported the use of RAS blockers in patients with persistent proteinuria beyond three months. Mild IgAVN, defined as normal eGFR and early morning urine protein to creatinine ratio (PCR) up to 250 mg/mmol, would be treated with oral prednisolone as the first-line agent. If proteinuria does not resolve, then the addition of azathioprine, cyclosporine, or mycophenolate mofetil may be considered as second-line agents or corticosteroid-sparing strategies [120]. Moderate IgAVN, defined as < 50% crescents on biopsy with impaired eGFR (< 80 ml/min/1.73 m^2) or severe persistent proteinuria (PCR > 250 mg/mmol for 4 weeks), would warrant initiation of corticosteroids followed by the addition of azathioprine, mycophenolate mofetil, or intravenous cyclophosphamide as second-line treatments [120]. Severe IgAVN, defined as > 50% crescents on biopsy with impaired eGFR (< 80 ml/min/1.73 m^2) or severe persistent proteinuria (PCR > 250 mg/mmol for 4 weeks), should be treated like other small vessel vasculitis such as ANCA-associated vasculitis. The treatment would therefore require an induction phase including high-dose systemic corticosteroids and cyclophosphamide, followed by a maintenance phase using lower-dose corticosteroids and azathioprine or

mycophenolate mofetil [120]. All of these recommendations were based on expert opinion, as the data available for the treatment of IgAVN is mostly retrospective or based on case series. These guidelines reflect the widespread use of immunosuppression in the setting of IgAVN in clinical practice. The CureGN trial reported that among 161 IgAVN and 506 IgAN participants across the age spectrum, 79.5% of IgAVN patients had received at least one immunosuppressive drug versus 54% of IgAN patients. Furthermore, adults with IgAVN were twice as likely to receive immunosuppressant drugs as children (24.1% vs. 12.2% of the cohort) [12]. European treatment guidelines are largely based on expert opinion. Perhaps the most controversial is the use of any immunosuppression in mild case of IgAVN with mild proteinuria in which the risk of immunosuppression may outweigh the benefit. More data are needed to determine the lower threshold of proteinuria beyond which treatment should be escalated. Perhaps some of the newer agents with a better safety profile that are being investigated in IgAN could ultimately be extended for use in IgAVN and pediatric patients. A particularly promising agent is oral targeted-release budesonide which affects the Peyer's patches in the ileum where the disease process (i.e., production of Gd-IgA1) is thought to originate. Such new therapies, if applicable to IgAVN, may change the risk-benefit balance of therapeutic interventions and recommendations.

More recently, treatment with rituximab, an anti-CD20 monoclonal antibody which has been successfully used in the treatment of ANCA vasculitis, has been explored in IgAVN. In a small case series of children with corticosteroid-dependent IgAVN, rituximab was associated with weaning of corticosteroids, reduced number of hospitalizations, and remission in most subjects [122]. Similarly, a few case series in adults suggest it may be beneficial [123–125]. Rituximab is expected to block hits 1 and 2 by reducing synthesis of Gd-IgA1 and autoantibody. However, in an open-label multicenter randomized study in adult IgAN, this agent failed to reduce the level of proteinuria when compared to standard therapy with RAS blockade and did not change serum levels of Gd-IgA1 and autoantibody [126]. The mechanism by which it benefits IgAVN patients remains therefore unknown.

New agents targeting complement activation pathways are showing promise for the treatment of IgAN in adults [33]. As they target pathogenic hit 4, it is reasonable to assume that such agents may be effective for severe IgAVN as well, although future studies are needed to confirm this theoretical benefit. Bortezomib, a proteasome inhibitor used in the treatment of multiple myeloma, has been described as a successful rescue therapy in one case report of refractory IgAVN [127].

Several attempts at therapeutic interventions to prevent the development of nephritis after the onset of IgAV have failed to show benefit. Therefore, the consensus, based on systemic reviews of the data, is to avoid corticosteroid use as a preventive therapy [128, 129]. A more recent placebo-controlled trial included 352 children with newly diagnosed IgAV who were randomized to receive prednisolone versus placebo for 14 days confirmed this guideline. At the end of the trial, there was no difference at 12 months in the primary outcomes of proteinuria (defined as PCR > 20 mg/mmol) or the need for additional treatments (such as use of anti-hypertensives, additional kidney treatment or biopsy) [130].

In patients transplanted after kidney failure caused by IgAN, prednisone significantly decreased the serum levels of IgA1, Gd-IgA1, and IgA-IgG complexes during the first 6 months after engraftment [131]. In a French study of pediatric IgAVN, patients with ISKDC class 2 histology (which best correlates with Oxford M1) had improved outcome if they had been treated with corticosteroids [132].

Biomarkers

Unlike IgAN, IgAVN can often be diagnosed with currently available laboratory data in the right clinical context, obviating the need for a diagnostic biomarker. However, a biomarker that would predict the development of nephritis in patients with IgAV would be very helpful. In addition, prognostic/severity marker(s) could help determine the timing of kidney biopsy and guide therapy.

Based on pathogenesis data available from IgAN, Allen et al. [133] investigated whether Gd-IgA1 was also involved in IgAV. Using a lectin-based assay in a cohort of adults and children with IgAV, they found that abnormal glycosylation of serum IgA1 was detected only in those with kidney involvement [133]. The major limitation of this study was that the serum Gd-IgA1 levels were not adjusted to total serum IgA which varies physiologically across the age range and hence the contribution of galactose deficiency may have been unrecognized in the IgAV group of children with nephritis who were much younger and likely had lower serum total IgA levels [133].

Using a different lectin assay, Lau et al. showed no difference in serum Gd-IgA1 levels between IgAVN and IgAV in a cohort of adults and children; however, IgAV patients who had persistent hematuria had higher serum levels of Gd-IgA1 than those in whom the hematuria resolved with time [38]. Pillebout et al. [39] looked at a panel of serum and urine biomarkers obtained at the time of IgAV diagnosis among 85 adults and 50 children. They showed that patients with IgAVN had significantly higher levels of serum Gd-IgA1, as well as higher urinary concentrations of IgA, IgG, IgM, IL-6, IL-8, IL-10, IgA-IgG complexes and IgA-sCD89 complexes [39]. Urinary IgA and IgM assays performed best, with areas under the curve of 0.86 and 0.87, respectively [39]. Subsequently, Berthelot et al. analyzed more rigorously the value of these biomarkers in the subset of adult IgAV patients in this same cohort. They found that, in addition to previously mentioned results, serum IgE as well as urinary IgM, NGAL and IL-1β were significantly higher in the IgAVN compared to IgAV group [134]. While all these biomarkers were associated with IgAVN at the time of diagnosis, only a high urinary IgA level predicted a poor outcome in their multivariate model [134].

A more recent lectin-independent ELISA for detection of Gd-IgA1 uses a monoclonal antibody known as KM55 [135]. Using KM55, Wada et al. showed that serum Gd-IgA1 levels and presence of mesangial Gd-IgA1 were identical among IgAN and IgAVN patients [136]. However, a recent study concluded that immunostaining by KM55 was not specific for primary IgAN [65]. The degree of galactose deficiency of the IgA1 hinge-region glycans may distinguish patients with IgAV from those who develop evidence of nephritis, with serum levels of Gd-IgA1 significantly lower in the former group [42]. In addition, the serum level of Gd-IgA1-specific IgG autoantibody (which accounts for hit 2 of the proposed

disease pathogenesis) was higher in IgAVN; patients without nephritis had autoantibody levels comparable to those of healthy controls [42]. After EBV immortalization, peripheral blood mononuclear cells from IgAVN and IgAN patients secreted IgA1 that was similarly galactose-deficient. The amount of Gd-IgA1 secreted was also higher than that secreted by cells from IgAV patients without nephritis [42]. This finding was further supported by the reduced expression of genes encoding glycosyltransferases (e.g., C1GalT1 and its molecular chaperone Cosmc) in IgA1-producing cells from IgAVN patients. Gd-IgA1-specific IgG autoantibody production was also higher in EBV-immortalized cells from IgAVN patients, particularly in those with active disease as evidenced by hematuria and significant proteinuria [42]. These results suggest that serum levels of Gd-IgA1 and its specific autoantibody could be used in the future to stratify patients at risk of developing nephritis, and could serve to monitor for disease activity. Although results from studies remain preliminary at this time, biomarkers promise to be a potential avenue for monitoring response to interventions and thus may promote future therapeutic trials (Table 3).

Conclusion

The four-hit hypothesis may best explain the pathogenesis of both IgAN and IgAVN with production of Gd-IgA1 [24], generation of circulating IgG autoantibodies specific for Gd-IgA1 [26–29], formation of pathogenic Gd-IgA1-containing immune complexes [26, 30–33], and the subsequent mesangial deposition of these immune complexes resulting in glomerular injury. Genetic factors likely play a role in the pathogenesis of IgAV, as there are ethnic and geographic differences in the incidence of IgAV [76, 77], familial segregation of IgAV [18, 19], and genetic-association studies to suggest involvement of common variants. However, there is currently no published large-scale GWAS for IgAV, although several studies are ongoing in the United States and Europe.

Poor clinical outcomes, including kidney failure, have been shown in some series of pediatric IgAVN cases [13, 86, 87]. Unfortunately, the use of surrogate outcome markers and a lack of uniformity in the definition of risk factors across studies complicate the interpretation of these studies. Chronic kidney disease at time of diagnosis, degree of proteinuria, presence of hypertension, older age of onset, and female sex have all been associated with loss of kidney function [104–105].

There is no widely validated and accepted pathological scoring system that fits with our current understanding of the pathogenesis of IgAVN. The MEST-C Oxford classification developed for IgAN may be validated and applied to IgAVN in the near future. This classification scheme offers a better assessment of active versus chronic kidney lesions and is an improvement over the older ISKDC classification. Biomarkers predicting the development of nephritis in IgAV or associated with severity of nephritis in IgAVN would be clinically useful. Serum Gd-IgA1 levels and Gd-IgA1-specific IgG autoantibody have been associated with the development of nephritis in some studies and may be useful in monitoring disease severity, based on preliminary studies.

Currently, there are no evidence-based guidelines for the treatment of IgAVN. The past few years have witnessed an exponential increase in clinical trials to test novel treatments in

adults with IgAN. Given the clear parallels in the pathogenesis of IgAN and IgAVN, these therapeutics trials are likely to be extended to pediatric populations and to IgAVN cases in the foreseeable future.

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References

1. Heberden W (1806) Commentaries on the history and cure of diseases, London.
2. Schönlein JL (1837) Allgememe und Specielle Pathologe und Therapie.
3. Henoch E (1874) Über ein eigenthümliche Form von Purpura. Berl Klin Wochenschr 11:641–643.
4. Henoch E, in Herschward A (ed): Vorlesungen uber kinderkranheiten, vol 10, Berlin, Aufl, p 839 (1899) Vorlesungen uber kinderkranheiten. In: Herschward A (ed) Vorlesungen uber kinderkranheiten, Berlin, pp Aufl, p 839.
5. Davin JC, Coppo R (2014) Henoch-Schönlein purpura nephritis in children. Nat Rev Nephrol 10:563–573 [PubMed: 25072122]
6. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA (2013) 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 65:1–11 [PubMed: 23045170]
7. Berger J (1969) IgA glomerular deposits in renal disease. Transplant Proc 1:939–944 [PubMed: 4107073]
8. Urizar RE, Michael A, Sisson S, Vernier RL (1968) Anaphylactoid purpura. II. Immunofluorescent and electron microscopic studies of the glomerular lesions. Lab Invest 19:437–450 [PubMed: 4880770]
9. Evans DJ, Williams DG, Peters DK, Sissons JG, Boulton-Jones JM, Ogg CS, Cameron JS, Hoffbrand BI (1973) Glomerular deposition of properdin in Henoch-Schönlein syndrome and idiopathic focal nephritis. Br Med J 3:326–328 [PubMed: 4579400]
10. Conley ME, Cooper MD, Michael AF (1980) Selective deposition of immunoglobulin A1 in immunoglobulin A nephropathy, anaphylactoid purpura nephritis, and systemic lupus erythematosus. J Clin Invest 66:1432–1436 [PubMed: 6777400]
11. Wyatt RJ, Julian BA (2013) IgA nephropathy. N Engl J Med 368:2402–2414 [PubMed: 23782179]
12. Selewski DT, Ambruzs JM, Appel GB, Bomback AS, Matar RB, Cai Y, Cattran DC, Chishti AS, D'Agati VD, D'Alessandri-Silva CJ, Gbadegesin RA, Hogan JJ, Iragorri S, Jennette JC, Julian BA, Khalid M, Lafayette RA, Liapis H, Lugani F, Mansfield SA, Mason S, Nachman PH, Nast CC, Nester CM, Noone DG, Novak J, O'Shaughnessy MM, Reich HN, Rheault MN, Rizk DV, Saha MK, Sanghani NS, Sperati CJ, Sreedharan R, Srivastava T, Swiatecka-Urban A, Twombley K, Vasylyeva TL, Weaver DJ, Yin H, Zee J, Falk RJ, Gharavi AG, Gillespie BW, Gipson DS, Greenbaum LA, Holzman LB, Kretzler M, Robinson BM, Smoyer WE, Flessner M, Guay-Woodford LM, Kiryluk K (2018) Clinical characteristics and treatment patterns of children and adults with IgA nephropathy or IgA vasculitis: Findings from the CureGN study. Kidney Int Rep 3:1373–1384 [PubMed: 30450464]
13. Levy M, Broyer M, Arsan A, Levy-Bentolila D, Habib R (1976) Anaphylactoid purpura nephritis in childhood: natural history and immunopathology. Adv Nephrol Necker Hosp 6:183–228 [PubMed: 139081]
14. Nakamoto Y, Asano Y, Dohi K, Fujioka M, Iida H, Kida H, Kibe Y, Hattori N, Takeuchi J (1978) Primary IgA glomerulonephritis and Schönlein-Henoch purpura nephritis: Clinicopathological and immunohistological characteristics. Q J Med 47:495–516 [PubMed: 375278]

15. Kamei K, Ogura M, Sato M, Ito S, Ishikura K (2016) Evolution of IgA nephropathy into anaphylactoid purpura in six cases--further evidence that IgA nephropathy and Henoch-Schonlein purpura nephritis share common pathogenesis. Pediatr Nephrol 31:779–785 [PubMed: 26679340]
16. Meadow SR, Scott DG (1985) Berger disease: Henoch-Schönlein syndrome without the rash. J Pediat 106:27–32 [PubMed: 2981307]
17. Julian BA, Quiggins PA, Thompson JS, Woodford SY, Gleason K, Wyatt RJ (1985) Familial IgA nephropathy. Evidence of an inherited mechanism of disease. N Engl J Med 312:202–208 [PubMed: 3855328]
18. Levy M (1989) Familial cases of Berger's disease and anaphylactoid purpura: more frequent than previously thought. Am J Med 87:246–248 [PubMed: 2757072]
19. Lavigne KA, Woodford SY, Barker CV, Julian BA, Novak J, Moldoveanu Z, Gharavi AG, Wyatt RJ (2010) Familial IgA nephropathy in southeastern Kentucky. Clin Nephrol 73:115–121 [PubMed: 20129018]
20. Suzuki H, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, Wyatt RJ, Scolari F, Mestecky J, Gharavi AG, Julian BA (2011) The pathophysiology of IgA nephropathy. J Am Soc Nephrol 22:1795–1803 [PubMed: 21949093]
21. Lau KK, Suzuki H, Novak J, Wyatt RJ (2010) Pathogenesis of Henoch-Schönlein purpura nephritis. Pediatr Nephrol 25:19–26. [PubMed: 19526254]
22. Waldo FB (1988) Is Henoch-Schönlein purpura the systemic form of IgA nephropathy? Am J Kidney Dis 12:373–377 [PubMed: 3055961]
23. Davin JC, Ten Berge IJ, Weening JJ (2001) What is the difference between IgA nephropathy and Henoch-Schönlein purpura nephritis? Kidney Int 59:823–834 [PubMed: 11231337]
24. Moldoveanu Z, Wyatt RJ, Lee J, Tomana M, Julian BA, Mestecky J, Huang W-Q, Anreddy S, Hall S, Hastings MC, Lau KK, Cook WJ, Novak J (2007) Patients with IgA nephropathy have increased serum galactose-deficient IgA1 levels. Kidney Int 71:1148–1154 [PubMed: 17342176]
25. Tomana M, Novak J, Julian BA, Matousovic K, Konecny K, Mestecky J (1999) Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. J Clin Invest 104:73–81 [PubMed: 10393701]
26. Suzuki H, Fan R, Zhang Z, Brown R, Hall S, Julian BA, Chatham WW, Suzuki Y, Wyatt RJ, Moldoveanu Z, Lee JY, Robinson J, Tomana M, Tomino Y, Mestecky J, Novak J (2009) Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity. J Clin Invest 119:1668–1677 [PubMed: 19478457]
27. Huang ZQ, Raska M, Stewart TJ, Reily C, King RG, Crossman DK, Crowley MR, Hargett A, Zhang Z, Suzuki H, Hall S, Wyatt RJ, Julian BA, Renfrow MB, Gharavi AG, Novak J (2016) Somatic mutations modulate autoantibodies against galactose-deficient IgA1 in IgA nephropathy. J Am Soc Nephrol 27:3278–3284 [PubMed: 26966014]
28. Rizk DV, Saha MK, Hall S, Novak L, Brown R, Huang ZQ, Julian BA, Novak J (2019) Glomerular immunodeposits of patients with IgA nephropathy are enriched for IgG autoantibodies specific for galactose-deficient IgA1. J Am Soc Nephrol 30:2017–2026 [PubMed: 31444275]
29. Novak J, Tomana M, Matousovic K, Brown R, Hall S, Novak L, Julian BA, Wyatt RJ, Mestecky J (2005) IgA1-containing immune complexes in IgA nephropathy differentially affect proliferation of mesangial cells. Kidney Int 67:504–513 [PubMed: 15673298]
30. Novak J, Raskova Kafkova L, Suzuki H, Tomana M, Matousovic K, Brown R, Hall S, Sanders JT, Eison TM, Moldoveanu Z, Novak L, Novak Z, Mayne R, Julian BA, Mestecky J, Wyatt RJ (2011) IgA1 immune complexes from pediatric patients with IgA nephropathy activate cultured mesangial cells. Nephrol Dial Transplant 26:3451–3457 [PubMed: 21828345]
31. Moura IC, Arcos-Fajardo M, Sadaka C, Leroy V, Benhamou M, Novak J, Vrtovsnik F, Haddad E, Chintalacharuvu KR, Monteiro RC (2004) Glycosylation and size of IgA1 are essential for interaction with mesangial transferrin receptor in IgA nephropathy. J Am Soc Nephrol 15:622–634 [PubMed: 14978164]
32. Maillard N, Wyatt RJ, Julian BA, Kiryluk K, Gharavi A, Fremeaux-Bacchi V, Novak J (2015) Current understanding of the role of complement in IgA nephropathy. J Am Soc Nephrol 26:1503–1512 [PubMed: 25694468]

33. Rizk DV, Maillard N, Julian BA, Knoppova B, Green TJ, Novak J, Wyatt RJ (2019) The emerging role of complement proteins as a target for therapy of IgA nephropathy. Invited Review. Front Immunol 10:504
34. Lai KN, Leung JC, Chan LY, Saleem MA, Mathieson PW, Lai FM, Tang SC (2008) Activation of podocytes by mesangial-derived TNF-α: glomerulo-podocytic communication in IgA nephropathy. Am J Physiol Renal Physiol 294:F945–955 [PubMed: 18256312]
35. Lai KN, Tang SC, Schena FP, Novak J, Tomino Y, Fogo AB, Glassock RJ (2016) IgA nephropathy. Nat Rev Dis Primers 2:16001 [PubMed: 27189177]
36. Saulsbury FT (1997) Alterations in the O-linked glycosylation of IgA1 in children with Henoch-Schönlein purpura. J Rheumatol 24:2246–2249 [PubMed: 9375892]
37. Nakazawa S, Imamura R, Kawamura M, Kato T, Abe T, Iwatani H, Yamanaka K, Uemura M, Kishikawa H, Nishimura K, Tajiri M, Wada Y, Nonomura N (2019) Evaluation of IgA1 O-glycosylation in Henoch-Schönlein purpura nephritis using mass spectrometry. Transplant Proc 51:1481–1487 [PubMed: 31084922]
38. Lau KK, Wyatt RJ, Moldoveanu Z, Tomana M, Julian BJ, Hogg RJ, Lee JY, Huang W-Q, Mestecky J, Novak J (2007) Serum levels of galactose-deficient IgA in children with IgA nephropathy and Henoch-Schoenlein purpura. Pediatr Nephrol 22:2067–2072 [PubMed: 17943324]
39. Pillebout E, Jamin A, Ayari H, Housset P, Pierre M, Sauvaget V, Viglietti D, Deschenes G, Monteiro RC, Berthelot L (2017) Biomarkers of IgA vasculitis nephritis in children. PLoS One 12:e0188718
40. Mizerska-Wasiak M, Gajewski L, Cichon-Kawa K, Maldyk J, Dziedzic-Jankowska K, Leszczynska B, Rybi-Szuminska A, Wasilewska A, Pukajlo-Marczyk A, Zwolinska D, Bienias B, Sikora P, Szczepanska M, Stelmaszczyk-Emmel A, Gorska E, Panczyk-Tomaszewska M (2018) Serum GDIgA1 levels in children with IgA nephropathy and Henoch-Schönlein nephritis. Cent Eur J Immunol 43:162–167 [PubMed: 30135628]
41. Zhang X, Xie X, Shi S, Liu L, Lv J, Zhang H (2020) Plasma galactose-deficient immunoglobulin A1 and loss of kidney function in patients with immunoglobulin A vasculitis nephritis. Nephrol Dial Transplant 35:2117–2123. 10.1093/ndt/gfz151 [PubMed: 31377786]
42. Suzuki H, Moldoveanu Z, Julian BA, Wyatt RJ, Novak J (2019) Autoantibodies specific for galactose-deficient IgA1 in IgA vasculitis with nephritis. Kidney Int Rep 4:1717–1724 [PubMed: 31844808]
43. Gharavi AG, Moldoveanu Z, Wyatt RJ, Barker CV, Woodford SY, Lifton RP, Mestecky J, Novak J, Julian BA (2008) Aberrant IgA1 glycosylation is inherited in familial and sporadic IgA nephropathy. J Am Soc Nephrol 19:1008–1014 [PubMed: 18272841]
44. Kiryluk K, Li Y, Moldoveanu Z, Suzuki H, Reily C, Hou P, Xie J, Mladkova N, Prakash S, Fischman C, Shapiro S, LeDesma RA, Bradbury D, Ionita-Laza I, Eitner F, Rauen T, Maillard N, Berthoux F, Floege J, Chen N, Zhang H, Scolari F, Wyatt RJ, Julian BA, Gharavi AG, Novak J (2017) GWAS for serum galactose-deficient IgA1 implicates critical genes of the O-glycosylation pathway. PLoS Genet 13:e1006609
45. Kiryluk K, Moldoveanu Z, Sanders JT, Eison TM, Suzuki H, Julian BA, Novak J, Gharavi AG, Wyatt RJ (2011) Aberrant glycosylation of IgA1 is inherited in both pediatric IgA nephropathy and Henoch-Schönlein purpura nephritis. Kidney Int 80:79–87 [PubMed: 21326171]
46. Yamada K, Kobayashi N, Ikeda T, Suzuki Y, Tsuge T, Horikoshi S, Emancipator SN, Tomino Y (2010) Down-regulation of core 1 β1,3-galactosyltransferase and Cosmc by Th2 cytokine alters O-glycosylation of IgA1. Nephrol Dial Transplant 25:3890–3897 [PubMed: 20551088]
47. Yamada K, Huang Z-Q, Raska M, Reily CR, Aderson J, Suzuki H, Ueda H, Moldoveanu Z, Kiryluk K, Suzuki Y, Wyatt RJ, Tomino Y, Gharavi AG, Weinmann A, Julian BA, Willey CD, Novak J (2017) Inhibition of STAT3 signaling reduces IgA1 autoantigen production in IgA nephropathy. Kidney Int Rep 2:1194–1207 [PubMed: 29270528]
48. Yamada K, Huang ZQ, Raska M, Reily C, Anderson JC, Suzuki H, Kiryluk K, Gharavi AG, Julian BA, Willey CD, Novak J (2020) Leukemia inhibitory factor signaling enhances production of galactose-deficient IgA1 in IgA nephropathy. Kidney Dis 6:168–180

49. Reily C, Ueda H, Huang ZQ, Mestecky J, Julian BA, Willey CD, Novak J (2014) Cellular signaling and production of galactose-deficient IgA1 in IgA nephropathy, an autoimmune disease. J Immunol Res 2014:197548
50. Knoppova B, Reily C, Maillard N, Rizk DV, Moldoveanu Z, Mestecky J, Raska M, Renfrow MB, Julian BA, Novak J (2016) The origin and activities of IgA1-containing immune complexes in IgA nephropathy. Front Immunol 7:117 [PubMed: 27148252]
51. Novak J, Barratt J, Julian BA, Renfrow MB (2018) Aberrant glycosylation of the IgA1 molecule in IgA nephropathy. Semin Nephrol 38:461–476 [PubMed: 30177018]
52. Placzek WJ, Yanagawa H, Makita Y, Renfrow MB, Julian BA, Rizk DV, Suzuki Y, Novak J, Suzuki H (2018) Serum galactose-deficient-IgA1 and IgG autoantibodies correlate in patients with IgA nephropathy. PLoS One 13:e0190967
53. Levinsky RJ, Barratt TM (1979) IgA immune complexes in Henoch-Schönlein purpura. Lancet 2:1100–1103 [PubMed: 91839]
54. Kauffmann RH, Van Es LA, Daha MR (1981) The specific detection of IgA in immune complexes. J Immunol Methods 40:117–129 [PubMed: 7019333]
55. Coppo R, Basolo B, Martina G, Rollino C, De Marchi M, Giacchino F, Mazzucco G, Messina M, Piccoli G (1982) Circulating immune complexes containing IgA, IgG and IgM in patients with primary IgA nephropathy and with Henoch-Schönlein nephritis. Correlation with clinical and histologic signs of activity. Clin Nephrol 18:230–239 [PubMed: 7151337]
56. Tanaka H (1984) Circulating immune complex and complement in children with various glomerulonephritides, especially the cases with IgA nephropathy or Henoch-Schönlein purpura nephritis. Nihon Jinzo Gakkai Shi 26:1131–1142 [PubMed: 6513184]
57. Westedt ML, Daha MR, de Vries E, Valentijn RM, Cats A (1985) IgA containing immune complexes in rheumatoid vasculitis and in active rheumatoid disease. J Rheumatol 12:449–455 [PubMed: 4045842]
58. Blanco Quiros A, Blanco C, Alvarez J, Solis P, Conde F, Gomez S (1994) Anti-immunoglobulin antibodies in children with Schönlein-Henoch syndrome. Absence of serum anti-IgA antibodies. Eur J Pediatr 153:103–106 [PubMed: 8157014]
59. Saulsbury FT (1987) The role of IgA1 rheumatoid factor in the formation of IgA-containing immune complexes in Henoch-Schönlein purpura. J Clin Lab Immunol 23:123–127 [PubMed: 3669060]
60. Hilhorst M, van Paassen P, van Breda Vriesman P, Cohen Tervaert JW (2011) Immune complexes in acute adult-onset Henoch-Schönlein nephritis. Nephrol Dial Transplant 26:3960–3967 [PubMed: 21441402]
61. Novak J, Moldoveanu Z, Renfrow MB, Yanagihara T, Suzuki H, Raska M, Hall S, Brown R, Huang WQ, Goepfert A, Kilian M, Poulsen K, Tomana M, Wyatt RJ, Julian BA, Mestecky J (2007) IgA nephropathy and Henoch-Schoenlein purpura nephritis: aberrant glycosylation of IgA1, formation of IgA1-containing immune complexes, and activation of mesangial cells. Contrib Nephrol 157:134–138 [PubMed: 17495451]
62. Allen AC, Bailey EM, Brenchley PEC, Buck KS, Barratt J, Feehally J (2001) Mesangial IgA1 in IgA nephropathy exhibits aberrant O-glycosylation: Observations in three patients. Kidney Int 60:969–973 [PubMed: 11532091]
63. Hiki Y, Odani H, Takahashi M, Yasuda Y, Nishimoto A, Iwase H, Shinzato T, Kobayashi Y, Maeda K (2001) Mass spectrometry proves under-O-glycosylation of glomerular IgA1 in IgA nephropathy. Kidney Int 59:1077–1085 [PubMed: 11231363]
64. Suzuki H, Yasutake J, Makita Y, Tanbo Y, Yamasaki K, Sofue T, Kano T, Suzuki Y (2018) IgA nephropathy and IgA vasculitis with nephritis have a shared feature involving galactose-deficient IgA1-oriented pathogenesis. Kidney Int Rep 93:700–705
65. Zhao L, Peng L, Yang D, Chen S, Lan Z, Zhu X, Yuan S, Chen G, Liu Y, Liu H (2020) Immunostaining of galactose-deficient IgA1 by KM55 is not specific for immunoglobulin A nephropathy. Clin Immunol 217:108483 [PubMed: 32479989]
66. Endo M, Ohi H, Ohsawa I, Fujita T, Matsushita M (2000) Complement activation through the lectin pathway in patients with Henoch-Schönlein purpura nephritis. Am J Kidney Dis 35:401–407 [PubMed: 10692265]

67. Hisano S, Matsushita M, Fujita T, Iwasaki H (2005) Activation of the lectin complement pathway in Henoch-Schönlein purpura nephritis. Am J Kidney Dis 45:295–302 [PubMed: 15685507]
68. Dumont C, Merouani A, Ducruet T, Benoit G, Clermont MJ, Lapeyraque AL, Phan V, Patey N (2020) Clinical relevance of membrane attack complex deposition in children with IgA nephropathy and Henoch-Schönlein purpura. Pediatr Nephrol 35:843–850 [PubMed: 31932958]
69. Jia M, Zhu L, Zhai YL, Chen P, Xu BY, Guo WY, Shi SF, Liu LJ, Lv JC, Zhang H (2020) Variation in complement factor H affects complement activation in immunoglobulin A vasculitis with nephritis. Nephrology 25:40–47 [PubMed: 30838755]
70. Selvaskandan H, Kay Cheung C, Dormer J, Wimbury D, Martinez M, Xu G, Barratt J (2020) Inhibition of the lectin pathway of the complement system as a novel approach in the management of IgA vasculitis-associated nephritis. Nephron 144:453–458. 10.1159/000508841 [PubMed: 32721954]
71. Besbas N, Saatci U, Ruacan S, Ozen S, Sungur A, Bakkaloglu A, Elnahas AM (1997) The role of cytokines in Henoch Schönlein purpura. Scand J Rheumatol 26:456–460 [PubMed: 9433407]
72. Ha TS (2005) The role of tumor necrosis factor-α in Henoch-Schönlein purpura. Pediatr Nephrol 20:149–153 [PubMed: 15627167]
73. Del Vecchio GC, Penza R, Altomare M, Piacente L, Aceto G, Lassandro G, De Mattia D, Giordano P (2008) Cytokine pattern and endothelium damage markers in Henoch-Schönlein purpura. Immunopharmacol Immunotoxicol 30:623–629 [PubMed: 18668398]
74. Su Z, Lv X, Liu Y, Zhang J, Guan J, Gai Z (2016) Circulating midkine in children with Henoch-Schönlein purpura: Clinical implications. Int Immunopharmacol 39:246–250 [PubMed: 27497193]
75. Jaszczura M, Mizgala-Izworska E, Swietochowska E, Machura E (2019) Serum levels of selected cytokines [interleukin (IL)-17A, IL-18, IL-23] and chemokines (RANTES, IP10) in the acute phase of immunoglobulin A vasculitis in children. Rheumatol Int 39:1945–1953 [PubMed: 31468124]
76. Lin CY, Yang YH, Lee CC, Huang CL, Wang LC, Chiang BL (2006) Thrombopoietin and interleukin-6 levels in Henoch-Schönlein purpura. J Microbiol Immunol Infect 39:476–482 [PubMed: 17164950]
77. Jen HY, Chuang YH, Lin SC, Chiang BL, Yang YH (2011) Increased serum interleukin-17 and peripheral Th17 cells in children with acute Henoch-Schönlein purpura. Pediatr Allergy Immunol 22:862–868 [PubMed: 21929599]
78. Galla JH, Kohaut EC, Alexander R, Mestecky J (1984) Racial difference in the prevalence of IgA-associated nephropathies. Lancet 2:522
79. Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR (2002) Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet 360:1197–1202 [PubMed: 12401245]
80. Lopez-Mejias R, Castaneda S, Genre F, Remuzgo-Martinez S, Carmona FD, Llorca J, Blanco R, Martin J, Gonzalez-Gay MA (2018) Genetics of immunoglobulin-A vasculitis (Henoch-Schönlein purpura): An updated review. Autoimmun Rev 17:301–315 [PubMed: 29353097]
81. Feehally J, Farrall M, Boland A, Gale DP, Gut I, Heath S, Kumar A, Peden JF, Maxwell PH, Morris DL, Padmanabhan S, Vyse TJ, Zawadzka A, Rees AJ, Lathrop M, Ratcliffe PJ (2010) HLA has strongest association with IgA nephropathy in genome-wide analysis. J Am Soc Nephrol 21:1791–1797 [PubMed: 20595679]
82. Gharavi AG, Kiryluk K, Choi M, Li Y, Hou P, Xie J, Sanna-Cherchi S, Men CJ, Julian BA, Wyatt RJ, Novak J, He JC, Wang H, Lv J, Zhu L, Wang W, Wang Z, Yasuno K, Gunel M, Mane S, Umlauf S, Tikhonova I, Beerman I, Savoldi S, Magistroni R, Ghiggeri GM, Bodria M, Lugani F, Ravani P, Ponticelli C, Allegri L, Boscutti G, Frasca G, Amore A, Peruzzi L, Coppo R, Izzi C, Viola BF, Prati E, Salvadori M, Mignani R, Gesualdo L, Bertinetto F, Mesiano P, Amoroso A, Scolari F, Chen N, Zhang H, Lifton RP (2011) Genome-wide association study identifies susceptibility loci for IgA nephropathy. Nat Genet 43:321–327 [PubMed: 21399633]
83. Yu XQ, Li M, Zhang H, Low HQ, Wei X, Wang JQ, Sun LD, Sim KS, Li Y, Foo JN, Wang W, Li ZJ, Yin XY, Tang XQ, Fan L, Chen J, Li RS, Wan JX, Liu ZS, Lou TQ, Zhu L, Huang XJ, Zhang XJ, Liu ZH, Liu JJ (2011) A genome-wide association study in Han Chinese identifies multiple susceptibility loci for IgA nephropathy. Nat Genet 44:178–182 [PubMed: 22197929]

84. Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H, Eitner F, Snyder HJ, Choi M, Hou P, Scolari F, Izzi C, Gigante M, Gesualdo L, Savoldi S, Amoroso A, Cusi D, Zamboli P, Julian BA, Novak J, Wyatt RJ, Mucha K, Perola M, Kristiansson K, Viktorin A, Magnusson PK, Thorleifsson G, Thorsteinsdottir U, Stefansson K, Boland A, Metzger M, Thibaudin L, Wanner C, Jager KJ, Goto S, Maixnerova D, Karnib HH, Nagy J, Panzer U, Xie J, Chen N, Tesar V, Narita I, Berthoux F, Floege J, Stengel B, Zhang H, Lifton RP, Gharavi AG (2012) Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. PLoS Genet 8:e1002765

85. Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, Fasel D, Lata S, Prakash S, Shapiro S, Fischman C, Snyder HJ, Appel G, Izzi C, Viola BF, Dallera N, Del Vecchio L, Barlassina C, Salvi E, Bertinetto FE, Amoroso A, Savoldi S, Rocchietti M, Amore A, Peruzzi L, Coppo R, Salvadori M, Ravani P, Magistroni R, Ghiggeri GM, Caridi G, Bodria M, Lugani F, Allegri L, Delsante M, Maiorana M, Magnano A, Frasca G, Boer E, Boscutti G, Ponticelli C, Mignani R, Marcantoni C, Di Landro D, Santoro D, Pani A, Polci R, Feriozzi S, Chicca S, Galliani M, Gigante M, Gesualdo L, Zamboli P, Battaglia GG, Garozzo M, Maixnerova D, Tesar V, Eitner F, Rauen T, Floege J, Kovacs T, Nagy J, Mucha K, Paczek L, Zaniew M, Mizerska-Wasiak M, Roszkowska-Blaim M, Pawlaczyk K, Gale D, Barratt J, Thibaudin L, Berthoux F, Canaud G, Boland A, Metzger M, Panzer U, Suzuki H, Goto S, Narita I, Caliskan Y, Xie J, Hou P, Chen N, Zhang H, Wyatt RJ, Novak J, Julian BA, Feehally J, Stengel B, Cusi D, Lifton RP, Gharavi AG (2014) Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet 46:1187–1196 [PubMed: 25305756]

86. Li M, Foo JN, Wang JQ, Low HQ, Tang XQ, Toh KY, Yin PR, Khor CC, Goh YF, Irwan ID, Xu RC, Andiappan AK, Bei JX, Rotzschke O, Chen MH, Cheng CY, Sun LD, Jiang GR, Wong TY, Lin HL, Aung T, Liao YH, Saw SM, Ye K, Ebstein RP, Chen QK, Shi W, Chew SH, Chen J, Zhang FR, Li SP, Xu G, Tai ES, Wang L, Chen N, Zhang XJ, Zeng YX, Zhang H, Liu ZH, Yu XQ, Liu JJ (2015) Identification of new susceptibility loci for IgA nephropathy in Han Chinese. Nat Commun 6:7270 [PubMed: 26028593]

87. Lopez-Mejias R, Carmona FD, Castaneda S, Genre F, Remuzgo-Martinez S, Sevilla-Perez B, Ortego-Centeno N, Llorca J, Ubilla B, Mijares V, Pina T, Miranda-Filloy JA, Navas Parejo A, de Argila D, Aragues M, Rubio E, Luque ML, Blanco-Madrigal JM, Galindez-Aguirregoikoa E, Jayne D, Blanco R, Martin J, Gonzalez-Gay MA (2017) A genome-wide association study suggests the HLA Class II region as the major susceptibility locus for IgA vasculitis. Sci Rep 7:5088 [PubMed: 28698626]

88. Meadow SR, Glasgow EF, White RH, Moncrieff MW, Cameron JS, Ogg CS (1972) Schönlein-Henoch nephritis. Q J Med 41:241–258 [PubMed: 4538491]

89. Counahan R, Winterborn MH, White RH, Heaton JM, Meadow SR, Bluett NH, Swetschin H, Cameron JS, Chantler C (1977) Prognosis of Henoch-Schönlein nephritis in children. Br Med J 2:11–14 [PubMed: 871734]

90. Yoshikawa N, White RH, Cameron AH (1981) Prognostic significance of the glomerular changes in Henoch-Schoenlein nephritis. Clin Nephrol 16:223–229 [PubMed: 7030544]

91. Yoshikawa N, Ito H, Yoshiya K, Nakahara C, Yoshiara S, Hasegawa O, Matsuyama S, Matsuo T (1987) Henoch-Schoenlein nephritis and IgA nephropathy in children: a comparison of clinical course. Clin Nephrol 27:233–237 [PubMed: 3594938]

92. Goldstein AR, White RH, Akuse R, Chantler C (1992) Long-term follow-up of childhood Henoch-Schönlein nephritis. Lancet 339:280–282 [PubMed: 1346291]

93. Ronkainen J, Nuutinen M, Koskimies O (2002) The adult kidney 24 years after childhood Henoch-Schönlein purpura: a retrospective cohort study. Lancet 360:666–670 [PubMed: 12241872]

94. Foster BJ, Bernard C, Drummond KN, Sharma AK (2000) Effective therapy for severe Henoch-Schönlein purpura nephritis with prednisone and azathioprine: a clinical and histopathologic study. J Pediatr 136:370–375 [PubMed: 10700695]

95. Kawasaki Y, Suzuki J, Sakai N, Nemoto K, Nozawa R, Suzuki S, Suzuki H (2003) Clinical and pathological features of children with Henoch-Schoenlein purpura nephritis: risk factors associated with poor prognosis. Clin Nephrol 60:153–160 [PubMed: 14524577]

96. Shin JI, Park JM, Shin YH, Kim JH, Lee JS, Kim PK, Jeong HJ (2005) Can azathioprine and steroids alter the progression of severe Henoch-Schönlein nephritis in children? Pediatr Nephrol 20:1087–1092 [PubMed: 15889281]

97. Mir S, Yavascan O, Mutlubas F, Yeniay B, Sonmez F (2007) Clinical outcome in children with Henoch-Schönlein nephritis. Pediatr Nephrol 22:64–70 [PubMed: 17024391]

98. Shenoy M, Bradbury MG, Lewis MA, Webb NJ (2007) Outcome of Henoch-Schönlein purpura nephritis treated with long-term immunosuppression. Pediatr Nephrol 22:1717–1722 [PubMed: 17647023]

99. Lucas Garcia J, Alvarez Blanco O, Sanahuja Ibanez MJ, Ortega Lopez PJ, Zamora Martin I (2008) Outcome of Henoch-Schönlein nephropathy in pediatric patients. Prognostic factors. Nefrologia 28:627–632 [PubMed: 19016636]

100. Fu H, Mao J, Huang J, Gu W, Lu Z (2016) Higher pathological grading is associated with unfavorable outcome of Henoch-Schonlein purpura nephritis in children. Int J Clin Exp Pathol 9:4633–4640.

101. Feng D, Huang WY, Hao S, Niu XL, Wang P, Wu Y, Zhu GH (2017) A single-center analysis of Henoch-Schonlein purpura nephritis with nephrotic proteinuria in children. Pediatr Rheumatol 15:15

102. Koskela M, Ylinen E, Ukonmaanaho EM, Autio-Harmainen H, Heikkila P, Lohi J, Jauhola O, Ronkainen J, Jahnukainen T, Nuutinen M (2017) The ISKDC classification and a new semiquantitative classification for predicting outcomes of Henoch-Schönlein purpura nephritis. Pediatr Nephrol 32:1201–1209 [PubMed: 28197887]

103. Coppo R, Mazzucco G, Cagnoli L, Lupo A, Schena FP (1997) Long-term prognosis of Henoch-Schönlein nephritis in adults and children. Italian Group of Renal Immunopathology Collaborative Study on Henoch-Schönlein purpura. Nephrol Dial Transplant 12:2277–2283 [PubMed: 9394311]

104. Scharer K, Krmar R, Querfeld U, Ruder H, Waldherr R, Schaefer F (1999) Clinical outcome of Schönlein-Henoch purpura nephritis in children. Pediatr Nephrol 13:816–823 [PubMed: 10603128]

105. Butani L, Morgenstern BZ (2007) Long-term outcome in children after Henoch-Schönlein purpura nephritis. Clin Pediatr (Phila) 46:505–511

106. Coppo R, Andrulli S, Amore A, Gianoglio B, Conti G, Peruzzi L, Locatelli F, Cagnoli L (2006) Predictors of outcome in Henoch-Schönlein nephritis in children and adults. Am J Kidney Dis 47:993–1003 [PubMed: 16731294]

107. Edstrom Halling S, Soderberg MP, Berg UB (2010) Predictors of outcome in Henoch-Schönlein nephritis. Pediatr Nephrol 25:1101–1108 [PubMed: 20174831]

108. Assadi F (2009) Childhood Henoch-Schonlein nephritis: a multivariate analysis of clinical features and renal morphology at disease onset. Iran J Kidney Dis 3:17–21 [PubMed: 19377254]

109. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, Alpers CE, Amore A, Barratt J, Berthoux F, Bonsib S, Bruijn JA, D'Agati V, D'Amico G, Emancipator S, Emma F, Ferrario F, Fervenza FC, Florquin S, Fogo A, Geddes CC, Groene HJ, Haas M, Herzenberg AM, Hill PA, Hogg RJ, Hsu SI, Jennette JC, Joh K, Julian BA, Kawamura T, Lai FM, Leung CB, Li LS, Li PK, Liu ZH, Mackinnon B, Mezzano S, Schena FP, Tomino Y, Walker PD, Wang H, Weening JJ, Yoshikawa N, Zhang H (2009) The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int 76:534–545 [PubMed: 19571791]

110. Niaudet P, Habib R (1998) Methylprednisolone pulse therapy in the treatment of severe forms of Schönlein-Henoch purpura nephritis. Pediatr Nephrol 12:238–243 [PubMed: 9630046]

111. Hennies I, Gimpel C, Gellermann J, Moller K, Mayer B, Dittrich K, Buscher AK, Hansen M, Aulbert W, Wuhl E, Nissel R, Schalk G, Weber LT, Pohl M, Wygoda S, Beetz R, Klaus G, Fehrenbach H, Konig S, Staude H, Beringer O, Bald M, Walden U, von Schnakenburg C, Bertram G, Wallot M, Haffner K, Wiech T, Hoyer PF, Pohl M (2018) Presentation of pediatric Henoch-Schönlein purpura nephritis changes with age and renal histology depends on biopsy timing. Pediatr Nephrol 33:277–286 [PubMed: 28983704]

112. Szeto CC, Choi PC, To KF, Li PK, Hui J, Chow KM, Leung CB, Lui SF, Mac-Moune Lai F (2001) Grading of acute and chronic renal lesions in Henoch-Schönlein purpura. Mod Pathol 14:635–640 [PubMed: 11454994]
113. Trimarchi H, Barratt J, Cattran DC, Cook HT, Coppo R, Haas M, Liu ZH, Roberts IS, Yuzawa Y, Zhang H, Feehally J (2017) Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. Kidney Int 91:1014–1021 [PubMed: 28341274]
114. Davin JC, Coppo R (2013) Pitfalls in recommending evidence-based guidelines for a protean disease like Henoch-Schönlein purpura nephritis. Pediatr Nephrol 28:1897–1903 [PubMed: 23832137]
115. Xu K, Zhang L, Ding J, Wang S, Su B, Xiao H, Wang F, Zhong X, Li Y (2018) Value of the Oxford classification of IgA nephropathy in children with Henoch-Schönlein purpura nephritis. J Nephrol 31:279–286 [PubMed: 29185209]
116. Cakici EK, Gur G, Yazilitas F, Eroglu FK, Gungor T, Arda N, Orhan D, Ozalp Ates FS, Bulbul M (2019) A retrospective analysis of children with Henoch-Schönlein purpura and re-evaluation of renal pathologies using Oxford classification. Clin Exp Nephrol 23:939–947 [PubMed: 30895528]
117. Jimenez A, Chen A, Lin JJ, South AM (2019) Does MEST-C score predict outcomes in pediatric Henoch-Schönlein purpura nephritis? Pediatr Nephrol 34:2583–2589 [PubMed: 31402405]
118. Koskela M, Ylinen E, Autio-Harmainen H, Tokola H, Heikkila P, Lohi J, Jalanko H, Nuutinen M, Jahnukainen T (2020) Prediction of renal outcome in Henoch-Schönlein nephritis based on biopsy findings. Pediatr Nephrol 35:659–668 [PubMed: 31797094]
119. Wyatt RJ, Hogg RJ (2001) Evidence-based assessment of treatment options for children with IgA nephropathies. Pediatr Nephrol 16:156–167 [PubMed: 11261686]
120. Ozen S, Marks SD, Brogan P, Groot N, de Graeff N, Avcin T, Bader-Meunier B, Dolezalova P, Feldman BM, Kone-Paut I, Lahdenne P, McCann L, Pilkington C, Ravelli A, van Royen A, Uziel Y, Vastert B, Wulffraat N, Kamphuis S, Beresford MW (2019) European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis-the SHARE initiative. Rheumatology (Oxford) 58:1607–1616 [PubMed: 30879080]
121. Radhakrishnan J, Cattran DC (2012) The KDIGO practice guideline on glomerulonephritis: reading between the (guide)lines--application to the individual patient. Kidney Int 82:840–856 [PubMed: 22895519]
122. Crayne CB, Eloseily E, Mannion ML, Azerf SP, Weiser P, Beukelman T, Stoll ML, Feig DI, Prescott Atkinson T, Cron RQ (2018) Rituximab treatment for chronic steroid-dependent Henoch-Schonlein purpura: 8 cases and a review of the literature. Pediatr Rheumatol 16:71
123. Fenoglio R, Naretto C, Basolo B, Quattrocchio G, Ferro M, Mesiano P, Beltrame G, Roccatello D (2017) Rituximab therapy for IgA-vasculitis with nephritis: a case series and review of the literature. Immunol Res 65:186–192 [PubMed: 27449502]
124. Lundberg S, Westergren E, Smolander J, Bruchfeld A (2017) B cell-depleting therapy with rituximab or ofatumumab in immunoglobulin A nephropathy or vasculitis with nephritis. Clin Kidney J 10:20–26 [PubMed: 28638602]
125. Maritati F, Fenoglio R, Pillebout E, Emmi G, Urban ML, Rocco R, Nicastro M, Incerti M, Goldoni M, Trivioli G, Silvestri E, Mohammad AJ, Jayne D, Eriksson P, Segelmark M, Novikov P, Harris H, Roccatello D, Vaglio A (2018) Brief Report: Rituximab for the Treatment of Adult-Onset IgA Vasculitis (Henoch-Schönlein). Arthritis Rheumatol 70:109–114 [PubMed: 28973844]
126. Lafayette RA, Canetta PA, Rovin BH, Appel GB, Novak J, Nath KA, Sethi S, Tumlin JA, Mehta K, Hogan M, Erickson S, Julian BA, Leung N, Enders FT, Brown R, Knoppova B, Hall S, Fervenza FC (2017) A randomized, controlled trial of Rituximab in IgA nephropathy with proteinuria and renal dysfunction. J Am Soc Nephrol 28:1306–1313 [PubMed: 27821627]
127. Van de Perre E, Smith RM, Bardsley V, Crawley C, Willcocks LC, Jayne DR (2016) Successful outcome using bortezomib in adult refractory IgA vasculitis: a case report. Rheumatology (Oxford) 55:2089–2091 [PubMed: 27453187]
128. Chartapisak W, Opastiraku S, Willis NS, Craig JC, Hodson EM (2009) Prevention and treatment of renal disease in Henoch-Schönlein purpura: a systematic review. Arch Dis Child 94:132–137 [PubMed: 18701559]

129. Szemenyei C, Hahn D (2015) Prevention of nephritis in Henoch-Schönlein purpura. J Paediatr Child Health 51:236–239 [PubMed: 25677491]

130. Dudley J, Smith G, Llewelyn-Edwards A, Bayliss K, Pike K, Tizard J (2013) Randomised, double-blind, placebo-controlled trial to determine whether steroids reduce the incidence and severity of nephropathy in Henoch-Schönlein Purpura (HSP). Arch Dis Child 98:756–763 [PubMed: 23845696]

131. Kim MJ, Schaub S, Molyneux K, Koller MT, Stampf S, Barratt J (2016) Effect of immunosuppressive drugs on the changes of serum galactose-deficient IgA1 in patients with IgA nephropathy. PLoS One 11:e0166830

132. Delbet JD, Hogan J, Aoun B, Stoica I, Salomon R, Decramer S, Brocheriou I, Deschenes G, Ulinski T (2017) Clinical outcomes in children with Henoch-Schönlein purpura nephritis without crescents. Pediatr Nephrol 32:1193–1199 [PubMed: 28204946]

133. Allen AC, Willis FR, Beattie TJ, Feehally J (1998) Abnormal IgA glycosylation in Henoch-Schönlein purpura restricted to patients with clinical nephritis. Nephrol Dial Transplant 13:930–934 [PubMed: 9568852]

134. Berthelot L, Jamin A, Viglietti D, Chemouny JM, Ayari H, Pierre M, Housset P, Sauvaget V, Hurtado-Nedelec M, Vrtovsnik F, Daugas E, Group HS, Monteiro RC, Pillebout E (2018) Value of biomarkers for predicting immunoglobulin A vasculitis nephritis outcome in an adult prospective cohort. Nephrol Dial Transplant 33:1579–1590 [PubMed: 29126311]

135. Yasutake J, Suzuki Y, Suzuki H, Hiura N, Yanagawa H, Makita Y, Kaneko E, Tomino Y (2015) Novel lectin-independent approach to detect galactose-deficient IgA1 in IgA nephropathy. Nephrol Dial Transplant 30:1315–1321 [PubMed: 26109484]

136. Wada Y, Matsumoto K, Suzuki T, Saito T, Kanazawa N, Tachibana S, Iseri K, Sugiyama M, Iyoda M, Shibata T (2018) Clinical significance of serum and mesangial galactose-deficient IgA1 in patients with IgA nephropathy. PLoS One 13:e0206865

137. Novak J, Julian BA, Mestecky J, Renfrow MB (2012) Glycosylation of IgA1 and pathogenesis of IgA nephropathy. Semin Immunopathol 34:365–382 [PubMed: 22434325]

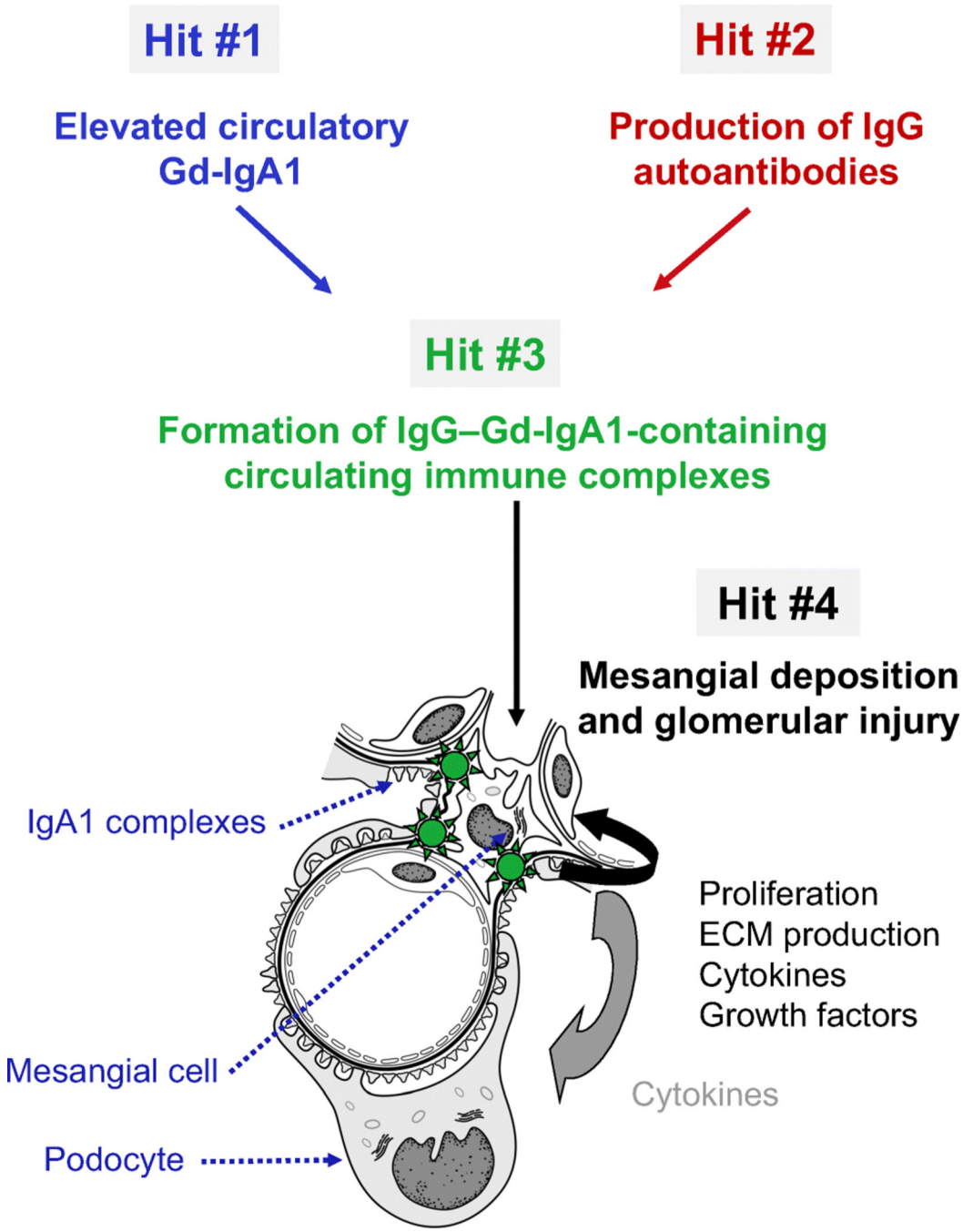

Fig. 1. Hypothesis for the pathogenesis of IgAN and IgAVN

IgAN and IgAVN appear to share the same pathogenesis, i.e., aberrantly glycosylated IgA1 (galactose-deficient in some hinge-region *O*-glycans; Gd-IgA1) is an autoantigen recognized by IgG autoantibodies, resulting in the formation of circulating pathogenic immune complexes. Some of these complexes, in turn, deposit in the kidney and induce glomerular injury. Figure modified from [137], used with permission.

Table 1.

Comparison of IgA nephropathy and IgA vasculitis with nephritis.

Features	IgA Vasculitis with Nephritis (IgAVN)	IgA Nephropathy (IgAN)
❖ **Clinical Presentation**		
➢ **Incidence (per million persons)**	Children: 15–70 Adults: 4–13	Children: 5–50 Adults: 10–40
➢ **Median Age at diagnosis (years)**	12.7	28.8
➢ **Macroscopic hematuria**	Common, coincides with mucosal infection	Less common
➢ **Nephrotic-range proteinuria (UPCR ≥ 3 g/g)**	38%	25%
➢ **Extra-renal manifestations**	Common (arthralgia, GI vasculitis, dermal leukocytoclastic vasculitis)	Rare
➢ **Immunosuppressive treatment**	80%	54%
❖ **Histopathology**		
➢ **Immunofluorescence**	Lambda = kappa light chains	Lambda > kappa light chains
➢ **Light microscopy**	Crescents and necrosis more common	Rare crescents
➢ **Electron microscopy**	More subendothelial immune deposits	Rare glomerular capillary-loop deposits
❖ **Pathogenesis**		
➢ **Gd-IgA1 (circulation)**	High levels	High levels
➢ **Gd-IgA1 antibody (circulation)**	High levels	High levels
➢ **Gd-IgA1-containing circulating immune complexes (circulation)**	Present. Complexes larger than in IgAV and with IgG	Present. Complexes with IgG
➢ **Complement activation (glomerular immunodeposits)**	Alternative and lectin pathways	Alternative and lectin pathways
❖ **Kidney Outcomes**		
➢ **Clinical remission**	98%	30–50%
➢ **CKD 5**	Develops in 1 to 3% of children, with higher risk if clinical onset in adulthood	Develops in 20–40% of patients within 20 years since diagnosis
➢ **Transplantation**	Frequent	Frequent
▪ **IgA deposits in allograft** ▪ **Loss of allograft at 5 years**	~8%	~10%
❖ **Genetics**		
➢ **Familial clustering**	Rare IgAN and IgAVN can occur in same family	5% of family members can have IgAN or hematuria. IgAN and IgAVN can occur in same family
➢ **Gd-IgA1 blood levels**	Heritable trait	Heritable trait
Genome-wide association studies	No studies to date. GIGA-kids study in progress	At least 20 susceptibility loci associated with disease

Gd-IgA1, Galactose-deficient IgA1; GIGA-kids, Genomics of IgA-related disorders in kids; CKD 5, stage 5 chronic kidney disease.

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Table 2.

Updated Oxford MEST-C Classification of IgA Nephropathy.

Histological Feature	Score
Mesangial hypercellularity	M0: ≤ 50% of glomeruli M1: > 50% of glomeruli
Endocapillary hypercellularity	E0: Absent E1: Present
Segmental glomerulosclerosis	S0: Absent S1: Present
Interstitial fibrosis and tubular atrophy	T0: 0–25% of cortical area T1: 26–50% of cortical area T2: > 50% of cortical area
Cellular or fibrocellular crescent	C0: Absent C1: < 25% of glomeruli C2: ≥ 25% of glomeruli

M: Mesangial hypercellularity; E: Endocapillary hypercellularity; S: Segmental glomerulosclerosis; T: Tubular atrophy/Interstitial fibrosis; C: Cellular or fibrocellular crescents.

Table 3.

Summary of the four hits involved in the pathogenesis of IgA vasculitis with nephritis and possible biomarkers and therapeutic approaches.

Hit	Pathogenic Process	Putative Environmental Factors Involved	Putative Genetic Factors Involved	Potential Clinical Biomarkers	Potential Novel Therapeutic Approaches
1	Elevated levels of circulatory galactose-deficient IgA1	Potential role of mucosal exposure to infectious or dietary antigens	Strong evidence for high heritability of serum galactose-deficient IgA1 level GWAS indicated roles of *C1GALT1* and *C1GALTC1*	Elevated serum levels of galactose-deficient IgA1	Suppression of synthesis of galactose-deficient IgA1 Enzymatic boost of galactose transfer to IgA1 hinge-region *O*-glycans
2	IgG autoantibody specific for galactose-deficient IgA1	Potential role of mucosal exposure to infectious or dietary antigens	MHC class II region	Elevated serum levels of IgG autoantibodies	Targeted B-cell depletion therapy Blockade of antigen-binding sites
3	Formation of pathogenic IgA1-containing immune complexes	Unknown		IgG-Gd-IgA1 immune complexes in blood and/or urine	Competitive blockade of immune complex formation by targeting the IgG autoantibodies of the autoantigen (galactose-deficient IgA1)
4	Mesangial deposition of IgA1-containing immune complexes, cell activation and initiation of glomerular injury	Unknown		Complement activation and degradation products in blood and/or urine	Suppression of the alternative or lectin complement pathway Blocking mesangial-cell activation induced by nephritogenic IgA1-containing immune complexes