Treatment of severe Henoch-Schönlein nephritis: justifying more immunosuppression

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The prognosis of Henoch-Schönlein purpura (HSP) nephritis is more severe than originally thought, with a significant portion progressing to deterioration of renal function in adulthood. Proteinuria adversely affects the outcome.

The aim of this study was to evaluate the initial single-center results of a treatment protocol for severe HSP nephritis based on the Heaton classification.

Age, gender, clinical features and duration of disease follow-up were assessed. Glomerular filtration rate (GFR), urinalysis and 24-hour urinary protein excretion were analyzed. All patients with severe renal involvement were biopsied and a treatment plan was assigned: Class II received oral steroids, Class III (with crescentic nephritis) received additional oral cyclophosphamide 2 mg/kg/d for 12 weeks, and Classes IV and V received azathioprine for 9 months subsequent to the treatment for Class III. All patients received angiotensin converting enzyme (ACE) inhibitors regardless of their blood pressure values.

Eighteen patients presenting with severe HSP nephritis, defined as heavy proteinuria and/or decreased renal function, were evaluated. Based on the renal histology, 5, 10, 1 and 2 of the patients were classified as Classes II, III, IV and V, respectively. At presentation, 7 of the patients had impaired renal function with GFR below 75 ml/min/1.73 m^2. With the presented treatment schema, all GFR returned to normal at the end of four years of follow-up. There was no proteinuria in any of the patients; only 8 had microscopic hematuria.

This preliminary study suggests a stepwise treatment according to the renal histology. The excellent results with complete disappearance of proteinuria and normal renal function justify the use of the aforementioned immunosuppressive protocol with ACE inhibition. Long-term, multicenter controlled studies are needed to verify our results.

Key words: Henoch-Schönlein purpura, nephritis, biopsy, immunosuppressive treatment.

Henoch-Schönlein purpura (HSP) is the most common form of vasculitis in childhood in most parts of the world. It mainly affects the small vessels of the skin, joints, gastrointestinal system, and kidneys[1]. The deposition of immunoglobulin A (IgA) containing immune complexes within the walls of the small vessels and within the mesangium have been held responsible for the pathogenesis of the disease. Usually, renal involvement is detected during the first four weeks of the illness in the form of hematuria. Although less common, severe nephritis with proteinuria may also be encountered in children. Renal involvement is the major cause of late morbidity. In one series of childhood, HSP nephritis accounted for 10-15% of glomerulonephritis and 3% of end stage renal disease (ESRD)[2].

Previous literature has agreed that renal involvement of HSP had an overall good prognosis. The risk of renal insufficiency or mortality was found to be 2-8% in children with HSP nephritis[3,4]. However, recent studies have shown that a considerable percentage of severe HSP nephritis progresses to renal failure[5,6]. In a recent report, one-quarter of the pediatric HSP nephritis cases had renal impairment at 4.8 years follow-up[4]. Several studies have shown that heavy proteinuria at the onset had a poor prognosis[3,7-17]. On the other hand, the presence of crescentic glomeruli in more than 50% of the biopsy specimens of the patients with HSP accounts for a poor outcome[8,12-14,18,19]. A study from Finland reported that HSP arising in childhood may cause renal disease and even renal failure later in life in a significant portion of patients[10]. There is no consensus on how to treat HSP patients with renal involvement, but the importance and efficacy of early induction of therapy in HSP patients with severe proteinuria have been previously emphasized[20]. The treatment choices have varied from steroids alone to combined heavy immunosuppressant therapy. However, we lack Level I evidence data for the best treatment in these patients.

The aim of our study was to present the results of our treatment algorithm that was based on the clinicopathological features in the kidney. Although the results are from a single center, we believe that the excellent results in a mean of four years deserve emphasis.

Material and Methods

This was a prospective, single-center study in patients originally diagnosed as HSP between April 1999 and April 2004. They all had presented to the pediatric nephrology and rheumatology outpatient clinics of Hacettepe Medical Faculty, Ankara, Turkey. The diagnosis of HSP was based on the typical clinical features and all met both the European League Against Rheumatism/Paediatric Rheumatology European Society (EULAR/PRES) criteria for childhood HSP and the American College of Rheumatology (ACR) criteria[21,22]. Thirty-three HSP patients presenting during this period had renal involvement defined by the presence of gross or microscopic hematuria (>5 cells per high power field from a centrifuged specimen) with or without proteinuria. Severe HSP nephritis was defined as heavy or nephrotic range proteinuria (>40 mg/m^2/h) and/or impaired renal function (defined as a reduced glomerular filtration rate (GFR) <75 ml/min/1.73 m^2) at presentation. If the patient met the criteria for severe HSP nephritis, he/she was admitted for a renal biopsy.

Eighteen of the aforementioned patients met the definition of severe HSP nephritis and underwent renal biopsy and were the subjects of this study.

The epidemiological data collected were age, sex, clinical features, and duration of disease follow-up. Laboratory assessment included GFR, urinalysis and 24-hour urinary protein excretion. Urinary protein excretion was expressed as mg protein/mg creatinine ratio (Up/Uc) and was then measured quantitatively.

Hypertension was defined according to the 4th report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents by the National Institutes of Health (NIH)[23].

Nephrotic syndrome was defined as proteinuria >1 g/m^2 per day and serum albumin <2.5 g/dl with or without edema. Nephritic syndrome was defined as hematuria, proteinuria, hypertension, and azotemia.

The biopsy specimens were graded according to the classification developed by Heaton[24]. According to this classification, absence of crescent formation was classified as Grade II and <50% crescents as Grade III, whereas 50-75% and >75% crescent formation were classified as Grades IV and V, respectively. None of our patients had minimal glomerular abnormalities (Grade I) or membranoproliferative glomerulonephritis.

Oral prednisolone was started in all these cases who met the definition of severe HSP nephritis. If the histological diagnosis was Grade II, no other immunosuppressive drug was added (Table I). If the renal histology was reported as ≥ Grade III by Heaton classification, oral cyclophosphamide was started at a dose of 2 mg/kg/day and continued for 12 weeks (168 mg/kg total dose). If the renal histology was classified as ≥ Grade IV, a nine-month course of azathioprine (at 1.5-2 mg/kg/day oral) was prescribed to follow the 12-week course of cyclophosphamide. If renal failure or

Table I. Treatment Protocol Based on Histopathological Features

Biopsy (for nephrotic proteinuria and/or reduced glomerular filtration rate)	Treatment
Grade II	Oral prednisolone 1 mg/kg/day tapered and switched to every other day at 1 month
Grade III	As above and oral cyclophosphamide 2 mg/kg/day for 12 weeks (168 mg/kg/total)
Grade IV and above	As above and oral azathioprine 1.5-2 mg/kg/day subsequent to cyclophosphamide continued for 9 months

life-threatening gastrointestinal complications were present, pulse methylprednisolone at 500 mg/m^2/d intravenously for three consecutive days was given. All patients received an angiotensin converting enzyme (ACE) inhibitor (0.3 mg/kg per day) regardless of their blood pressure values.

Results

The age of the patients with severe HSP nephritis ranged from 4 to 15 years (mean: 11.2±4.0 years). Ten were boys and eight were girls with a male/female ratio of 1.25. All children presented with characteristic purpura of HSP. Arthralgia and/or arthritis were present in 15 cases. Abdominal symptoms were evident in 17 patients, while severe abdominal symptoms were seen in 12 of these patients. Twelve (67%) had purpura for more than one month. The median follow-up time was four years.

The first sign of nephropathy was detected during the first month of the disease in 16 cases and during the second month of follow-up in the remaining two. Range of proteinuria varied from moderate to severe. One patient had nephrotic syndrome, 13 had nephritic features with heavy proteinuria and four had nephritic syndrome. Children presenting without heavy proteinuria had decreased creatinine clearances meeting the definition of severe HSP nephritis. Seven of these patients had a decreased GFR (<75 ml/min per 1.73 m^2, range: 17-70) with serum creatinine levels of 1.3-2.5 mg/dl.

By light microscopy, 8-34 glomeruli per sample were examined and the glomerular changes were graded according to the classification of Heaton. The majority were defined as Class III HSP nephritis. Only two children were classified as Grade V. Table II describes the nephrological features present in each class.

With the aforementioned treatment protocol, proteinuria completely disappeared in all patients by 4-6 months of treatment. All had normal blood pressure and normal renal function tests. No side effects were observed. Eight patients had microscopic hematuria at the last visit. Three were lost to follow-up after a year. The follow-up period for the remaining group was a mean of four years.

Discussion

Henoch Schönlein purpura is the most common vasculitis in most parts of the world, and it is thus ironic that there is no evidence-based data on how to treat its most dreadful long-term complication, severe renal disease. This report suggests an algorithm for the treatment of severe HSP nephritis based on the renal classification. We hope this will serve as a basis for multi-center studies that will provide us with more substantial data.

Henoch Schönlein purpura nephritis is a disease that pediatricians need to consider more fully in terms of the adequacy of their treatment. Reports that suggest current treatment practices yield a good prognosis for children may have affected

Table II. Clinicopathological Correlation of Henoch-Schönlein Purpura Nephritis

	Heaton Classification			
Clinical Findings	II	III	IV	V
Acute nephritic syndrome	1	3	–	–
Nephritic+nephrotic syndrome or heavy proteinuria	4	6	1	2
Nephrotic syndrome	–	1	–	–
Decreased glomerular filtration rate	1	6	–	–

our management of this condition resulting in a reluctance to use immunosuppressive-based treatments. Series of unselected children used to indicate that most children entered full remission of kidney disease, with only 2-13% developing ESRD[2]. However, recent reports have questioned the so-called good outcome of HSP. Reference centers have reported remission in less than half of the patients[5,25]. Coppo and colleagues[26] have shown that a quarter of the children presenting with HSP ended up with renal function impairment. They showed that the prognosis was similar and indeed not better than in adults[26].

In a multicenter study, proteinuria has been shown to be the main prognostic factor adversely affecting renal outcome[26]. In fact, the alleviation of proteinuria has been shown to parallel the resolution of renal disease in other kidney ailments. In this investigation, we were able to successfully treat proteinuria with steroids, immunosuppressives and ACE inhibitors in patients who presented with severe HSP nephritis with crescent formation. Similar treatment protocols have previously been suggested for severe HSP nephritis, especially in those with renal failure. Only patients presenting with severe proteinuria or deteriorating renal function were the subject of the study. The management of patients with only mild urine abnormalities does not require immunosuppressive treatment as such.

Based on the results of this investigation, we suggest a stepwise protocol with treatment decisions based on the classification of the renal biopsy and on crescent formation. Tarshish et al.[27] used cyclophosphamide 90 mg/m^2/day for 42 days in all instances of HSP nephritis; however, proteinuria persisted in a significant portion of patients and they were not able to achieve remission in all patients: 12.5% of patients identified with HSP nephritis reached ESRD in a mean follow-up of 3.7 years.

We suggest that if the patient has a disease severity of Class III or more, the dose of cyclophosphamide should be 168 mg/kg (cumulative dose at 12 weeks) and should be followed by a course of azathioprine for more severe classes. In a meta-analysis, a cumulative dose of up to 200-250 mg/kg was considered safe for most children in terms of gonadal toxicity[28]. The complete disappearance of proteinuria and restoration of all renal functions indicate the effectiveness of the suggested therapy after a four-year follow-up. Flynn et al.[29] also observed a significant reduction in proteinuria with steroids and 12-week course of cyclophosphamide in children with crescentic HSP nephritis.

Angiotensin converting enzyme inhibition has also contributed to the favorable outcome in our series. Recent studies in IgA nephritis have highlighted the effectiveness of ACE inhibition in the management of this disease[30]. HSP nephritis shares certain features of IgA nephritis. These two diseases are thought to be within the spectrum of one disease although they have differences in etiopathogenesis. Thus, we concluded that ACE inhibition would be beneficial in the treatment of HSP nephritis. This may be through the anti-transforming growth factor (TGF) effect introduced by ACE inhibition or other potential effects[30,31].

Previous reports have suggested that older children with persistent purpura tended to be associated with more severe symptoms[32]. This was true in our study as well when compared to the HSP patients in the same center.

In conclusion, we suggest a treatment algorithm in the hope of preventing long-term kidney sequelae in children with crescentic, severe HSP nephritis. We believe we can substantially improve our ability to prevent this condition by classifying the pathology. We suggest that the presented immunosuppressive treatment with ACE inhibitors will improve the long-term prognosis, although multicenter controlled studies are required to provide the best data in treatment.

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