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ORIGINAL ARTICLE

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Severe Henoch-Schönlein nephritis: resolution with azathioprine and steroids

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Abstract *Aim*: The aim of this study was to assess the efficacy of long-term azathioprine and steroids for treatment of severe nephritis in children with Henoch-Schönlein purpura (HSP). *Methods*: Analysis of case records of children with HSP followed up for a mean duration of 4.7 years (range 6 months–6.5 years) was performed. All underwent clinical status evaluation followed by percutaneous kidney biopsies. Renal histological changes were graded according to the International Study of Kidney Disease in Childhood (ISKDC) classification. Nine children with severe nephritis (grades III and IV) received steroids (mean duration 12.1 months) and long-term azathioprine (mean duration 14.7 months), while two children received steroids alone. *Results*: All nine children in the former category showed sustained clinical and biochemical remission, while the two children in the latter category did not. *Conclusion*: Severe nephritis seen in association with HSP can be effectively treated with a combination of azathioprine and steroids.

Keywords Henoch-Schönlein nephritis · Immunosuppressive therapy · Azathioprine · Steroids

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Introduction

Henoch-Schönlein purpura (HSP) is an IgA-mediated multisystem vasculitis that predominantly involves the skin, joints, gastrointestinal tract, and kidneys [1, 2, 3]. Renal involvement (HSP nephritis, or HSN) occurs in approximately 40% of HSP patients [4], with the majority of patients having only minor urinary abnormalities that resolve spontaneously. However, a subset of patients with severe nephritis may progress to end-stage renal disease (ESRD). The management of severe HSN has so far remained controversial. While some believe that no therapeutic regimen is really effective, others have tried oral and intravenous pulses of steroids, immunosuppressives (azathioprine, cyclophosphamide, chloramabucil), antiplatelet drugs, anticoagulants, rifampicin, or plasmapheresis either alone or in various combinations [5]. As severe HSN, which requires therapy, is uncommon, controlled therapeutic trials have never been carried out [6] and may, in fact, not even be possible due to its rarity. However, there is some evidence that therapy with steroids combined with an immunosuppressive such as azathioprine may indeed have a beneficial effect [6, 7, 8, 9]. We analyzed the clinical course of 11 children with severe HSN who were treated in our unit over the last 8 years.

Patients and methods

Of the 110 HSP patients who attended the Pediatric Rheumatology and Immunology Clinic of the Advanced Pediatric Centre, Post Graduate Institute of Medical Education and Research in Chandigarh between January 1993 and January 2001, 28 (25.5%) were diagnosed as having nephritis. The diagnosis of HSN was based on the presence of hematuria and/or proteinuria along with characteristic purpuric rash and abdominal or joint pain, or both, plus evidence of leukocytoclastic vasculitis on skin biopsy. Fourteen (50%) had minor urinary abnormalities that resolved spontaneously on follow-up. The other 14 had nephritis severe enough to be considered for a renal biopsy and specific therapy. One patient reported elsewhere [10] could not undergo biopsy, and two others were lost to follow-up. These three patients were excluded from further analysis. Of the

remaining 11, two patients whose biopsies showed little or no changes on light microscopy received oral steroids only. Nine patients received aggressive therapy with steroids and azathioprine. The clinical course of these eleven patients treated for severe nephritis was evaluated by reviewing the records.

Definitions used

1. Hematuria: "microscopic" if urine examination showed five or more RBCs/HPF and "gross" if visible to the naked eye [11]
2. Gross proteinuria: >40 mg/m^2 per h with or without edema [11]
3. Acute nephritic syndrome: hematuria with at least two conditions among hypertension, increased plasma creatinine, and oliguria caused by nephritis [8]
4. Hypertension: systolic or diastolic blood pressure >95th percentile for the specific age, based on the Second Task Force recommendations [12]

Clinical status evaluation

Clinical status was evaluated on initial encounter with the patient and at the latest observation, and each patient was classified into clinical state A, B, C, or D as adapted from the Goldstein et al. [13] classification on outcome in HSN:

A. Normal: normal physical examination, urine and renal function
B. Minor urinary abnormalities: microscopic hematuria or proteinuria (<40 mg/m^2 per h) but normal physical examination
C. Active renal disease: proteinuria of 40 mg/m^2 per h or more and serum creatinine <3 mg% with or without hematuria and hypertension
D. Renal insufficiency: serum creatinine >3 mg%, ESRD

Ten out of 11 patients were categorized with clinical status C, while one patient had clinical status B at the time of initial evaluation (Table 1). The majority of our patients had hypoalbuminemia, the mean serum albumin being 3.3 g/dl (range 2.8–3.6 g/dl).

Renal biopsies

All patients underwent percutaneous renal biopsies. The histopathological sample of one patient and immunofluorescence samples of two patients were found inadequate for opinion. The glomerular changes were graded according to the classification of the International Study of Kidney Disease in Childhood (ISKDC) [14] as follows:

Grade 1. Minor glomerular abnormalities
Grade 2. Pure mesangial proliferation
Grade 3. Minor glomerular abnormalities or mesangial proliferation with crescents/segmental lesions (sclerosis, adhesions, thrombosis, necrosis) in less than 50% of glomeruli
Grade 4. As grade 3 but with crescents/segmental lesions in 50–75% of glomeruli
Grade 5. As grade 3 but with crescents/segmental lesions in more than 75% of glomeruli
Grade 6. Membranoproliferative-like lesions

Further description was made of crescents as cellular, fibrocellular, or fibrous [15] and small or large [11].

Treatment protocol

Nine patients were assigned to receive steroids and azathioprine. Seven out of them received initial pulse steroids intravenously (methylprednisolone 30 mg/kg per day or dexamethasone 5 mg/kg per day) for 3 days followed by oral prednisolone, while the remaining two received oral steroids, right from the beginning, along with azathioprine (usually 2 mg/kg per day). Prednisolone was given as 1–2 mg/kg per day in three divided doses for approximately 8 weeks followed by maintenance with single dose of 1–2 mg/kg per day every alternate day. This was tapered off once the urinary abnormalities had stabilized for 2–3 months. The duration of prednisolone therapy ranged from 6–16 months (mean 12.1). Azathioprine was given for a mean duration of 14.7 months (range 6–24) and tapered off over 1–2 months. Supportive therapy was given for other manifestations (e.g., hypertension) as and when required.

As already mentioned, two patients with HSN who did not have significant changes on renal biopsy were treated with oral prednisolone alone.

Follow-up

All children were followed up initially every 2–4 weeks and later 1–2 months until remission and every 3–6 months thereafter. Urine examination for proteinuria and hematuria was done on each visit. Renal functions and hemograms were repeated every 3–6 months and as and when otherwise indicated. The mean follow-up period is 4.7 years (range 6 months–6.5 years).

Results

Table 1 summarizes the clinical and laboratory data of nine patients treated with steroids and azathioprine

Table 1. Clinical and laboratory data of patients with HSN. *ANS* acute nephritic syndrome, *GP* gross proteinuria, *HTN* hypertension, *RI* renal insufficiency, *Mic* microscopic

Patient no.	Age (years)/ sex	Mode of onset of ANS/GP	Associated features of HTN/RI	Initial proteinuria (g/m^2 per day)	Time taken to resolve (months)	Initial hematuria (gross/mic)	Time taken to resolve (months)	Follow-up period (years)	Clinical status at onset/at latest observation
1	6/F	+/+	+/+	4	6	Mic	6	6	C/A
2	10/M	+/+	+/–	9	7.5	Gross	7.5	5.5	C/A
3	12/M	+/+	+/–	2	9	Mic	9	5.5	C/A
4	8.5/F	+/+	+/+	4	8	Gross	8	5.3	C/A
5	8/M	+/+	+/–	4.3	10	Mic	4	5.1	C/A
6	8/M	+/+	+/+	3.3	8	Gross	8	4.5	C/A
7	11/M	+/+	+/–	7.5	2	Gross	12	3.5	C/A
8	9/F	+/+	+/–	1.3	3.5	Gross	3	0.5	C/A
9	11/M	+/+	+/–	2.4	7	Mic	5	3.5	C/A
10	9.5/F	+/–	–/–	Nil	–	Gross	17	2.5	B/B

(patient nos. 1–9) and two treated with steroids only (nos. 10, 11). The mean age at onset of HSN was 9.4 years (range 6–12), reaffirming the belief that severe nephritis is more common in older children [8, 16]. The total duration of illness averaged 30 days (range 10–75) and the mean interval between onset of disease to onset of nephritis was 19.5 days (range 8–30). The mode of onset was mixed nephritic-nephrotic in all patients except one (no. 11) who had an acute nephritic picture at onset. Five patients had facial edema. Three had evidence of renal insufficiency (mean serum creatinine level 3.6 mg%, range 3.2–4.0 mg%), which resolved over 3 to 6 months after the start of therapy. None has so far developed ESRD. Hypertension was noted in nine patients and was managed with nifedipine, enalapril, and propranolol used singly or in combination.

All patients had initial gross proteinuria (mean 3.9 g/m^2 per day) except one (no. 11) who developed proteinuria later in the course of the disease. It normalized over a mean period of 6.5 months. Recurrence of proteinuria occurred twice in one of the nine patients (no. 4) in the azathioprine-treated group. The first recurrence (1.32 g/day) resolved spontaneously while the child was on azathioprine, whereas the second recurrence (1.2 g/day) required a short course of steroids. In patient 10, normalization occurred in 7 months with recurrence (0.3 g/day) 8 months later, again resolving over the subsequent 5 months. In patient 11, proteinuria (1.8 g/day) developed at 1 year of follow-up which resolved over 1 month, with subsequent recurrence (1–3 g/day) 1 year later which has persisted till now.

Hematuria was gross in six patients and microscopic in five. Resolution occurred over a mean of 6.6 months in patients treated with azathioprine without any subsequent recurrence. In contrast, initial hematuria resolved in 5 months in patient 10, which recurred 1 year later and resolved in 6 months. In patient 11, initial resolution took 17 months and recurrence occurred 5 months later, which remains unresolved till now.

The clinical status of all patients who were treated with azathioprine and one patient (no. 10) treated with steroids alone improved from status C at onset to status A at the latest observation. Patient 11 ultimately underwent a repeat renal biopsy 2.2 years after disease onset and has been started on combination therapy (i.e., azathioprine + prednisolone) for the last 3 months.

Renal histopathological evaluation

Table 2 shows the histological data of the 11 patients under study. The mean interval between onset of nephritis and performance of kidney biopsy was 50.6 days. The average number of glomeruli per specimen was 20.5. Features of activity (mesangial hypercellularity, cellular crescents, increased matrix, lobular accentuation) were noted in 10/12 specimens, while

Table 2. Histopathological details of patients with HSN

Patient no.	Period from onset to biopsy (days)	Total no. of glomeruli	Percentage of glomeruli with large crescents	mesangial hypercellularity	Increased matrix	Synechiae formation	Fibrocellular crescents	Fibrous crescents	Tubulointerstitial damage	ISKDC classification (grade)
1	67	31	18	+	–	+	+	–	+	III
2	45	14	15	+	–	–	–	–	–	III
3	45	17	30	+	–	+	+	+	+	III
4	30	23	24	+	–	+	–	–	–	III
5	75	22	27	+	+	–	–	–	–	III
6	45	5	–	–	–	–	–	–	–	IV
7	4	16	13	+	–	–	+	–	+	III
8	45	Inadequate	Specimen							
9	135	51	–	–	–	–	–	–	–	Minimal lesions
10	21	12	–	+	–	–	–	–	–	I
Repeat biopsy	810	20	25	+	–	–	+	–	–	III

features of chronicity (fibrous crescents, synechiae formation, tubulointerstitial damage, glomerulosclerosis) were seen in 4/12 specimens. Hyaline arteriosclerosis was present in one patient (no. 4) only. According to the ISKDC classification, the glomerular changes were of grade 3 in seven patients and grade 4 in one. The specimen was inadequate for categorization in one patient (no. 8). Patient 10 had minimal glomerular lesions (unclassifiable). Patient 11 showed grade 1 changes on initial biopsy that progressed to grade 3 on repeat biopsy. Immunofluorescence studies revealed significant deposition (2+ to 3+) of IgA mainly in the mesangium and variable deposits of C3 and fibrin in the mesangium and capillary loops.

No clinical or laboratory parameters could be singled out to correlate with the severity of renal histopathological findings and the latest clinical status, as the outcome has been favorable in all patients treated with azathioprine so far. No significant therapy-related complications were observed in any patient. One patient (no. 7) developed chickenpox while on tapering doses of azathioprine. He was put on acyclovir and recovered over a week. Azathioprine had to be abruptly stopped in this case.

Discussion

Since the first precise description by Henoch a century ago [17], nephritis has been recognized as the most worrisome of all clinical manifestations of HSP, being the single most important cause of long-term morbidity and mortality in these patients [18]. Renal involvement in HSP has been reported to occur in almost 40% of patients (range 10%–100%), but the majority have minor urinary abnormalities [8, 19]. Nephritis was seen in 28/110 (~25%) of our patients but, in as many as 50%, the involvement was severe. Minor renal disease may be transient and can be easily missed if repeated urinalyses are not carried out [8]. As ours is a tertiary care hospital, late referrals to us would mean missing a substantial number of patients with minor renal disease [18].

Attempts have been made to prognosticate the outcome of HSN on the basis of mode of onset and clinical status at presentation (with or without histological grading of renal biopsies), but there is no consensus [13]. The percentage of patients with grade C and D outcomes ranges from nil in biopsy grade 1 to 67% in grade 5 [13]. More recently, scoring of biopsy specimens has been suggested [6, 13] with particular emphasis on tubulointerstitial changes predicting poorer outcomes. The majority of our patients had mixed nephritic-nephrotic onset. This has been found to be predictive of poor outcome (clinical grades C and D) in 52% of patients [13]. Again, in the nine patients treated with azathioprine, the renal histological changes were severe, indicating poor prognosis.

The two patients treated with steroids only had minimal histological abnormalities, suggesting a good outcome [20]. It may be inferred from the above discussion that combination therapy of azathioprine and steroids had modified the clinical course from grade C to grade A in the first nine patients, at least in the short term, and that oral steroids alone probably did not affect the clinical course much. However, the course of HSN is believed to be unpredictable, and long-term prognosis should always be kept guarded. Late complications have been known to occur many years later [18] and especially during pregnancy [13]. Late sequelae in our patients cannot, therefore, be ruled out.

Patients with severe HSN who have significant changes on biopsy are likely to do better with a combination of azathioprine and prednisolone rather than steroids alone. However, in such patients, if the renal biopsy shows minimal or no change, oral prednisolone should be started and the patient kept under close follow-up. Azathioprine should be added to the regimen if proteinuria and/or hematuria do not resolve within a couple of months or if the patient relapses after achieving remission. Repeat renal biopsy is also indicated at this time. Some authors have performed repeat renal biopsies on follow-up with a view to determine prognosis and the duration of azathioprine therapy [6, 21]. We, however, did not consider this necessary, as the children had shown complete clinical and biochemical recovery, and under such circumstances the procedure would not have been ethically justifiable.

Eight years back, when we started treating HSN with combination therapy (i.e., azathioprine and steroids), the view on usefulness of this approach was based only on anecdotal reports. Evidence accumulated over the ensuing years has confirmed its efficacy [6, 9]. We chose azathioprine in preference to other cytotoxic drugs such as cyclophosphamide and chlorambucil because of its relatively lower toxicity [22].

Even though all our patients treated with azathioprine had unfavorable clinical and histological grades, the possibility that some of them might have improved on their own without therapy cannot be excluded, as some patients have been known to have spontaneous remissions in HSN [20]. In our opinion, however, early aggressive therapy is justified because the outcome is difficult to predict in this disease. Further validation of scoring systems with multicentric trials may improve prognostication and settle this controversy, but these would be very difficult to conduct in view of the rarity of this condition.

To the best of our knowledge and belief, ours is only the third study on long-term use of azathioprine in severe HSN, but it is by no means a controlled study. As severe HSN is an uncommon occurrence, double-blind studies may be almost impossible to conduct [6]. For more accurate information, multicentric studies would be required to validate our results. In conclusion, our experience indicates that a combination of azathioprine and steroids significantly improves outcome in patients with severe HSN at least at 5-year follow-up.

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