



Renal manifestations of Henoch–Schönlein purpura in a 6-month prospective study of 223 children

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ABSTRACT

Objective To assess the risk factors for developing Henoch–Schönlein purpura nephritis (HSN) and to determine the time period when renal involvement is unlikely after the initial disease onset.

Design A prospective study of 223 paediatric patients to examine renal manifestations of Henoch–Schönlein purpura (HSP). The patient's condition was monitored with five outpatient visits to the research centre and urine dipstick testing at home.

Results HSN occurred in 102/223 (46%) patients, consisting of isolated haematuria in 14%, isolated proteinuria in 9%, both haematuria and proteinuria in 56%, nephrotic-range proteinuria in 20% and nephrotic-nephritic syndrome in 1%. The patients who developed HSN were significantly older than those who did not (8.2 ± 3.8 vs 6.2 ± 3.0 years, $p < 0.001$, CI for the difference 1.1 to 2.9). Nephritis occurred a mean of 14 days after HSP diagnosis, and within 1 month in the majority of cases. The risk of developing HSN after 2 months was 2%. Prednisone prophylaxis did not affect the timing of the appearance of nephritis. The risk factors for developing nephritis were age over 8 years at onset (OR 2.7, $p = 0.002$, CI 1.4 to 5.1), abdominal pain (OR 2.1, $p = 0.017$, CI 1.1 to 3.7) and recurrence of HSP disease (OR 3.1, $p = 0.002$, CI 1.5 to 6.3). Patients with two or three risk factors developed nephritis in 63% and 87% of cases, respectively. Laboratory tests or blood pressure measurement at onset did not predict the occurrence of nephritis.

Conclusion The authors recommend weekly home urine dipstick analyses for the first 2 months for patients with HSP. Patients with nephritis should be followed up for more than 6 months as well as the patients with HSP recurrence.

INTRODUCTION

Henoch–Schönlein purpura (HSP) is a generalised vasculitis characterised by various combinations of skin, joint, gastrointestinal and renal involvement. HSP can occur at any age, but is most common in childhood. It is usually a self-limited disease.¹ The extrarenal symptoms typically resolve rapidly without complications, and the long-term prognosis is mainly dependent on the severity of renal involvement.^{2–4} Renal disease affects approximately one-third of patients, varying from intermittent haematuria and proteinuria to severe nephrotic-nephritic syndrome.⁵ Hypertension may be found in the presence of renal involvement. Although renal involvement is in most cases mild and self-limited, it has been claimed that about 1% of patients progress to

What is already known on this topic

- ▶ Henoch–Schönlein purpura nephritis (HSN) occurs mostly in the early course of Henoch–Schönlein purpura.
- ▶ In most cases HSN is mild and self-limiting.
- ▶ Corticosteroid treatment does not prevent the occurrence of HSN.

What this study adds

- ▶ Weekly urine dipstick tests are indicated for 2 months after the onset of Henoch–Schönlein purpura (HSP). The length of follow-up time should be increased at least up to 6 months individually in the case of HSP recurrence and in those developing nephritis.
- ▶ A follow-up of 6 months is not enough for patients with Henoch–Schönlein purpura nephritis, not even for those with mild transient nephritis.
- ▶ Prednisone prophylaxis does not affect the timing of the appearance of nephritis.

end-stage renal disease.^{4 6 7} The aims here were to evaluate the renal features of HSP in unselected patients during a 6-month prospective follow-up, to identify the risk factors for developing Henoch–Schönlein purpura nephritis (HSN) and to determine the follow-up time needed for diagnosing renal involvement.

PATIENTS AND METHODS

The patients were recruited unselectively a mean of 7 days (SD 10.5, range 0–65 days) after disease onset during the period 1999–2006. The criteria for inclusion were age ≤ 16 years and a clinical diagnosis of HSP including typically distributed palpable purpura or petechiae and at least one of the following findings: arthralgia or arthritis, abdominal pain or nephritis. Exclusion criteria were thrombocytopenia and systemic vasculitis at onset. The diagnosis of HSP fulfils the 1990 criteria of the American College of Rheumatology.⁸ Of the 223 patients (122 boys and 101 girls), 176 were primarily recruited into a trial of early corticosteroid

treatment for the prevention of nephritis⁹ and 23 into a trial comparing Cyclosporine A (CyA) with methylprednisolone (MP) pulses for the treatment of severe HSN.¹⁰ In addition to these drugs, 21 patients were treated with angiotensin-converting enzyme inhibitors during the 6-month follow-up. The mean age of the patients at the onset of the trial was 7.1 years (SD 3.5, range 1.6–16.7 years). Specific details of the patients' extrarenal symptoms are contained in our previous report.¹¹

There were five control visits to the centre during the 6 months of the trial (at inclusion and 1–2 weeks, 1, 3 and 6 months after diagnosis), including a clinical examination, laboratory tests and blood pressure measurement. The patients of the prednisone study (176/79%) monitored haematuria and proteinuria at home with daily urine dipstick tests for a month. Patients with increasing proteinuria or haematuria were advised to contact the centre for a diagnosis of HSN.

Blood samples for describing the acute phase of HSP were obtained at the time of enrolment. Normal ranges for the patient's age and sex were used to interpret the laboratory test results. Previous streptococcal infection was diagnosed if the antistreptolysin O titre or streptodornase antibodies were elevated or if a throat swab culture was positive for group A β -haemolytic streptococcus. Other blood tests included erythrocyte sedimentation rate, C reactive protein, serum albumin, creatinine, immunoglobulin A, E, G and M, and complement components C3 and C4. The urine analyses included dipsticks, microscopy and protein assays.

The criteria for haematuria, proteinuria and nephrotic-nephritic syndrome are described in table 1. Nephritis was considered to be prolonged if it lasted over 1 month. A recurrence of HSP disease was considered when a patient who had been asymptomatic for at least 1 month presented with a new flare-up of skin lesions or other symptoms related to HSP. The mean blood pressure at the first three control visits was taken to describe the blood pressure at the acute phase of HSP. Hypertension was defined as systolic or diastolic blood pressure greater than the 95th percentile for the patient's age, sex and height according to the Update on the 1987 Task Force Report.¹²

A total of 21 patients underwent renal biopsy during the 6-month follow-up, at a mean of 67 days after HSP diagnosis (range 18–168 days) on account of nephrotic-range proteinuria or prolonged nephritis lasting over 6 weeks. Additionally, four patients in the CyA versus MP study underwent kidney biopsy after finishing the 6-month follow-up. HSN with diffuse IgA mesangial deposits was confirmed in all cases. The glomerular changes were graded according to the classification devised by the International Society of Kidney Disease in Children (ISKDC), as follows: gradus I: minimal alterations; gradus II: mesangial proliferation; gradus III: focal or diffuse proliferation or sclerosis with <50% crescents; gradus IV: focal or diffuse mesangial proliferation or sclerosis with 50–75% crescents; gradus V: focal or diffuse mesangial proliferation

or sclerosis with >75% crescents; and gradus VI: membrano-proliferative-like lesions.¹³ Gradus II was recorded for seven biopsies, gradus III for 12 biopsies, gradus IV for one biopsy and gradus VI for one biopsy. The patients with biopsies after 6 months all had ISKDC gradus III changes.

STATISTICAL ANALYSIS

The statistical analyses were performed with SPSS (version 16.0 for Windows), using the χ^2 test for categorical variables and Student's two-tailed t test for continuous variables. Forward stepwise logistic regression was used for multivariate analysis. Nephritis-free survival was calculated by the Kaplan–Meier method. Statistical significance was set at $p < 0.05$.

RESULTS

HSN occurred in 102/223 (46%) of the patients, consisting of isolated haematuria in 14/14%, isolated proteinuria in 9/9%, both haematuria and proteinuria in 58/56%, nephrotic-range proteinuria in 20/20% and nephrotic-nephritic syndrome in 1/1%. Of these patients 40 had received early prednisone treatment. The age distribution of the patients with and without nephritis is presented in figure 1. The occurrence of nephritis (table 2) increased significantly with age ($p < 0.001$ for linear trend). The patients with nephritis were significantly older than those without (8.2 ± 3.8 vs 6.2 ± 3.0 years, $p < 0.001$, CI for the difference 1.1 to 2.9), but renal manifestations also occurred in young children, 24% being aged 1–4 years. Nephrotic-range proteinuria or prolonged nephritis lasting over 1 month affected 42 patients. These patients were older than those with nephritis lasting under 4 weeks and with non-nephrotic proteinuria (9.1 ± 3.8 vs 7.5 ± 3.6 years, $p = 0.038$, CI for the difference 0.9 to 3.1).

Nephritis occurred on average 14 days after the disease onset (range 0–101 days). The tidal trend is shown in detail in figure 2. Thirty-six of the 223 patients (16%) presented with haematuria or proteinuria at the time of HSP diagnosis. In the vast majority of cases, that is 87%, renal manifestations developed within 1 month, the incidence rates of nephritis after 1 and 2 months being 14% and 2%, respectively. The patient with the latest nephritis onset in our series presented with a recurrence of HSP skin manifestations at the time of diagnosis of HSN. As seen in figure 3, early prednisone treatment did not affect the frequency or timing of the appearance of nephritis.

In 60/102 (59%) of patients with nephritis this lasted for less than 1 month and did not require treatment. These included two patients with mild intermittent haematuria and proteinuria existing for only 3 and 5 days, respectively. None of the patients with HSN developed renal failure or end-stage renal disease during the 6-month follow-up. The patient having nephrotic-nephritic syndrome in the early course of HSP disease developed renal failure 20 months later and received a kidney transplant 6 years after the onset.

Table 1 Criteria for renal manifestations of Henoch–Schönlein purpura

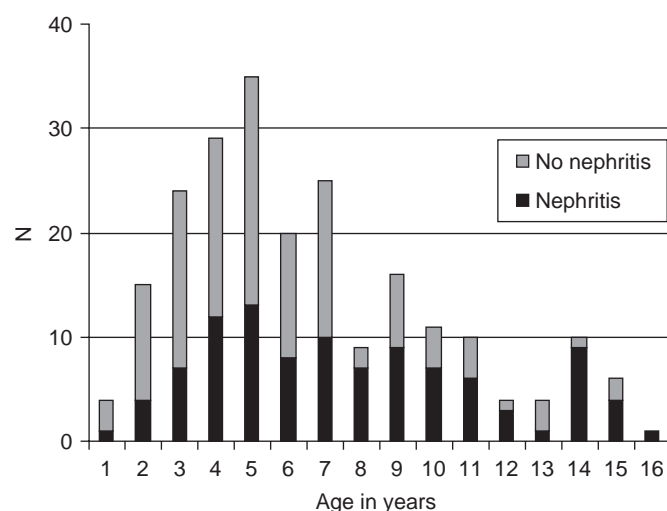
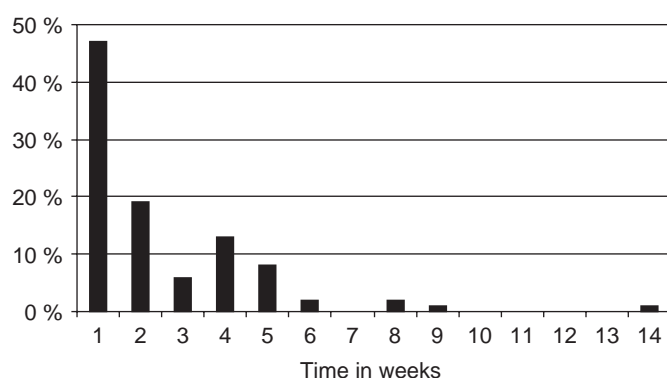
Renal symptom	Criteria
Haematuria	≥ 5 Red blood cells/field or positive dipstick tests*
Proteinuria	Urine protein > 200 mg/l, urine albumin > 30 mg/l or positive dipstick tests*
Haematuria and proteinuria	See above
Nephrotic-range proteinuria	24 h urine protein > 40 mg/m ² /h
Nephrotic-nephritic syndrome	> 200 Red blood cells/field and 24 h urine protein > 40 mg/m ² /h and at least two of the following findings: oliguria, hypertension, renal dysfunction

*+ to ++ in 3 consecutive days or +++ in 2 consecutive days.

Table 2 Occurrence of Henoch–Schönlein purpura nephritis by age at onset

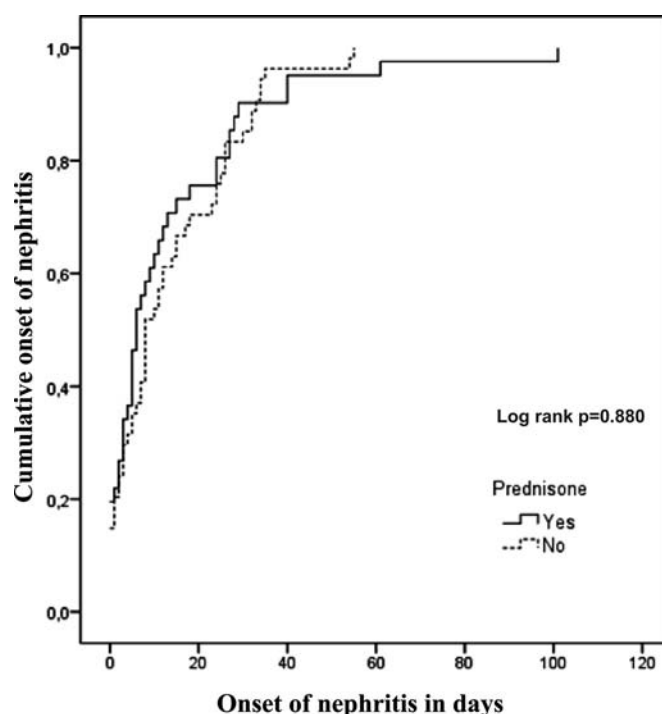
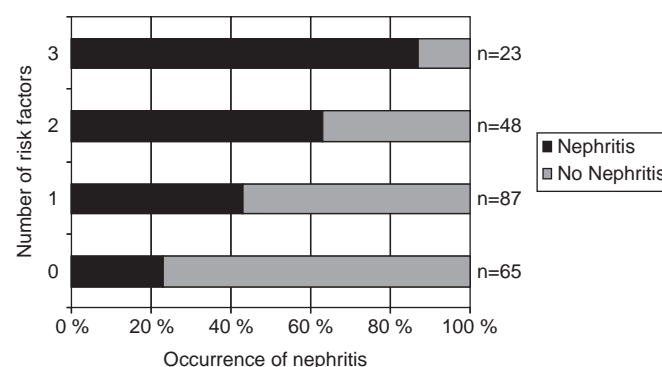
Age group (years)	All	Nephritis	No nephritis
0–3	19	5 (26%)	14 (74%)
3–6	88	32 (36%)	56 (64%)
6–10	70	34 (49%)	36 (51%)
10–16	46	31 (67%)	15 (33%)
All	223	102 (46%)	121 (54%)

$p < 0.001$ for χ^2 test for linear trend.

**Figure 1** Age distribution and occurrence of nephritis in 223 children with Henoch–Schönlein purpura.**Figure 2** Time from the onset of Henoch–Schönlein purpura to the development of nephritis.

Multivariate analysis showed that age over 8 years at onset (OR 2.7, $p=0.002$, CI 1.4 to 5.1), abdominal pain (OR 2.1, $p=0.017$, CI 1.1 to 3.7) and a recurrence of HSP disease (OR 3.1, $p=0.002$, CI 1.5 to 6.3) were independent risk factors for developing nephritis, but we found no correlation between melena and the occurrence of renal findings (table 3). An accumulation of risk factors increased the risk of HSN (figure 4), that is the patients having two or three risk factors developed nephritis in 63% and 87% of cases, respectively.

Upper respiratory tract infection (URTI) (51% vs 68%; $p=0.058$) and previous streptococcal infection (42% vs 30%; $p=0.077$) seemed to associate with the development of HSN (table 3). Previous streptococcal infection was not associated with the level of C3, and none of the other numerous laboratory tests performed at the onset of HSP predicted the development of renal manifestation (table 4).

**Figure 3** Timing of the onset of Henoch–Schönlein purpura nephritis in patients treated with early prednisone ($n=40$) and non-treated patients ($n=62$). Only the patients presenting with nephritis were included in the analyses.**Figure 4** Predictive model for the occurrence of nephritis in patients with 0–3 risk factors, including age over 8 years, abdominal pain and recurrence of Henoch–Schönlein purpura.

During the first month hypertension was detected in 20/160 (13%) cases, but this was mild, the mean systolic pressure being 5 mm Hg (SD 4, range 0–13 mm Hg) and diastolic pressure 2 mm Hg (SD 3, range 0–8 mm Hg) above the 95th percentile for the patient's age, sex and height. Significant hypertension was diagnosed and treated only in one patient with nephrotic-nephritic syndrome.

DISCUSSION

Nephritis occurred in 46% of the 223 unselected HSP patients studied here, consisting of isolated haematuria in 14%, isolated proteinuria in 9%, both haematuria and proteinuria in 56%, nephrotic-range proteinuria in 20% and nephrotic-nephritic syndrome in 1%. The patients who were followed up without any treatment represent the natural course of HSP disease, prospective data on which are scarce. To our knowledge, this is the largest prospective study of childhood HSN.

Table 3 Multivariate analysis (n=223) and univariate analysis (n=87–176) of aetiological factors and clinical symptoms as prognostic factors for the development of nephritis in Henoch–Schönlein purpura

Prognostic factor	Nephritis (n=102)	No nephritis (n=121)	p Value	OR (95% CI)
Multivariate analysis				
Male sex	55 (54%)	67 (55%)	0.828	
Age >8 years at onset	47 (46%)	24 (20%)	0.002	2.7 (1.4 to 5.1)
Joint symptoms	95 (93%)	105 (87%)	0.139	
Abdominal pain	70 (69%)	56 (46%)	0.017	2.1 (1.1 to 3.7)
Melena	8 (8%)	10 (8%)	0.908	
Recurrences	40 (39%)	15 (12%)	0.002	3.1 (1.5 to 6.3)
Univariate analysis				
Orchitis in boys (n=122)	6/55 (11%)	11/67 (16%)	0.601	
Blood pressure (n=160)	8/74 (11%)	12/86 (14%)	0.635	
Previous upper respiratory tract infection (n=143)	32/63 (51%)	54/80 (68%)	0.058	
Streptococcus positive (n=199)	40/95 (42%)	31/104 (30%)	0.077	

Table 4 Occurrence of abnormal laboratory values at onset of Henoch–Schönlein purpura in patients with and without nephritis

	Nephritis	No nephritis	p Value
Elevated ESR (n=181)	45% (38/84)	57% (55/97)	0.124
Elevated CRP (n=206)	36% (34/95)	39% (43/111)	0.663
Elevated IgA (n= 182)	25% (20/81)	33% (33/101)	0.255*
Elevated IgE (n=117)	36% (18/50)	27% (18/67)	0.290
Elevated IgG (n=131)	5% (3/56)	11% (8/75)	0.351*
Elevated IgM (n=176)	0% (0/79)	4% (4/97)	0.065*
Increased C3	5% (4/79)	6% (6/96)	0.999*
Decreased C3	1% (1/79)	1% (1/96)	0.999*
Increased C4	4% (3/78)	1% (1/95)	0.328*
Decreased C4	5% (4/78)	1% (1/95)	0.176*
Positive ANCA (n=168)	9% (7/77)	18% (17/91)	0.077

*Fisher's exact test.

ANCA, antineutrophil cytoplasmic antibodies; CRP, C reactive protein; ESR, erythrocyte sedimentation rate.

The occurrence of urinary findings in our series is consistent with a systematic review of 12 unselected studies covering a total of 1133 unselected patients, in whom nephritis occurred in 34%, including 79% who had isolated haematuria and/or proteinuria and 21% who had acute nephritic syndrome or nephrotic syndrome.⁵ The figures arrived at in our study were the same. A total of 9% of our patients with HSN presented with isolated proteinuria without haematuria, which has been considered to be rare by some authors.^{1 2 14} On the other hand, isolated proteinuria as a symptom of HSN has been reported to occur in 7–28% of cases.^{15–17} This inconsistency probably arises from the wide variations in the reported frequencies and reliabilities of urine testing.

The reported incidence of HSN varies greatly, depending both on the definition of the renal disease and the method of detection and also according to the nature of the patient series (from primary care vs a tertiary referral centre). In our unselected HSP patient group 46% developed a renal manifestation during the 6-month follow-up. In this series the primary diagnoses of HSP had been arrived at very early, a mean of 7 days after onset, and most of the patients were then followed up with frequent urine testing at home and at control visits. In a recent prospective study of 74 patients, the reported incidence of HSN was 26%, which is low for patients diagnosed in a tertiary referral care centre with frequent urine testing.¹⁸ The exact criteria for proteinuria were not defined in that study, however, which hampers comparison of the results.

Our results are in accordance with previous observations that 75–100% of patients developing HSN do so within the first 4 weeks after the onset of HSP, and virtually all within 3 months.^{3 14 18} Pabunruang *et al*¹⁹ reported that 27% of their HSN cases were discovered more than 6 months after the HSP diagnosis, but they did not describe the frequency of urine testing in their retrospective study, and the delay in diagnosing HSN may have originated from differences within the local healthcare system, study setup and the late testing of urine. We found the occurrence of nephritis to be infrequent after 1 month, that is 10 had to be screened, respectively, in order to diagnose a new case of nephritis 1 month after the onset of HSP and as many as 50 patients 2 months after. According to the systematic review by Narchi⁵ the cumulative proportion of patients with HSP developing HSN by 2 months was 90% and by 6 months 97%, respectively. This data may be interpreted to suggest that all patients with HSP should be tested at least for 6 months. On the basis of our prospectively and systematically collected data we suggest that weekly urine dipstick tests should be continued for 2 months from the onset of HSP. Beyond that point frequent routine follow-up is neither cost-effective nor necessary in patients with no urine abnormalities during follow-up. However, the length of follow-up time should be increased at least up to 6 months individually in the case of HSP recurrence and in those developing nephritis.

Frequent urine analysis and follow-up is important, as even patients with mild renal findings at the onset of HSP may run a risk of severe long-term complications,^{4 20–22} and a renal manifestation may be missed because of the short duration of the symptoms and the lack of frequent testing. The intermittent nephritis of two patients in our series, for example, would have been missed without weekly dipstick tests. Even patients with transient renal manifestation in the course of HSP should be followed up for more than 6 months, since 19% of those in the early prednisone group and 43% in the placebo group in our earlier report still had some renal findings after 6 months.⁹ The resolution of all HSP symptoms, including nephritis, in the whole cohort is described in our previous paper by subgroups (prednisone-treated, non-treated and those having severe nephritis treated with CyA or MP). Of the patients with only prednisone prophylaxis or without any treatment, 12% and 15%, respectively, still had renal symptoms at the 6-month control visit.¹¹ Additionally, it must be kept in mind that HSP recurrences may occur some years after apparent resolution of HSN, especially in women during pregnancy.^{4 22} Individually longer follow-up must be planned, especially if

the initial symptoms of HSP consisted of nephrotic-range proteinuria or severe haematuria, as the prognosis is usually poor among these patients.^{4 22 23}

Renal involvement in HSP has been reported to be more frequent and more severe in children older than 4–10 years,^{3 15 20} and in agreement with this, we found a linear trend between age at onset and the occurrence of nephritis ($p < 0.0001$), so that age over 8 years carried a 2.7-fold risk. HSN may develop at any age, however, as witnessed by the fact that 24% of our patients with nephritis were aged ≤ 4 years. Abdominal pain, bloody stools, persistent purpura and relapse have been described as independent risk factors for the occurrence of HSN,^{15 17 20 24} and we observed that the occurrence of renal involvement was 2.1-fold in patients with abdominal pain and 3.1-fold in patients with HSP recurrences. In addition, if the patient had two or three of these risk factors, nephritis developed in 63% and 87% of cases, respectively, in accordance with the results of Shin *et al.*²⁰ Gastrointestinal symptoms and recurrences could be indicators of extensive, active HSP vasculitis, while there are virtually no theories to explain why older age is associated with an elevated risk of nephritis.

Data on other risk factors implicated in HSN are contradictory. Arthritis has been reported both to protect the patient from nephritis⁹ and to increase the risk.²¹ We found no association between the occurrence of arthritis and nephritis. URTI²⁵ or streptococcal infection²⁶ has been suggested to precede HSN. This was the trend also in our patients (table 3). Previous streptococcal infection did not induce changes in the level of C3, which is a known feature of poststreptococcal glomerulonephritis.²⁷ HSP is often preceded by bacterial and viral infections,¹ as was also seen in our patients (table 3). In our experience, HSN and relapses of HSP often occur during episodes of URTI or other infections, and it would therefore be worth investigating whether urine tests are indicated during URTI in patients who have had HSP.

Early laboratory markers associated with HSN have been widely studied. Fretzayas *et al* reported elevated serum IgA in 73% of all patients with HSP and in 95% of patients with HSN.¹⁸ These figures are high compared with the 8–62% reported by other authors in patients with HSP^{2 14 16 28} and with the 29% found in our study. Similä *et al* reported S-IgM to increase in patients with HSN during follow-up,²⁹ but we did not find that serum IgA, IgM or any other test performed at the onset of the disease differed between those who later developed nephritis and those who did not. We therefore conclude that these laboratory tests administered at the onset of HSP do not predict the development of nephritis.

Corticosteroid treatment has been reported both to reduce^{3 30} and to increase¹⁶ the risk of nephritis. In addition, several reports support the view that corticosteroid treatment does not alter the clinical course of HSP.^{4 14 15 17} Our present data (figure 3) clearly demonstrate that early prednisone treatment does not prevent or mask the development of HSN. This is in accordance with our previous report showing that early prednisone treatment did not prevent nephritis although it did help to obviate renal manifestations, since the prevalence of nephritis in the patients treated with prednisone was significantly lower at the 6-month control visit.⁹

CONCLUSIONS

Our results based on an unselected prospective patient series demonstrate that renal findings in HSP are common and develop early. Prednisone prophylaxis does not affect the

timing of appearance of nephritis. In accordance with our results on the timing of HSN, we suggest that weekly urine dipstick tests should be continued for 2 months after the onset of HSP. Close attention should be paid especially to patients aged over 8 years at onset, those experiencing abdominal pain and those with a recurrence of the disease, as the risk of developing nephritis is significantly increased in these circumstances. Even in cases of transient nephritis the follow-up should be continued for more than 6 months, and even for some years or throughout life in individual cases, as renal symptoms may re-appear after apparent healing of HSN.

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Competing interests None.

Patient consent Obtained.

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