STM JOURNALS

International Journal of
Cell Biology and Cellular Functions

Volume 2, Issue 1, 2024
January–June
DOI: 10.37591/IJCBCF

https://journals.stmjournals.com/ijcbcf

Review IJCBCF

Exploring the Pathophysiology of Henoch-Schönlein Purpura (HSP): A Comprehensive Review

Himanshu Jain[1,*], Kuljeet Kaur[2]

Abstract

Blood from tiny veins can leak into nearby tissues, causing purpura, a disorder marked by red spots or patches on the skin that may have an impact on the kidneys. Henoch-Schönlein purpura (HSP) is associated with vasculitis and inflammation of blood vessels. The range of renal conditions associated with purpura includes severe glomerulonephritis and mild proteinuria. For instance, immunological complex accumulation in the renal glomeruli of HSP patients might result in inflammation and renal injury. The pathophysiology of HSP is largely dependent on immunological pathways, including complement activation and immune complex deposition. Effective management of these renal symptoms depends on rapid identification and action. In addition to skin discoloration and renal involvement, purpura may present with other symptoms, including fatigue, joint pain, and mucosal bleeding. Though the precise etiology of HSP is unknown, it is thought to be related to an unbalanced immune system reaction that may be brought on by an infection or other circumstances. Treatment strategies depend on the underlying cause and may involve immunosuppressive therapy, plasmapheresis, or supportive care. For the most effective treatment for patients with HSP, a multidisciplinary strategy comprising gastroenterologists, nephrologists, and rheumatologists is recommended. Supportive treatment for gastrointestinal and renal disorders may include fluid replacement, pain relief, and, in certain situations, immunosuppressive medication. A long-term follow-up is necessary to evaluate renal function and keep an eye out for disease recurrence. This study aims to give a thorough overview of HSP, including information on its pathophysiology, diagnosis, possibilities for treatment, and clinical signs and symptoms.

Keywords: Henoch-Schönlein purpura (HSP), renal disorder, IgA vasculitis, galactose-deficient IgA1, anti-endothelial cell antibodies, nephritic

INTRODUCTION

Dr. William Heberden recognized HSP (Henoch-Schönlein purpura) as a systemic vasculitis in 1802. Johann Schönlein and his pupil Eduard Henoch combined all the symptoms and gave the ailment a common name [1]. According to the new nomenclature established during the International Chapel Hill Consensus Conference 2012 (CHCC 2012), HSP, also known as IgA vasculitis, is a group of disorders that involves inflammation of blood vessels, including capillaries, and typically involves the skin, joints, gastrointestinal tract, and kidneys. The disease is characterized by deposits of immune complexes, primarily IgA1 and C3 complement components, and is often accompanied by arthralgia and arthritis [2].

It is a common childhood vasculitis that is most prevalent in Southeast Asia and Europe, with an

***Author for Correspondence**
Himanshu Jain
E-mail: himanshu31jain@gmail.com

[1]Lecturer, Department of Pharmaceutical Sciences, University Institute of Pharmaceutical Sciences and Research, Baba Farid University of Health Sciences, Faridkot, Punjab, India
[2]Research Scholar, Department of Pharmaceutical Sciences, University Institute of Pharmaceutical Sciences and Research, Baba Farid University of Health Sciences, Faridkot, Punjab, India

Received Date: March 20, 2024
Accepted Date: May 04, 2024
Published Date: May 27, 2024

Citation: Himanshu Jain, Kuljeet Kaur. Exploring the Pathophysiology of Henoch-Schönlein Purpura (HSP): A Comprehensive Review. International Journal of Cell Biology and Cellular Functions. 2024; 2(1): 30–40p.

annual incidence of 10-30 cases per 100,000 children. It primarily affects children under 10 years of age and equally affects males and females. Its pathogenesis is triggered by upper respiratory tract infections with common recurrence [3]. It occurs more frequently during colder months and is reported globally [2, 4–14]. Genetic predisposition may play a role, with mutations in the *MEFV* gene (associated with familial Mediterranean fever) and certain human leukocyte antigen haplotypes influencing susceptibility to HSP [15]. A Spanish study found that HLA-DRB1*01 and HLAB*41:02 are protective against IgAV/HSP with HLA-DRB1×03 phenotypes. IgAV/HSP is more common in patients with familial Mediterranean fever [16].

SYMPTOMS OF HSP

HSP, an autoimmune or immune-mediated disorder, is believed to be caused by an abnormal immune response within an individual's body, influenced by genetic predisposition, environmental triggers, and immune system dysregulation, without the need for transmission between individuals [17, 15]. HSP is characterized by four main clinical manifestations known as the "classic tetrad": The classic symptoms of HSP include [18]:

1. *Purpura:* This skin rash appears as tiny red or purple dots. The rash usually occurs on the lower extremities (legs and buttocks) but can also appear on other parts of the body. Purpura occurs because of bleeding from the skin as a result of blood vessel inflammation.
2. *Joint Pain:* Joint pain and swelling, particularly in the knees and ankles, are common; whereas arthritis is rare. Arthralgias are common, affecting approximately two-thirds of patients, and may also occur without increased CPK (Creatine Phosphokinase) levels [19].
3. *Abdominal Pain:* Inflammation of the gastrointestinal tract frequently causes pain and discomfort. Gastrointestinal bleeding can occur in certain circumstances. Approximately two-thirds of the children with HSP experience intestinal involvement. Abdominal symptoms precede the typical purpuric rash in 11% of cases and major complications such as intussusception [17].
4. *Kidney Involvement:* Blood and protein in the urine are signs of renal involvement and may indicate glomerulonephritis, an inflammation of the kidney filtering units [19]. Hypertension was present in approximately one-third of the cases. Renal failure is more common in adults at the time of diagnosis, occurring in approximately 30% of cases but is rare in children. IgA vasculitis is responsible for a small percentage of adult nephropathy cases [3, 19]. Between 10% and 60 percent of people have renal involvement; variables associated with a poor prognosis include proteinuria from the beginning, age greater than 7 years, obesity, chronic purpura, and male sex [1]. A study assessing 417 patients between 1975 and 2012 found complete recovery in most cases of Hemolytic Splenic Pulmonary Infection (HSP), with relapses in almost one-third of the cases. This study supports HSP as a typical vasculitis in children, with a favorable prognosis mainly due to renal involvement [20].
5. *Cutaneous Involvement:* Cutaneous hemorrhage, which may result from necrotizing vasculitis of tiny capillaries in the dermis, is a diagnostic need caused by red blood cells leaking into the skin or mucous membranes. In the acute stage of the illness, symptoms generally disappear and do not require medical attention [3, 19].
6. *Others:* Less common clinical manifestations of HSP include cerebral vasculitis, testicular hemorrhage [21], and interstitial pulmonary hemorrhage. Central nervous system involvement is rare but can lead to symptoms such as headaches, seizures, emotional instability, and behavioral changes [15]. Other rare but dangerous side effects include cholecystitis, intestinal stenosis, duodenal blockage, enteropathy with protein loss, intussusception, and intestinal necrosis [1]. Posterior Reversible Encephalopathy Syndrome (PRES) has been described in patients with HSP and may result from inflammation of the nervous system vessels or hypertension. CNS (Central Nervous System) imaging examinations may reveal foci of edema [1, 22–28].

PATHOPHYSIOLOGY OF HSP

Two models have been proposed to explain the pathogenesis of vasculitis and glomerulonephritis [3]. The first model explains IgAV and IgAVN symptoms by increasing Gd-IgA1 levels, which are

influenced by environmental and genetic factors. The second model explains systemic symptoms by involving IgA and FcαRI interactions, neutrophil activation, and vascular hemorrhage.

Role of IgA and IgA Receptors in the Pathogenesis of HAS

IgA is a member of the human immunoglobulin family that activates complement proteins, binds to, and activates multiple receptors, and induces pro-inflammatory reactions. The prototypical IgA receptor is FcαRI, which exists in both soluble and transmembrane forms in myeloid cells. Numerous autoimmune disorders, including rheumatoid arthritis (RA), ulcerative colitis, and linear IgA bullous disease (LABD) have been linked to their interactions. In ex vivo models, tissue damage can be decreased by blocking the interaction between IgA and FcαRI [3].

HSA is triggered by IgA1 immune deposits including galactose deficiency, complement factors, and neutrophil infiltration. Through the IgA Fc receptor FcαRI (CD89), IgA complexes can activate neutrophils, causing neutrophil migration and activation, ultimately resulting in tissue damage in IgAV [29].

IgA, a monomeric molecule in the blood, is present in 90% of circulation as IgA1, with 10% being IgA2 [30]. It can activate complement proteins, induce lectin, and activate multiple receptors, including transferrin receptor (CD71) [31, 32]. Overexpression of this receptor can facilitate the formation of IgA1-containing immune complexes, thereby reducing susceptibility to autoimmune and inflammatory diseases [33]. IgA monomers can attach to FcαRI but are unable to cross-link it, resulting in anti-inflammatory reactions. FcαRI creates an 'inhibisomes' that hinder neighboring receptors' signaling. This process, known as inhibitory ITAM (ITAMi), downregulates immune activation, leading to pro-inflammatory functions and tissue destruction [34–39].

The Role of Galactose-deficient IgA1 in IgA Vasculitis

Glycosylation affects immunoglobulin structure and function, with genetic predisposition, infection, and IL-6 production causing abnormal glycosylation [40]. Because IgA1 in IgAN and IgAVN lacks galactose, subjacent GalNAc residues were observed. Autoantibodies form immune complexes with Gd-IgA1, which affect disease severity and progression. Gd-IgA1's Although studies have not revealed any differences between patients with IgAV and healthy controls, the role of IgA vasculitis remains unclear. In IgAVN, Gd-IgA1-immune complexes form in mesangial cells, leading to increased liver levels. This is due to the inability of large immune complexes to enter the liver via the Disse space [41–44].

The Role of Anti-endothelial Cell Antibodies in IgA Vasculitis

Henoch-Schönlein purpura is highly likely to cross-react with various pathogens including *Streptococcus pyogenes*, *Neisseria meningitidis*, *Mycoplasma pneumoniae*, and other bacteria. Other triggers include drugs, vaccinations, toxins, food allergens, and tumor antigens [1, 45–50].

Microorganisms with antigenic structures similar to blood vessel walls produce cross-reactive anti-endothelial cell antibodies (AECA) [20]. These antibodies accumulate in vascular walls, activate the complement cascade, and cause vessel damage. Pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8 stimulate neutrophil migration, adhesion, and infiltration, resulting in leukocytoclastic vasculitis. Elevated interleukin-33 concentrations may contribute to increased IgA autoantibody production and disease severity [1, 51].

IgA vasculitis is a condition characterized by IgA1-autoantibodies binding to AECA (although no pathogen has been identified, cross-reactive AEC A may be produced as a result of microbial infection. Because IgA from IgAV patients adhered more strongly to β2-glycoprotein I (β2GPI) than to control IgA, this antigen may be a potential contender. Remarkably, IgA AECA from patients with IgAVN adhered to bovine glomerular endothelial cells, indicating that patients with IgAV and IgAVN may have different antigen specificities for AECA. The complement system, hereditary variables, and

modulation of endothelial activity have been implicated in IgAV. Illnesses may contribute to the genesis of IgA vasculitis, which frequently manifests in the fall following bacterial or viral illnesses [3].

By identifying Gd-IgA1, GalNAc on the pathogen surfaces may promote the synthesis of cross-reactive IgA and IgG. Microorganisms harbor antigenic structures that can produce autoantibodies. Mucosal infection upregulates IL-6, leading to Gd-IgA1 development by altering glycosylation machinery. Helicobacter pylori is associated with the disease, whereas *S. pneumoniae* and *Haemophilus influenzae* release IgA1 proteases that are capable of cleaving Gd-IgA1 and the IgA1 hinge [3].

CASE STUDIES OF HSP IN CHILDREN

The Ankara 2008 classification criteria suggest that a child is classified as having IgAV/HSP if they have palpable purpura, diffuse abdominal pain, IgA deposition, arthritis, hematuria, or proteinuria [16). 52]. This study found that IgA antibodies in childhood Henoch-Schönlein purpura (HSP) patients can enhance IL-8 production in human umbilical vein endothelial cells (HUVEC). IgA autoantibodies bind to endothelial cells and when incubated with HUVEC cells, enhance IL-8 production. This study revealed that TNF-α in the sera of patients with HSP can enhance IL-8 production by HUVEC; however, antibody blocking did not completely inhibit IL-8 production. The presence of IgA in the serum is crucial for this effect. PD98059, an inhibitor of ERK (Extracellular signal-Regulated Kinase) phosphorylation, reduces the effect of IgA autoantibodies on IL-8 production. This interaction could contribute to the inflammatory response and tissue damage observed in HSP [53].

A study in Saudi Arabia found that 45% of children with HSP had a history of upper respiratory tract infection history [21], 12.2% of children with IgA vasculitis had renal involvement, and 22.2% developed it at follow-up [54, 55]. Children with nephrotic syndrome and large crescent or sclerosing lesions have the highest risk of long-term renal impairment [56]. Another case study of a 10-year-old patient treated with Tramadol and Ibuprofen showed that his renal function was monitored for six months, with no renal function disorder [52]. The later age of onset is a possible risk factor for nephropathy [4, 5]. It is very rare among Black people [4, 12, 57, 58]**.** A case of fulminant HSP in 1994 involved intrathoracic bleeding, intestinal perforation, nephritis, and a skin rash. After cyclosporine therapy, symptoms returned [59]. Antiplatelet agents are useful but potentially dangerous. Heparin is effective but should be administered cautiously [60]. Corticosteroid use did not have a protective effect on patient outcomes. Given the possibility of renal involvement and recurrence, the recommended follow-up period is often >6 months [61].

A retrospective study from 2011 to 2017 found no association between age or sex and poorer outcomes in 61 patients, with a median age of 6 years. Early treatment including hydration, nutrition, and electrolyte balance can relieve intussusception. Immunosuppressive treatment is necessary for patients with severe renal involvement [61]. Plasmapheresis may be beneficial for rapidly progressive HSPN (Henoch-Schönlein Purpura Nephritis), but its benefits are not as definitive as those for ANCA-associated vasculitis. Early and accurate diagnosis remains a challenge for effective management. The European SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) initiative aims to improve care for pediatric rheumatic diseases and has developed consensus-based, evidence-based recommendations for the diagnosis and treatment of various conditions, including IgA vasculitis and nephritis [18, 52].

EFFECT OF HSP ON KIDNEY FUNCTIONING

Nephritic or nephrotic syndrome is present in 20% of patients with HSPN, whereas chronic renal failure occurs in 1 – 15 percent of children. Several histological categories are used to diagnose hypoxic kidney disease (HSPN), the most used being the International Study of Kidney Disease in Children (ISKDC) classification. It has been suggested that the Oxford classification, which is employed in IgA nephropathy, may predict the course of renal disease in HSPN. The most accurate and promising method for predicting patient outcomes in HSPN is the modified semi-quantitative classification (SQC).

However, more research is needed to validate its effectiveness. The existence and quantity of crescents, which are linked to capillary wall damage from fibrinoid necrosis, determines the ISKDC classification. Studies have demonstrated that individuals with higher histological stages may undergo spontaneous lesion healing, and even those with low-grade histological lesions may endure chronic renal failure, indicating that the relationship between crescents and outcomes is not always reliable [62].

Rituximab may help lower the oral CS (Corticosteroids) burden in chronically steroid-dependent patients. Patients are more likely to experience renal involvement but experience arthralgia or arthritis less frequently as they age. The study postulated that in patients with varying onset ages, the relative significance of white blood cell (WBC) and IgA in the etiology of IgAV varies [63].

Other symptoms included leg edema, fever, testicular swelling, pain, headache, and dizziness [63, 64]. The disease primarily affects the gastrointestinal tract, joints, and kidneys, with 50% of cases occurring in children under five years of age [65].

Classification of HSP Nephritis Severity Based on Expert Opinion from the SHARE Initiative

Table 1 given below consists of some important definitions regarding severity.

DIAGNOSIS AND TREATMENT

The clinical standards set by the European League Against Rheumatism (EULAR) and other organizations serve as the foundation for HSP. Acute abdominal syndrome (HSP) is characterized by knee and ankle pain, palpable purpura, and other symptoms [67]. Diagnosis involves tests, such as urinalysis, imaging, and skin and kidney biopsies. It can manifest with other symptoms and affect the internal organs. Erythrocyte sedimentation rate, C-reactive protein level, platelet count, WBC count, and immunoglobulin A levels are examples of laboratory tests that are neither specific nor diagnostic [21]. Laboratory tests are crucial for assessing a patient's condition, monitoring treatment, and detecting potential complications. IgAV, a small-vessel vasculitis, has no established diagnostic criteria, and its morbidity and mortality are mainly determined by renal involvement severity [1, 2, 12, 52, 68]. For adult patients, the ACR 1990 categorization criteria are less useful and do not distinguish them effectively from other small-vessel vasculitides [69]. The most important diagnostic criteria are presented in Table 2.

The current diagnostic criteria for HSP are sensitive and specific, and there is ongoing research to identify less invasive and more specific biomarkers for accurate diagnosis. Understanding the pathogenesis of HSP is important for identifying potential disease-specific biomarkers that can aid in its diagnosis [68].

Treatment

Traditional treatments, such as hydration, bed rest, analgesics, and non-steroidal anti-inflammatory drugs, are effective in most cases [21]. HSP cases are often managed symptomatically, as follows:

1. *Immunosuppressive or immunomodulating:* immunosuppressive or immunomodulatory options include mycophenolate mofetil, cyclosporine A, rituximab [70], and dapsone. Colchicine inhibits immune cell movement to inflammation sites, whereas dapsone has antioxidant and immunomodulatory effects [71].
2. *Blood Pressure Management:* To preserve the kidneys, blood pressure control, dietary changes, and drugs such as angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors may be employed.
3. *Corticosteroids:* Corticosteroids are used in the treatment of systemic lupus erythematosus, primary IgA nephropathy, antineutrophil cytoplasmic antibody vasculitis, and other types of glomerulonephritis to prevent and treat short- and long-term kidney damage. Intravenous cyclophosphamide and high-dose steroid therapy are recommended for severe nephritis, followed

by azathioprine or mycophenolate mofetil as a maintenance treatment. Although specialists advise against the routine use of corticosteroids, they can be used to treat renal involvement in HSP [72]. Corticosteroids have shown efficacy in reducing abdominal and joint pain, and immunosuppressive medications such as azathioprine or cyclophosphamide may be considered. Corticosteroids are often used to manage symptoms but are not consistently beneficial for skin purpura [2, 19, 58, 73].

4. *Adjuvant Therapies:* Adjuvant therapies such as anticoagulants, plasmapheresis, and tonsillectomy have been proposed, but require further investigation.
5. *Steroids:* Usually Steroids are not recommended for prophylactic use, but high-dose steroids, cyclosporine, and mycophenolate have shown success in treating complications, such as glomerulonephritis. A study comparing steroids and pulse cyclophosphamide for treating severe adult Henoch-Schönlein purpura found no benefit in adding cyclophosphamide compared to steroids alone, with no severe adverse events observed [66].

Table 1. Severity definition [66].

S.N.	Severity	Definition
1	Mid nephritis	GFR (Glomerular Filtration Rate) >80 mL/min/1.73 m^2 and early morning UP:UC (Urine Creatinine)
2	Moderate	250 mg/mmol for at least 4 weeks
3	Severe	>50% crescents on renal biopsy findings and GFR of 250 mg/mmol for at least 4 weeks (Ozen et al.)

Table 2. Diagnostic criteria.

Criteria	Terms	Definition
ACR classification criteria	Palpable purpura	Slightly raised 'palpable' hemorrhagic skin lesions, not related to thrombocytopenia. Patient 20 years or younger at the onset of first symptoms and granulocytes in small blood vessel walls on biopsy.
	Bowel angina wall	Diffuse abdominal pain, worse after meals, or the diagnosis of ischemia, usually including bloody diarrhea.
EULAR/PRINTO/PRES classification	Purpura	Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance, is not related to thrombocytopenia.
	Abdominal pain	Acute-onset, diffuse, colicky stomach pain that is evaluated by a physical examination and history; may accompany GIT (Gastrointestinal Tract) hemorrhage and intussusception.
	Arthritis or arthralgias	Acute-onset arthritis is characterized by joint swelling or pain that limits movement, while acute-onset arthralgia is characterized by joint pain that is unaccompanied by joint swelling or mobility restriction.
	Renal involvement	involvement of the kidneys Hematuria or red blood cell casts; proteinuria greater than 0.3 g/24 hours or greater than 30 mg/mmol of urine albumin/creatinine ratio on a spot morning sample: Greater than five red blood cells/HFF, red blood cell casts in the urine sediment or two inches on a dipstick.
Michel's Criteria (1992) [68]	Palpable purpura, bowel angina, gastrointestinal bleeding, hematuria, age ≤20 years at disease onset, and no history of medication intake at disease onset.	
Chapel Hill Consensus Criteria (1994)	HSP is defined as a small-vessel vasculitis with IgA-dominant immune deposits, involving skin, gut, and glomeruli, and associated with arthralgia or arthritis.	
Helander's Criteria (1995)	Palpable purpura, vascular IgA deposition, age ≤20 years at disease onset, gastrointestinal involvement, upper respiratory tract infection prodrome, and mesangioproliferative glomerulonephritis with or without IgA deposition.	

CONCLUSION

Based on the above review, it can be concluded that purpura disease, a complex condition affecting children of various ages, requires accurate diagnosis and treatment strategies. It involves palpable

purpura, joint, and abdominal pain, and renal involvement. Treatment focuses on managing underlying causes, alleviating symptoms, and preventing complications. Corticosteroids or immunosuppressive agents should be considered in severe cases. Researchers and medical professionals are constantly investigating novel treatments and diagnostic standards to enhance pediatric patient care.

REFERENCES

1. Jaszczura M, Dyga K, Bryłka A, Góra A, Machura E. IgA vasculitis, formerly known as Henoch–Schönlein purpura–the most common vasculitis in children. Pediatr Pol. 2018;93:336–42. DOI: 10.5114/polp.2018.78000.
2. Trnka PH. Henoch-Schönlein purpura in children. J Paediatr Child Health. 2013;49:995–1003. DOI: 10.1111/jpc.12403.
3. Heineke MH, Ballering AV, Jamin A, Ben Mkaddem SB, Monteiro RC, Van Egmond M. New insights in the pathogenesis of immunoglobulin A vasculitis (Henoch-Schönlein purpura). Autoimmun Rev. 2017;16:1246–53. DOI: 10.1016/j.autrev.2017.10.009.
4. Trapani S, Micheli A, Grisolia F, Resti M, Chiappini E, Falcini F, De Martino M. Henoch Schonlein purpura in childhood: Epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature. Rheumatism. 2005;35:143–53. DOI: 10.1016/j.semarthrit.2005.08.007.
5. Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schonlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet. 2002;360:1197–202. DOI: 10.1016/S0140-6736(02)11279-7.
6. Calviño MC, Llorca J, García-Porrúa C, Fernández-Iglesias JL, Rodriguez-Ledo P, González-Gay MA. Henoch-Schönlein purpura in children from northwestern Spain: A 20-year epidemiologic and clinical study. Medicine. 2001;80:279–90. DOI: 10.1097/00005792-200109000-00001.
7. Watson L, Richardson ARW, Holt RCL, Jones CA, Beresford MW. Henoch Schonlein Purpura – A 5-Year Review and Proposed Pathway. PLOS ONE. 2012;7. DOI: 10.1371/journal.pone.002 9512.
8. Tizard EJ. Henoch-Schönlein purpura. Arch Dis Child. 1999;80:380–3. DOI: 10.1136/adc.80.4. 380.
9. Prais D, Amir J, Nussinovitch M. Recurrent Henoch-Schönlein purpura in children. J Clin Rheumatol. 2007;13:25–8. DOI: 10.1097/01.rhu.0000255692.46165.19.
10. Calvo-Río V, Hernández JL, Ortiz-Sanjuán F, Loricera J, Palmou-Fontana N, González-Vela MC, et al. Relapses in patients with Henoch–Schönlein purpura: Analysis of 417 patients from a single center. Medicine. 2016;95. DOI: 10.1097/MD.0000000000004217.
11. Lei WT, Tsai PL, Chu SH, Kao YH, Lin CY, Fang LC, et al. Incidence and risk factors for recurrent Henoch-Schönlein purpura in children from a 16-year nationwide database. Pediatr Rheumatol Online J. 2018;16:25. DOI: 10.1186/s12969-018-0247-8.
12. Piram M, Mahr A. Epidemiology of immunoglobulin A vasculitis (Henoch–Schönlein): Current state of knowledge. Curr Opin Rheumatol. 2013;25:171–8. DOI: 10.1097/BOR.0b013e32835d 8e2a.
13. Saulsbury FT. Henoch–Schönlein purpura. Curr Opin Rheumatol. 2010;22:598–602. DOI: 10.1097/BOR.0b013e32833af608.
14. Butt G, Anees M, Rana M. Frequency of renal manifestations in patients of Henoch-Schonlein purpura. J Pak Assoc Dermatol. 2021;31:146–52.
15. Hetland LE, Susrud KS, Lindahl KH, Bygum A. Henoch-Schönlein purpura: A literature review. Acta Derm Venereol. 2017;97:1160–6. DOI: 10.2340/00015555-2733.
16. Sag E, Arici ZS, Ozen S. IgA vasculitis (Henoch–Schönlein purpura) in children. Expert Opin Orphan Drugs. 2017;5:405–10. DOI: 10.1080/21678707.2017.1311783.
17. Abbas S, Geetha S, Deepthi RV, Kamar J, Uthup S. Clinical profile and outcome of Henoch Schonlein purpura in a tertiary care hospital in South India. Int J Contemp Pediatr. 2017;4:822–6. DOI: 10.18203/2349-3291.ijcp20171493.
18. Ozen S, Marks SD, Brogan P, Groot N, de Graeff N, Avcin T, et al. European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis—The SHARE initiative. Rheumatology. 2019;58:1607–16. DOI: 10.1093/rheumatology/kez041.

19. Audemard-Verger A, Pillebout E, Guillevin L, Thervet E, Terrier B. IgA vasculitis (Henoch–Shönlein purpura) in adults: Diagnostic and therapeutic aspects. Autoimmun Rev. 2015;14:579–85. DOI: 10.1016/j.autrev.2015.02.003.
20. Calvo-Río V, Loricera J, Mata C, Martín L, Ortiz-Sanjuán F, Alvarez L, et al. Henoch-Schönlein purpura in northern Spain: Clinical spectrum of the disease in 417 patients from a single center. Medicine. 2014;93:106–13. DOI: 10.1097/MD.0000000000000019.
21. Alharthi AA. Henoch-Schonlein purpura in Saudi Arabia: A retrospective study of 27 children in Taif region. Curr Pediatr Res. 2016;20:126–31.
22. Watson L, Richardson ARW, Holt RCL, Jones CA, Beresford MW. Henoch Schonlein Purpura – A 5-year review and proposed pathway. PLOS ONE. 2012;7. DOI: 10.1371/journal.pone.0029512.
23. Zhao YL, Liu ZJ, Bai XM, Wang YC, Li GH, Yan XY. Obesity increases the risk of renal involvement in children with Henoch–Schönlein purpura. Eur J Pediatr. 2015;174:1357–63. DOI: 10.1007/s00431-015-2547-z.
24. Narchi H. Risk of long term renal impairment and duration of follow up recommended for Henoch-Schönlein purpura with normal or minimal urinary findings: A systematic review. Arch Dis Child. 2005;90:916–20. DOI: 10.1136/adc.2005.074641.
25. Modi S, Mohan M, Jennings A. Acute scrotal swelling in Henoch-Schonlein purpura: Case report and review of the literature. Urol Case Rep. 2016;6:9–11. DOI: 10.1016/j.eucr.2016.01.004.
26. Dos Santos D, Langer FW, Dos Santos T, Rafael Tronco Alves G, Feiten M, Teixeira de Paula Neto W. Posterior reversible encephalopathy syndrome as a complication of Henoch-Schönlein purpura in a seven-year-old girl. Scott Med J. 2017;62:34–7. DOI: 10.1177/0036933017690467. PubMed: 28152662.
27. Hwang JJ, Ahn J, Kim KP, Choi HI, Choi JY, Song R, et al. Henoch-Schönlein purpura with muscle involvement, presenting as myositis. J Clin Rheumatol. 2017;23:60–2. DOI: 10.1097/RHU.0000000000000476. PubMed: 28002161.
28. Michas G, Grigoriou K, Syrigos D, Alexopoulos N, Evdoridis C, Trikas A. A rare cause of myocarditis resulting in acute heart failure in the setting of Henoch-Schönlein purpura. Hellenic J Cardiol. 2017;58:439–42. DOI: 10.1016/j.hjc.2017.05.002. PubMed: 28528257.
29. Woof JM, Kerr MA. The function of immunoglobulin A in immunity. J Pathol. 2006;208:270–82. DOI: 10.1002/path.1855. PubMed: 16961578.
30. Crago SS, Kutteh WH, Moro I, Allansmith MR, Radl J, Haaijman JJ, Mestecky J. Distribution of IgA1-, IgA2-, and J chain-containing cells in human tissues. J Immunol. 1984;132:16–8. DOI: 10.4049/jimmunol.132.1.16. PubMed: 6418796.
31. Roos A, Bouwman LH, van Gijlswijk-Janssen DJ, Faber-Krol MC, Stahl GL, Daha MR. Human IgA activates the complement system via the mannan-binding lectin pathway. J Immunol. 2001;167:2861–8. DOI: 10.4049/jimmunol.167.5.2861. PubMed: 11509633.
32. Hiemstra PS, Gorter A, Stuurman ME, Van Es LA, Daha MR. Activation of the alternative pathway of complement by human serum IgA. Eur J Immunol. 1987;17:321–6. DOI: 10.1002/eji.1830170304. PubMed: 3569402.
33. Aleyd E, Heineke MH, van Egmond M. The era of the immunoglobulin A Fc receptor FcαRI: its function and potential as target in disease. Immunol Rev. 2015;268:123–38. DOI: 10.1111/imr.12337.
34. Blank U, Launay P, Benhamou M, Monteiro RC. Inhibitory ITAMs as novel regulators of immunity. Immunol Rev. 2009;232:59–71. DOI: 10.1111/j.1600-065X.2009.00832.x. PubMed: 19909356.
35. Pasquier B, Launay P, Kanamaru Y, Moura IC, Pfirsch S, Ruffié C, Hénin D, Benhamou M, Pretolani M, Blank U, Monteiro RC. Identification of FcαRI as an inhibitory receptor that controls inflammation: dual role of FcRγ ITAM. Immunity. 2005;22:31–42. DOI: 10.1016/j.immuni.2004.11.017. PubMed: 15664157.
36. Ben Mkaddem SB, Rossato E, Heming N, Monteiro RC. Anti-inflammatory role of the IgA Fc receptor (CD89): From autoimmunity to therapeutic perspectives. Autoimmun Rev. 2013;12:666–9. DOI: 10.1016/j.autrev.2012.10.011. PubMed: 23201915.

37. Heineke MH, van Egmond M. Immunoglobulin A: Magic bullet or Trojan horse? Eur J Clin Invest. 2017;47:184–92. DOI: 10.1111/eci.12716.
38. Aleyd E, van Hout MW, Ganzevles SH, Hoeben KA, Everts V, Bakema JE, van Egmond M. IgA enhances NETosis and release of neutrophil extracellular traps by polymorphonuclear cells via Fcα receptor I. J Immunol. 2014;192:2374–83. DOI: 10.4049/jimmunol.1300261. PubMed: 24493821.
39. van der Steen LP, Bakema JE, Sesarman A, Florea F, Tuk CW, Kirtschig G, Hage JJ, Sitaru C, van Egmond M. Blocking Fcα Receptor I on Granulocytes Prevents Tissue Damage Induced by IgA Autoantibodies. J Immunol. 2012;189:1594–601. DOI: 10.4049/jimmunol.1101763.
40. Jennewein MF, Alter G. The immunoregulatory roles of antibody glycosylation. Trends Immunol. 2017;38:358–72. DOI: 10.1016/j.it.2017.02.004. PubMed: 28385520.
41. Launay P, Grossetête B, Arcos-Fajardo M, Gaudin E, Torres SP, Beaudoin L, Patey-Mariaud de Serre N, Lehuen A, Monteiro RC. Fcα receptor (CD89) mediates the development of immunoglobulin A (IgA) nephropathy (Berger's disease): evidence for pathogenic soluble receptor–IgA complexes in patients and CD89 transgenic mice. J Exp Med. 2000;191:1999–2009. DOI: 10.1084/jem.191.11.1999. PubMed: 10839814.
42. Tissandié E, Morelle W, Berthelot L, Vrtovsnik F, Daugas E, Walker F, Lebrec D, Trawalé JM, Francoz C, Durand F, Moura IC, Paradis V, Moreau R, Monteiro RC. Both IgA nephropathy and alcoholic cirrhosis feature abnormally glycosylated IgA1 and soluble CD89-IgA and IgG–IgA complexes: common mechanisms for distinct diseases. Kidney Int. 2011;80:1352–63. DOI: 10.1038/ki.2011.276. PubMed: 21866091.
43. Vuong MT, Hahn-Zoric M, Lundberg S, Gunnarsson I, Van Kooten C, Wramner L, Seddighzadeh M, Fernström A, Hanson LA, Do LT, Jacobson SH, Padyukov L. Association of soluble CD89 levels with disease progression but not susceptibility in IgA nephropathy. Kidney Int. 2010;78:1281–7. DOI: 10.1038/ki.2010.314. PubMed: 20811333.
44. Wilkinson A. Early recognition and treatment of Henoch-Schönlein purpura in children. Nurs Child Young People. 2019;31:36–40. DOI: 10.7748/ncyp.2019.e1118. PubMed: 31486599.
45. Watanabe T. Henoch-Schönlein purpura following influenza vaccinations during the pandemic of influenza A (H1N1). Pediatr Nephrol. 2011;26:795–8. DOI: 10.1007/s00467-010-1722-8. PubMed: 21120537.
46. Jariwala S, Vernon N, Shliozberg J. Henoch-Schönlein purpura after hepatitis A vaccination. Ann Allergy Asthma Immunol. 2011;107:180–1. DOI: 10.1016/j.anai.2011.05.006. PubMed: 21802028.
47. Mitsui H, Shibagaki N, Kawamura T, Matsue H, Shimada S. A clinical study of Henoch-Schönlein purpura associated with malignancy. J Eur Acad Dermatol Venereol. 2009;23:394–401. DOI: 10.1111/j.1468-3083.2008.03065.x. PubMed: 19207675.
48. Blanco R, González-Gay MA, Ibáñez D, Alba C, Pérez de Llano LA. Henoch-Schönlein purpura as a clinical presentation of small cell lung cancer. Clin Exp Rheumatol. 1997;15:545–7.
49. Angelier AS, Petit L, Wynckel A, Vuiblet V, Birembaut P, Toubas O, et al. Schoenlein-Henoch purpura as a presentation of squamous cell bronchial carcinoma. Rev Mal Respir. 2011;28:372–6. DOI: 10.1016/j.rmr.2010.09.033. PubMed: 21482344.
50. Nozato K, Morishima Y, Furuta J, Fujita J, Miyazaki K, Ogawa R, et al. A case of Henoch-Schönlein purpura which was difficult to distinguish from a skin rash associated with gefitinib. Nihon Kokyuki Gakkai Zasshi. 2010;48:529–34.
51. Maritati F, Canzian A, Fenaroli P, Vaglio A. Adult-onset IgA vasculitis (Henoch-Schönlein): update on therapy. Presse Med. 2020;49:104035. DOI: 10.1016/j.lpm.2020.104035. PubMed: 32645417.
52. Kango SC, Palet JE, Bognin OB, Ouaimon D, Houndjahoue GF. Diagnostic difficulties in a case of Henoch-Schönlein purpura at the pediatric University Hospital complex of Bangui. J Med Case Rep Case Series. 2022;3:19.
53. Yang YH, Huang YH, Lin YL, Wang LC, Chuang YH, Yu HH, Lin YT, Chiang BL. Circulating IgA from acute stage of childhood Henoch-Schönlein purpura can enhance endothelial interleukin (IL)-8 production through MEK/ERK signalling pathway. Clin Exp Immunol. 2006;144:247–53. DOI: 10.1111/j.1365-2249.2006.03076.x. PubMed: 16634798.

54. Demir S, Candan C, Turhan P, Ergüven M. Henoch Schönlein Purpura / Ig A Vasculitis in Children and Risk Factors for Renal Involvement. Acta Medica. 2021;52:230–38. DOI: 10.32552/2021.ActaMedica.585.
55. Szemenyei C, Hahn D. Prevention of nephritis in Henoch-Schönlein purpura. J Paediatr Child Health. 2015;51:236–39. DOI: 10.1111/jpc.12785. PubMed: 25677491.
56. Bogdanović R. Henoch-Schönlein purpura nephritis in children: Risk factors, prevention and treatment. Acta Paediatr. 2009;98:1882–89. DOI: 10.1111/j.1651-2227.2009.01445.x.
57. Atkinson SR, Barker DJ. Seasonal distribution of Henoch-Schönlein purpura. Br J Prev Soc Med. 1976;30:22–25. DOI: 10.1136/jech.30.1.22. PubMed: 949569.
58. Reamy BV, Servey JT, Williams PM. Henoch-Schönlein purpura (IgA Vasculitis): Rapid Evidence Review [IgA vasculitis]. Am Fam Physician. 2020;102:229–33. PubMed: 32803924.
59. Lee DH, Lee ES, Hong J, Park KH, Pai KS. A case of Henoch-Schönlein purpura with fulminant complications and its long-term outcome. Child Kidney Dis. 2019;23:128–33. DOI: 10.3339/jkspn.2019.23.2.128.
60. Chan H, Tang YL, Lv XH, Zhang GF, Wang M, Yang HP, Li Q. Risk factors associated with renal involvement in childhood Henoch-Schönlein purpura: A meta-analysis. PLOS ONE. 2016;11. DOI: 10.1371/journal.pone.0167346.
61. Gaia MJ, Capela M, Borges JP, Marques E, Ferreira G, Vinhas da Silva A. Purpura HS. What to expect. Port J Nephrol Hypert, Lisboa. 2019;33:212–16.
62. Jelusic M, Sestan M, Cimaz R, Ozen S. Different histological classifications for Henoch-Schönlein purpura nephritis: Which one should be used? Pediatr Rheumatol Online J. 2019;17:10. DOI: 10.1186/s12969-019-0311-z. PubMed: 30819179.
63. Liao CH, Tsai M, Yang YH, Chiang BL, Wang LC. Onset age is a risk factor for refractory pediatric IgA vasculitis: A retrospective cohort study. Pediatr Rheumatol Online J. 2020;18:86. DOI: 10.1186/s12969-020-00480-3. PubMed: 33172497.
64. Wang X, Zhu Y, Gao L, Wei S, Zhen Y, Ma Q. Henoch-Schönlein purpura with joint involvement: Analysis of 71 cases. Pediatr Rheumatol. 2016;14:1–8.
65. Dawood SA, Abodiah AM, Alqahtani SM, Shati AA, Alqahtani YA, Alshehri MA, Mahmood SE. Clinico-epidemiological profile and outcome of children with IgA vasculitis in Aseer region, Southwestern Saudi Arabia. Inhealthcare. 2021 Dec 7;9(12):1694.
66. Pillebout E, Alberti C, Guillevin L, Ouslimani A, Thervet E; Cesar Study Group. Addition of cyclophosphamide to steroids provides no benefit compared with steroids alone in treating adult patients with severe Henoch Schönlein purpura. Kidney Int. 2010;78:495–502. DOI: 10.1038/ki.2010.150. PubMed: 20505654.
67. Han DH. Clinical analysis on 106 cases of Henoch–Schönlein purpura. J Intern Korean Med. 2007;28:570–85.
68. Yang YH, Yu HH, Chiang BL. The diagnosis and classification of Henoch–Schönlein purpura: An updated review. Autoimmun Rev. 2014;13:355–58. DOI: 10.1016/j.autrev.2014.01.031. PubMed: 24424188.
69. Van de Perre E, Jones RB, Jayne DRW. IgA vasculitis (Henoch–Schönlein purpura): Refractory and relapsing disease course in the adult population. Clin Kidney J. 2021;14:1953–60. DOI: 10.1093/ckj/sfaa251. PubMed: 34345419.
70. 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. Brief report: Rituximab for the treatment of adult-onset IgA vasculitis (Henoch-Schönlein). Arthritis Rheumatol. 2018;70:109–14. DOI: 10.1002/art.40339. PubMed: 28973844.
71. Audemard-Verger A, Terrier B, Dechartres A, Chanal J, Amoura Z, Le Gouellec N, Cacoub P, Jourde-Chiche N, Urbanski G, Augusto JF, Moulis G, Raffray L, Deroux A, Hummel A, Lioger B, Catroux M, Faguer S, Goutte J, Martis N, Maurier F, Rivière E, Sanges S, Baldolli A, Costedoat-Chalumeau N, Roriz M, Puéchal X, André M, Lavigne C, Bienvenu B, Mekinian A, Zagdoun E,

Girard C, Bérezné A, Guillevin L, Thervet E, Pillebout E; French Vasculitis Study Group. Characteristics and management of IgA vasculitis (Henoch-Schönlein) in adults: Data from 260 patients included in a French multicenter retrospective survey. Arthritis Rheumatol. 2017;69:1862–70. DOI: 10.1002/art.40178. PubMed: 28605168.

72. Gohari A, Matsell DG, Mammen C, Goldman RD. Henoch-Schönlein purpura in children: Use of corticosteroids for prevention and treatment of renal disease. Can Fam Physician. 2020;66:895–97. DOI: 10.46747/cfp.6612895. PubMed: 33334956.
73. Butt G, Anees M, Rana M. Frequency of renal manifestations in patients of Henoch-Schonlein purpura. J Pak Assoc Dermatol. 2021;31:146–52.

