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REVIEW

Clinical practice:

Diagnosis and management of Henoch–Schönlein purpura

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Abstract Henoch–Schönlein purpura (HSP) is the most common vasculitis of childhood. In this review, the main clinical features and complications are described. Although most features are self-limiting, renal disease is the most likely to result in long-term morbidity. Treatment of HSP nephritis is controversial, and the evidence for both prevention and treatment of established disease is reviewed. Follow-up for children presenting with HSP should be for at least 6 months and should include regular urine testing for proteinuria and haematuria and a blood pressure measurement. Women with a history of HSP during childhood are at increased risk of complications (such as proteinuria and hypertension) during pregnancy and should be monitored closely. This paper describes current practice with regard to investigation and management and proposes a practical care pathway of the management of a child with HSP.

Keywords Purpura · IgA · Glomerulonephritis · Intussusception · Corticosteroids · Treatment

Introduction

In 1802, William Heberden (of Heberden's nodes) published a 5-year-old boy with oedema, arthralgia, haematuria, abdominal pain with melaena and 'bloody points' over his legs [16]. Later, in 1837, Johann Schönlein described the association between arthralgia and purpura. His former pupil, Eduard Henoch, went on to recognise gastrointestinal (GI) and later renal involvement in this syndrome, and thus, it acquired the title of Henoch–Schönlein purpura (HSP) [17].

HSP is the most common vasculitis in childhood and affects the small vessels. Its course is often self-limiting although may manifest long-term renal morbidity. The clinical features are now well-recognised; however, there remains uncertainty about the pathogenesis, and there is a lack of consensus about treatment and optimal follow-up for HSP. This article will describe current clinical practice and propose a practical care pathway.

Epidemiology

HSP can affect all age groups but most commonly children between 2 and 6 years of age [1, 13]. The incidence in children is reported as between 10.5 and 20.4/100,000 children per year [5, 13]. The latter is from a comprehensive study in the UK with information collected from primary and secondary care. The incidence was highest in the 4–6-year age group, with up to 70.3/100,000 per annum [13]. There is a slight male preponderance of 1.2:1, with a lower incidence in black children compared with white or Asian [13].

Diagnostic criteria

In 2006, the European League against Rheumatism and Paediatric Rheumatology European Society published a new classification of childhood vasculitis, which superseded the 1990 American College of Rheumatology classification of HSP [27].

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Diagnosis of HSP (EULAR/PReS consensus criteria)

Palpable purpura (essential) in the presence of one of the following:

- Diffuse abdominal pain
- Any biopsy showing predominant IgA
- Acute arthritis/arthralgia
- Renal involvement defined as any haematuria or proteinuria.

Clinical features

The rash of HSP is classical; however, it is not always the primary sign or presenting complaint. Joint involvement and/or abdominal pain precedes the rash in 30–43% of patients by up to 14 days, which may prohibit accurate diagnosis at this stage [4, 35]. The spectrum of clinical features is shown in Table 1 (Figs. 1, 2, and 3).

Laboratory features

No test is diagnostic for HSP, and recommended initial investigations are shown below in Table 2.

If the diagnosis is in doubt or if there is significant renal involvement, then further investigations may be warranted as shown in Table 3.

Imaging

Imaging may be required to diagnose complications of HSP. The most common modalities are shown in Table 4. However, in more severe cases, such as those with neurological involvement, other specialist imaging may be required.

Table 1 Clinical features associated with Henoch–Schönlein purpura

Organ involvement	Incidence	Description
Skin	100%	Essential for diagnosis. Initially, it may resemble an urticarial or erythematous macular-papular rash before developing into a palpable purpura, symmetrically distributed over the extensor surfaces of the lower legs, buttocks and arms (Fig. 1)
		Lesions may spread to trunk and face. Bullous lesions may develop [35] (Fig. 2)
		Rash fades within weeks
Joints	Up to 82%	Usually an oligoarthritis
		Mainly affects lower limb joints particularly ankles or knees
		Self-resolving
Gastrointestinal (GI)	50–75%	May be limited to mild colicky abdominal pain +/or vomiting, but in some cases abdominal pain can be severely debilitating
		Some form of bleeding is common although massive haemorrhage only occurs occasionally [5]
		Intussusception is a well recognised but rare complication (Fig. 3)
		Pancreatitis, hydrops of the gallbladder and protein-losing enteropathy are also recognised, but rare features
Renal	20–60%	Most common features are isolated microscopic haematuria with or without proteinuria
		Macroscopic haematuria also common
		Hypertension—may be isolated or related to renal involvement
		Acute nephritis or nephrotic syndrome or a mixed picture (6–7% of children with HSP)
		Acute renal failure
		91% of those who develop renal complications do so within 6 weeks and 97% within 6 months [24]
Urogenital	Up to 27% of boys	Usually manifests as orchitis
		However, may mimic torsion and require surgical exploration to differentiate [15, 35]
		There are single case reports in the literature of ureteral (often bilateral) stenosis associated with HSP [36]
Neurological	2%	Seizures, intracranial haemorrhage and cerebral vasculitis are reported but rare
		Headache is common but may not be recognised as a separate phenomenon [42]
Pulmonary	<1%	Rare especially in children
		Clinically may present as an interstitial pneumonia with histology normally showing diffuse alveolar haemorrhage [23]

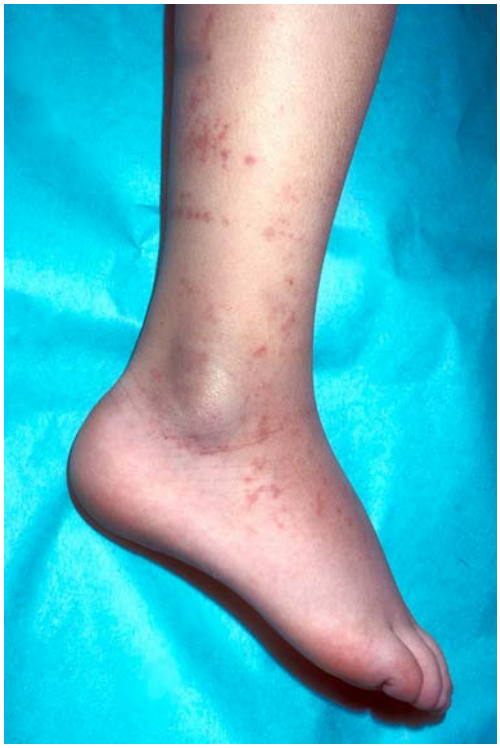

Fig. 1 The purpuric rash of HSP (note the pressure effect of the top of the sock line)

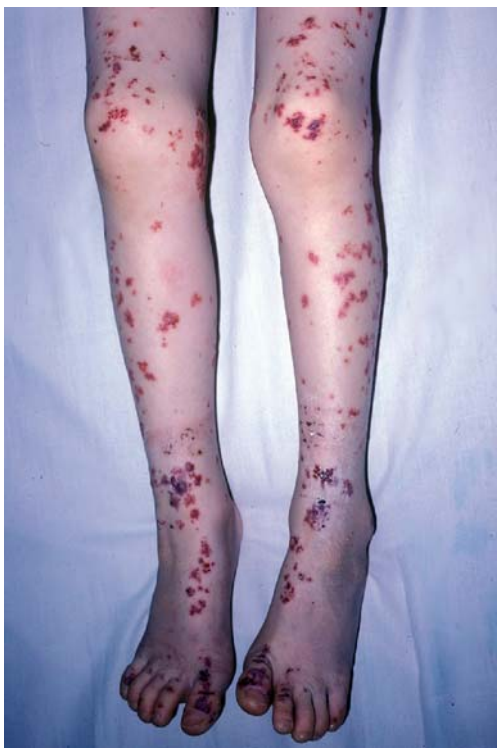

Fig. 2 The purpuric rash with bullous lesions

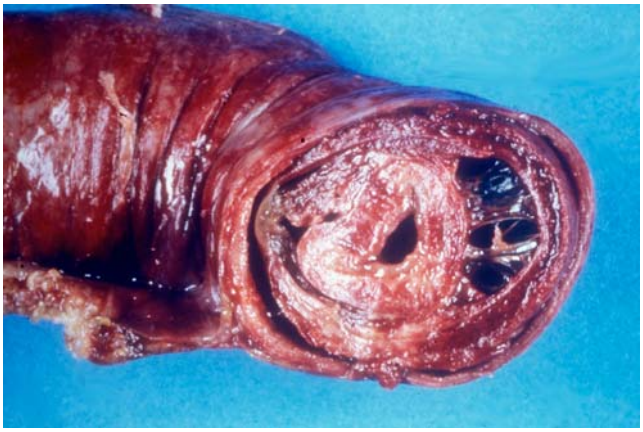

Fig. 3 A cross-section of large bowel demonstrating intussusception

Aetiology

The pathogenesis of HSP is not yet clearly understood, although it is known to be an immune complex-mediated disease. Preceding upper respiratory tract infections are common particularly with group A β-haemolytic streptococcus, but many other organisms have been implicated such as mycoplasma, adenovirus, parvovirus B19, varicella and herpes simplex [4, 35].

It is possible that there is a genetic predisposition to developing HSP and subsequent renal involvement. Multiple factors have been implicated including human leucocyte antigen class II genes, genetic polymorphisms of the renin angiotensin system and cytokines such as IL-1 β [3, 10, 28]. HSP is also more common in children with familial Mediterranean fever [26].

However, any predisposition to HSP is most likely to be a combination of factors, which influence susceptibility, likelihood of renal involvement and eventual outcome.

Immunology

IgA complexes are formed and deposited in the skin, gut and glomeruli triggering a localised inflammatory response. A leucocytoclastic vasculitis subsequently develops with necrosis of the small blood vessels.

Normally, IgA is found in the serum and in mucosal fluids. It has two isotypes: IgA1 and IgA2. Mucosal IgA is mainly polymeric and 60% IgA2, whereas serum IgA is mainly IgA1 and 90% monomeric. In HSP, the complexes are formed with polymeric IgA1.

An abnormal form of the IgA1 known as Gal-d IgA1 (referring to a galactose deficiency of the O-linked glycans in the hinge region of IgA1) has also been identified, which has been found to be higher in HSP nephritis (HSPN) compared with HSP without nephritis and non-disease controls [2].

Table 2 Recommended initial investigations for Henoch–Schönlein purpura

Full blood count	May show anaemia and/or a leucocytosis
Erythrocyte sedimentation rate	Normal or raised
Clotting	Normal
Biochemical profile	Renal function may be altered with raised creatinine. Low albumin (may be related to renal or gastrointestinal disease)
Anti-streptolysin O titre (ASOT) and anti-deoxyribonuclease B (anti-DNase B)	To confirm preceding streptococcal infection (this does not exclude HSP as it may precede HSP)
Urine dipstick and protein:creatinine ratio	Haematuria, proteinuria
Septic screen	If diagnosis is unclear and purpura are present

Other IgA antibodies may be raised, such as IgA rheumatoid factor and IgA antineutrophil cytoplasmic antibodies may be positive [25, 35].

Pathology

In the skin, a biopsy of the purpura (but also of the non-affected areas) reveals IgA deposition. In the kidney, the histological findings are similar to that of IgA nephropathy. Primarily, there is mesangial proliferation with hypercellularity. There may be focal necrosis and segmental capillary collapse. Epithelial crescent formation represents more significant inflammatory damage. Histological changes are graded in a classification by the International Study for Kidney Disease in Children [9].

Treatment

The natural course of the disease is usually one of complete resolution, often without the need for therapeutic intervention. Patients often require admission to hospital, particularly for symptom control; this is dependent on the degree of primary care available out of hospital. Bed rest may be necessary for those with acute arthralgia or abdominal pain, although in the opinion of the authors, this does not influence disease progression. It is possible that the condition may be modified in some cases either by controlling acute symptoms or by influencing the long-term morbidity, particularly following renal involvement. Some of the possible therapeutic interventions are shown below.

Skin

The vasculitic skin manifestations rarely need therapy, but, particularly with bullous lesions, there are reports of the successful use of steroids. Steroid sparing agents such as dapsone or colchicine have also been used [38].

Joint

The sometimes debilitating arthropathy is often treated with non-steroidal anti-inflammatory drugs (NSAIDs) normally with rapid resolution. However, in a randomised control trial of 171 patients randomised to receive oral prednisolone (1 mg $kg^{-1}day^{-1}$ for 2 weeks, weaning over the next 2 weeks) or placebo, oral prednisolone reduced the severity of joint symptoms and showed a tendency towards shorter duration of pain (reduced by 1.3 days, but this was not significant) [32]. The use of NSAIDs and the impact on renal disease in HSP have not been determined.

Gastrointestinal tract

Corticosteroid therapy has long been employed in acute HSP to alleviate GI symptoms, but until recently, there had not been any randomised control trials (RCTs) performed to determine the efficacy. Retrospective studies have suggested that there may a benefit with low-dose oral steroids [29, 34]. In the non-randomised study by Rosenblum and those treated with steroids who appeared to have a more rapid resolution of abdominal pain but by 72 h, there was no difference between the groups. Similarly, in the retrospective study by Reinehr et al., children with HSP and GI symptoms who were treated with steroids appeared to have more rapid resolution of symptoms.

Table 3 Recommended secondary investigations in Henoch–Schönlein purpura (or if diagnosis not clear)

Anti-nuclear antibodies, double-stranded DNA, anti-neutrophil cytoplasmic antibody (ANCA)	To differentiate from systemic lupus erythematosus or ANCA positive vasculitic
Complement 3, complement 4	Usually normal in HSP/Occasionally low C3/4
Immunoglobulins	Usually normal IgG and M but IgA may be raised in HSP

Table 4 Common modalities of imaging employed in the investigation of Henoch–Schönlein purpura

Mode	Indication	Possible findings
Renal tract ultrasound	Renal impairment	Echo bright kidneys Hydronephrosis
Plain Abdominal X-ray/supine chest X-ray	Suspected perforated GI tract	Air leak
Abdominal ultrasound	Severe GI involvement or suspected Intussusception	Thickened bowel wall, reduced peristalsis, intussusception

More recently, in a study of 40 patients prospectively randomised to receive either oral prednisolone for 2 weeks (2 mg $kg^{-1}day^{-1}$ for 1 week and weaned over the second) or placebo, no difference was seen in the rate of GI involvement [18]. However, in the study by Ronkainen et al., described above, 171 children with HSP were randomised and received either placebo or prednisolone (dose described above) on diagnosis. The steroid group described significantly less pain in a symptom diary and had a shorter duration of these symptoms by 1.2 days, which was also significant [32].

Provided significant abdominal pathology such as intussusception has been excluded, then prednisolone in a dose of 1 mg/kg (maximum, 60 mg) should be considered in children with significant HSP-associated abdominal pain. Steroids may also be indicated with other evidence of significant GI disease—e.g. protein-losing enteropathy. In some children with abdominal pain, feeding may precipitate further pain; however, most will tolerate a simple diet. Intravenous fluids may be required in cases of severe pain or vomiting. In extreme cases, an elemental diet or parenteral nutrition may be necessary.

The presence of severe GI pain or significant bleeding (either as haematemesis, melena or fresh bloody stools) would warrant careful clinical monitoring of haemodynamic status and consideration of endoscopy after discussion with a gastroenterologist.

In severe GI tract vasculitic disease, there are case reports of the successful use of immunoglobulin infusions, intravenous methylprednisolone and plasma exchange in otherwise intractable disease [19, 41, 43].

Persistent or chronic abdominal pain following HSP is uncommon but has been described and successfully treated with methotrexate and mycophenolate mofetil [21, 30].

Renal disease

Do early corticosteroids prevent or ameliorate the development of HSP nephritis?

In 1992, Mollica published a prospective study of 164 children with HSP without evidence of nephritis that were alternately given prednisolone or no treatment. Of the steroid group, none developed nephropathy within 6 weeks compared to 12% (10/84) in those not treated. A further two patients in the untreated group developed nephropathy at 24 and 72 weeks following acute presentation. However, of these 12 patients, only two had persistent nephropathy 12 months after onset, and the study was non-randomised and non-placebo-controlled [22]. The evidence for a reduction in the incidence of nephritis with oral steroids early in HSP has been conflicting. Neither of the two RCTs by Huber and Ronkainen (described above) found any benefit of steroids in the prevention of renal disease [18, 32].

More recently, the largest RCT (double-blind, placebo-controlled) performed to date has been undertaken [11]. Three hundred and fifty-three children with new onset HSP were randomised on presentation to receive either prednisolone (2 mg/kg for 1 week followed by 1 mg/kg for 1 week) or placebo. There was no reduction in the prevalence of nephropathy at 12 months in those treated with steroids compared with those treated with placebo. In a recent Cochrane review, a meta-analysis was performed on the four studies described above and found no difference in persistent renal disease at up to 12 months following treatment with steroids at presentation of HSP compared with placebo and therefore concluded that corticosteroids do not prevent renal involvement in HSP [7].

When is a renal biopsy necessary?

One of the difficulties facing the clinician in making a decision about treatment of a child with HSPN is determining the severity of the renal involvement from the clinical features alone coupled with the variable outcome, including favourable outcome in some with severe disease at presentation. In a follow-up of 78 children, both severity of clinical presentation and histological features were related to outcome, but no features were absolutely predictive [14]. In a systematic review, the relative risk of long-term renal impairment was 11.9 comparing a nephritic nephrotic presentation with microscopic haematuria alone [24]. However, even those with a severe clinical presentation may make a full recovery. It is therefore recommended that, in this situation, histological information may help to

guide treatment. The authors therefore recommend renal biopsy in the following clinical situations.

Indications for renal biopsy include the following:

- Acute renal impairment/nephritic syndrome at presentation
- Nephrotic syndrome with normal renal function persisting at 4 weeks
- Nephrotic range proteinuria (urine protein/creatinine ratio, >250 mg/mmol) at 4–6 weeks (if not improving spontaneously)
- Persistent proteinuria—urine protein/creatinine ratio >100 mg/mmol for more than 3 months consider biopsy particularly if the diagnosis is not clear.

Treatment of renal disease

Treatment is directed at preventing what can be severe long-term renal morbidity in those patients considered most at risk. Other than the degree of clinical renal involvement at presentation, there are certain factors that have been associated with a less favourable prognosis. These include age at onset above 8 years, abdominal involvement, persistent purpura and increasing severity of grade of renal histology [6, 32].

In view of the relatively small number of children with severe HSPN, there is a lack of RCTs to establish the benefit of treatment. The recent Cochrane review also performed a meta-analysis of treatment of severe established renal disease. Only two RCTs were identified. One compared cyclophosphamide alone with no specific treatment in children with HSP and nephrotic range proteinuria and did not show any benefit of cyclophosphamide [39]. The second study suggested that cyclosporine A may be more effective than methylprednisolone or prednisolone in inducing remission but was not statistically significant [31].

Most reports in the literature are case series or retrospective studies involving small numbers of patients. In a literature review by Zaffanello and Fanos [44], the level of evidence derived from many of these studies was assessed. These included reports of treatment with prednisolone, methylprednisolone, cyclophosphamide, azathiaprine, cyclosporine, dypiridamole, warfarin and plasma exchange. The authors concluded that there was insufficient firm evidence to guide best practice in the management of established HSPN. A more recent, single-centre, retrospective review looking at treatment of severe HSP nephropathy and IgA nephropathy demonstrated that therapy with differing combinations of steroids, cyclophosphamide, ACE inhibitors and angiotensin receptor blockers produced a good outcome in 54% of

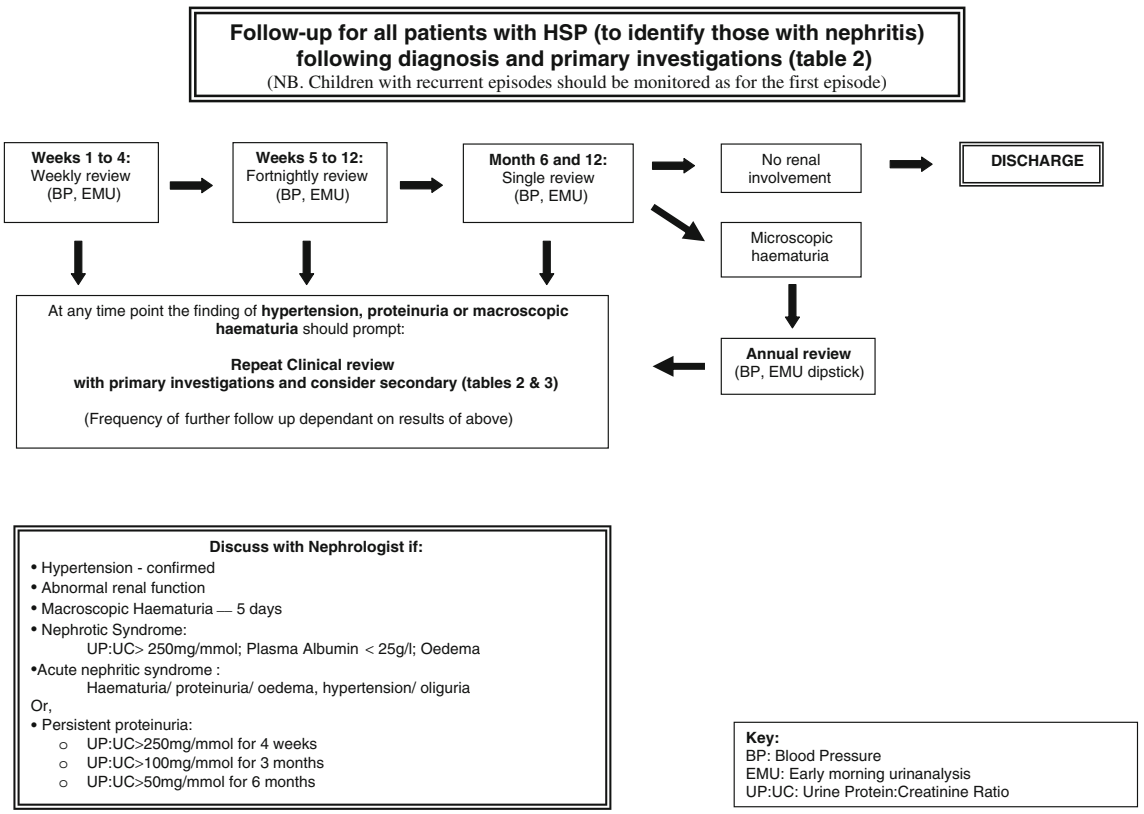

Fig. 4 Detection and referral of patients with HSP nephritis (adapted from local guidelines developed by Dal Hothi and Bristol Paediatric Nephrologists reprinted with the kind permission of the BMJ publishing group) [40]

children with severe (>stage III) histological changes on initial renal biopsy [12].

In those children with severe disease, there is some low-grade evidence for the benefit of intensive therapy, and in these patients, some form of steroid/immunosuppressive therapy is often initiated. In view of the possible long-term consequences of HSPN, early discussion with the paediatric nephrologist is recommended. A suggested referral plan is shown in Fig. 4.

Angiotensin-converting enzyme inhibition has been shown to effectively decrease proteinuria and slow progression of renal impairment in IgA nephropathy. Given the similarities in pathology between the two conditions, ACE inhibition should be considered in the management of persistent proteinuria and considered as a first-line therapy for hypertension secondary to HSP [8]. Any long-term protective effect has not been proven, and follow-up studies are required.

Follow-up and outcome

HSP without nephritis is a self-limiting disease, and the most common outcome is complete resolution. The duration of the acute illness varies between studies, but for most patients, it resolves within 8 weeks [35]. Recurrence within the first year is not uncommon, affecting about 30–40% of patients, although these episodes are generally less symptomatic and of shorter duration [35].

In a systematic review, Narchi reported that 97% of children developing renal involvement of HSP would do so within 6 months of presentation [24]. Therefore, this is the minimum length of follow-up recommended. At the Bristol Royal Hospital for Children, a practical pathway to guide monitoring for 6–12 months post-diagnosis has been developed. Factors prompting immediate discussion with a nephrologist include hypertension, abnormal renal function, acute nephritis or nephrotic syndrome (Fig. 4).

The risk of long-term renal impairment is reported to be between 15% and 2% in follow-up studies of unselected patients [24, 37], where renal impairment includes persistent hypertension, proteinuria or decreased glomerular filtration rate. The same studies describe a risk of end-stage renal failure as <1%. In the UK, HSPN accounts for 1.5% of children requiring renal replacement therapy (ninth annual report of the UK renal registry) [20].

In reports describing long-term follow-up of patients with HSPN, most demonstrate a correlation between severity at onset and eventual outcome [14, 24, 33]. In the systematic review by Narchi, which included 1,133 children with HSP, 1.6% of those that had isolated haematuria or non-nephrotic proteinuria on presentation developed long-term renal impairment compared with 19.5% of those with nephritic or nephrotic presentations [24]. Other studies have reported that 11–13% of those children with HSP who presented with or developed isolated haematuria/proteinuria and 35–44% of those with nephritic or nephrotic presentations develop long-term renal impairment [14, 33]. In the systematic review by Narchi, no long-term renal impairment occurred after normal urinalysis for 6 months [24]. Therefore, these patients may be discharged from follow-up. In view of the possibility of late deterioration in those with mild renal involvement, long-term albeit annual follow-up is recommended in these patients [24].

Pregnancy

Pregnancy may be affected in women who have had HSP during childhood. In one long-term follow-up study of children with HSPN, 16 of 44 full-term pregnancies were complicated by proteinuria and or hypertension [14]. This finding was replicated in another long-term follow-up study in which 16 of 23 pregnancies were similarly complicated [33]. It is recommended that women who have had HSP during childhood be followed carefully during pregnancy for the development of proteinuria or hypertension.

Summary

Although HSP is the most common childhood vasculitis and has been recognised for over 200 years, there remains uncertainty regarding optimal monitoring and therapy. Non-renal involvement is common, and there may be a role for steroids in treating GI involvement. There is, however, no evidence that early steroids reduce the risk of developing renal complications. Renal involvement can be severe but may resolve completely. However, some children will develop long-term sequelae, and renal biopsy is helpful in determining the need for treatment with immunosuppression in the acute phase. A practical care pathway for monitoring patients following a diagnosis of HSP and indicating when to refer to tertiary nephrology is presented.

Conflict of interest The authors declare that they have no conflict of interest.

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