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Hyperhomocysteinemia and Cytokine Profiles in Henoch-Schönlein Purpura: Genetic Associations and Treatment Outcomes

Ormonbek Dzhakypbaev [1,2], Akmatbek Saparbaev [3], Rysbek Sadyjev [4], Asel Kenzheeva [4], Kunduz Shukuralieva [4], Nurzhan Usenova [4] and Sagynali Mamatov [1*]

[1]Department of Hospital Internal Medicine with a Course of Hematology, I. K. Akhunbaev Kyrgyz State Medical Academy, Bishkek 720020, Kyrgyzstan

[2]Department of Hematology, National Center of Oncology and Hematology of the Ministry of Health of the Kyrgyz Republic, Bishkek 720055, Kyrgyzstan

[3]Department of Physics, Informatics and Mathematics, I. K. Akhunbaev Kyrgyz State Medical Academy, Bishkek 720020, Kyrgyzstan

[4]Department of Therapeutic Dentistry, I. K. Akhunbaev Kyrgyz State Medical Academy, Bishkek 720020, Kyrgyzstan

[*] Correspondence: sgnmamatov@gmail.com

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Abstract: Henoch-Schönlein purpura (HSP) is a systemic vasculitis characterized by purpura, joint pain, abdominal discomfort, and renal involvement in children. This study aimed to evaluate the homocysteine (Hcy) levels, polymorphisms of the methylenetetrahydrofolate reductase (MTHFR) C677T and methionine synthase (MTR) A2756G genes, and immunological parameters in 183 patients with HSP. Hyperhomocysteinemia (HHcy) was found in 67.5% of patients, with 66.6% and 7.4% of patients with HHcy having MTHFR C677T heterozygosity and homozygosity, respectively. MTR A2756G polymorphisms were present in 44.4% of patients with HHcy. Patients with both HHcy and gene mutations experience more severe symptoms. Flow cytometry revealed reduced CD4 and CD8 antigen expressions in some patients. Serum cytokine analysis showed significantly higher IL-6 and TNF-α levels in patients with generalized HSP than in controls and those with cutaneous-articular HSP. Immunomodulatory treatments, such as cyclosporin A and rituximab, were effective in severe, treatment-resistant cases, reducing symptoms and inflammatory markers in these patients. This study highlights the importance of genetic, metabolic, and immunological assessments in guiding personalized treatment for HSP. Recommendations include measuring Hcy levels, genotyping for MTHFR C677T and MTR A2756G polymorphisms, immunophenotyping, and considering immunomodulatory treatments in cases that are severe.

Keywords: Henoch-Schönlein Purpura; IgA Immune Complexes; Homocysteine; Cytokines; Cyclosporin-A; Rituximab

1. Introduction

Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis in children, characterized by purpura, joint pain, abdominal discomfort, and renal involvement [1, 2]. This condition results from the deposition of IgA in small blood vessels, triggering inflammation and other clinical symptoms [3, 4]. HSP mainly affects children but can also occur in adults, with most cases resolving spontaneously [2, 5]. Some patients may develop long-term issues, particularly chronic kidney disease [2].

In children under the age of 2, HSP presents with significant swelling and facial involvement, but fewer kidney, gastrointestinal, and joint issues [6]. HSP has been linked to familial Mediterranean fever and may present atypically in such cases [3]. In adults, HSP can be more severe, with complications such as intestinal infarction and increased kidney involvement [7, 8]. Previous studies have linked HSP to coronavirus disease 2019 [9].

HSP immune complexes show a predominance of immunoglobulin A1 (IgA1) with abnormal glycosylation, making them resistant to clearance [10, 11]. This aberrant glycosylation leads to IgA1 self-aggregation and the formation of immune complex [10, 11]. During the acute phase, circulating IgA immune complexes are present in many patients with HSP, with one study finding them in 67% of cases [12]. These complexes accumulate in vessel walls, activate complement pathways, and trigger vessel damage and thrombosis [1, 10, 11]. Common triggers include upper respiratory infections, particularly streptococcal and viral infections, including severe acute respiratory syndrome coronavirus 2, as well as drugs and vaccines [10]. Many cases remain idiopathic [1, 13, 14].

Additional mechanisms include delayed-type hypersensitivity and autoimmunity, with some patients showing elevated IgA anticardiolipin and anti-β2-glycoprotein I antibodies [1, 14–16]. During flares, patients exhibit increased levels of pro-inflammatory cytokines, especially vascular endothelial growth factor (VEGF), tumor necrosis factor alpha (TNF-α), and interleukin (IL)-6 [1]. These cytokines enhance endothelial permeability, leukocyte extravasation, and vascular injury, contributing to systemic complications [1, 2, 14]. HSP typically presents with purpura, arthritis, abdominal pain, and renal involvement, which may progress to chronic kidney disease [1, 2, 13]. Although spontaneous resolution occurs frequently, glomerulonephritis remains a significant complication [1, 2, 13, 14].

While central nervous system complications are uncommon, increases in pro-inflammatory cytokines have been documented in systemic circulation, contributing to endothelial dysfunction [1, 2]. Studies in Wistar rats have shown that elevated homocysteine (Hcy) levels raise these cytokines in the brain, connecting vasculitic processes to neuroinflammation. Monocyte chemoattractant protein-1 enables monocyte migration across the blood-brain barrier, potentially increasing neurovascular damage.

Under specific conditions, HSP patients with high Hcy levels may face an increased risk of central nervous system involvement [1]. Hyperhomocysteinemia (HHcy) promotes endothelial dysfunction via oxidative stress, enhancing vascular inflammation. Elevated fibrinogen, von Willebrand factor, and D-dimer levels indicate the activation of coagulation pathways, corresponding to microvascular damage in HSP [1]. This hypercoagulable state may lead to increased microthrombus formation and organ ischemia [1, 17]. D-dimer and von Willebrand factor levels correlate with disease activity [1, 17], whereas the neutrophil-to-lymphocyte ratio and mean platelet volume serve as indicators of inflammation [17, 18]. While IgA1 deposition remains the primary cause [11, 12, 16], metabolic issues, such as HHcy may be significant in severe cases. Testing for Hcy and coagulation markers could help identify high-risk patients, and therapies targeting HHcy might offer benefits, although clinical trial evidence is limited [1, 14].

Hcy, derived from methionine demethylation, is crucial for folate and B-vitamin metabolism. Methylenetetrahydrofolate reductase (MTHFR) converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (5-MTHF), thereby enabling Hcy remethylation through methionine synthase (MTR). This process requires vitamin B_{12} as a coenzyme, which is maintained by methionine synthase reductase [19, 20]. Hcy converts to cysteine via cystathionine beta-synthase with vitamin B_6 [19, 21]. MTHFR C677T, MTR A2756G, or MTRR A66G polymorphisms, as well as vitamin deficiencies, can cause HHcy [20, 22, 23].

Hcy damages endothelial cells through oxidative stress and reduces nitric oxide production [20, 21]. HHcy enhances tissue factor expression and disrupts fibrinolytic balance [20, 21]. It causes DNA hypomethylation, which affects endothelial function [19, 21]. HSP features IgA1-dominant immune complex deposition and vessel injury [1, 2, 11, 12]. Patients show endothelial activation similar to that of HHcy [17, 18]. While no direct link exists between HHcy and HSP, the vascular effects of Hcy suggest its role in HSP complications. Elevated Hcy levels contribute to microvascular injury [20, 21], warranting metabolic screening in severe cases. B-vitamin supplementation reduces plasma Hcy levels [21, 23], although its impact on HSP remains unconfirmed.

Hcy is an intermediate amino acid in methionine metabolism, controlled by remethylation and transsulfuration pathways. The MTHFR C677T mutation reduces enzyme activity, particularly in individuals with the TT genotype, thereby elevating Hcy levels. Individuals with the TT genotype and low folate levels exhibit increased plasma Hcy levels [22, 23]. The MTR A2756G polymorphism affects enzyme efficiency and increases the risk of folate deficiency

[22]. Combined MTHFR C677T and MTR A2756G risk alleles can synergistically increase the risk of folate deficiency [22]. This genetic predisposition affects immune-mediated vascular disease. HSP is an IgA-mediated vasculitis that affects multiple organs, potentially leading to renal insufficiency [1, 2]. Its pathogenesis involves IgA immune complexes and vascular inflammation [1, 2, 11, 12].

While elevated cytokine levels are documented in HSP [1, 17], HHcy could worsen vascular injury. Hcy damages the endothelium, promotes oxidative stress, and disrupts vascular balance [19, 21]. Through epigenetic mechanisms, it affects the gene expression in vascular cells [19, 21]. Understanding MTHFR and MTR genotypes facilitates risk assessment, as these combinations increase the likelihood of complications, particularly in individuals with low folate levels [20, 22, 23]. Evaluating the relationships between genotype, metabolism, and clinical outcomes may help identify patients at high risk [12, 17].

The proposed treatment plan for HSP involves a methodical strategy based on disease severity, organ involvement, and symptom persistence. Current research supports this multidisciplinary approach, particularly in immune modulation, for resistant cases, and in supportive care. Supportive measures, including bed rest and dietary modifications, are used in acute HSP to reduce stress on the inflamed vessels and minimize immune triggers. These interventions are essential for children, who typically have self-limiting diseases, but are critical for those with significant gastrointestinal or renal involvement [2, 14].

Gastrointestinal capillaritis may require fasting and gut decontamination due to the risk of enteric bleeding or perforation. While evidence is limited, intestinal decontamination using non-absorbable antibiotics is warranted in cases of severe mucosal damage to prevent complications, especially in immunosuppressed conditions [2, 14]. These agents aim to reduce microthrombus formation and support vascular integrity. Clinical evidence for their effectiveness in HSP is lacking, except in severe cases. The literature supports the use of anticoagulation primarily for thromboembolic events or nephrotic syndrome, while antiplatelet agents are used without strong outcome data [1, 2]. Fibrinolytic agents and prostacyclin remain experimental and are based on case-based evidence.

Corticosteroids alleviate symptoms related to joint, abdominal, and skin issues and are prescribed for intense pain, gastrointestinal complications, or early-stage nephritis [1, 14]. However, randomized trials have shown that corticosteroids do not prevent the onset or progression, or alter the course of the disease in mild cases [1, 14, 24]. Medium-dose treatments with anticoagulant and antiplatelet measures are reserved for severe conditions. Plasmapheresis is used for rapidly advancing glomerulonephritis or severe systemic involvement requiring immune complex removal [25, 26]. Evidence suggests that it may reduce proteinuria and renal inflammation, although controlled trial data are limited [26].

Cyclosporin-A (CyA) has proven effective for treating HSP with significant nephritis that is resistant to corticosteroids. Studies have documented the resolution of nephritic syndrome and renal recovery following CyA treatment after initial treatment failure [1, 25, 27]. Its use is considered in both children and adults with ongoing proteinuria, hematuria, or nephrotic syndrome.

Rituximab (RTX), a monoclonal antibody targeting CD20, is effective in severe, treatment-resistant HSP cases with kidney and heart involvement [1, 28, 29]. It enables quick remission, reduces steroid use, and serves as an alternative when cytotoxic drugs are unsuitable; however, larger controlled trials are needed [29]. Mycophenolate mofetil is effective in treating steroid-resistant nephritis in children with severe kidney disease [1, 30].

Addressing HHcy with folic acid prevents this vascular damage. The multi-tiered HSP approach includes supportive care, immunomodulation, and metabolic management. CyA and RTX improve outcomes in resistant diseases [1, 25, 27–29]. However, treatments beyond supportive care lack strong evidence from randomized trials, requiring personalized treatment and multicenter studies [1, 24, 26].

HSP has complex causes, and studies have aimed to clarify how genetic and metabolic factors may worsen vascular inflammation and disrupt immune function. A key area of interest is HHcy, which is increasingly being considered a factor in endothelial damage through oxidative stress and epigenetic changes. These effects mirror the vascular issues found in HSP, suggesting a combined effect in individuals with genetic predispositions. While direct evidence linking HHcy to HSP onset remains limited, the vascular harm from high Hcy levels deserves investigation, especially in patients with severe symptoms.

Understanding the genetic basis of HHcy, including variations in MTHFR and MTR genes, is essential. These genetic differences can disrupt Hcy metabolism, leading to systemic buildup and inflammation. Research has linked the MTHFR C677T and MTR A2756G genotypes to elevated Hcy levels, particularly in individuals with inadequate

folate intake. This genetic tendency may affect treatment outcomes in patients with HSP when conventional therapies fail. Examining these gene polymorphisms, Hcy levels, and immune parameters could provide insights into disease variability and enable the development of tailored therapeutic approaches.

This study aimed to evaluate the level of Hcy in blood serum, polymorphism of the MTHFR C677T and MTR A2756G genes, and immunological parameters in patients with HSP.

2. Materials and Methods

This study involved 183 patients with HSP who were treated at the Hematology Department of the National Center for Oncology and Hematology under the Ministry of Health of the Kyrgyz Republic.

All patients underwent comprehensive clinical and laboratory evaluations. Diagnosis was established through clinical and laboratory assessments. Laboratory tests were performed using standard procedures. During the treatment phase, we analyzed the patients' complete blood count with platelet count, full urine analysis, blood biochemistry (including bilirubin and its fractions, alanine aminotransferase, aspartate aminotransferase, total protein, glucose, urea, creatinine, and lactate dehydrogenase), markers for viral hepatitis B and C, HIV, and a comprehensive hemostatic screening tests (covering platelet aggregation, prothrombin time, prothrombin index, international normalized ratio, thrombin time, activated partial thromboplastin time, fibrinogen, and soluble fibrin monomer-fibrinogen complex).

Among the specialized tests, we employed the following methods: 1. Cytokine analysis was performed using enzyme-linked immunosorbent assay kits (Quantikine ELISA Kits, R&D Systems, United States), 2. Two-color flow cytometry was used to evaluate CD4+ and CD8+ T cells, with antibodies sourced from eBioscience (California, United States), 3. Hcy measurement using an Enzyme-linked immunosorbent assay Kit (Homocysteine Enzyme Immunoassay Kit, Bio-Rad Lab, United States), 4. MTHFR and MTR gene analyses were conducted using real-time polymerase chain reaction.

Fasting venous blood samples were collected from patients to investigate the Hcy concentrations and genetic variations in the MTHFR and MTR genes. DNA was extracted using the phenol-chloroform method and ethanol precipitation. MTHFR C677T and MTR A2756G polymorphisms were genotyped using allele-specific real-time PCR with fluorescent probes. Genotype identification was automated using an ABI Prism 7500 Real-Time PCR System (Applied Biosystems, USA). Internal controls and duplicates ensured the precision of the results. Plasma Hcy levels were measured using an enzymatic cycling assay, with reference ranges standardized to the WHO guidelines. Patients were divided into subgroups based on Hcy levels and genetic polymorphism profiles for comparative analysis.

In addition to genetic and cytokine analysis, immunological assessments were performed to quantify circulating IgA immune complexes and examine B cell subsets. The measurement of these complexes used an ELISA-based technique for IgA. B-cell phenotyping of peripheral blood mononuclear cells via multicolor flow cytometry (BD FACSCanto II) identified naïve, memory, and IgA-producing B cells. To assess endothelial dysfunction, plasma von Willebrand factor, fibrinogen, and D-dimer levels were determined using immunoturbidimetry. Patients with elevated prothrombotic markers and cytokine levels were observed during and after treatment to evaluate outcomes. All procedures followed standardized protocols, and the equipment was regularly calibrated to ensure consistent results.

Combined treatment of patients with HSP: bed rest, then semi-bed rest, hypoallergenic diet, in case of gastrointestinal tract capillary damage–complete fasting with intestinal decontamination/sterilization using antibacterial drugs that are not absorbed in the intestine; basic therapy using anticoagulants, antiplatelet agents, fibrinolysis activators and prostacyclin; in cases of grades II and III activity of the autoimmune/immune complex process–steroid hormonal drugs in medium doses under the cover of anticoagulants, antiplatelet agents and therapeutic plasmapheresis sessions. In 12 cases of patients with severe and refractory HSP, immunomodulatory treatments such as CyA and RTX are used to manage the condition, reducing steroid dependency and securing prolonged remission. Patients with HHcy were simultaneously prescribed folic acid and folate complex preparations.

Statistical analysis of the study data was performed using Statistica v8.0 (StatSoft Inc., Tulsa, USA). Data are presented as n (%) or the mean ± standard deviation. The Student's t-test was used to assess any intergroup differences in characteristics that followed a continuous distribution. Statistical significance was calculated as follows: values of different groups of patients or $p < 0.05$ (*), patients compared to controls or $p < 0.01$ (**), group of patients

at different periods of treatment, or $p < 0.001$ (***). The study was conducted with the full consent of the patients' parents and was approved by the Bioethics Committee of the I.K. Akhunbaev Kyrgyz State Medical Academy (Protocol No. 32, dated April 12, 2022).

3. Results

In a study involving 67 patients, the patients were divided into two groups based on the localization of microvascular lesions: cutaneous-articular form of HSP (n = 38) and generalized form of HSP (n = 29). Serum cytokine analysis revealed that patients with the generalized form of HSP exhibited significantly higher levels of IL-6 and TNF-α than those in the control group and those with the cutaneous-articular form. The mean IL-6 concentration in generalized cases was 12.0 ± 0.093 pg/mL, whereas it was 7.9 ± 0.074 pg/mL in the cutaneous-articular group ($p < 0.001$). Likewise, TNF-α levels were substantially elevated at 7.2 ± 0.026 pg/mL compared to 5.8 ± 0.305 pg/mL ($p < 0.001$). Following treatment, there was a decrease in IL-6 and TNF-α levels by 10% and 18.3%, respectively, in patients with generalized HSP. However, IL-6 levels remained above the baseline, indicating ongoing inflammation in some patients (Table 1).

Table 1. Concentration of proinflammatory cytokines in patients with HSP during therapy.

	Groups	IL-1ß, pg/ml	IL-6, pg/ml	TNF-α, pg/ml
1.	Control (n=12)	4.9±0.045	6.4±0.008	4.5±0.078
2.	Cutaneous-articular form (n=38, before treatment)	6.8±0.016*	7.9±0.074**	5.8±0.305**
3.	Cutaneous-articular form (n=38, after treatment)	6.3±0.003	8.5±0.204	4.9±0.068
4.	Generalized form (n=29, before treatment)	10.4±0.107**	12.0±0.093**	7.2±0.026**
5	Generalized form (n=29, after treatment)	9.1±0.063*	10.8±0.036	5.9±1.002*

Note: Values are presented as the mean±standard deviation. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. IL-1ß = interleukin-1ß, IL-6 = interleukin-6, TNF-α = Tumor necrosis factor alpha.

Among the included patients, skin capillary lesions were observed in all patients, and 21 (11.4%) had atrophic ulcers. Joint issues, primarily affecting major weight-bearing joints such as the knees and ankles, were linked to microthrombosis in 86.8% of these cases. Gastrointestinal microvascular involvement, as indicated by symptoms such as abdominal pain and melena, was confirmed in 29 patients (15.8%).

Proteinuria and hematuria, indicating kidney involvement, were detected in 15 patients (8.1%), four of whom had diabetic nephropathy as an underlying condition. These patients exhibited more severe symptoms and slower responses to treatment. Among elderly patients over 70 years of age (n=21), comorbidities included chronic hepatitis (20%), diabetes mellitus (15%), cancer (10%), and osteomyelitis (5%). However, in half of these cases, no comorbidities were directly associated with the onset of HSP.

In a study involving 36 peripheral blood lymphocyte samples, flow cytometry revealed a reduction in CD4 and CD8 antigen expression in some of the patients. Notably, eight patients (22.2%) exhibited lower CD4 levels, and 11 (30.6%) had a marked decrease in absolute CD4 count ($p < 0.05$), suggesting a decline in helper T-cell activity. This immunological imbalance points to the potential involvement of compromised cellular immunity in the development and progression of the disease.

This study evaluated the Hcy metabolism of 80 patients. HHcy was identified in 54 patients, accounting for 67.5% of the total. Genetic testing showed that 66.6% of patients with HHcy had MTHFR C677T heterozygosity, while 7.4% were homozygous. In contrast, these genetic variations were present in 42.3% and 3.8% of patients with normal Hcy levels. MTR A2756G polymorphisms appeared in 44.4% of patients with HHcy and 38.4% of normohomocysteinemic controls, with one case of homozygosity in the HHcy group. These findings indicate a statistically significant link between these gene polymorphisms and increased Hcy levels ($p < 0.05$) (Table 2).

Subgroup analysis showed that patients with both elevated Hcy levels and MTHFR/MTR gene mutations often experienced more severe systemic symptoms, especially affecting the kidneys and causing persistent purpura, than those without. Additionally, patients with the homozygous MTHFR TT genotype had notably higher Hcy levels ($p < 0.01$) and showed greater resistance to standard treatments, frequently necessitating immunomodulatory therapies, such as CyA and RTX.

Table 2. Indicators of genetic abnormalities in patients with HSP.

	Genetic Polymorphism	Group of Patients with Normal HHcy in the Blood (n = 26)	Group of Patients with HHcy in the Blood (n = 54)
1.	MTHFR C677T homozygous	1 (3.8%)	4 (7.4%)
2.	MTHFR C677T heterozygote	11 (42.3%)*	36 (66.6%)*
3.	MTR A2756G homozygous	-	1 (1.8%)
4.	MTR A2756G heterozygote	10 (38.4%)*	24 (44.4%)*

Note: Values are presented as the n (%). *$p < 0.05$. MTHFR = Methylenetetrahydrofolate reductase, MTR = Methionine synthase, Hcy = Homocysteine, HHcy = Hyperhomocysteinemia.

In a group of 12 patients with severe, treatment-resistant HSP, CyA was used as an immunomodulatory treatment. These patients showed insufficient response to corticosteroids, skin ulcerations, worsening kidney issues, or disease flare-ups. CyA was administered at 3–5 mg/kg/day, with adjustments based on clinical response and serum creatinine levels. After four weeks, nine of the 12 patients showed significant clinical improvements, including the disappearance of purpura, decreased proteinuria, and stabilized kidney function. Three patients achieved partial remission, with reduced inflammatory markers, but continued low-grade proteinuria. Cytokine analysis revealed a 25% reduction in IL-6 and a 30% reduction in TNF-α levels ($p < 0.01$), indicating suppression of systemic inflammation. No major side effects, such as nephrotoxicity or hypertension, were observed during treatment. These results suggest that CyA could be a safe and effective alternative to steroids for managing severe HSP, especially in patients with immune-complex-driven kidney issues and high proinflammatory cytokine levels.

RTX was administered to five patients with severe, recurring HSP, characterized by widespread vasculitic skin lesions, kidney involvement, and poor response to corticosteroids and standard immunosuppressive treatments. These patients exhibited high serum levels of IL-6 and TNF-α, as well as abnormal B cell profiles, including increased circulating $CD19^+$ and IgA+ memory B cells, indicating a B cell-driven immune pathology. RTX was administered as two intravenous infusions of 375 mg/m^2, one week apart. Clinical response occurs within 2–3 weeks after the initial dose. Four patients experienced complete resolution of skin purpura and normalization of inflammatory markers, with significant decreases in serum IL-6 (from 12.4 ± 0.36 pg/mL to 6.1 ± 0.18 pg/mL, $p < 0.001$) and TNF-α (from 7.8 ± 0.24 pg/mL to 4.2 ± 0.16 pg/mL, $p < 0.01$) levels. One patient achieved partial remission, with stable kidney parameters, but continued to experience low-grade skin symptoms. No adverse effects, infusion reactions, or infectious complications were observed during the follow-up period. These findings suggest the potential of B-cell depletion therapy in refractory HSP cases with immunological dysregulation and systemic symptoms unresponsive to first-line treatments.

Categorizing patients based on genetic polymorphisms revealed patterns in cytokine expression and immune markers. Individuals with the MTHFR TT genotype showed higher Hcy levels and increased IL-6 and TNF-α levels, indicating a gene-environment interaction that intensifies inflammation. These patients had lower CD4+ T cell counts and increased IgA+ memory B cells, suggesting compromised cellular immunity and enhanced B cell-mediated immune complex formation. The combination of metabolic imbalance and immune dysfunction may contribute to severe outcomes, including renal complications and resistance to treatment.

Our findings indicate that metabolic and genetic screening can guide the treatment of patients with HSP. Folate supplementation in individuals with HHcy, especially those with risk genotypes, is associated with decreased Hcy levels and improved inflammatory markers. However, these improvements do not consistently lead to clinical remission, highlighting the need for personalized treatment. Patients with HHcy and abnormal immune profiles responded better to immunomodulatory treatments, such as CyA and RTX. These results demonstrate the benefits of genetic, metabolic, and immunological assessments in enhancing outcomes in HSP.

4. Discussion

This study examined HSP by exploring the interactions among genetic susceptibility, metabolic imbalances, and immune system malfunctions. The strong link between HHcy and MTHFR/MTR polymorphisms highlights a gene-environment interaction that worsens vascular inflammation and endothelial damage in patients with HSP. The irregularities in cytokine profiles, with heightened IL-6 and TNF-α levels, align with earlier studies indicating that inflammatory components are crucial for disease severity and treatment resistance [20, 21]. Further research

is needed to elucidate the role of HHcy in HSP vascular damage. These mechanisms include nitric oxide inhibition, immune-regulatory gene disruption, and oxidative stress pathways, all of which contribute to IgA-mediated injury. Analyzing cytokine profiles may provide insights into disease-specific immune patterns.

Patients with HSP show increased levels of proinflammatory cytokines, including IL-1β, IL-6, and TNF-α. The function of TNF-α is complex, with studies showing mixed outcomes when TNF-α inhibitors are used for HSP treatment. TNF-α is involved in cytokine production in HSP [31]. Patients with IgA nephropathy show elevated TNF-α, IL-1β, and IL-6 compared to healthy individuals, indicating the' role of cytokines in vascular damage [32]. IgA-containing complexes activate NF-κB, ERK1/2, and MEK/REK pathways, leading to neutrophil infiltration in HSP [33, 34]. Cytokine-induced chemokines cause glycocalyx shedding and increase the expression of cell adhesion molecules, promoting cell attachment to the vascular wall.

The results of this study revealed that individuals with the MTHFR TT genotype have increased Hcy levels and more intense inflammatory responses with higher proinflammatory cytokine levels. This aligns with research showing that genetic differences in Hcy metabolism genes can make individuals susceptible to HHcy, potentially causing vascular damage and severe HSP outcomes [22, 23]. The metabolic imbalance in our study group highlights the role of Hcy as an indicator and driver of disease activity. While folate supplementation improved inflammatory markers, these treatments did not consistently achieve full clinical remission, suggesting that metabolic management may only complement, rather than replace, immunomodulatory therapies.

Flow cytometry results showing decreased CD4+ T cell numbers and a modified B cell profile with increased IgA+ memory cells suggest compromised cellular and humoral immunity. This finding aligns with research associating immune imbalance with HSP pathogenesis [2, 3].

The positive response to immunomodulatory therapies, such as CyA and RTX, highlights the need for tailored treatment plans. In severe, treatment-resistant HSP, CyA and RTX alleviated symptoms and lowered proinflammatory cytokine levels. These findings support a personalized approach, where immunophenotyping and genetic screening guide therapeutic choices, especially in patients unresponsive to corticosteroid therapy. CyA reduces proteinuria and inflammatory markers [25, 26]. Similarly, RTX, by depleting B cells, has succeeded where B cell-mediated pathology predominates, resulting in rapid improvements in skin and kidney symptoms [28, 29].

This highlights the importance of tailored management for severe HSP through immunomodulatory therapies, such as CyA and RTX. CyA, a calcineurin inhibitor, has been effective in managing renal complications by reducing proteinuria and inflammatory markers when other treatments are ineffective. Studies on children with HSP nephritis have shown that CyA can induce rapid remission and improve renal histopathology through T-cell modulation, which disrupts immune-mediated glomerular damage in the pathogenesis of HSP nephritis [25–27]. The literature increasingly recognizes CyA as a promising treatment for steroid-resistant nephritis, alongside evidence that mycophenolate mofetil may benefit specific cases [1].

RTX, a monoclonal antibody targeting CD20+ B cells, has shown effectiveness in treating children and adults with HSP, particularly in cases where B-cell pathology is dominant or traditional treatments fail. Case studies have reported the resolution of kidney issues and severe extrarenal symptoms after RTX treatment. In cases where cyclophosphamide was unsuitable, RTX reversed cardiac complications, skin conditions, and nephritis, serving as the sole immunomodulatory therapy in some refractory cases [28, 29, 35]. These improvements coincide with decreased proinflammatory cytokine levels, which are crucial targets in refractory diseases.

Making broad recommendations is challenging due to the rarity of severe HSP and the reliance on case-based evidence. Adult groups show higher rates of persistent kidney and skin disease, with cases often resistant to standard treatments, necessitating alternatives such as CyA and RTX [36]. HSP involves immune dysregulation of T- and B-cells, with genetic variations affecting outcomes and the effectiveness of drugs [14, 24]. Identifying immune markers through immunophenotyping or genetic screening could inform treatment choices for patients unresponsive to initial corticosteroid therapy [14, 24, 26].

The positive effects of CyA and RTX in treating severe HSP support the use of immunophenotypic and genetic data to guide treatment. This aligns with recent insights into HSP pathogenesis and is suitable for patients with persistent proteinuria, major extrarenal complications, or those unresponsive to corticosteroids.

The C677T polymorphism in MTHFR exon 4 has been linked to reduced folate levels for methionine production [37, 38]. MTHFR genetic variations are associated with an increased risk of cancer. In Caucasians, the C677T variant increases the risk of breast cancer but shows no significant association with ovarian cancer [39].

The MTR A2756G gene polymorphism has been investigated for its role in HSP due to its impact on Hcy metabolism. MTR produces methionine synthase, which converts Hcy to methionine using 5-methyltetrahydrofolate and vitamin B_{12}. The A2756G variant causes an amino acid change (Asp919Gly), resulting in decreased enzyme activity and impaired Hcy clearance [40]. This study showed that 44.4% of HSP patients with HHcy had the MTR A2756G heterozygous genotype, versus 38.4% of those with normal Hcy levels, suggesting a gene–environment interaction.

The MTR A2756G polymorphism, particularly when combined with variants such as MTHFR C677T, could increase the risk of metabolic disturbances and vascular harm. Elevated plasma Hcy levels cause oxidative stress, disrupt endothelial nitric oxide production, and promote inflammation and thrombosis, which are factors linked to HSP-related vasculitis [41, 42]. The coexistence of Hcy-elevating genotypes and proinflammatory cytokines in this study patients suggests a complex pathophysiology. These findings support the inclusion of MTR A2756G screening in HSP risk evaluation, especially for severe cases. Further research is needed to understand the effects of these polymorphisms on HSP outcomes.

Biomarkers beyond traditional inflammatory mediators can enhance the prediction of HSP severity. Serum galactose-deficient IgA1 has been identified as a promising biomarker, with increased levels associated with nephritis in patients with HSP and IgA nephropathy [43, 44]. The patients with HSP nephritis had higher circulating galactose-deficient IgA1 levels than healthy individuals [44]. Additionally, urinary biomarkers such as neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 have shown early increases in patients with renal involvement, informing monitoring and treatment [45].

The gut microbiome may influence immune responses during HSP development. Dysbiosis has been associated with autoimmune and vasculitic conditions, including HSP. Changes were found in the gut microbiota of children with active HSP, showing decreased Bacteroides and increased Proteobacteria, indicating inflammation [46, 47]. These microbial changes can affect mucosal immunity and IgA production. Additionally, microbial metabolites, such as short-chain fatty acids, regulate T-cell differentiation and epithelial barrier function, suggesting that microbiome-targeted therapies (probiotics, prebiotics, or dietary changes) may offer a new approach for treating HSP.

These findings reveal the complexity of HSP, where genetic factors, metabolic disruptions, and immune irregularities affect disease severity and treatment efficacy. Including Hcy metabolism and immunological markers in clinical assessments can improve risk categorization and treatment strategies. While immunomodulatory drugs show promise in resistant cases, multicenter studies are needed to validate their safety and efficacy. Future research should explore the functional genomics of the MTHFR and MTR pathways, as well as examine the microbiota and epigenetic influences on immune responses. A personalized medicine approach based on genetic, metabolic, and immunological biomarkers can improve outcomes for this condition.

Previous or simultaneous treatments, such as corticosteroids, anticoagulants, or dietary changes, may have impacted the study results. These treatments can alter inflammatory markers, cytokine levels, and immune cell profiles, potentially complicating the observed associations between genetic polymorphisms and Hcy levels. Corticosteroids reduce the expression of IL-6 and TNF-α, which may partly account for the differences in cytokine levels among the patient groups. Likewise, administering folic acid to patients with HHcy may have mitigated Hcy-related endothelial dysfunction. As the treatments were neither randomized nor standardized, future controlled studies are necessary to separate pharmacological intervention effects from inherent genetic and metabolic factors in HSP pathogenesis.

5. Limitations

This study was conducted at a single location in Kyrgyzstan, limiting the applicability of the results to broader populations. Subgroup analyses of patients treated with cyclosporin A (n = 12) and rituximab (n = 5) were limited by small sample sizes, which reduced statistical power and increased the risk of selection bias. The cross-sectional design of this study prevents causal conclusions between HHcy, gene polymorphisms (MTHFR C677T and MTR A2756G), and clinical outcomes. Longitudinal research is needed to evaluate the temporal relationships and progression of HSP in terms of genetic and metabolic profiles. The study did not measure vitamin B6, B12, and folate levels, which limits the interpretation of gene–nutrient interactions. As these vitamins are essential cofactors in Hcy metabolism, their exclusion hinders the understanding of the metabolic contributions to HHcy and disease severity. The use of parametric tests may not be suitable for all datasets, particularly those without verified normality. No adjustments for multiple comparisons increased the risk of Type I error. Treatments, including CyA, RTX, and

folate supplementation, were neither randomized nor standardized, introducing confounding factors and limiting the attribution of clinical improvements to these interventions. The study lacked long-term patient follow-up for monitoring outcomes such as chronic kidney disease progression, relapse, or immunological changes. Thus, conclusions regarding treatment efficacy and prognosis remain provisional. Patients received various supportive and pharmacological treatments that may have influenced their immune markers and clinical responses. The lack of standardized treatment protocols complicates the attribution of outcomes to specific interventions.

6. Clinical Implications

This study provides key insights into the treatment of HSP, particularly in severe cases. The association between HHcy and MTHFR C677T and MTR A2756G gene polymorphisms suggests the inclusion of metabolic and genetic assessments in HSP diagnosis. Identifying patients with HHcy could help predict severe manifestations and guide early interventions. The observed immune dysregulation, including reduced CD4+ T cells and increased IgA+ memory B cells, indicates the value of immunophenotyping in treatment strategies. Patients with specific immune profiles may require customized immunomodulatory treatments rather than standard corticosteroids. The successful use of CyA and RTX in severe HSP demonstrates the benefits of immunotherapy, which effectively reduces cytokine levels and manages inflammation. Non-invasive biomarkers such as IL-6, TNF-α, and Hcy could help track disease activity and treatment response. These findings emphasize the importance of combining clinical, genetic, immunological, and metabolic data for comprehensive disease management, especially in adult patients prone to complications. These insights support the shift from empirical management to precision medicine for HSP treatment.

7. Recommendations

This study advocates for metabolic and genetic evaluations as part of HSP assessment. Measuring plasma Hcy levels and genotyping MTHFR C677T and MTR A2756G polymorphisms are recommended in severe cases. Hhcy and genetic variant detection enable early intervention with folate and B-complex supplements to reduce vascular damage. Flow cytometry analysis of CD4+ T cells and IgA+ memory B cells may reveal immune imbalances linked to disease severity, guiding the selection of immunosuppressive treatments. CyA and RTX should be considered early in patients with proteinuria or inadequate response to standard therapies. Follow-up should monitor inflammatory cytokines, Hcy, and coagulation markers of disease activity. A multidisciplinary team is vital for managing complex HSP cases. Larger studies are required to refine treatment strategies based on genotypes and biomarkers. Future research should explore therapeutic targets, including the microbiome and epigenetic regulation, and investigate the safety of CyA and RTX in diverse populations.

8. Conclusions

This study highlights the complex nature of HSP, demonstrating that genetic factors, metabolic imbalances, and immune system disruptions influence disease severity and treatment efficacy. A link was identified between HHcy and polymorphisms in the MTHFR C677T and MTR A2756G genes, particularly in patients with severe symptoms and poor treatment responses.

This study showed that patients with high Hcy levels and genetic variations displayed increased inflammatory reactions, with higher IL-6 and TNF-α levels and lower CD4+ T cell counts, supporting the role of HHcy in vascular damage and immune pathology. Immunomodulatory therapies, such as CyA and RTX, showed benefits in difficult cases by reducing proinflammatory cytokines and symptoms. While folic acid supplementation improved HHcy biochemically, it did not consistently achieve clinical remission, indicating that metabolic correction alone is insufficient in severe cases.

This study advocates for a precision medicine approach, recommending comprehensive assessments that include genetic testing, Hcy measurements, and immune profiling. Future longitudinal and multicenter studies are needed to confirm these findings and refine personalized therapeutic strategies for complex HSP forms.

Author Contributions

Conceptualization, O.D., and A.S.; methodology, R.S.; software, S.M.; validation, A.K., and K.S.; formal analysis, S.M.; investigation, O.D., A.S., R.S., A.K., and K.S.; data curation, N.U.; writing—original draft preparation, K.S., and N.U.; writing—review and editing, S.M. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Bioethics Committee of the I.K. Akhunbaev Kyrgyz State Medical Academy (Protocol No. 32, dated April 12, 2022).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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