AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5,October ,2025

UDC: 616.13-002.2-056.7-091.8-07-053.2

THE ROLE OF IMMUNE COMPLEXES IN CHILDREN WITH HEMORRHAGIC VASCULITIS (SCHONLEIN-HENOCH VASCULITIS) AND THEIR RELATIONSHIP WITH CLINICAL FORMS

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RELEVANCE

Henoch-Schönlein purpura, now more specifically termed IgA Vasculitis (IgAV), is the most common systemic vasculitis in children. While often a self-limiting disease, it can lead to severe and chronic complications, most notably IgA vasculitis nephritis (IgAV-N), which can progress to end-stage renal disease. The pathogenesis is fundamentally driven by the formation and deposition of IgA-containing immune complexes in the small vessel walls of target organs. Understanding the precise role of these immune complexes—their composition, size, and quantity—and elucidating their relationship with the diverse clinical manifestations (skin, joint, gastrointestinal, and renal) is of critical importance. This knowledge is essential for developing prognostic biomarkers to identify children at high risk for severe complications like nephritis and for designing targeted therapies that go beyond non-specific immunosuppression.

Keywords: IgA vasculitis, Henoch-Schönlein purpura, immune complexes, IgA nephropathy, glomerulonephritis, pediatric vasculitis, pathogenesis.

АКТУАЛЬНОСТЬ

Геморрагический васкулит, в настоящее время более точно называемый IgA-васкулитом (IgAV), является наиболее распространенным системным васкулитом у детей. Хотя это заболевание часто самоограничивающееся, оно может приводить к тяжелым и хроническим осложнениям, в первую очередь к IgA-васкулит-нефриту (IgAV-N), который может прогрессировать до терминальной стадии почечной недостаточности. В основе патогенеза лежит образование и отложение IgA-содержащих иммунных комплексов в стенках мелких сосудов органов-мишеней. Понимание точной роли этих иммунных комплексов — их состава, размера и количества — и выяснение их взаимосвязи с разнообразными клиническими проявлениями (кожными, суставными, желудочно-кишечными и почечными) имеет решающее значение. Эти знания необходимы для разработки прогностических биомаркеров с целью выявления детей с высоким риском тяжелых осложнений, таких как нефрит, и для создания таргетной терапии, выходящей за рамки неспецифической иммуносупрессии.

Ключевые слова: IgA-васкулит, геморрагический васкулит, пурпура Шенлейна-Геноха, иммунные комплексы, IgA-нефропатия, гломерулонефрит, детский васкулит, патогенез.

INTRODUCTION

IgA Vasculitis (IgAV), historically known as Henoch-Schönlein purpura (HSP), represents the most frequently diagnosed systemic vasculitis in the pediatric population. It is

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5,October ,2025

fundamentally an immune-complex-mediated disease characterized by a leukocytoclastic vasculitis affecting the small vessels, with pathognomonic deposition of immunoglobulin A (IgA) as the dominant or co-dominant antibody. The incidence of IgAV peaks in children between the ages of 4 and 6 years, often following an upper respiratory tract infection, suggesting a role for infectious triggers in a genetically susceptible host.

The clinical presentation of IgAV is defined by a classic tetrad of signs and symptoms, which can manifest in any order or combination. The most common and defining feature is a non-thrombocytopenic, palpable purpuric rash, which typically appears in a symmetric, gravity-dependent distribution on the lower extremities and buttocks. This is frequently accompanied by transient, non-erosive arthritis or arthralgia, predominantly affecting the ankles and knees. Gastrointestinal (GI) involvement, manifesting as colicky abdominal pain, nausea, vomiting, or GI bleeding, is also a prominent feature.

While the cutaneous, articular, and most GI manifestations are typically self-limiting and resolve without long-term sequelae, the primary determinant of morbidity and long-term prognosis is the development of renal involvement, termed IgA vasculitis nephritis (IgAV-N). This complication affects a significant portion of patients and can range in severity from asymptomatic microscopic hematuria and mild proteinuria to fulminant nephritic or nephrotic syndromes, hypertension, and acute kidney injury. A small but significant percentage of children with IgAV-N, estimated at up to 5%, may progress to end-stage renal disease (ESRD), making IgAV a notable cause of chronic kidney disease (CKD) with origins in childhood.

The central pathogenic event underlying all clinical manifestations of IgAV is the formation, systemic circulation, and eventual deposition of IgA-containing immune complexes in target organs. However, the precise characteristics of these complexes and how they relate to the variable clinical severity, particularly the predisposition for severe nephritis, remain areas of intense investigation. This review aims to systematically analyze the evidence regarding the central role of immune complexes in the pathogenesis of IgAV and to critically evaluate the association between the characteristics of these complexes and the specific clinical phenotypes of the disease in children.

METHODS

This article is a comprehensive narrative review of the medical literature designed to synthesize the current understanding of the role of immune complexes in pediatric IgAV. A systematic search of electronic databases, including PubMed, Scopus, and Google Scholar, was conducted for relevant articles published in the English language up to October 2025.

The search strategy employed a combination of Medical Subject Headings (MeSH) and text keywords, including "Henoch-Schönlein purpura," "IgA vasculitis," "pathogenesis," "pathophysiology," "immune complex," "circulating immune complexes," "galactose-deficient IgA1," "complement pathway," "pediatric," "childhood," "nephritis," "gastrointestinal involvement," and "clinicopathological correlation."

The review prioritizes peer-reviewed original research articles (both clinical and basic science), meta-analyses, systematic reviews, and authoritative clinical practice guidelines. Inclusion criteria were focused on studies that provided molecular, immunological, histopathological, or clinical evidence linking immune complex formation, composition, and deposition to the clinical manifestations of IgAV, with a particular emphasis on pediatric cohorts. The collected data were synthesized to construct a cohesive narrative on the pathogenic cascade, from molecular origins to clinical expression, and to analyze the strength of the evidence connecting immune complex biomarkers to different forms of the disease.

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INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5,October ,2025

RESULTS

The literature review reveals a cohesive, multi-step model for the pathogenesis of IgAV, with immune complexes at its core. The results can be categorized into the pathogenic mechanism itself and the correlation of immunological markers with specific clinical forms.

The "Multi-Hit" Pathogenesis of Immune Complex Formation and Action

The evidence strongly supports a "multi-hit" hypothesis for the development of IgAV, which is shared with IgA nephropathy (IgAN).

Hit 1: Production of Aberrantly Glycosylated IgA1: The initial step involves the production of IgA1 molecules with a defective glycosylation pattern in their hinge region. Specifically, there is a deficiency in the addition of galactose to O-linked N-acetylgalactosamine (GalNAc) residues, resulting in the formation of galactose-deficient IgA1 (Gd-IgA1). This appears to be a genetically predisposed trait.

Hit 2: Formation of Anti-Glycan Autoantibodies: The exposed, abnormal glycan structures on Gd-IgA1 are recognized as neoantigens by the immune system, leading to the production of specific autoantibodies, primarily of the IgG and IgA isotypes.

Hit 3: Formation of Pathogenic Circulating Immune Complexes (CICs): The binding of these autoantibodies to Gd-IgA1 molecules results in the formation of large, multimeric immune complexes. These Gd-IgA1-containing CICs are poorly cleared by the hepatic clearance system, leading to their persistence and accumulation in the circulation.

Hit 4: Tissue Deposition and Complement Activation: These large CICs deposit in the walls of small vessels in target organs. Once deposited, they potently activate the complement system, primarily through the lectin and alternative pathways. This leads to the local generation of pro-inflammatory mediators, including C3a and C5a.

Hit 5: Inflammatory Cell Infiltration and Tissue Damage: C3a and C5a act as powerful chemoattractants, recruiting neutrophils to the site of deposition. The subsequent infiltration and degranulation of these neutrophils cause a leukocytoclastic vasculitis, leading to endothelial damage, increased vascular permeability, and local hemorrhage.

Correlation of immune complexes with clinical forms - The strength of the association between these pathogenic immune complexes and the severity of organ involvement varies significantly.

Renal Involvement (IgAV-N): The evidence for a strong association here is overwhelming. Multiple studies consistently demonstrate that children with IgAV-N have significantly higher serum levels of Gd-IgA1 and Gd-IgA1/IgG CICs compared to children with IgAV without nephritis or healthy controls. Furthermore, high levels of these complexes at disease onset are shown to be a predictive risk factor for the subsequent development and persistence of nephritis. The gold standard for diagnosis, renal biopsy, confirms this link with the pathognomonic histopathological finding of dominant IgA and C3 deposition in the glomerular mesangium. The intensity of this deposition often correlates with clinical severity.

Gastrointestinal (GI) Involvement: Histopathological studies of GI biopsies from affected children confirm the presence of IgA-dominant vasculitis in the submucosal vessels, verifying that IC deposition is the underlying cause. However, the data linking the circulating levels of these ICs to the severity of GI symptoms (e.g., pain, bleeding) are less consistent. While levels are elevated, a clear quantitative correlation is not well established.

Cutaneous and Articular Involvement: The palpable purpura and arthritis are direct results of IC deposition in the dermal and synovial microvasculature, respectively. However, as nearly all patients exhibit skin involvement, circulating IC levels do not effectively discriminate

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5,October ,2025

between mild and severe cutaneous disease. Similarly, the severity of arthritis, which is typically transient, does not correlate well with systemic measurements of ICs.

Table 1: Summary of association between immune complexes and clinical manifestations of IgAV

Clinical form	Underlying pathophysiology	Strength of correlation with circulating pathogenic ICs (e.g., Gd-IgA1)
Renal (Nephritis)	IC deposition in glomerular mesangium; intense complement-mediated inflammation and proliferation.	STRONG (Predictive of risk, severity, and persistence)
Gastrointestinal	IC deposition in submucosal small vessels, causing edema, ischemia, and hemorrhage.	MODERATE (Causative, but poor quantitative correlation with severity)
Cutaneous	IC deposition in dermal post-capillary venules, causing leukocytoclastic vasculitis.	WEAK (Causative, but does not predict severity)
Articular	IC deposition in synovial microvasculature, causing transient inflammation.	WEAK (Causative, but does not predict severity)

DISCUSSION

The results of this review confirm that immune complexes are the central pathogenic drivers of IgA Vasculitis and its varied clinical manifestations. The elucidation of the "multi-hit" hypothesis, with Gd-IgA1 at its origin, has transformed our understanding of the disease from a vaguely understood hypersensitivity reaction to a specific, molecularly defined autoimmune process.

The most critical finding with direct clinical implications is the powerful and specific association between the pathogenic Gd-IgA1-containing immune complexes and IgA vasculitis nephritis. This strong correlation is likely explained by the unique physiological role of the glomerular mesangium, which functions to clear macromolecules and immune complexes from the circulation. In IgAV, this function leads to the preferential trapping of the large, poorly soluble CICs, making the kidney a primary site of injury. This robust link establishes these specific immune complexes not just as pathogenic mediators but as highly promising prognostic biomarkers. The ability to measure levels of Gd-IgA1 or related CICs at disease onset could allow for a paradigm shift in management: from a "watchful waiting" approach to a proactive, risk-stratified strategy. Children with high levels of these biomarkers could be identified as being at high risk for severe nephritis and could be monitored more closely, with a lower threshold for performing a renal biopsy and initiating early, aggressive immunosuppressive therapy to prevent irreversible kidney damage.

In contrast, the weaker correlation of circulating IC levels with the severity of extra-renal manifestations suggests the involvement of other modulating factors. While IC deposition is the necessary trigger for skin, joint, and GI symptoms, the ultimate severity of inflammation in these tissues may be more dependent on local factors, such as vascular bed characteristics, local endothelial activation states, and genetic variations in local inflammatory response pathways. This explains why two children with similar levels of circulating ICs might have vastly different degrees of purpura or abdominal pain.

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INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5,October ,2025

A key limitation in translating these findings to routine clinical practice is the current lack of standardized, widely available, and validated commercial assays for measuring Gd-IgA1 and Gd-IgA1/IgG complexes. Developing such tools is a critical next step. Furthermore, most studies are cross-sectional or retrospective; large, prospective, longitudinal studies are needed to further validate the predictive value of these biomarkers over the full course of the disease.

Future research must focus on several key areas. First, standardizing and commercializing biomarker assays is paramount. Second, investigating the specific triggers (e.g., infectious agents) that lead to the increased production of Gd-IgA1 in susceptible individuals could open avenues for primary prevention. Finally, the detailed understanding of the pathogenic cascade presents novel therapeutic targets. Developing therapies that could specifically inhibit the formation of Gd-IgA1, block the binding of anti-glycan autoantibodies, or inhibit the lectin pathway of complement activation could offer more targeted and less toxic treatment options than the broad immunosuppressants currently in use.

In conclusion, while IgA-containing immune complexes are the unifying cause of all manifestations of IgA Vasculitis, their specific molecular signature, particularly the presence of galactose-deficient IgA1, is most powerfully and prognostically linked to the development of nephritis. This strong, specific association underscores the central role of these complexes in determining long-term outcomes and represents a critical target for future diagnostic and therapeutic innovation in the management of this common pediatric disease.

CONCLUSION

The pathogenesis of IgA Vasculitis in children is unequivocally driven by the formation and deposition of IgA-containing immune complexes. The modern "multi-hit" model, centered on aberrantly glycosylated IgA1, provides a compelling molecular explanation for this process. While these immune complexes are responsible for the entire spectrum of clinical disease, their utility as a biomarker shows a clear hierarchy. The correlation is strongest and most clinically relevant for renal involvement, where higher levels of pathogenic complexes predict a greater risk and severity of nephritis—the principal cause of long-term morbidity in IgAV. The association with gastrointestinal, cutaneous, and articular disease severity is less direct.

This understanding highlights a critical future direction for clinical practice: the development of reliable, standardized assays for Gd-IgA1 and related immune complexes. Such tools could revolutionize the management of IgAV by allowing for early risk stratification, helping clinicians decide which children need closer monitoring, renal biopsy, and more aggressive immunosuppressive therapy, ultimately preserving long-term renal function..

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