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REVIEW ARTICLE

Articular involvement in Henoch-Schönlein Purpura: A review of literature

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Abstract

Background: Henoch-Schönlein purpura (HSP), the most typical kind of pediatric vasculitis, can also affect adults. Over the last 10 years, research has been increasing on improvements in HSP diagnosis, physiopathology, symptoms, and therapy. Joint involvement is highly frequent in this condition; however, it typically undergoes spontaneous resolution and does not lead to long-term complications.

Objective: To provide a deeper understanding of the constituting pathogenic mechanisms and clinical presentation of articular involvement, focusing on the effect of neutrophil activation on systemic small vessels.

Methods: This literature review utilized a systematic search of academic databases, employing specific keywords to select recent peer-reviewed articles and scholarly sources on the topic.

Results: The manifestations of joint involvement in HSP can vary in severity and frequency. Non-steroidal anti-inflammatory medications or acetaminophen are considered the first-line treatment for joint pain; however, corticosteroids may help achieve quick remission. In cases where standard treatment fails or manifestations persist, immunosuppressive drugs like rituximab, methotrexate, cyclophosphamide, or azathioprine have been used.

Conclusions: While it tends to resolve without lasting joint damage, accurate diagnosis and appropriate management are crucial to ensure optimal patient outcomes.

Key words: IgA vasculitis, arthralgia, arthritis, treatment, physiopathology, Henoch - Schoenlein purpura

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Introduction

IgA vasculitis (IgAV), also known as Henoch-Schönlein purpura (HSP), is the most common vasculitis in children; however, it is not restricted to the pediatric population. HSP is a small-vessel leukocytoclastic vasculitis caused by IgA1-dominant immune deposits. It can be divided into two forms: skin-limited IgAV, characterized by palpable cutaneous purpura, and the systemic form, which involves arthritis, renal involvement, gastrointestinal bleeding, and abdominal pain.[1–4] The incidence of HSP varies geographically.

The hospitalization rate in the US was 2.4/100,000, but this figure is likely underestimated due to most patients being managed as outpatients.[5] There is an apparent correlation between the presentation of IgAV with genetic and environmental factors, and currently, the main associated factor is a prior infection.[6] Although HSP is a self-limiting disease, the prognosis depends on the severity of gastrointestinal or renal involvement.[7]

Joint involvement may be the first and most common manifestation alongside purpura, with the elbows, knees, and ankles being the most frequently affected joints.[8] It is characterized by painful joint inflammation, and the treatment generally involves analgesia and supportive care. In more severe cases, corticosteroid use has been reported. Joint involvement in IgAV typically exhibits a benign course and does not result in long-term sequelae. However, gaining a deeper understanding of the constituting pathogenic mechanisms and clinical presentation may help achieve a more comprehensive diagnosis and management guidelines for this pathology in its early stages. This article aims to review the current understanding of articular involvement in IgAV in the existing literature and identify the gaps where further research is still needed.

Epidemiology

Most cases of IgAV occur between the ages of 4 and 6, and it is more common in males than females (male-to-female ratio of 1.5:1).[1] The incidence of HSP has remained stable over time and varies among countries. For instance, the annual incidence per 100,000 people is 3.5 in Japan, 26.7 in Scotland, 17.5 in Sweden, 18.6 in France, 6.7 in Croatia, 6.1 in the Netherlands, 6.2 to 20.4 in the UK, 12.9 in Taiwan of China, and 55.9 in Korea. In Colombia, HSP is the most common vasculitis in children, presenting in 24% of the cases of vasculitis in adults and children, which is consistent with the situation in other Latin American countries.[1,9,10] Moreover, HSP exhibits ethnic variations, with the incidence being 3-4 times higher in Asian or Caucasian children than in Black children.[1]

Furthermore, HSP has been reported at any age, with a higher occurrence in childhood, at a rate of 2 to 33 times greater than in adults.[1,9] In children, most cases are observed between the ages of 4 and 6, and different clinical manifestations are associated depending on the age group. Arthritis/arthralgia is more frequent in children younger than 6 years old, whereas renal involvement is more common in children aged 6 to 12 years old.[9,11]

The hospitalization rate in the US was 2.4/100,000 during 2006–2014, but it is likely underestimated because most patients are managed as outpatients due to the mild and self-limiting nature of most cases.[5] According to authors from an epidemiology and resource study for HSP in the US, the hospitalization cost was $3,254.70 in 2014, with an average length of stay of 2.8 days.[5]

Pathophysiology

As its name indicates, the most characteristic pathogenic feature of IgA vasculitis is the deposition of IgA1-dominant immune complexes within the endothelium of small vessels.[1] Another key concept regarding the pathogenesis of IgAV is aberrant IgA glycosylation.[12] To better understand IgAV pathophysiology, it has been compared to IgA nephropathy (IgAN) due to the similarities in histopathology and clinical presentation.[13] Additionally, two main pathogenic models have been proposed to interpret the phenotype of vasculitis (**Figure 1**).[1]

The first widely accepted hypothesis was proposed by Novak et al. as a multi-hit model for IgA nephropathy. It was later found that the model was also applicable to IgAV.[12] The model consists of a four-hit chain that leads to a tissue inflammatory process mediated by IgA immune complexes, resulting in organ injury.[14] The first hit is an increased production of galactose-deficient IgA1 (Gd-IgA1), followed by its binding to specific IgA1 autoantibodies, consequently forming pathogenic immune complexes. The fourth hit is their deposition in small vessels.[1,12,13]

The most recent hypothesis was presented in 2017 by M. H. Heineke et al., partly based on the propositions by Chiang et al. This model explains the systemic manifestations of IgAV through a multi-hit mechanism, highlighting the effect of neutrophil activation on systemic small vessels.[1,14] The first hit involves an increased serum level of IgA1 anti-endothelial cell antibodies (AECA), followed by the binding of IgA1 AECA to B2GP1 receptors on endothelial cells in small vessels, which augments the production of IL-8 and other proinflammatory factors, thereby attracting neutrophils. Subsequently, neutrophils are activated by the interaction between IgA1 and IgA1 Fc Alpha receptor 1 (FcaR1). The net effect is vascular endothelial cell damage through antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and reactive oxygen species (ROS). Furthermore, other immune factors such as LTB4, TNFα, endothelial antigens, and AECA antibodies contribute to a positive feedback loop, further increasing inflammation and vascular hemorrhaging.[13,14]

The aberrant glycosylation of IgA has been shown to significantly impact its immune function. In IgAV, Gd-IgA1 is reportedly involved in initiating inflammation in small vessels by activating cellular NF-kB and upregulating the production of immune mediators.[15] The hinge region of IgA1 contains three to six O-linked glycan sites, where Gal, GalNAc, and Neu5ac form glycosidic linkages with oxygen atoms of serine or threonine. An alteration in the expression or function of catalytic enzymes in O-glycosylation in B cells can lead to a galactose deficiency in IgA1, resulting in the exposure of terminal GalNAc residues or the production of sialylated Gd-IgA1, both of which act as neoepitopes.[1,12] Circulatory IgA1 with glycans deficient in Gal is considered a disease-specific abnormality. However, this alteration alone is not enough to cause systemic manifestations; it requires the formation of immune complexes.[16] Concomitantly, autoantibodies that recognize GalNAc residues can form immune complexes by binding to Gd-IgA and FcαR1.[17] These circulating immune complexes perpetuate vascular damage via ADCC, CDC, and ROS, as mentioned earlier, and by their deposition in small vessels.[12,16] While it is unclear if this alteration relates to disease severity, it has been linked to kidney involvement.[16]

Understanding the underlying pathogenesis of IgAV, particularly the roles of neutrophils and Gd-IgA1, is crucial to comprehend the systemic presentation of this pathology and its organ-specific manifestations. Joint involvement is the second most frequent manifestation of the disease and follows the small-vessel vasculitis pathogenesis described earlier. The inflammatory and destructive processes lead to

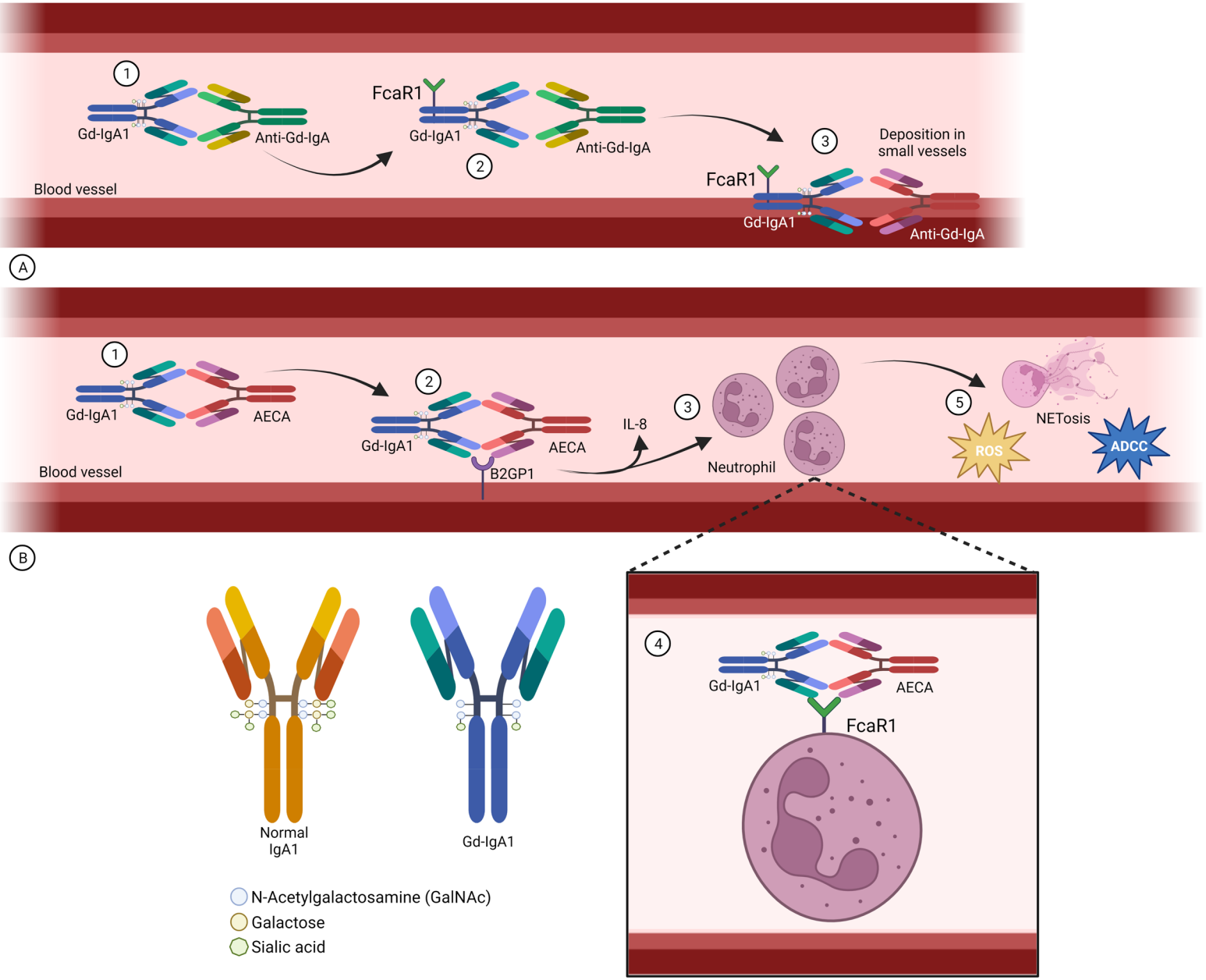

Figure 1. Pathogenic models of Henoch-Schölen purpura. (A) Four-hit chain inflammatory process hypothesis proposed by Novak et al. (B) Hypothesis presented by M. H. Heineke et al. highlighting the effect of neutrophil activation in small systemic vessels.
AECA: anti-endothelial cell antibodies; ROS: reactive oxygen species; ADCC: Antibody-dependent cellular cytotoxicity

painful joint inflammation.[18] Since most cases of IgAV occur during winter and autumn, the most widely believed trigger for HSP is respiratory infections, among others. The possible infectious agents identified include *Streptococcus*, *Helicobacter pylori*, Parainfluenza, Respiratory Syncytial Virus, *Mycoplasma*, *Toxoplasma gondii*, Epstein-Barr Virus, and SARS-Cov-2.[19–21]

Vaccines such as influenza, papillomavirus, Hepatitis B, and measles have been identified as potential triggers for HSP. Some drugs, such as antibiotics and TNF-α blockers, have also been associated with IgAV. Other triggers, such as certain foods and insect bites, have been described as well.[19,22]

Moreover, novel findings emphasize the importance of genetic factors and polymorphisms in the predisposition and severity of IgAV.[23,24] Genetic association studies assessing HLA-A and HLA-B allele variability have strongly influenced the susceptibility to IgAV. Specifically, R. Lopez Mejias et al. mentioned a correlation between HLA-A03 and HLA-B44 with increased joint involvement.

Clinical aspects

Henoch-Schönlein vasculitis comprises systemic damage due to inflammation, IgA deposition, and leukocytoclastic activity.[25] In a study of 417 patients, disease onset after infection was associated with 43%.[26] The clinical spectrum is variable and includes manifestations characterized by renal, joint, cutaneous, and gastrointestinal involvement.[27] In 90% of patients, cutaneous manifestations constitute the initial finding. Patients with IgAV develop palpable, symmetrical purpura, predominantly in the lower extremities. Renal involvement is present in 20–80% of patients. Gastrointestinal manifestations emerge with severe pain, with intussusception being the most severe of these. Joint involvement emerges as arthralgia in 63.1% and arthritis in 37.4%, with a predominance of oligoarticular pattern, predominantly in the lower extremities.[27]

Target organ involvement should be intentionally sought at the time of diagnosis and throughout the clinical course of the disease. Renal function, specifically, should be monitored for 12 months after diagnosis.

Joint involvement

Joint involvement displays a wide spectrum; nonetheless, this condition exhibits a benign evolution and undergoes spontaneous resolution. It is the second most common manifestation after purpura, and its incidence could be as high as 78%.[6] Onset is usually simultaneous with skin manifestations or occurs in the following days, and 15% of children, it may even precede the rash.[6,13,23] A retrospective study of 71 patients with the disease reported arthralgia in 100% of the patients, with only 13% having no other joint involvement, while the rest of the patients presented any of the following: pain, edema, or restriction of mobility.[6] The semiology of pain is diverse; nonetheless, a predominant feature entails migratory and recurrent behavior patterns.[6,28] According to the findings of this study, the main descriptions of pain include distending, sore, hot, and undiscriminated pain. Heavy loads often exacerbate arthralgias.[6]

Joint involvement is less frequent in patients with a relapse; however, the most common presentation of joint involvement is arthralgia, followed by arthritis in an oligoarticular pattern with a predisposition for lower limb extremity joints such as knees, feet, ankles, and toes.[6,13,26] Other joints that are also affected include elbows, hands, and wrists.[13] Furthermore, a symmetrical distribution was observed when two or more joints were affected.[28] Other manifestations, such as fever, scrotal involvement, and subcutaneous edema, were more frequent in patients with persistent joint involvement than others.[29]

An infrequent manifestation of the disease includes lumbar, sacral, or cervical edema accompanied by pain and the inability to ambulate. Three case reports describe this finding with different clinical courses. In the first case, cutaneous symptoms developed later in the course of the disease.[30] Another case report described the onset of cutaneous and gastrointestinal symptoms, followed by acute onset lumbosacral edema accompanied by pain.[31] The third case presents a patient with edema, low back pain, and oligoarticular pain in the lower extremities. Additionally, this patient presented edema in the lower extremities and palpable purpura.[32]

Joint manifestations can vary in severity and frequency. Therefore, ongoing research should continue to gather evidence regarding the wide spectrum of joint involvement in this pathology.

Management

HSP is usually self-limiting, and general measures such as rest, adequate hydration, and monitoring vital signs are useful.[25] The first-line of treatment includes non-steroidal anti-inflammatory medications or acetaminophen, which have effectively resolved joint symptoms in the mildest cases within 3 to 12 days. Additionally, they are not contraindicated in the absence of nephritis or microscopic hematuria when it is the only renal manifestation; however, they are contraindicated in the presence of gastrointestinal bleeding.[29,33]

Corticosteroids are indicated when there is evidence of nephritis or complications such as orchitis, cerebral vasculitis, pulmonary hemorrhage, and severe gastrointestinal involvement.[33] However, it has been observed that persistent joint manifestations resolved with steroid administration with no long-term adverse effects during the follow-up. Similarly, patients treated with steroids have shown faster improvement in rash, edema, and joint pain compared to patients who did not receive steroids.[6,30]

Case reports of patients managed with corticosteroids, particularly methylprednisolone, at 1–2 mg/kg per day for 1–4 weeks, state that the average time for joint symptom recovery was 2.65 days. Additionally, the recovery rate was faster than in patients who did not receive corticosteroids.[6]

Immunosuppressive treatment with drugs such as rituximab, methotrexate, cyclophosphamide, or azathioprine has been used when there is a failure in standard treatment or when manifestations persist.[23] It has been observed that using rituximab improves the persistence of joint manifestations. Likewise, a systematic review of 20 studies

showed that 94.3% of patients experienced clinical improvement, and 74.3% achieved remission when rituximab was used.[23,31] The efficacy of cyclophosphamide and azathioprine has been studied when combined with corticosteroids.[23] Similarly, it has been reported that methotrexate has been effective in improving persistent manifestations in the absence of kidney disease.[32] In severe cases where life is endangered, plasma exchange may be needed.[33]

Overall, this information suggests a personalized approach to HSP treatment, with various options available depending on the severity and specific manifestations of the disease.

Differential diagnosis and prognosis

The short-term renal outcomes of IgAV are favorable in most patients, with complete recovery noted in 94% of children and 89% of adults after an average of approximately 18 months. The long-term renal prognosis of IgAV nephritis was worse in adults than in children in most studies, which may be partly attributed to concurrent chronic kidney disease or a longer time lag between disease onset and clinical presentation.[19]

In children, manifestations of active IgAV usually resolve spontaneously. However, relapse of IgAV is common and occurs in up to one-third of patients, with a higher likelihood in children with renal involvement, even though joint involvement and subcutaneous edema in extremities are less frequent.[2,3,32,34] Recurrent symptoms and signs, which usually mimic the original episode (but tend to be less severe), are typically observed within four months after the initial symptoms have resolved.[13,21] Recurrent disease does not necessarily predict a worse long-term course. Xuehong Wang et al. reported a 37% recurrence rate, with 15% occurring within the first month, 10% in the following 1 to 3 months, and the rest within 6–17 months.[6]

Joint symptoms resembling those of IgAV can be a sign of autoimmune illnesses such as Systemic Lupus Erithematosus (SLE), juvenile idiopathic arthritis, and rheumatic fever. However, patients with IgAV often have normal test results for serum complement, antinuclear and anti-dsDNA antibodies, and rheumatoid factor. Even though at least 15% of IgAV patients may also experience temporary hypocomplementemia, abnormal findings for any of these investigations may aid in distinguishing IgAV from SLE and JIA.[18,21]

The diagnosis is more challenging if there is an incomplete presentation of IgAV or if the skin manifestations are absent at disease onset. In these circumstances, other causes for purpura, arthritis, abdominal pain, and kidney disease must be considered. Patients in whom the diagnosis is in doubt should have a complete blood count, prothrombin time, and urinalysis. The presence of thrombocytopenia or coagulopathy largely excludes the diagnosis of IgAV.[12,23,24]

Conclusion

Recent developments are highlighted in this review article, including a better understanding of this condition's pathophysiology, which has led to a name change, as well as knowledge derived from extensive genetic susceptibility studies, environmental population studies, and scientific research on IgA abnormalities. The diagnosis and treatment of these individuals will be greatly standardized because of the recent release of worldwide consensus recommendations, which will also serve as a foundation for further research, although the data supporting these concepts are currently insufficient to change clinical practice.

Although most patients have excellent outcomes, renal repercussions remain a concern, and unfavorable results have not shown improvement. Suppose we could stratify patients based on their likelihood of developing subsequent issues. In that case, we believe that the period of renal surveillance, particularly in children, offers a perfect "window of opportunity" for early management. Improved early biomarkers are therefore required to accurately predict these individuals. Urgent international collaboration is needed to uncover novel biomarkers, validate clinical recommendations and severity scores, and establish core outcome sets for this illness, utilizing multi-center disease cohorts. Large-scale comparisons can be established with this setup, providing a framework for successful randomized controlled trials.

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