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*Case Report*

# Abrupt and durable remission of Henoch–Schönlein purpura nephritis with cyclosporine A

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**Abstract**

Henoch–Schönlein purpura glomerulonephritis (HSP-GN) is a common form of systemic small vessel vasculitis in children. Although prognosis is usually favourable, the disease is occasionally associated with a risk of renal insufficiency. Various immunosuppressive agents have been used in patients with severe HSP-GN, but none have shown convincing favourable effects. We report a case of biopsy-proven HSP-related GN in a 4-year-old girl that responded remarkably well to cyclosporine A (CsA), following failure to respond to other immunosuppressive agents. At 8 months post-CsA treatment, repeat renal biopsy findings were consistent with histological improvement. We conclude that CsA treatment not only exerts beneficial effects on resistant HSP-related GN but may also arrest progression of the disease.

**Keywords:** cyclosporine A; glomerulonephritis; Henoch–Schönlein purpura

## Introduction

Henoch–Schönlein purpura (HSP) is the most common form of systemic small vessel vasculitis in childhood. The dominant clinical features of HSP are cutaneous purpura, arthritis, abdominal pain and glomerulonephritis (GN) [1]. Although prognosis is mostly favourable, the condition is occasionally associated with a risk of renal insufficiency. In particular, the combination of nephrotic-range proteinuria and hypertension predicts a poor prognostic outcome [2]. Renal prognosis can also be predicted by the renal biopsy findings [1]. Among reports of immunosuppressive agents used in patients with severe forms of HSP-related GN, a few have indicated beneficial effects of cyclosporine A (CsA) in resistant forms of the disease [3–5].

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We report a case of HSP-related GN with nephrotic-range proteinuria in a 4-year-old girl that responded remarkably well to CsA following failure to respond to other immunosuppressive agents. After 8 months of CsA treatment, the patient achieved clinical remission and repeat renal biopsy findings showed histological improvement. We conclude that treatment with CsA exerts beneficial effects in resistant HSP-related GN and may arrest progression of the disease.

## Case report

A 4-year-old girl was admitted for purpura on the legs. There was no arthritis, abdominal pain or oedema. Blood pressure was 95/60 mmHg. Urine analysis revealed microscopic haematuria, proteinuria and granular casts. Within a week she developed nephrotic-range proteinuria (5 g/24 h), urine protein/urine creatinine (mg/g) that varied from 5 to 7, as well as macroscopic haematuria and hypoalbuminaemia (2.5 g/dl). Upon renal biopsy, we examined 47 glomeruli that had focal and diffuse proliferative lesions and deposits of $IgA^{+++}$, $C^{3+}$ and $IgM^{+}$. There was no vasculitis. Half of the tubules were necrotic (Table 1). The lesions were graded according to the International Study of Kidney Disease in Children (ISKDC) and were classified as stages IIIB–IV (Figure 1A).

Treatment was initiated with prednisolone, 2 mg/kg/day, for 1 month. Proteinuria persisted and azathioprine (2 mg/kg/day was added while steroids were gradually tapered to 2 mg/kg every other day. Although proteinuria decreased from 5 to 1 g/day, it increased 5 weeks later to 3 g/day. Azathioprine was withdrawn and the child was started on cyclophosphamide (2 mg/kg/day) for 2 weeks, without substantial improvement in the nephrotic/nephritic syndrome. Intravenous pulses of methylprednisolone, 30 mg/kg/day, for three consecutive days followed by the same dosage on alternate days for 6 days did not affect the nephrotic syndrome. Within 3 months the patient was cushingoid and hypertensive (130/60 mmHg). Serum creatinine was 0.58 mg/dl. The nephrotic syndrome persisted. Considering the lack of efficacy and the poor tolerance of

**Table 1.** Renal biopsy findings at initial diagnosis (first) and 8 months (second) after initiation of CsA treatment

| | First biopsy | Second biopsy |
|---|---|---|
| *No. of glomeruli* | 47 | 40 |
| Normal | 12 | 24 |
| Immature | 6 | 0 |
| Sclerosed | 6 | 6 |
| *Proliferation* | | |
| Endocapillary | 17 | 0 |
| Mesangial | | |
| MPGN-like | 6 | 0 |
| *Segmental necrosis* | | |
| Crescents | 0 | 0 |
| Type of crescents | | |
| *Tubules* | | |
| Normal | 50% | 95% |
| Necrosis | 50% | 0% |
| Atrophy | 0% | 5% |
| *Vessels* | | |
| Normal | + | + |
| Necrosis | − | − |
| Sclerosis | − | − |
| *Interstitium* | | |
| Normal | + | + |
| Inflammation | − | − |
| Fibrosis | − | − |
| *Immunofluorescence* | 11 gloms | 6 gloms |
| IgG | ++ | − |
| IgA | ++ | ++ |
| IgM | + | − |
| $C_{1q}$ | − | − |
| $C_3$ | + | + and in small vessel walls |
| $C_4$ | − | − |

the foregoing measures, she was started on CsA (Neoral®, Novartis Pharma, Basel, Switzerland, 150 mg/m$^2$/day) with continuation of prednisolone at a dose of 1 mg/kg every other day. CsA blood levels were monitored twice a week for 1 month and once monthly thereafter for 1 year. Adjustment of dosage was based on $C_0$ and $C_2$ blood levels, assessed by monoclonal antibody assay, that aimed to achieve a $C_2$ target level of 750 ng/ml. The effect of CsA was striking: within 3 weeks proteinuria was nil. Renal function remained normal (serum creatinine 0.51 mg/dl, GFR according to Schwartz's formula 110 ml/min/1.73 m$^2$). Steroid dosage was gradually tapered to 5 mg on alternate days and withdrawn within 5 months.

At 8 months after starting CsA, we examined 40 glomeruli in a repeat renal biopsy. The lesions had regressed to stages I–II (Figure 1B). A mild degree of mesangial proliferation persisted in 10 glomeruli that had IgA$^{++}$ deposits (Table 1). Five percent of the tubules were atrophic with no evidence of interstitial or vascular toxicity caused by CsA. CsA treatment was continued for 6 months and slowly tapered over the following 6 months to a stop. Total CsA treatment duration had been 20 months. Follow-up is now 4 years. Blood pressure is 100/60 mmHg. Proteinuria is nil. Urine erythrocyte counts are 1–2 per field. Serum creatinine is 0.5 mg/dl.

## Discussion

Persistent proteinuria or nephrotic-range proteinuria in the course of childhood HSP is frequently a forerunner of chronic renal insufficiency [1]. Renal prognosis is also predicted by the level of renal histopathology: 52% of grade IV HSP-GN progress to renal insufficiency [2]. Our patient fulfilled these criteria of poor prognosis.

Various therapeutic measures have been proposed to arrest the progression of HSP-GN [3]. Considering our lack of understanding of the pathophysiology of the disease, most, and perhaps all, therapies can be considered as blind trials, having the hope of favourable clinical and histological effects. Three main categories of drugs have been tested,

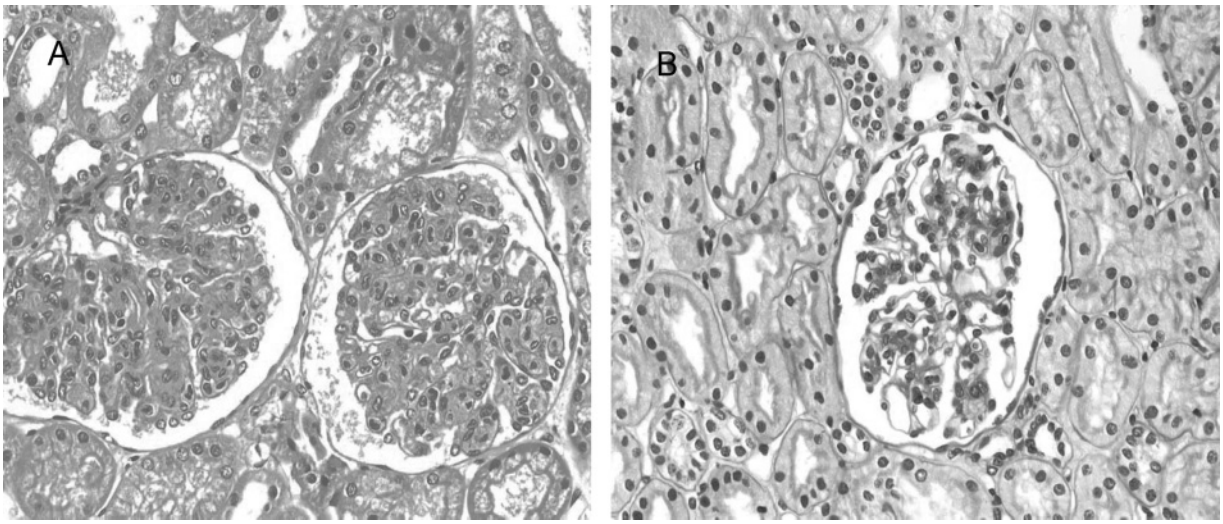


**Fig. 1.** Photomicrographs of kidney biopsy specimens, (**A**) before treatment and (**B**) 8 months after treatment. Panel **A** (haematoxylin/eosin stain) shows a rather severe degree of mesangiocapillary and endocapillary proliferate lesion that affects both glomeruli. There is also a severe degree of acute tubular injury with loss of the normal brush border. In panel **B** (PAS stain), mild segmental mesangioproliferative lesions are observed along with normal tubules and interstitium.

which include anticoagulants [3], corticosteroids and immunosuppressive agents, such as cyclophosphamide and azathioprine [6]. Corticosteroids, given alone or in combination with cytotoxic agents, are credited with remission of proteinuria in most cases [3]. However, in rare cases, the disease is stubbornly resistant to any of these drugs, as was the case with our patient.

Ronkainen *et al*. [4] evaluated the efficacy of CsA for treating seven paediatric HSP-GN patients with nephrotic-range proteinuria. They concluded that CsA provides promising treatment for resistant HSP-GN, since four of the seven patients enjoyed stable remission and all had retained renal function at 6 years following treatment. More recently, Shin *et al*. [5] reported a beneficial effect of CsA in seven children suffering from HSP-related nephrotic syndrome. Taken together, we believe that such encouraging and well-documented findings with CsA, combined with the present case, which was supported by repeated renal biopsy findings, justify interest in CsA as treatment for HSP-GN.

The favourable effect of CsA on proteinuria in HSP-GN has been ascribed to non-immunologic, pharmacologic effects on glomerular permeability to proteins [7]. However, if this were the case, complete remission would be rare and there should not be any effects on haematuria. More important, our findings showing regression of histologic glomerular lesions (Figure 1) argue against non-immunologic mechanisms.

The efficacy of CsA in combination with low-dose corticosteroids has been amply demonstrated in a minimal change disease and in a significant proportion of focal-segmental glomerulosclerosis cases [8]. It has been shown that CsA dependence is not the rule [7]. In these forms of nephrosis, CsA buys time until the unknown process that induces the nephrotic syndrome has reached a phase of extinction. We postulate that a similar mechanism may explain the stable, complete remission of HSP-GN obtained in our patient after prolonged treatment with CsA.

The issue of tolerability is critical for any trial using CsA to treat renal disease, irrespective of disease aetiology. As is already known, the most accepted method for detecting nephrotoxic effects of CsA in treated children with idiopathic nephritic syndrome is by means of a repeat renal biopsy rather than a stable serum creatinine concentration [7]. We believed that these criteria also applied to our HSP-GN patient, who was treated with CsA. In our patient, a repeat biopsy after 8 months of CsA treatment revealed findings of twofold interest. First, it showed minor, almost insignificant tubular lesions and ruled out CsA toxicity (Figure 1B). This good tolerance can be ascribed to the rather low dosage of the drug and to the meticulous monitoring of CsA blood levels. Second, it showed that our treatment option was likely responsible for the marked improvement in the primary renal disease.

The present findings warrant larger scale studies to confirm the favourable effects of CsA in severe forms of renal involvement.

*Conflict of interest statement*. None declared.

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