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Review Articles

Henoch-Schönlein Purpura Nephritis in Children: A Review

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Abstract:

Henoch-Schönlein purpura (HSP) is a systemic disorder which involves multiple organs including kidney. The characteristic pathology is leukocytoclastic vasculitis of the capillaries with deposition of IgA immune complexes. The principal cause of morbidity and mortality in this disease is due to renal involvement. Approximately half of the children with HSP develop nephritis (HSPN) within 4-6 weeks of initial presentation and HSPN is a major cause of end stage renal disease (ESRD) in children. So, it is important to be updated about aetio-pathogensis, clinico-pathological aspects and prognostic factors of nephritis related to Henoch Schonlein purpura. The most important is to identify the appropriate treatment options for HSPN. So, herein review has been done on the different aspects of HSPN including treatment.

Key words: *Henoch- Schönlein purpura, Nephritis, Children, Urokinase, Mycophenolate Mofetil, Mizoribin.*

Introduction:

Henoch-Schönlein purpura (HSP) is a small vessel vasculitis, the major manifestations of which include arthritis, non-thrombocytopenic purpura, abdominal pain and glomerulonephritis. It is one of the most common vasculitides of childhood and is considered to be self-limiting. But the renal involvement can result in life long problems.[1] Approximately 40%-50% children with HSP develop nephritis (HSPN) within 4-6 weeks of the initial presentation of which 1% to 17% progress to renal failure or end stage-renal disease (ESRD) .[2-6]

HSP nephritis accounts for 5.1% of children with ESRD in Europe.[4] The manifestations of HSPN includes microscopic or macroscopic haematuria, mild or heavy proteinuria with or without nephrotic syndrome, renal failure and hypertension.[4] The renal lesion of HSPN is characteristically a focal and segmental proliferative glomerulonephritis. A broad correlation exists between the clinical presentation and the histological changes on renal biopsy. Those with haematuria without significant proteinuria which encompasses majority of children have generally less severe histological changes, which mostly undergo spontaneous remission. But patients with massive proteinuria, with persisting nephritic or nephrotic syndrome are likely to have severe histological changes and usually show progressive course. In a few children nephritis may not occur until late in the disease and ESRD may appear a number of years later.[2-5] It is therefore important to be updated about the different aspects of the HSPN including presentation, histology and particularly management. Herein we review the literature on the different aspects of HSPN with particular emphasis on the management.

Epidemiology:

Gardner-Medwin *et al.* reported a large population based survey from a multi-ethnic region of UK and estimated the annual incidence of HSP in United Kingdom 22.1 per 1,00,000 children.[4] A greater incidence was found in children from Indian subcontinent(24per 100000).[4] The estimation done by other investigators previously was lower and it was 13.5 – 18.0 per 1, 00,000 population.[5,6]

Nephritis is a predominant feature of HSP and it develops 20%-55% children with HSP.[7] Follow-up urinalysis for one year showed the increased incidence

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of involvement.[7] The incidence of nephritis related to HSP was 2.7 cases per 1,00,000 population in the study done by Stewart et al.[5] In Asian children the incidence is higher and reported as 4.9 cases per 1,00,000 children per year. In a recent study from Japan the incidence of HSPN was 3.6 ± 1.0 per 1, 00,000 populations.[8] In the Italian registrar of renal biopsies the prevalence of nephritis due HSP was 11.6% of all the renal biopsies.[9]

Etio pathogenesis:

The pathogenesis of HSPN is still unclear. Recurrence of the HSPN in some patients after renal transplantations made postulation that it may be a systemic immune-complex mediated disease.[10] Elevated serum levels of IgA1 and deposition of IgA1 containing immune deposits in the capillaries of glomerulus, skin and GI tract is suggestive of involvement of immune system.[11,12] Most popular hypothesis is increased production of polymeric IgA1 by the mucosal immune system in response to a mucosally presented antigen such as bacteria, viruses or fungi as probable mechanism for the development of HSP.[13] One of the characteristic of IgA1 is the presence of an 18 amino acid long hinge region between complement fixing regions 1 and 2. The majority of these amino acid serine and threonine have elaborated sugar chains, connected through sugar chains (o-glycosylation). This process thought to stabilize the IgA molecule and make it less prone to proteolysis. In HSP and IgA nephropathy these sugar chain appear to be deficient. The exact reason for the abnormality is unknown.[14]

The Gd-IgA 1 immune-complex in the mesangial areas activates a complement pathway like alternate or lectin pathways.[15] Deposition of C3 and properdin suggests alternate pathway activation whereas recently others found complement activation through lectin pathway.[16,17] Moura et al suggested that the Gd-IgA 1 immune-complex in the mesangial areas activates mesangial cells which results in the proliferation of cells, such as macrophages and lymphocytes and the production of inflammatory cells and profibrogenic cytokines and chemokines, suggesting a pivotal role in mesangial cell proliferation, matrix expansion and inflammatory cell recruitment.[18]

Manifestation:

The manifestations of nephritis secondary to HSP may occur at any time of the disease process and include isolated microscopic or macroscopic hematuria, mild or heavy proteinuria with or without nephrotic syndrome, renal failure and hypertension.[19] The frequently found feature is microscopic hematuria which was found in 80% cases within 4 weeks of onset of the disease but it may occur later in the disease. Gross hematuria may present in few cases. The most severe form is acute nephritic syndrome which may lead to nephrotic syndrome or renal insufficiency.[19-21] Such type of features are not common and particularly found in referral centers. Recurrences of nephritic features are common and particularly found in severe renal involvement. Meadow et al found that 26% child with HSPN had relapse 2 months later.[22]

The urinary abnormalities detected in a cohort of 666 children showed varying degrees of hematuria, proteinuria and in combination.[23-27] [Figure-1]

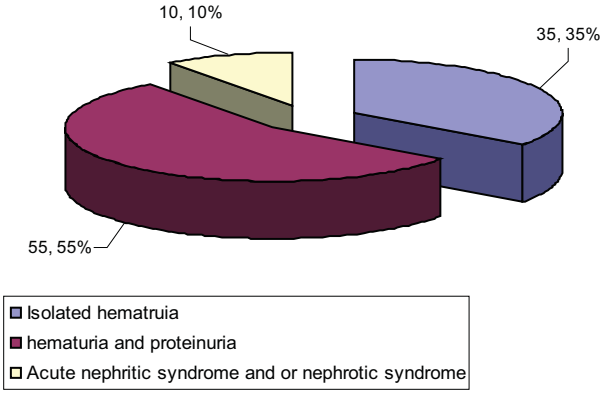

Fig.-1

Diagnosis:

No simple laboratory tests is available for the diagnosis of HSPN. Diagnosis is usually done by clinical manifestations related to renal involvement with typical skin rash(palpable purpura particularly on the extensor surfaces of the lower limbs, arms and buttock), arthralgia or arthritis and abdominal pain. Routine urinalysis, electrolytes and renal functional status are done on regular basis to see the extent and severity of renal involvement. Immunological investigations including complement levels and anti-nuclear anti bodies are normal. The IgA level is elevated in 50%-70% cases, and a small number show ANCA positivity. Platelet count is in the normal range and the activity of clotting factors is normal. Abnormalities and low levels of fibrin stabilizing factor (Factor XIII) have been reported, in addition increased Von Willebrand factor plasma level indicating an endothelial damage that favours fibrin deposition and crescent formation.[28]

Renal biopsy is considered in cases with[19]

- Nephritic/nephrotic presentation(urgent)
- Impaired renal function(GFR<80ml/min/1.73m^2 estimated by Haycock-Schwartz formula)
- Nephrotic range proteinuria(>250mg/mmol)
- Significant hypertension
- Plasma albumin <2.5gm/l
- Persistently abnormal urinalysis after one year

Renal Pathologic changes of HSPN :

The renal lesion in HSPN is characteristically a focal and segmental proliferative glomerulonephritis.

Immunofluroscence:

Most striking feature is widespread granular deposits of IgA and to a lesser extent, IgG or IgM. The mesangial deposition of C_3 and properdin found in 75%-85%.

% cases and less frequently C1q and C_4. Fibrin deposition is found in 60%-70% cases.[1-6]

Light microscopy:

The characteristic features of the disease is mesangial damage with different grades of hyper-cellularity ranging from isolated mesangial proliferation to focal segmental glomerulosclerosis (FSGS) and severe crescentic glomerulonephritis(GN).[29] Classification of HSPN are mostly based on the severity of proliferative lesion.[3,22] The international study of kidney diseases (ISKDC) classification of HSP was origanlly devised by Meadow et al and adopted in a modified form by the ISKDC. [Table-I].

Table-I

ISKDC histological classification of Henoch-Schönlein purpura nephritis[3]

I	Minimal alterations
II	Mesangial proliferation
IIIa	Focal proliferation or sclerosis with <50% crescents
IIIb	Diffuse proliferation or sclerosis with <50% crescents
IVa	Focal mesangial proliferation or sclerosis with 50-75% crescents
IVb	Diffuse mesangial proliferation or sclerosis with 50-75% crescents
Va	Focal mesangial proliferation or sclerosis with >75% crescents
Vb	Diffuse mesangial proliferation or sclerosis with >75% crescents
VI	Membranoproliferative-like lesion

Clinico-pathological correlation and prognosis:

HSP is a self-limiting disorder. Recurrence of symptoms like rash, arthralgia, gastrointestinal symptoms and hematuria may occur for several months to years after the initial episode.[27] However the long term morbidity associated with HSP was due to associated nephritis. Patients with grade II and IIIa histological findings tend to have better outcome with return to normal renal function or persistent microscopic hematuria and proteinuria. Whereas patient with grade IIIb, IV and V have persistent proteinuria and hematuria or progress to terminal renal failure. A few patients develop rapidly progressive renal failure accompanied by exuberant crescent formation.[29]

The longterm renal outcome of patient with HSPN (Study done by Coppo et al at Italy) showed out of 57 children 32 went to complete remission, 26 had mild proteinuria, 17 had moderate proteinuria, 3 had nephrotic range porteinuria, 12 had moderate CRF, 6 had severe CRF and 7 patient needed dialysis[29] (Figure-2)

A Series of patient study conducted by Meadow et al showed that at 2 years or more after diagnosis of HSPN 55% were entirely normal, 22% had residual urinary abnormality but with normal GFR, 10% had both abnormal urine sediment and reduced GFR and 8% had severe reduction of GFR receiving dialysis or had died of renal failure.[22]

Another long term follow-up study (1974-1997) done by Kawasaki et al which included 114 patients with HSPN.[20] Patients were divided into two groups based on the severity of the disease and designated as “favorable” and “unfavorable”.The different parameters like clinical features, laboratory data and pathological findings (TableII) showed that nephrotic syndrome, decreased factor XIII activity, hypertension and renal failure at onset were significantly higher in unfavorable group than the favorable group. Also the histological type Vb and VI were significantly higher in the unfavorable group and type II in the favorable group. Among the total 114 patients including both favorable and unfavorable group, 5 developed renal failure and the renal survival rate for 15 years or over was 95.6%.[20]

Table-II

Comparison of clinical manifestations, laboratroy data and pathological findings at onset in both groups.[20]

		"Favorable" (*n*=94)	"Unfavorable" (*n*=20)	
Clinical manifestation				
Purpura	114(100%)	94 (100%)	20 (100%)	NS
Abdominal pain	29 (25%)	23 (24%)	6 (30%)	NS
Arthralgia	11 (10%)	8 (9%)	3 (15%)	NS
Quincke edema	9 (8%)	7 (7%)	2 (10%)	NS
AGN	9 (8%)	3 (3%)	6 (40%)	*p* <0.01
NS	17 (15%)	9 (10%)	8 (60%)	*p* <0.01
RPGN	4 (4%)	0 (0%)	4 (25%)	*p* <0.05
School urinary screening	4 (4%)	4 (4%)	0 (0%)	NS
Intussusception	1 (1%)	1 (1%)	0 (0%)	NS
Laboratory data				
Proteinuria (mg/m^2/h)		58 (71)	146 (104)	*p* <0.05
Hematuria		92 (98%)	20 (100%)	NS
Serum albumin (g/dl)		36 ± 10	26 ± 8	*p* <0.05
Serum creatinine (mg/l)		4.9 ± 2.8	8.8 ± 5.0	*p* <0.05
24-h creatinine clearance (ml/min/1.73 m^2)		96.9 (29.9)	70.8 (20.4)	*p* <0.05
Mean blood pressure (mmHg)		80 ± 10	93 ± 14	*p* <0.05
ISKDC classification				
Type II		31 (33%)	0 (0%)	*p* <0.05
Type IIIa		24 (26%)	1 (5%)	NS
Type IIIb		21 (22%)	6 (30%)	NS
Type IVb		16 (17%)	7 (35%)	NS
Type Vb		2 (2%)	3 (15%)	*p* <0.05
Type VI		0 (0%)	3 (15%)	*p* <0.01

NS = not significant

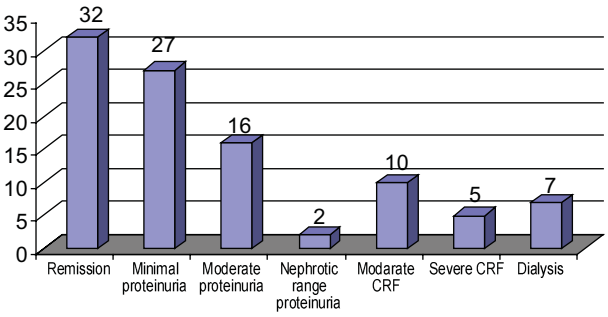

Fig.-2:

Differential diagnosis: The differential diagnosis of HSPN includes other vasculitis like systemic lupus erythematosus(SLE), polyarteritis nodosa(PAN), wegener's granulomatosis, hypesensitive vasculitis and sepsis particularly meningo-coccal septicaemia**.**[19]

Relationship of HSPN and primary IgA nephropathy: The main reason for searching relationship between these two entities is due to indistinguishable renal pathology.[23] Both share similar disturbances in the IgA system and both have high levels of circulating IgA particularly presence glycosylated IgA1. In a French nation survey on 40 families with two or more members affected by primary IgA nephropathy, five had members presented with complete HSP syndrome, confirming a possible genetic link between the two diseases.[30]

Treatment of HSPN:

Mild cases with HSP don't require any treatment provided regular monitoring for urine abnormality is ensured. However, attempts have been made to prevent the involvement of kidney in HSP cases with varying results.[31-34] Meta-analysis of four RCTs that

evaluated prednisolone therapy at the presentation of HSP was not significantly different from that with placebo or non-specific treatment.[35] but other recent studies verified these results and suggested the benefit of steroid administration in HSPN.[36,37] A recent systematic review of reported out comes by Niaudet *et al.* compared the children with HSP who were treated at diagnosis with corticosteroid with those of supportive care only and the conclusion was , it seem to be effective to prevent renal involvement if corticosteroid given early in the course of illness.[38]

When the kidneys are already involved it is possible to wait for spontaneous remission or to start therapy. A majority of patients with HSPN with mild symptoms do not require steroid therapy and usually managed symptomatically.[31]

Steroid therapy: Initially treatment with oral corticosteroid were believed to be ineffective based on the retrospective study by Counahan R *et al.* decades ago[3] subsequent studies showed that the result of treatment with oral prednisolone in moderate to severe nephritis was optimistic and there was significant improvement of histopathology ,clinical features and outcome[38,39] Niaudet *et al.*[38] reported that meyhyleprednisolone [MP] is effective in patients with risks of progression of the disease. Clinical manifestation and prognosis was observed in 56 children by Kawasaki *et al.* who received MP and urokinase pulse therapy and showed significant improvements of proteinuria after 6 months and significant decrease in disease activity index in all the 27 patients who underwent second renal biopsy.No patient showed any renal insufficiency and renal survival rate was 100%.for years.[40]

Multi-drug therapy: Nephrotic range proteinuria and crescents in>50% of glomeruli were mostly associated with poor outcome. So, it is important to halt the progression of the disease with efficient immunosuppressive therapy. Shenoy *et al.* found 15% patients progressed to ESRD and persistent renal abnormality with daily steroid and cyclophosphamide for 8-12 weeks followed by azathioprine and alternate day steroid for 8-12 weeks in severe form of HSP nephritis.[41] Good results obtained from more aggressive therapeutic regimen consisted with 3 Methyl Prednisolone(MP) pulses followed by 6 months course of prednisolone, depyridamole and 3 month course of cyclophosphamide with >60% complete remission by Oner et al.[42] Other reported studies with multi drug therapy supported this result.[43-46] The randomized controlled study by Kawasaki et al. showed combination of MP + urokinase pulses with cyclophosphamide was more effective than MP+urokinase pulses without cyclophosphamide in patients with>50% crescents.[47]

Cyclosporin A is also effective in association with steroids in reducing proteinuria in HSP patients with heavy proteinuria and improvement of follow up biopsy findings though it itself is a nephrotoxic drug.[48]

Recent trials with mycophenolate Mofetil(MMF) along with prednisolone in HSPN showed positive results. So, MMF might be useful in inducing remission and may be used as steroid sparing drug in the treatment of HSPN.[49-52] Further large scale studies are needed to establish this results. Other combination therapies such as MP+urokinase+Mizorabin was effective in ameliorating proteinuria and the histological severity of HSPN in patients with<50% crescents but not effective with>50% crescents.[53]

Plasmapheresis(PP): There are number of reports about PP for HSPN.[53-55] The retrospective study done by Hattori et al. showed that PP sole therapy was effective in improving the progression of rapidly progressive nephritis in HSP.[53] Other study by Kawasaki et al. showed PP with MP pulses, Urokinase pulses, oral prednisolone, dipyridamole and warfarin had convincing result on rapidly progressive HSPN.[47]

Tonsillectomy: Tonsillectomy thought to be effective for treatment of HSPN keeping in mind to limit the mucosal immune response.[56] Some studies have reported that tonsillectomy was effective for patients with severe HSPN.[57-58] But the overall analysis did not support the recommendation.

Other treatment options: Benefits of use of IVIg or leukocytapheresis are anecdotal and are not well established yet.[59-61] Further large scale studies are needed.

Follow-up:

- Isolated haematuria or haematuria and mild proteinuria at least two years afterl urinalysis become normal(?lifelong)
- Nephrotic, nephritic or nephritic- nephrotic presentation needs life-long follow-up as there is significant risk of renal impairment in the long term. [19]

Transplantation: HSPN may recur after transplantation.[62,63] Recipients of Living related donors face increased risk of recurrence. Meulders et al. reported the risk of recurrence and graft loss due to recurrence was35% and 11% respectively at 5 year post transplant.[61]

Conclusion:

HSPN is the most severe and fatal complication of HSP. So, in this review article emphasis has been given to the latest update of the different aspects of HSPN including aetio-pathogenesis, clinico-pathological correlation, prognostic factors and treatment options. Though there are scarcity of RCTs, it is suggested that early diagnosis and therapeutic intervention can prevent long term morbidity like ESRD. Multi- drug therapy with M-P pulses, prednisolone , cyclophosphamide with newer drugs like Urokinase, MMF and Mizoribin can prevent to some extent the progression of the disease in rapidly progressive HSPN. Although the large RCTs for the treatment of moderate to severe nephritis are still pending.

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