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Anaphylactoid purpura: characteristics of 16 patients who progressed to renal failure

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Abstract. Renal insufficiency occurs in at least 1.5% of children with anaphylactoid purpura (AP). We reviewed the records of 16 children who developed end-stage renal disease (ESRD group) secondary to AP and matched them for age, era of onset, renal histology, and clinical severity at onset with 16 children who had AP but whose creatinine clearance returned to and remained normal (recovery group). We reviewed creatinine clearances at 1, 3, 5, and 10 years after onset. A creatinine clearance >70 ml/min per 1.73 m^2 was present in 50% of the patients in the ESRD group at 3 years and in 25% at 5 years after onset. In contrast, all patients in the recovery group had a creatinine clearance >70 ml/min per 1.73 m^2 by 3 years (7 of 16 had a creatinine clearance >125 ml/min per 1.73 m^2) and all were normal 95–125 ml/min per 1.73 m^2) by 5 years. Thus, the presence of an increased creatinine clearance (>125 ml/min per 1.73 m^2) at 3 years predicted recovery, while failure to reach a creatinine clearance of >70 ml/min per 1.73 m^2 at 3 years predicted progression to ESRD. There was no evidence of recurrent systemic AP or nephritis in the 14 patients who underwent renal allograft transplantation. We conclude that long-term evaluation of patients over many years is required to identify those who will progress to ESRD from AP and that recurrence of AP in the renal transplant is uncommon.

Key words: Anaphylactoid purpura – Henoch-Schönlein purpura – Renal transplantation – Glomerulonephritis

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Introduction

Anaphylactoid purpura (AP), also called Henoch-Schönlein purpura, is a relatively uncommon disease occurring primarily in the first and second decades of life [1–4]. The usual presenting features include purpuric rash, abdominal pain, arthralgias [1–4] and in 40%–90% of patients, renal involvement [5]. The nephritis of AP is usually mild and not progressive, and in an unselected patient population, renal insufficiency occurred in only 1.5% [6]. AP is responsible for approximately 5% of all end-stage renal disease (ESRD) in childhood and at the University of Minnesota constitutes 22% of all glomerulonephritis in pediatric patients leading to ESRD. It is important to identify this population of patients at risk for renal failure early in their course, since this may influence therapeutic decisions.

Previous authors have defined variables at disease presentation which predict a high risk of development of ESRD and have pointed out that the progression to ESRD may not become evident until several years after onset [2]. However, previously described risk factors of a nephritic and nephrotic syndrome at presentation, coupled with a high proportion of crescents on renal biopsy specimens, were not shown to be accurate predictors, in that approximately half of the patients with these characteristics recovered and half developed severe sequelae [7].

This paper is an attempt to refine predictive indices for those children with early clinical and histological findings believed to be predictive of progression to ESRD. Finally, we have reviewed the outcome of the ESRD group to assess the benefits of renal transplantation in their management.

Patients and methods

The diagnosis of AP with nephritis was established by the commonly accepted clinical criteria of purpuric rash, gastrointestinal involvement, arthralgias, and renal disease, the latter verified in all cases by light, immunofluorescent, and electron microscopic changes on initial renal biopsy specimens.

The patients were derived from a review of the records of approximately 100 patients with AP nephritis who had renal biopsies between 1955 and 1981. Sixteen patients were identified who had progressed to end-stage renal disease (ESRD group). We compared these patients with a control group of 16 carefully matched patients who had a similar severity of clinical and renal pathological involvement at onset but in whom the creatinine clearance returned to normal (>95 ml/min per 1.73 m^2, recovery group). This design was adopted in order to retrospectively ascertain whether predictive indices would allow clear separation of these two groups. The two groups of patients were closely matched for age (mean 11.2 years, range 5–17 years), era of onset, similarity of histopathological involvement at onset, and clinical severity of nephrotic syndrome, hypertension, and measured creatinine clearance at onset, but were not matched for degree of hematuria. Both groups have been followed for 14±6 (X±SD) years since initial presentation of their AP and a mean of 9.6±5.7 years since reaching either ESRD or recovery.

Clinical and laboratory data at onset and at 1, 3, 5, and 10 years after onset were analyzed for the presence of hypertension (defined as equal to or greater than the 95th percentile for age [8] and/or requirement of blood pressure medication), nephrotic syndrome (defined as edema associated with serum albumin <2.5 mg/dl and >40 mg/kg per day of urinary protein), microscopic or gross hematuria, and glomerular filtration rate estimated by creatinine clearances in one or more 24-h urine collections. We classified creatinine clearances into the following four groups: (1) <70 ml/min per 1.73 m^2; (2) ≥70 but <95 ml/min per 1.73 m^2; (3) ≥95 but ≤125 ml/min per 1.73 m^2 (normal in our laboratory); and (4) >125 ml/min per 1.73 m^2.

The patients in the two groups were treated similarly. In the ESRD group, 12 of the 16 patients received prednisone and azathioprine for a mean of 1.5±0.71 years, 2 additional patients received cyclophosphamide, while 2 patients received prednisone alone. In the recovery group, 14 of the 16 received prednisone and azathioprine for 1.7±0.57 years, 1 patient received heparin and prednisone, and 1 patient received prednisone alone. There were no significant differences between the two groups in the dose or the duration of treatment with azathioprine and prednisone.

Analyses for recent streptococcal infection, antinuclear antibody, hypocomplementemia, rheumatoid factor, and hepatitis B antigenemia were negative in all 32 patients.

All patients had kidney biopsies within 3.4 months (range 1–7 months) of presentation. The kidney biopsy specimens were processed for light, immunofluorescent, and electron microscopy using established techniques. The initial kidney biopsy slides available in 28 of 32 patients were re-reviewed by one of us (RS) without knowledge of the clinical course. Glomerular changes were graded based upon the classification by the International Study of Kidney Diseases in Children [9]: (1) minor glomerular abnormalities; (2) mesangial proliferation either in some or all of the glomeruli; (3) crescents or segmental lesions in less than 50% of the glomeruli; (4) crescents or segmental lesions in 50%–75% of the glomeruli; (5) crescents or segmental lesions in greater than 75% of the glomeruli; and (6) membranoproliferative-like glomerulonephritis.

Chi-square statistical analysis was considered significant when the P value was <0.01.

Results

Evaluation of persistence of nephrotic syndrome or hypertension at onset or at intervals of 1, 3, and 5 and 10 years demonstrated no significant differences between the two groups, perhaps due to the small numbers of patients followed at 5 and 10 years. Chi-square analysis revealed a significantly ($P<0.01$) greater incidence of gross hematuria in the group that progressed to ESRD (Table 1). Although there was no difference between the two groups in the creatinine clearance at onset, the creatinine clearances were significantly greater in the recovery group at 1, 3, and 5 years (Fig. 1). In the ESRD group, 10 of 16 patients (62%) at 1 year, 8 of 16 patients (50%) at 3 years, and 12 of 16 patients (75%) at 5 years had creatinine clearances <70 ml/min per 1.73 m^2. The recovery group had 2 of 16 patients (12%) with a creatinine clearance <70 ml/min per 1.73 m^2 at 1 year, but all patients in this group had a creatinine clearance >70 ml/min per 1.73 m^2 at 3 years and all improved to a normal creatinine clearance by 5 years. The mean time from onset to ESRD in this group was 5.9 years (range 0.75–19 years). The mean time to recovery (creatinine clearance >95 ml/min per 1.73 m^2) in the recovery group was 1.9 years (range 0.75–4 years). Thus, in this study, failure to achieve a creatinine clearance ≥70 ml/min per 1.73 m^2 by 3 years predicted a poor outcome. Nonetheless, it should be pointed out that a return of the creatinine clearance to 70 ml/min per 1.73 m^2 by 3 years did not necessarily predict a good outcome, since 50% of the patients in the ESRD group had achieved this level by 3 years, and at 5 years 25% continued to have a creatinine clearance >70 ml/min per 1.73 m^2 (Fig. 1).

Table 1. Signs and symptoms at presentation

	ESRD (n = 16)	Recovery (n = 16)
Age (years)[a]	9.7± 3.3	11.7± 4.5
Nephrotic syndrome[b]	8	5
Hypertension[b]	10	7
Gross hematuria	12	4 ($P<0.01$)
Micro hematuria	2	7
Creatinine clearance[b] (ml/min/1.73 m^2)	64 ±31	72 ±27

[a] Mean ± SD
[b] Defined in text
ESRD: end-stage renal disease

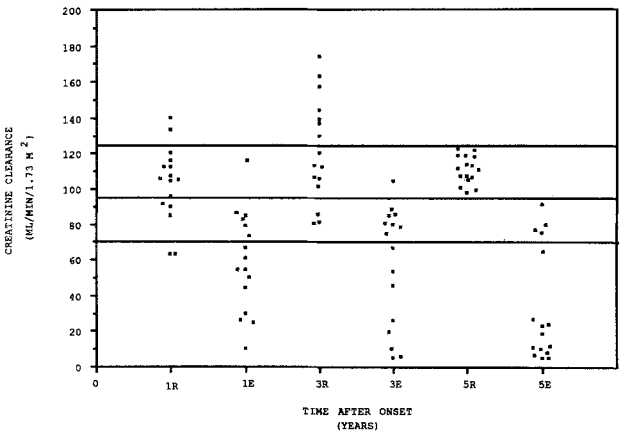

Fig. 1. Creatinine clearance (ml/min/1.73m^2) in recovery group (*R*) and end-stage renal disease group (*E*) at 1, 3 and 5 years after onset. Each *dot* represents an individual patient. All patients in the R group had clearance above 75 ml/min/1.73 m^2 at 3 years

Table 2. Morphological features

Pathological grades[a]	I	II	III	IV	V	VI
ESRD (n = 13)	1	0	2	3	4	3
Recovery (n = 15)	1	0	6	4	1	3

[a] Defined in text

In evaluating patients of both groups who had creatinine clearances between 70 and 125 ml/min per 1.73 m^2 at 3 years, there appeared to be no significant differences in the degree of hypertension or proteinuria that would further help to predict recovery or progression to ESRD.

Seven of the patients in the recovery group had evidence of an increased creatinine clearance (>125 ml/min per 1.73 m^2) at 3 years (Fig. 1). Three of these patients had proteinuria (1 was nephrotic and the other 2 had 25–30 mg/kg per day of urinary protein with normal serum albumin), while the other 4 patients had no significant proteinuria. All 7 of these patients had a normal creatinine clearance by 5 years without persistent proteinuria. No patient in the ESRD group had an increased creatinine clearance at any time.

There was no consistent relationship between the grades of morphological changes in the biopsy specimens and the ultimate course of the two groups of patients (Table 2). Two of the biopsy specimens in each group had peripheral glomerular loop deposits of IgA, while all patients had mesangial IgA deposits of similar intensity.

Fourteen of the 16 ESRD patients have received renal transplants; 1 currently receives maintenance hemodialysis because of multiple lymphocytotoxic antibodies and another with a creatinine clearance of 10 ml/min per 1.73 m^2 is currently awaiting kidney transplantation. The 14 transplanted patients have received 20 renal allografts and 6 kidneys were lost from rejection. Eleven of the 14 patients who received kidney transplants are alive, with a mean allograft survival time of 9.8 years (range 1–23 years). No patient has developed clinical signs or symptoms of recurrence of their original disease in the allograft. The 3 patient deaths were attributable to suicide, gram-negative sepsis, and post-transplant malignancy. Renal tissue was available from 18 of the 20 allografts either as renal biopsy specimens obtained for graft dysfunction or nephrectomy specimens obtained either from autopsies or removed due to chronic rejection, and none showed pathological evidence of recurrent disease.

Discussion

It has been stated that the prognosis for recovery of patients with AP is based upon the severity of the nephropathy [3]. Meadow et al. [2, 10] reported that up to 40% of patients with severe nephritis/nephrotic syndrome at onset had severe sequelae such as renal insufficiency, persisting hypertension or nephrotic syndrome. These authors further found that renal morphology at initial biopsy was roughly correlated with the severity of clinical expression and was of definite value in predicting outcome [2]. In a follow-up of those patients, Counahan et al. [7] found that although the presentation with severe clinical and histological disease was associated with poor prognosis, these characteristics were imprecise predictors of outcome, in that 50% of the patients in this category recovered while 50% had progressive disease.

As others have previously shown, we have not been able to identify any characteristics of either the initial clinical course or the initial renal pathology which allowed precise prediction of the eventual outcome of AP nephritis in our patients. However, this current study extends these earlier observations by discerning that failure at 3 years to regain a creatinine clearance of ≤70 ml/min per 1.73 m^2 was highly predictive of ESRD, while a high creatinine clearance at this time (>125 ml/min per 1.73 m^2) was highly predictive of recovery. Nonetheless, the prognosis of patients with values between these limits of creatinine clearances at 3 years was not predictable. Furthermore, the presence of gross hematuria at onset was a significant, albeit imperfect, negative prognosticator.

Recent long-term studies have found that up to two-thirds of patients with AP who develop renal insufficiency do so within the first 3 years from initial onset [3, 6, 11]. However, Cameron [11] reported a patient who did not develop renal insufficiency until 15 years after initial presentation.

In the present study, 50% of the patients in the ESRD group had a creatinine clearance >70 ml/min per 1.73 m^2 at 3 years and 25% had a creatinine clearance >70 ml/min per 1.73 m^2 at 5 years after diagnosis. One patient did not develop renal failure until 19 years after onset of AP. These observations emphasize that renal insufficiency can develop late in the course of the disease without clear warning provided by the initial and follow-up evaluations. All patients in our recovery group had a return of creatinine clearance >70 ml/min per 1.73 m^2 by 3 years. Therefore, later evaluation may be more useful than the initial findings in identification of those patients at risk for ESRD, since return of creatinine clearance to >70 ml/min per 1.73 m^2 by 3 years after onset was not an accurate predictor of recovery. However, failure of the creatinine clearance to reach 70 ml/min per 1.73 m^2 by 3 years or failure of normalization of the creatinine clearance by 5 years did predict a poor outcome.

An increased creatinine clearance at 3 years (>125 ml/min per 1.73 m^2) which was observed in 7 patients who recovered, has not been previously noted in other forms of glomerulonephritis during recovery. Three of these patients had significant proteinuria, which may be important to note, since proteinuria can spuriously elevate creatinine clearance [12]. None of the patients in the ESRD group had increased creatinine clearances at any time. It is possible that hypertrophy of nephrons relatively undamaged by AP nephritis when coupled with recovery of the relatively damaged nephrons may result in hyperfiltration, which may be expressed clinically as an elevated creatinine clearance. This observation is interesting in that is contradicts the current hypothesis that hyperfiltration leads to progressive renal disease [13, 14].

The ongoing debate of whether immunosuppressive treatment alters the natural course of the disease is not addressed in this study, since our study was uncontrolled and all patients were treated.

Leumann and Briner [15] reported a 40% chance of recurrence of AP in the transplanted kidney, which has been said to occur while the patient is receiving immunosuppressive therapy.

Review of the available literature [16–21] identified 6 possible cases of recurrence of this disease in the post-transplant period, resulting in 3 of 6 grafts being lost [16–18]. The 3 patients who lost their renal allografts demonstrated a rapid deterioration in their native kidney function and 2 had received renal transplants within months of onset of their original disease. All 3 of these patients also had evidence of systemic recurrence of disease such as purpura after renal transplantation. These data have been interpreted as suggesting that renal transplantation should be performed in these patients after a waiting period of at least 1 year from the time of resolution of the signs of active AP disease, in order to minimize the risk of recurrence. Others have reported that IgA is deposited in the mesangium of patients who unerwent transplant allograft biopsy for suspicion of rejection [22] and have suggested that this might indicate recurrent disease. Since deposition of IgA in the mesangium of the well-functioning transplant allograft occurs in patients whose original disease was neither AP or IgA nephropathy (Berger's disease) [23], we suggest that this finding alone should not be interpreted as definitive evidence of recurrence of the original disease but rather should be noted and the patient observed closely. Our data also indicate that recurrence of AP in the transplanted kidney is uncommon.

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