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Comprehensive Clinical and Immunological Analysis of Hemorrhagic Vasculitis in Children

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Abstract Hemorrhagic vasculitis is considered one of the most common and frequently occurring diseases in the pediatric population. Its incidence can vary significantly depending on several factors, including geographic region, the level of economic development, and the methods used for diagnosis and statistical reporting. The clinical presentation of hemorrhagic vasculitis is highly diverse, with the severity and potential complications of the disease largely influenced by the state of the hemostatic system—specifically the balance between coagulation and anticoagulation mechanisms. Additionally, the outcome of the disease is strongly affected by the organs involved. In particular, kidney involvement is associated with a notably higher risk of a severe disease course, potentially leading to long-term health issues and requiring more intensive medical intervention. This highlights the importance of early diagnosis, careful monitoring, and a tailored therapeutic approach based on individual patient conditions. The article presents the results of a retrospective analysis of the medical history of 416 children diagnosed with "Hemorrhagic Vasculitis" who were treated at the Cardiorheumatology Department of the Multidisciplinary Clinic of the Tashkent Medical Academy from 2012 to 2022. Additionally, it includes a prospective study of the clinical and immunological characteristics of the disease in 77 children over time. Key Findings: Hemorrhagic vasculitis most commonly develops after viral infections. The cutaneous-articular form is the most prevalent, accounting for 60% of cases. Inflammatory markers (ESR, CRP) correlate with the severity of symptoms. Glucocorticoid therapy facilitates the rapid regression of symptoms. Patients with this form require long-term monitoring, as 10% may develop chronic complications. These findings provide valuable insights into the clinical and immunological characteristics of hemorrhagic vasculitis, aiding in the optimization of diagnostic and therapeutic approaches.

Keywords Hemorrhagic vasculitis, Henoch-Schönlein purpura, Clinical features, Children, Immune status

1. Introduction

Hemorrhagic vasculitis (Henoch-Schönlein purpura, IgA vasculitis) is the most common type of primary vasculitis in children. Globally, approximately 3–27 children per 100,000 develop this disease annually. Although relatively rare among all pediatric diseases, it is the most frequently encountered vasculitis in children. The condition typically presents with a hemorrhagic rash (purpura) due to small vessel damage in the skin and has a systemic nature, also affecting the kidneys, joints, and intestines.

Hemorrhagic vasculitis mainly occurs in childhood, with approximately 75–90% of cases affecting children under 10 years old. The highest incidence is observed between 4–7 years of age, and it is extremely rare in infancy. In some cases, IgA vasculitis can also occur in adolescence and adulthood, but it is primarily considered a childhood disease [2,4,6,7,9,12].

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The pathogenesis of hemorrhagic vasculitis is primarily driven by immune-mediated damage to the intimal layer of small blood vessels in various organs, including the skin, joints, gastrointestinal tract, and kidneys. This damage is caused by the deposition of IgA-containing immune complexes, which trigger endothelial dysfunction [1,3,5,6]. Consequently, there is a reduction in fibrinolytic activity, increased activation of lipid peroxidation processes, and significant disruptions in the coagulation and platelet components of the hemostatic system. The significance of this study lies in its aim to identify specific clinical, laboratory, and immunological markers that can be used for the objective and dynamic evaluation of disease activity, thereby contributing to more precise monitoring and improved management of the condition.

Research Objective: This study aims to conduct a retrospective analysis of the clinical manifestations and variants of hemorrhagic vasculitis (Henoch-Schönlein purpura) in the pediatric population, with the goal of identifying specific clinical signs, laboratory indicators, and immunological markers that can serve as reliable tools for the objective and dynamic evaluation of disease activity throughout its course.

By analyzing these parameters, the study seeks to enhance the understanding of disease progression and support more accurate monitoring and personalized management strategies for affected children.

2. Materials and Methods

This study was conducted in the pediatric cardiology and rheumatology department of the multidisciplinary clinic at Tashkent Medical Academy. A retrospective analysis was performed on 416 medical histories of children aged 3 to 17 years diagnosed with hemorrhagic vasculitis between 2012 and 2022. Data were recorded in specially designed charts, and children were divided into groups based on age, gender, clinical course, seasonal occurrence, severity, and comorbidities.

In order to investigate the clinical and immunological characteristics of hemorrhagic vasculitis over time, a prospective study was carried out involving 77 pediatric patients diagnosed with the condition. The study cohort consisted of 42 boys (54.5%) and 35 girls (45.4%), allowing for a comprehensive assessment of gender-related features and the dynamic progression of the disease within this population. Patients were categorized into three clinical groups based on disease severity:

- **Group 1 (mild, n=48):** skin-joint form.
- **Group 2 (moderate, n=20):** skin-joint-abdominal form.
- **Group 3 (severe, n=9):** mixed form involving skin, joints, abdomen, and kidneys. A control group included 30 age-matched healthy children.

Based on disease duration:

- **66%** experienced acute illness lasting up to 1.5 months,
- **26%** had a prolonged course lasting up to 6 months,
- **8%** had chronic relapsing vasculitis lasting over 6 months.

Clinical Symptoms. At the onset of the disease:

- **14%** of patients had a body temperature increase to 37.6–38℃,
- **67%** experienced loss of appetite,
- **34%** had nausea and vomiting,
- **28%** had digestive disturbances (diarrhea or constipation).

The diagnostic approach included a comprehensive set of methods aimed at thoroughly evaluating the condition of the patients. These methods encompassed a general clinical examination, complete blood count, biochemical blood analysis, as well as urine and stool analysis. Coagulation tests were performed to assess hemostatic function, and renal ultrasound was conducted to evaluate kidney involvement. Additionally, an immunological assessment of peripheral blood was carried out, which included the measurement of immunoglobulin levels (IgA, IgM, IgG) using Mancini's method, and the determination of T- and B-lymphocyte levels through the Mendes method. Enzyme-linked immunosorbent assays (ELISA) were also utilized to obtain more detailed immunological data.

3. Results and Discussion

According to the results obtained, 71.7% of hemorrhagic vasculitis cases in children occurred in the age range of 7-14 years, 2.1% in the 1-3 years group, and 2.8% in the 15-18 years group. Among 416 children, 51.4% ±2.4% were boys and 48.6% ±2.4% were girls, indicating that the disease is more common in boys. This finding corresponds with data from previously studied literature.

A seasonal pattern in disease incidence was established, with an increase in cases observed in autumn (September, October, November) and spring (March, April, May)**.** Other researchers have also noted a decline in cases during summer. Notably, Kudryasheva M.A. (2015) justified in her study that in summer, the incidence rate is recorded 3-4 times lower than in other seasons, but severe forms of the disease are more frequently observed in the summer.

The duration of hospitalization for children with hemorrhagic vasculitis depends on the clinical form of the disease, its severity, and the presence of comorbidities. According to our results, the average length of hospital stay for children was 10 ±2.3 days.

One of the most prominent and clinically significant diagnostic features of hemorrhagic vasculitis in children is the presence of a palpable erythematous rash on the skin. This rash typically serves as a key indicator of the disease and is often one of the earliest and most recognizable symptoms during clinical evaluation. (Pic). Diagnosing the disease before the rash appears is challenging; however, once the rash is present, it confirms the diagnosis. The rash primarily appears on the legs and arms of patients from the 3rd to 4th day of illness.

Clinical signs such as acute respiratory infections were frequently observed before the manifestation of hemorrhagic vasculitis symptoms:

- **Nasopharyngitis** - 221 cases (**53.1% ±2.4%**),
- **Tonsillitis** - 266 cases (**23.7% ±2.0%**),
- **Fever** - 99 cases (**63.9% ±2.3%**).

These findings emphasize the correlation between upper respiratory tract infections and the onset of hemorrhagic vasculitis in children.

Numerous studies investigating hemorrhagic vasculitis in children have highlighted the presence of an allergic predisposition and a history of frequent acute respiratory infections (ARI) as significant contributing factors in the onset and development of the disease. These underlying conditions are believed to play a key role in triggering immune system dysregulation, thereby increasing susceptibility to vascular inflammation characteristic of this pathology. [2,3,4,12,10]. The onset of the disease is often accompanied by nasopharyngeal or intestinal infections, as well as food allergies [11]. The presence of an infectious disease before the onset of hemorrhagic vasculitis (HV) (most commonly a nasopharyngeal or intestinal infection) maintains constant interest in the role of various infectious agents in the development of the disease. According to various data, upper

respiratory tract infections occur before the onset of HV in 30-65% of cases [10]. Moreover, several studies have shown a high prevalence of chronic infection foci, particularly chronic sinusitis or tonsillitis, in 74% of children with HV [12].

According to the literature, the most common form of the disease is the cutaneous and cutaneous-articular form [2,4,8]. In our observations, all patients predominantly had the cutaneous and cutaneous-articular form as well, with hemorrhagic skin rash observed in 100% of the patients. However, in 93 patients (22.3±2.0%), a normal (cutaneous) form was identified, characterized by purpuric eruptions with a hemorrhagic tint (Fig. 1).

The rash associated with hemorrhagic vasculitis typically presents with a symmetrical distribution and has characteristic localization, most commonly appearing around the joints, on the buttocks, and on the lower extremities. It is often palpable, slightly raised above the surface of the skin [11]. As the rash resolves, residual pigmentation develops, and the affected skin areas tend to become dry and flaky. In the majority of cases—specifically, in 74 patients (17.7±1.8%) diagnosed with cutaneous-hemorrhagic syndrome—an accompanying arthritic syndrome was also observed. In pediatric patients, the joints of the legs and arms were more frequently affected, while the involvement of the knee joints and spine was comparatively less common. Overall, joint involvement in the form of arthritis or arthralgia is observed in approximately 90% of patients. The most commonly affected joints include the ankles and knees, though the elbows and wrists may also be involved in some cases. A distinctive feature of hemorrhagic vasculitis is the absence of joint complications and complete recovery, with only rare cases showing residual changes. In hemorrhagic vasculitis, arthritis (joint involvement) often coincides with the onset of the rash and typically presents as joint pain, hyperemia, and periarticular edema.

The frequency of comorbidities in children with hemorrhagic vasculitis was observed in 252 (60.5±2.3%) patients. The cutaneous-articular form was identified in 183 (43.9±1.4%) patients, of whom 45.3% (98 patients) had associated comorbidities. In particular, 13.0% of children experienced recurrent arthritis symptoms.

According to the literature, gastrointestinal tract involvement is detected in 80% of patients with HV [9,11]. The main clinical symptoms include abdominal pain (88%), bleeding (75%), diarrhea (30%), and vomiting (25%). Our study found that this pathology was present in 62.0% of children. These patients reported symptoms such as abdominal pain, diarrhea, vomiting, and loss of appetite. Pain intensity varied from mild epigastric pain to severe lateral abdominal pain, with the clinical picture often resembling an acute abdomen. In 20-50% of cases, gastrointestinal symptoms preceded the appearance of skin rashes. In 16-30% of children, abdominal pain intensified due to gastrointestinal bleeding caused by thrombosis and necrosis of the intestinal mucosal veins, and less frequently due to intussusception and intestinal perforation [7].

The cutaneous-abdominal form was identified in 38 patients (9.1±1.4%). It was noted that this type of hemorrhagic vasculitis was twice as common in children with comorbid conditions. Among these children, 25% were diagnosed with Helicobacter infection, 18% had helminthic infestations, and 10% had gastritis or duodenitis. The timely detection and treatment of comorbid conditions in this type of HV led to prolonged hospitalization and an increase in the duration of treatment.

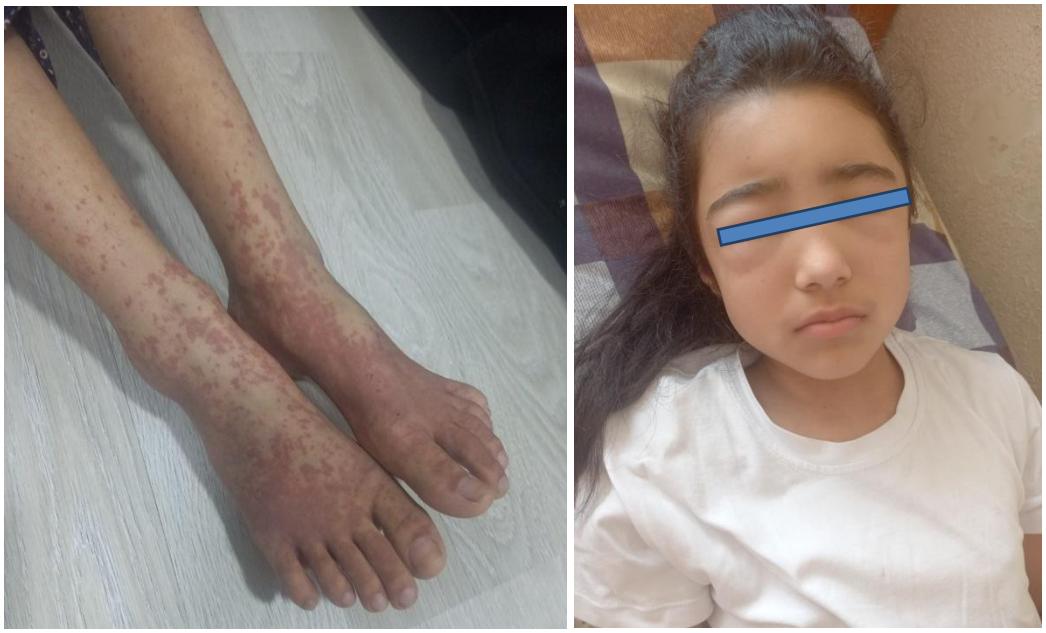

Figure 1. Severe Recurrent Henoch-Schönlein Purpura (IgA Vasculitis) with Cutaneous-Abdominal and Nephrotic Manifestations in an 12-Year-Old Patient

Clinically significant kidney damage in the form of nephritis develops in an average of 40% of children with HV within the first 4-6 weeks after disease onset. However, according to various authors, this rate varies from 20% to 80% [10,12]. Microscopic hematuria and proteinuria are common, and in some cases, nephrotic syndrome with massive proteinuria may develop. In certain cases, nephritic syndrome may be accompanied by atrial hypertension [7]. Morphological kidney changes most commonly manifest as mesangioproliferative glomerulonephritis [4].

Renal involvement in hemorrhagic vasculitis in children worsens the disease prognosis. The severity of kidney syndrome in patients can range from mild proteinuria and microscopic hematuria to acute kidney damage. Our study found that renal involvement occurred in approximately half of the children with comorbidities, with an overall frequency of 30.4%. The mixed form (cutaneous + articular + abdominal + renal) was observed in 7.4±1.2% of patients. These patients experienced prolonged hospital stays, with 47% of them being hospitalized for more than 20 days. High disease activity was noted in 43% of children with comorbidities, while among those without comorbidities, high disease activity was observed in only 18%.

According to the literature, the majority of patients with Henoch-Schönlein purpura (HSP) do not exhibit significant changes in erythrocyte sedimentation rate (ESR), leukocyte count, IgA, or antistreptolysin-O (ASLO) levels in peripheral blood, reflecting moderate inflammatory activity of the disease. However, our data showed that laboratory parameter alterations in children were common. ESR values varied widely from 2 to 80 mm/hour, with 34 children (44.0±3.8%) having ESR levels exceeding 20 mm/hour. ESR levels in our patients did not correlate with the severity or extent of the cutaneous-hemorrhagic syndrome ($r=0.003$), nor with the presence ($r=0.24$) or severity of arthritic syndrome ($r=0.17$). However, a positive correlation between ESR levels and nephritis was established ($r=0.45$, $p<0.05$).

Leukocyte levels in children with HV ranged from 4.1 to 29.0×10^9/L. Moderate leukocytosis ($10–20\times10^9$/L) was detected in the first group, while severe leukocytosis (above 20×10^9/L) was observed in the second and third groups. Elevated leukocyte levels were recorded in patients with various forms of HV; however, most of them had kidney involvement—21 patients (12.6±2.6%). Hyperleukocytosis was noted in the third group in patients with kidney damage, macroscopic hematuria, and/or extensive skin lesions.

During the progression of vasculitis, an imbalance in T-cell subpopulations occurs. Specifically, the Th1/Th2 ratio is disrupted, with Th2 cells becoming hyperactive, which in turn stimulates B cells, increasing the production of immunoglobulins, particularly IgA. This process may contribute to the exacerbation of vasculitis. These immune system changes lead to an increase in IgA levels in the bloodstream. In severe cases, kidney damage may occur, evidenced by the presence of red and white blood cells in the urine, as well as an increase in protein (proteinuria) in the urine. These processes are associated with high IgA levels and a decrease in complement system components C3 and C4 [5,6,9].

In the immunological analysis of peripheral blood, patients with the cutaneous-articular form of the disease showed a significantly higher mean level of CD4-marked T-lymphocytes compared to the control group, while CD8-marked T-lymphocytes were lower than in the control group. In particular, the identified imbalance in T-lymphocyte subpopulations was accompanied by an increased CD4/CD8 ratio. The mean levels of CD3- and CD16-marked T-lymphocytes also significantly differed from those of healthy children.

In patients with mixed forms (cutaneous + articular + abdominal) and (cutaneous + articular + abdominal + renal), a significant increase in CD4+ T-lymphocytes ($p<0.05$) and an elevated CD4/CD8 ratio were observed compared to the control group. Additionally, in the mixed forms of the disease, the number of CD3- and CD95-marked cells in peripheral blood was significantly higher than in the control group.

When immune complexes accumulate in blood vessel walls, they activate the complement system. This process recruits neutrophil granulocytes, further intensifying inflammation within blood vessels. As a result, this can lead to glomerulonephritis, a condition where the small blood vessels in the kidneys become damaged. Additionally, IgE immunoglobulin levels may also be elevated. Studies indicate that increased IgE levels are linked to proteinuria (protein leakage in urine), and that Type I hypersensitivity reactions contribute to an increase in capillary permeability. Children with hemorrhagic vasculitis have been found to exhibit a decrease in natural killer (NK) cell numbers. NK cells play a crucial role in protecting the body from viral infections and are an essential part of the immune system. Their reduced activity may exacerbate immune-related damage to the intestines and kidney tissues.

4. Conclusions

1. Hemorrhagic vasculitis in children presents with diverse clinical manifestations, with cutaneous, articular, gastrointestinal, and renal involvement being the most significant. Hospitalization duration was 2.5–3 times longer in children with comorbidities. Allergic conditions and secondary infections (including helminthic infestations) were identified as predisposing factors for the disease.
2. Immunological disturbances in patients included increased CD4+ T-lymphocyte levels and decreased CD8+ T-cells, along with elevated IgA and IgG levels, particularly in mixed forms of the disease. The immune changes observed contribute to the progression of capillary toxicity and prolonged disease course.
3. Currently, immunological markers and molecular research are improving early disease detection and helping to determine appropriate treatment strategies**.** Medical and scientific investigations are playing a key role in understanding the underlying mechanisms of

vasculitis and developing more effective treatment approaches.

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