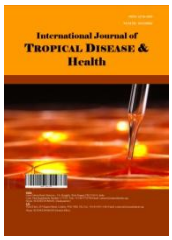

International Journal of TROPICAL DISEASE & Health

43(17): 14-20, 2022; Article no.IJTDH.90259
ISSN: 2278–1005, NLM ID: 101632866

Progress in the Treatment of Henoch-Schonlein Purpura in Children

Zhaoyu Yang [a], Jiemin Wang [b] and Fuyong Jiao [b*]

[a] Xi'an Medical College, China.
[b] Children's Hospital of Shaanxi Provincial People's Hospital, China.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2022/v43i1730657

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/90259

Review Article

Received 13 June 2022
Accepted 20 August 2022
Published 27 August 2022

ABSTRACT

Henoch-Schonlein Purpura (HSP) is the most common leukocyte fragmentary vasculitis with IgA immune complex deposition in childhood, which may affect capillaries, arterioles and venules in various systems of the body. Henoch-Schonlein purpura nephritis (HSPN) can be diagnosed when kidney damage occurs in children with HSP, which is the most severe complication of HSP. However, if the treatment of children with HSPN is delayed or recurrent, more than 20% of these children eventually develop chronic renal failure, seriously affecting the prognosis and quality of life of the children. Therefore, early diagnosis and treatment are crucial to the prognosis of children with HSP. This article reviews the treatment of HSP and HSPN.

Keywords: Henoch-Schonlein purpura; nephritis; treatment.

1. INTRODUCTION

HSP, also known as IgA vasculitis, [1] is one of the most common vasculitis in children. Its characteristic clinical manifestations are rashes, mainly distributed in the lower limbs and buttocks. The rashes are symmetrical, with different shapes and sizes, protrusion of the skin surface and non-discoloring under pressure. About 2/3 of children with HSP may develop paroxysms of colic (around the umbilicus or in the lower abdomen), blood in the stool, vomiting and other

**Corresponding author: Email: 3105089948@qq.com, 15083101256@163.com;*

gastrointestinal symptoms, but most of the abdominal signs are only mild tenderness, and a few children may develop more severe complications, such as intussusception, intestinal obstruction, intestinal perforation, and other acute abdominal complications. Joint swelling and pain can occur in about 1/3 of the cases, mainly involving the knee, ankle, elbow and other large joints, the lesions are transient. And generally will not lead to joint deformity. According to relevant domestic reports, about 30%-50% of children with HSP may develop kidney damage, [2] called HSPN, which is manifested as hematuria, proteinuria, or tubular urine, accompanied by increased blood pressure and edema. HSPN is a self-limited, benign disease, most of which will recover completely with correct and aggressive treatment, but still more than 20% of children with HSPN will eventually develop chronic renal failure if treatment is delayed or recurrent.

As for the treatment of HSP and HSPN, there is no unified plan at home and abroad, and the primary treatment includes the following aspects:

2. GENERAL TREATMENT

2.1 Rest

The acute phase should rest in bed, avoid extensive exercise and long-time lower limb ptosis, clinical symptoms within three months of remission, prohibition of vigorous exercise, the recovery period can be appropriate physical exercise.

2.2 Diet

Eat food that is easy to digest, and gradually add other kinds of food after the skin purpura and digestive tract symptoms are significantly reduced or the child's condition is completely recovered. The general order of food is given is grain, vegetable→fruit→pork, [3] and keep away from the allergenic environment. If the allergen of the child is not clear, the allergen test should be given.

2.3 Other

Vitamin C can be added to reduce vascular permeability and edema. In addition, attention should be paid to the amount of access to maintain water and electrolyte balance.

3. SYMPTOMATIC TREATMENT

3.1 Rash

Antihistamines and calcium should be given to children with HSP with urticaria or angioneurotic edema. Montelukast sodium can also be given orally, which can reduce vascular permeability and inflammatory response. Montelukast sodium may also play a role in promoting fibrosis in the pathogenesis of HSP [4]. In clinical treatment, more antihistamines and montelukast sodium combined application. According to the principle of randomized control, Lu Zhijian divided 96 children with HSP into two groups, both of which had received basic treatment. Montelukast sodium was added to the control group, and antihistamines and montelukast sodium were added to the observation group. The results showed that the observation group had shorter symptom disappearance time, lower recurrence rate, lower incidence of adverse reactions and higher safety [5].

3.2 Symptoms of Digestive Tract

A H2 receptor blocker, can not only inhibit gastric acid secretion, relieve digestive tract symptoms, but also enhance immunity. However, long-term or high-dose those medication can cause breast swelling and lactation, so it should be used with caution in adolescent and preadolescent male children [6]. The synthesis of coagulation factors Ⅱ、Ⅶ、Ⅸ、Ⅹ depends on vitamin K. The use of vitamin K in small doses has hemostatic effect, and the use of vitamin K in large dose can relieve the pain caused by gastrointestinal spasms. When gastrointestinal bleeding is obvious, strict fasting and intravenous nutritional support should be given.

3.3 Symptoms of Joint

When arthritis or joint pain, NSAIDs should be used on the basis of general treatment. When joint symptoms are more obvious and the above treatment effect is not good, hormones should be added.

3.4 Other

Children with helicobacter pylori (HP) infection may be treated with omeprazole in combination with two antibiotics. Chen Cheng randomly divided children with HSP positive into the

treatment group and the control group, and compared the two groups, the results showed that the abdominal pain symptoms of children with HSP in the treatment group treated with omeprazole, clindamycin and metronidazole were relieved faster and the recurrence rate was lower than those in the control group without those drugs [7]. The children with positive mycoplasma pneumoniae antibodies were treated with macrolide antibiotics. When accompanied by infection, sensitive antibiotic treatment is given. pneumoniae

4. TREATMENT OF HSPN

There is no unified protocol for the treatment of HSPN, which needs to be individualized according to its clinical classification and/or pathological grade.

4.1 Glucocorticoid (GC)

GC is not recommended when purpura is simple or accompanied by slight abdominal pain or joint pain. GC is a basic drug for the treatment of HSPN. It has strong anti-inflammatory effect and can effectively control the inflammatory response, relieve severe arthralgia, abdominal pain and other symptoms in children. It can also act on the glomerular basement membrane, reduce hematuria and proteinuria in children with HSPN, and protect renal function. However, its effect is limited, and massive long-term use of GC may lead to aggravation of infection, hypercoagulability of blood, osteoporosis, etc. In addition, GC cannot prevent the occurrence of kidney damage, shorten the course of disease in children with HSPN, or reduce the recurrence rate. Therefore, GC alone is not recommended at present, and GC combined with immunosuppressive agents is preferred for the treating of HSPN.

4.2 Immunosuppressor

4.2.1 Cytoxan (CTX)

GC combined with CTX shock therapy for HSPN is commonly used in clinical practice, and the curative effect is relatively positive. It has been reported that long-term use of CTX can increase the incidence of alopecia, gonad damage, hemorrhagic cystitis and other complications, it can also cause nephrotoxicity and myocardial damage when the dose more than 120mg/kg, so the use of CTX is restricted [8]. According to Liu Fengzhi, the cumulative dose of CTX in the treatment of HSPN children should not exceed 300mg/kg [9].

4.2.2 Mycophenolate Mofetil (MMF)

MMF is a new immunosuppressant that can selectively block the proliferation of B and T lymphocytes and rapidly inhibit the proliferation of macrophages and the formation of antibodies, thus exerting immunosuppressive effects [10]. Geng Haiyun et al. analyzed 68 patients with macroproteinuria (macroproteinuria: HSPN children with 24h urinary protein quantitative ≥50mg/kg or morning urinary protein/creatinine (mg/mg) ≥2.0 [11] were randomly divided into CTX group and MMF group. The treatment regimen of CTX group was MP+ACEI+CTX, and the MMF group was MP+ACEI+MMF. The complete response rate, response rate, urine protein turning negative time and adverse reactions were compared between the two groups, and the results showed that CTX and MMF had comparable efficacy and safety in the treatment of HSPN children with massive proteinuria [12]. However, MMF has the advantage of convenient administration and no gonadal damage compared with CTX.

4.2.3 Cyclosporin A (CyA)

CyA is a potent inhibitor. CyA combined with GC can treat refractory HSPN. It has also been reported that for children with nephrotic proteinuria who are resistant to prednisone, CTX and AZA at the same time, CyA can significantly reduce urinary protein [13]. CyA can not only lead to changes in glomerular structure and function, but also cause adverse reactions such as hepatotoxicity, nervous system lesions and gastrointestinal reactions. Time and dose of medication are related to the occurrence of adverse reactions, so the above side effects can usually disappear after dosage reduction or withdrawal.

4.2.4 Azathioprine（AZA）

AZA is a highly effective immunosuppressant, which produces immunosuppressive effects by inhibiting the proliferation of B and T lymphocytes. The main adverse reactions are bone marrow suppression and liver damage. AZA combined with GC is a common treatment for HSPN. Fotis et al. showed in a study that AZA+GC could effectively control the long-term symptoms of children with HSPN, while allowing earlier GC discontinuation without serious adverse reactions [14].

4.2.5 Tacrolimus (FK506)

FK506 is highly immunosuppressive and has a similar mechanism of action to CyA, but the immunosuppressive effect is 100 times stronger than CyA. In the treatment of children with HSPN, FK506 combined with GC is superior to CTX combined with GC, and the incidence of adverse reactions is lower [15].

4.2.6 Mizoribine (MZR)

MZR is a metabolic immunosuppressant that can inhibit cell proliferation in the lymphatic system [16]. Clinical studies have shown that MZR has mild gastrointestinal symptoms and bone marrow suppression, which is positively dose-dependent and sometimes leads to increased uric acid. Studies have reported that MZR combined with GC has a higher remission rate and a smaller incidence of adverse reactions in children with severe HSPN compared with CTX intravenouspercussion therapy [17].

4.2.7 Leflunomide (LEF)

LEF is an immunomodulator. A meta-analysis of LEF treatment for HSPN showed that LEF treatment for HSPN has certain advantages and is safer [18]. Another meta-analysis of LEF in the treatment of refractory nephropathy showed that the effectiveness of LEF was comparable to CTX and LEF had fewer adverse reactions [19]. The study of Zhang Miaoge et al showed that LEF had a significant effect on the disappearance of hematuria and urinary protein and the improvement of renal function [20].

5. RITUXIMAB (RTX)

RTX is a monoclonal antibody. It is now used to treat a variety of refractory and recurrent kidney diseases. Yin Jing et al reported 2 cases of refractoy IgA in children with recurrent rash, abdominal pain and gastrointestinal bleeding. High-dose hormone therapy was effective. Although immunosuppressants were also used, the symptoms of hormone reduction were repeated, and the symptoms disappeared rapidly after RTX administration, and hormone withdrawal was successfully stopped within two months and continued remission [21]. The sample size of this study is small, so how to select suitable IgAV patients for RTX treatment, the timing of RTX use, appropriate dose and course of treatment, and the impact on long-term prognosis need to be observed in a larger sample and for a longer period of time.

6. ANGIOTENSIN CONVERTING ENZYME INHIBITOR (ACEI) /ANGIOTENSIN RECEPTOR ANTAGONISM AGENT (ARB)

The main functions of ACEI and ARB are to dilate glomerular arteries, reduce glomerular pressure, protect renal function, prevent kidney damage, reduce proteinuria, relieve hypertension and edema. ACEI/ARB was routinely used for children with proteinuria [12].

7. ANTIPLATELET AGGLUTINATION DRUGS/ ANTICOAGULANTS

Antiplatelet agglutination drugs/anticoagulants Aspirin and dipyridamole can inhibit platelet adhesion and aggregation, and reduce the formation of coagulation and microthrombus. Dipyridamole is often used clinically. Low molecular weight heparin can not only reduce the hypercoagulability of children with HSPN, but also regulate the complement level and antagonize the type Ⅳ allergy mediated by immune cells [22]. Other studies have reported that the addition of thrombolytic urokinase therapy for severe HSPN can reduce glomerular lesions [23].

8. GAMMAGLOBULIN

GC combined with gamma globulin can significantly relieve gastrointestinal symptoms of children with severe HSP and reduce secondary kidney damage, with good long-term efficacy [24]. High-dose gamma globulin shock therapy can effectively relieve symptoms of HSPN children with hormone dependence or hormone resistance [25].

9. OTHER DRUGS

9.1 Hydroxychloroquine (HCQ)

HCQ reduces the damage of autoantibodies to human cells. A foreign clinical trial confirmed that could relieve the disease of children with HSP [26]. Due to its effectiveness, safety and extremely low cost, as well as its anti-thrombosis and anti-lipid disorders, it may be used as an immune modulator to treat HSP in the future, but its potential side effects on children with HSP need further study.

9.2 Dapsone

Dapsone is an anti-inflammatory drug, which can reduce the permeability of capillaries and provide a basis for the treatment of vascular inflammatory diseases. Dapsone can significantly reduce the expression of IL-6 and IL-8 in serum of children with HSP, and has a significant effect on regulating the cascade reaction of cytokines in serum, and has a significant therapeutic effect on children with HSP [27]. However, its specific side effects on children with HSP remain to be further studied.

9.3 Anisodamine (654-2)

654-2 can be used to treat refractory HSP. It is an M choline receptor blocker, which has the effects of relieving vasospasm, anti-septic shock, analgesia, etc. Clinically, other drugs combined with 654-2 are used to treat CHILDREN with HSP.

9.4 Alfacalcitol

Alfacalcitol is a calcium modulator that acts in the liver in the formation of 1, 25-(OH)2D3. 1, 25-(OH) 2D3 can regulate calcium and phosphate metabolism, promote bone mineralization, and regulate immune function and inflammatory response. Fu Qiang et al showed that the addition of alfacalccitol to children with HSP can increase the level of 1, 25-(OH)2D3 in serum, reduce the level of inflammatory factors in vivo and improve cellular immune function, and reduce the recurrence rate and the incidence of renal damage in children with HSP [28].

10. NON-DRUG TREATMENT

10.1 Blood Purification

Commonly used blood purification techniques include plasmapheresis (PE), hemoperfusion (HP) and hemodialysis (HD), which are mainly used for the treatment of HSPN children with acute nephritis or HSP children with severe complications. PE is to extract the blood from the body of children with HSP, and then separate the pathogenic components in the extracted plasma and discard them. Finally, the non-pathogenic components in the plasma and the supplemental albumin or balance liquid are transfused back to the body of children. The mechanism of action of HP is similar to that of PE, and compared with PE, HP can avoid the occurrence of blood infections and the loss of plasma components. HD uses the principle of semi-permeable membrane to complete blood purification, correct water and electrolyte disorders, and maintain acid-base balance. Studies have reported that HP combined with HD has a more significant effect on children with severe HSP [29]. Blood purification technology can rapidly relieve the symptoms of children, reduce proteinuria, alleviate kidney injury, and improve the long-term prognosis of children, but whether it can prevent and treat kidney injury remains to be supported by clinical evidence-based medical evidence.

10.2 Tonsillectomy

Tonsil is the first defense barrier of the human body. When stimulated by antigen, tonsil can stimulate B lymphocytes to produce IgA1, accelerate the deposition of IgA1 immune complex in the glomerular basement membrane, and renal damage function. Tonsillectomy can reduce pharyngeal infection, reduce hematuria and proteinuria, maintain the stability of renal function, and reduce the recurrence of the disease. This is surgical treatment, and clinical indications should be strictly grasped, especially for children with recurrent tonsillar infection who still have hematuria and proteinuria after routine treatment. Tonsillectomy should be performed after 2-5 weeks of local inflammation control. However, there is no clear conclusion about the effect of HSPN on tonsillectomy in children at home and abroad.

10.3 Kidney Transplantation

If kidney failure eventually develops, kidney transplantation may be used, but recurrence is still possible.

11. CONCIUSION

The treatment of HSP should be determined according to the severity of the disease and organ involvement. If the disease is mild, only symptomatic supportive treatment can be given. HSPN is the most serious complication of HSP. The treatment of HSPN depends on clinical classification and/or pathological grade. Effective treatment can significantly improve the prognosis of children with HSPN. GC is the basic drug for the treatment of HSPN, but it is generally not recommended to use it alone. GC combined with immunosuppressive agents is recommended for the treatment of HSPN. There are many types of immunosuppressive agents, which should be

selected according to the specific conditions of children in clinical practice. ACEI/ARB is a routine drug for children with proteinuria. In addition, RTX, anticoagulants, gamma globulin and other drugs and non-drug therapy, such as blood purification, tonsillectomy are also used to treat children with HSPN.

12. FUTURE PROSPECTS

Relevant clinical studies have proved that traditional Chinese medicine（TCM） treatment of children with HSP/HSPN can improve their immune function, reduce side effects caused by hormones and immunosuppressants, reduce their inflammatory response, and alleviate their hypercoagulable state [30]. But at present, there are still the following problems: the diagnosis and treatment norms of TCM clinical syndrome differentiation and therapeutic effect evaluation standard are not unified; There are many self-designed prescriptions by doctors, which is not conducive to clinical promotion. Therefore, it is suggested to reach a consensus on the basis of syndrome differentiation and treatment, and provide a standardized TCM diagnosis and treatment plan, so as to better promote and apply the characteristics and advantages of TCM treatment of this disease. At present, the evidence-based medical evidence on HSPN treatment is still relatively small. Given the relatively low incidence of HSPN, more large-sample, multicenter prospective studies need to be carried out.

FUNDING

(1) Shaanxi Province Key Research and Development Program in 2020 (International Cooperation) (Project No. 2020KW-052);
(2) Program of Shaanxi Province (International Cooperation Project . No.2022KW-13)

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Saulsbury FT. Clinical update. Henoch—schonlein purpura. Lan—cet. Lancet. 2007;369(9566):976-8.
2. Yamei H, Zaifang J, Kunling S, et al. Zhu Futang practical pediatrics [M]. 8th ed. Beijing: People's Medical Publishing House. 2015; 733-44.
3. Hailing X, Xiaoyu C, Liyan F et al. Clinical significance of dietary management in children with Henoch schonlein Purpura. Chin Med Sci. 2019;4:52-4,138.
4. Lu ZJ. Clinical efficacy and safety of montelukast sodium combined with loratadine in the treatment of pediatric allergic purpura. 2021;27(15):55-7.
5. Wu SH, Liao PY, Yin PL, Zhang YM, Dong L. Inverse temporal changes of lipoxin A4 and leukotrienes in children with Henoch-Schonlein purpura. Prostaglandins Leukot Essent Fatty Acids. 2009;80(4):177-83.
6. Immunology Group, Pediatrics Branch, Shanghai Medical Association. Expert consensus on the clinical use of immunomodulators in children (Shanghai). Chin J Clin Pediatr. 2018;33(9):651-64.
7. Cheng C, Guodong Ouyang, Changfu G. Efficacy of sequential therapy against Helicobacter pylori in children with Henoch schonlein Purpura abdominal type. Chinese modern medicine application. 2014;8(7):177-8.
8. Santeusanio AD, Menon MC, Liu C, et al. Influence of patient characteristics and immunosuppressant management on mortality in kidney transplant recipients hospitalized with coronavirus19（COVID）. Clin Transpl. 2021;18(47):236-9.
9. FENGzhi L. Value analysis of high-dose cyclophosphamide and methyl-rednisolone in the treatment of allergic purpura nephritis. Electron J Cardiovasc Dis Integr Trad West Med. 2018;6(19):181.
10. Dan YU. Nephrology DO, hospital WC. Clinical efficacy of mycophenolate mofetil combined with low-dose hormone in the treatment of minimal change nephrotic syndromes. Chin J Pharmaceu Econo. 2019;12(17):236-9.
11. Nephrology Group, Pediatrics Branch of Chinese Medical Association. Evidence-based guidelines for the diagnosis and treatment of common kidney diseases in children (-): diagnosis and treatment of hormone-sensitive, recurrent/dependent nephrotic syndrome Evidence-based Guidelines (Trial). Chin J Pediatr. 2009; 47(3):167-70.
12. Haiyun G, Chaoying C, Huarong L et al. Mycophenolate and cyclophosphamide in the treatment of children with proteinuria type allergic purpura nephritis: a prospective randomized controlled study. Chin J Curr Pediatr. 2021;23(4):338-42.

13. Nephrology Group. Pediatrics Society of Chinese Medical Association. Evidence-based guidelines for diagnosis and treatment of Purpura nephritis (2016). Chin J Pediatr. 2017;9(55):647-50.
14. Fotis L, Tuttle PV, Baszis KW, Pepmueller PH, Moore TL, White AJ. Azathioprine therapy for steroid-resistant Henoch-Schönlein purpura : A report of 6 cases. Pediatr Rheumatol Online J. 2016; 14(1):37.
15. Juan Y, Yumei Z, Lijun Z. Clinical observation of low-dose prednisone combined with tacrolimus in treatment of children with Henoch-schonlein purpura nephritis. Chin Pharm. 2019;22(11):2055-7.
16. Qiang Y, Weiguo S, Hequn Z. New progress in clinical application of immunosuppressive imizolibin. Int J Urol. 2008;28(03):418-21.
17. Liangzhi L, Lei L, Xianhong H et al. Treatment of severe allergic purpura nephritis with mizolibin: a clinical observation of 21 cases. Chongqing Med Sci. 2010;39(14):1904-6.
18. Jinyu N, Hanfang Z, Bing LI, Wensheng Z. Leflunomide in the treatment of Purpura nephritis: A meta-analysis. 2020;24(6) :1061-6.
19. Fei W, Shunjin H, Hongyu W, et al. A meta-analysis of leflunomide and cyclophosphamide in the treatment of refractory nephrotic syndrome. Anhui Med. 2018;22(6):1182-6.
20. Gemiao Z, Jianjun C, Qiwei F. Clinical observation of leflunomide in the treatment of children with Henoch-Schonlein Purpura nephritis. Chin Med Clin. 2015;15(11) :1616-8.
21. Gong Q, Li Q. Clinical study of gamma globulin in the treatment of severe abdominal allergic purpura in children. Mod Digest Interv Ther. 2016;21(5):738-40.
22. Jing Y, Qianqian Z, Jijun M et al. Rituximab in the treatment of refractory immunoglobulin A vasculitis in children: two cases. Chin J Rheumatol. 2021; 25(12):823-6.
23. Ohara S, Kawasaki Y, Miyazaki K, Ono A, Suzuki Y, Suyama K et al. Miyazaki K eta1. Eficacy of cyclosporine A for steroid—resistant severe Henoch-Schonlein purpura nephriris. Fukushima J Med Sci. 2013;59(2):102-7. doi: 10.5387/fms.59.102, PMID 24500387.
24. Yao Y. Application and dose analysis of low molecular weight heparin calcium in the treatment of children with Purpura nephritis. Syst Med. 2018;3(14):87-9.
25. Liping X, Xu C, Yi J. Therapeutic effect of gamma globulin shock therapy on children with abdominal allergic purpura. Chin J Contemp Pediatr. 2016;18(10):988-90.
26. Casian A, Sangle S, D'Cruz DP. New use for an old treatment: hydroxychloroquine as a potential treatment for systemic vasculitis. Autoimmun Rev, 2018, 17. p. 660-4.
27. Zhijuan D. Clinical observation on the effect of dapsone on serum IL-6 and IL-8 in children with Henoch schonlein Purpura. China's Med Front. 2010;5(16):55-6.
28. Qiang F, Mingfang S, Ying C. A prospective randomized controlled study of alfacalccitol in the treatment of children with Henoch purpura. Chin J Contemp Pediatr. 2021;23(8):797-801.
29. Xin-Ying H, Yun X, Hui-ling X. Nursing experience of hemoperfusion tandem hemodialysis in treatment of severe allergic purpura in children. Pract Clin Med. 2009;10(4):122-6.
30. Lei S, Bo P, Linjie X et al. Research progress of traditional Chinese medicine in the treatment of Henoch-schonlein purpura nephritis in children. Chin J Trad Chin Med (Formerly Chin Med J). 2019;34(2):708-10.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/90259