Pediatric IgA Nephropathies: Clinical Aspects and Therapeutic Approaches

By Noel M. Delos Santos and Robert J. Wyatt

The pediatric IgA nephropathies are IgA nephrothapy (Berger's Disease) and Henoch-Schönlein purpura nephritis. Both conditions are reviewed in detail with respect to epidemiology, clinical features, outcome, prognostic markers, and therapeutic approaches. For both conditions variable disease severity and outcome along with the lack of conclusive evidence for efficacy of treatment based on randomized clinical trials makes it difficult to make strong recommendations regarding therapy.

BASED PRIMARILY ON inference from prevalence in biopsy series, IgA nephropathy (IgAN) is considered to be the world's most common type of chronic glomerulonephritis for adults.[1] This is probably the case for children as well. In Japan, IgAN was diagnosed in 24% of biopsies in Yonago[2] and 30% of the biopsies in Kobe.[3] Recently, 11% of pediatric biopsies in Seoul, Korea, showed IgAN.[4] Our experience in Memphis, Tennessee, from 1980 through 2002 indicates that IgAN occurred in 11.5% of 607 first biopsies (transplant biopsies excluded).

IgA NEPHROPATHY

Epidemiology

The overall population-based incidence of IgAN varies considerably based on the time-period and regions examined. Most of the studies include only adults and mostly individuals of European descent.[5] The highest incidence reported is 88 cases per one million population per year (MPPY) from Adelaide, Australia.[6] The most recent studies from Europe indicate an incidence in the range of 15 to 40 cases per MPPY, whereas the only U.S. study from Kentucky reported an incidence of 12 cases per MPPY for the period 1990 through 1994.[5] In the Kentucky study, the incidence of IgAN was 5.6 cases per MPPY for children aged 1 to 9 and 10.2 cases per MPPY for individuals aged 10 to 19 for the period 1985 through 1994.[5]

Data based on the percentage of biopsies diagnostic for IgAN suggest that IgAN is rare in blacks.[7] In addition, very few cases of IgAN have ever been reported from the continent of Africa.[8,9] However, in Shelby County (Memphis), Tennessee, we found that the incidence of IgAN was actually higher for black children than in white children for the period 1985 through 1994 (5.7 vs. 3.0 cases per MPPY).[10]

Recently, Utsunomiya et al.[11] reported the incidence of IgAN for children in Yonago City, Japan. This study included children first detected in a yearly screening program as well as those presenting with clinical features of disease and referred to the pediatric nephrologist for diagnosis. The incidence of pediatric IgAN was 45 cases per MPPY for children under age 15 for the period 1983 to 1999. The five- to 10-fold higher incidence in these Japanese children as compared with American children could simply reflect a racial difference in incidence. Other explanations include the detection of more cases through the Japanese screening programs, better diagnostic acuity of Japanese primary care physicians, and/or a more aggressive approach of Japanese pediatric nephrologists toward biopsies for children with microscopic hematuria alone or with low levels of proteinuria.

CLINICAL FEATURES

Presentation

Jean Berger's original report in 1969 included children as young as age 10 years and emphasized the occurrence of macroscopic hematuria during an episode of pharyngitis.[12] The earliest pediatric series were comprised mostly of children who presented with such an episode of macroscopic hematuria.[13-15] The largest and most extensive clinical reports on pediatric IgAN come from Europe,[16,17] the United States,[18-20] and Japan.[21-25] Although the mean age of presentation is approximately 10 years of age,[16-18,20,22,23] onset of symptoms can occur as early as 2 to 3 years of age.[2,16-18] The earliest a

From the Children's Foundation Research Center at the Le Bonheur Children's Medical Center and the Department of Pediatrics, University of Tennessee Health Sciences Center, Memphis, TN.

Address reprint requests to Robert J. Wyatt, MD, MS, Room 301 WPT, Children's Foundation Research Center, 50 North Dunlap, Memphis, TN 38103. E-mail: rwyatt@utmem.edu

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child has been diagnosed at our center is 25 months of age. Most pediatric series have shown a male predominance of approximately between 1.5 and 2.3 to one.[16,20,21,23] However, two Japanese series found no difference in male to female ratio.[2,22] In contrast, the Southwest Pediatric Nephrology Study Group (SPNSG) found a three to one male predominance for children in the southwestern and southeastern United States.[18]

The percentage of children presenting with macroscopic hematuria shows distinct regional variation. The Japanese studies find macroscopic hematuria at presentation in less than one-third of their patients,[2,23] as compared with approximately three-fourths for the French and U.S. studies.[14-16,18] However, in Sweden, only 43% presented with macroscopic hematuria.[17] Of the children who present only with microscopic hematuria and/or proteinuria, many will have one or more episodes of macroscopic hematuria at a later time.[2,16,23,26] This clinical course was documented for 17% of French children[16] and for 30% to 37% of Japanese children.[2,23,26]

In our experience, the most common association with isolated microscopic hematuria in children is not IgAN, but hypercalciuria.[27] Hypercalciuria is documented in approximately 40% of the white children evaluated for isolated hematuria in our clinic, and those affected children characteristically have eumorphic red blood cells and calcium oxalate crystals on examination of the urinary sediment. In contrast, children with isolated microscopic hematuria and IgAN are likely to have dysmorphic red blood cells and could have red blood cell casts. It is not surprising that both IgAN and hypercalciuria have been documented in the same child.[28] In fact, one of the subjects in the 1984 report failed to have resolution of hematuria in response to treatment with hydrochlorothiazide, and was biopsied and found to have IgAN with mild histology.[27]

Some children have both steroid-responsive–minimal change nephritic syndrome and IgAN.[29] These patients usually have normal histology and should be treated as steroid-responsive nephrotic syndrome patients.[30] Excluding such patients, up to 7% of children with IgAN present with nephrotic syndrome.[20,21] The initial report of the SPNSG found nephrotic syndrome at presentation in only one of 62 patients, whereas Yoshikawa found none with this presentation in his large series.[23] Another Japanese study found that preschool children were much more likely than school-aged children to have an acute onset with macroscopic hematuria, hypertension, and nephrotic syndrome.[2] However, these young children had eventual resolution of such symptoms.[2] The percent of children with heavy proteinuria at onset (>3 g/m^2 per day) is difficult to derive from the large series but is clearly much lower than that documented for adults. The largest proportion of children with this degree of proteinuria was 18% in the report by Kusumoto et al.[22]

Data for hypertension at presentation varies widely among the various series. In the report by Yoshikawa et al.,[23] hypertension was defined as diastolic blood pressure persistently $\geq$90 mm Hg and was only found in 1.5% of the patients. Levy et al.[16] defined hypertension as greater than the 97.5th percentile for gender and height and found that 3% of the patients were hypertensive. The 1995 report by Wyatt et al.[20] defined hypertension as greater than the 95th percentile for age using the 2nd Task Force on Blood Pressure Control in Children normative data[31] and found that 7% were hypertensive. Many of the patients were included in a subsequent study, and with the use of newer blood pressure standards based on gender, age, and height,[32] 25% of the patients were found to be hypertensive at presentation.[33] Although some selection bias toward severe disease could have affected the hypertension data from that study, it seems clear that the use of modern standards for assessment of children's blood pressure will result in a higher percent of hypertension at onset for pediatric IgAN.

Although approximately 10% of children could have a transient episode of mild renal insufficiency at onset of IgAN, presentation with chronic renal insufficiency (CRI) rarely occurs in the pediatric patient.[20,23] Only one of 103 patients in our 1995 report[20] and two of 65 patients from Cincinnati Children's Hospital presented with end-stage renal disease (ESRD).[34] This is in distinct contrast to adult series from the United States in which 40% to 50% of patients have CRI at presentation.[5,35,36]

Outcome

The initial reports on pediatric IgAN had mean follow up in the range of 5 years and contained few patients with CRI or progression to ESRD.[14,15,21,37,38] Subsequently, Levy et al.[16] from Paris and Welch

et al.[34] from Cincinnati reported progression to ESRD for 7% and 8% of their patients, respectively. All of those with ESRD in those two reports had significant crescentic involvement. However, as early as 1982, Linne et al.[39] found ESRD in 25% of 12 children in the absence of significant crescentic involvement at diagnosis and more than 9 years of follow up. In 1992, Yoshikawa et al.[25] reported that 5% of 200 Japanese children had developed CRI as defined by creatinine clearance below 60 mL/min/1.73 m^2 for over 3 months. In 1994, the SPNSG reported a rate of progression to ESRD of 15% for 80 pediatric patients with over 4 years of follow up from time of clinical onset.[18] In 1995, Wyatt et al.[20] found 12% of 103 patients followed in Lexington, Kentucky, or Memphis, Tennessee, progressed to ESRD. Some of the patients, including five with ESRD, from the latter report were also included in the SPNSG report.

Very limited kidney survival data for pediatric IgAN are available. Two Japanese reports show that 5% to 6% of pediatric patients were predicted to progress to ESRD at 10 years from onset[22,24] as compared with 13% of children from the southeastern United States.[20]

Long-term follow-up studies for patients with IgAN diagnosed in childhood indicate that 26% to 50% of the patients not progressing to ESRD will eventually develop a normal urinalysis.[16,19,25,40] In our recent study on angiotensin-converting enzyme (ACE) genotype in pediatric IgAN, the 62 subjects not progressing to ESRD had a minimum of 5 years with the mean length of follow up being almost 15 years.[33] At follow up, mean serum creatinine was 0.73 ± 0.19 mg/dL for females and 0.91 ± 0.24 mg/dL for males in this group. Of the 62 subjects, 46 had a urinary protein to creatinine ratio of less than 0.2; only three of these had microscopic hematuria. Including subjects with progression, 54% of the subjects in the study had a normal urinalysis at the time of last follow up. One can reasonably assume that few individuals who are more than 5 years from biopsy with a normal urinalysis will ever progress to ESRD and that the majority of children identified with IgAN will have a good outcome.

Prognosis

Clinical Markers of Outcome

The major clinical associations found in children are identical to those seen in large adult series: degree of urinary protein excretion and hypertension.[41] CRI at diagnosis, a well-documented association for adults,[41] cannot be evaluated for children as a result of its rarity at presentation.

Yoshikawa et al.[25] found that "heavy" proteinuria defined by urinary protein excretion >1 g/m^2 per day was significantly associated with CRI (glomerular filtration rate [GFR] <60 mL/min/1.73 m^2) at last follow up. The 1994 report of the SPNSG showed that proteinuria $\geq 2+$ at biopsy was the most significant clinical association by univariate analysis, differentiating patients with and without progression to ESRD.[19] Wyatt et al.[20] documented a similar association between proteinuria and progression to CRI or ESRD by comparing proteinuria at time of biopsy between that group and children with normal renal function 10 years after onset.

The 1994 SPNSG report found a significant association between hypertension at diagnosis and progression to ESRD.[19] This was not assessed in the reports of Yoshikawa et al.[25] as a result of the rarity of children meeting their criteria for hypertension.

Hypertension did not associate with progression to ESRD or CRI in the 1994 report by Wyatt et al.,[20] probably as a result of the low percentage of patients meeting this study's criteria for hypertension.

The report by Yoshikawa et al.[24] showed a significant association between older age at diagnosis and CRI at follow up, whereas the 1994 SPNSG report found no difference in outcome between children younger and older than age 9 at presentation.[19]

The controversial study of Beukhof et al.[42] in Dutch adults with IgAN suggested that absence of macroscopic hematuria was a poor prognosis marker. The authors even suggested that IgAN with and without macroscopic hematuria were separate and distinct diseases. Pediatric data do not support this conclusion. Macroscopic hematuria was not associated with outcome in the 1994 SPNSG report[19] or in the series of Yoshikawa et al.[25]

The 1994 SPNSG study[19] and the 1995 report by Wyatt et al.[20] found that outcome was significantly worse for black as compared with white children with IgAN. Since 1985, we have identified more black children with IgAN[10] and now believe that the outcomes are similar (unpublished observation)

and that the earlier observations could reflect selection bias with fewer children with mild disease being detected and referred for biopsy.

Zidar et al.[43] made the interesting observation that children with IgAN and a history of intrauterine growth retardation (IUGR) were significantly more likely have hypertension and more focal sclerotic lesions than the other children in their study. These authors speculate that reduction in number of nephrons associated with IUGR was responsible for the finding.

Histologic and Other Biopsy Markers of Outcome

Many studies of histologic markers of outcome use grading systems in which subjects are "lumped" into three to five categories with grade 1 always being normal or near-normal findings by light microscopy.[18,36,44,45] Pediatric studies differ somewhat from the adult studies in that findings of significant chronic tubular and interstitial injury only occur in a small percentage of patients at diagnosis.[25] The SPNSG 1994 report[19] and the Wyatt et al.[20] 1995 study used a three-category system of type 1—normal, type 2—mesangial hypercellularity alone, and type 3—any degree of scarring that could include any focal sclerosis, adhesions, and crescents.[19] Tubulointerstitial changes are not included in this system. The strength of this system is the separation of cases with mild histologic features, but does not consider the percentage of glomeruli with chronic changes. The SPNSG compared children that progressed to ESRD with those with long-term follow up and no progression and found a highly significant association between type 3 lesions with sclerosis and ESRD.[19] Greater than 20% of glomeruli with sclerotic lesions was found at diagnosis for 83% of patients progressing to ESRD as compared with 4% of those who did not progress ($P < 0.001$). Wyatt et al.[20] showed that biopsy grade significantly associated with ESRD/CRI. In that study, 88% of those with ESRD/CRI had grade 3 and 12% grade 2 biopsies as compared with 35% grade 3 and 35% grade 2 for those with stable renal function after 10 years of follow up. In addition to confirming the association between severity of renal histology and outcome, this study indicates that many children with grade 3 histology will eventually have a good outcome. In our more recent study,[33] almost half of the patients having one or more markers of poor outcome at diagnosis, i.e., hypertension, proteinuria >3 g/m^2 per day, grade 3 biopsy, eventually developed a normal urinalysis.

Yoshikawa et al.[25] analyzed histologic features based on the mean percentage of glomeruli affected. Patients were placed in four groups based on outcome. Mesangial proliferation, global sclerosis, segmental sclerosis, crescents, capsular adhesions, and moderate or severe tubulointerstitial changes were all significantly associated with progression to CRI.[25] Nine of 27 (33%) patients with $\geq$30% of glomeruli showing sclerosis, crescents, or adhesions developed CRI as compared with one of 173 patients with $<$30% of glomeruli having such lesions.[25]

In a small study from Andreoli et al.,[46] patients with capillary loop deposition of IgA by immunofluorescence were significantly more likely to have urinary protein excretion of more than 1 g/24 hours as compared with those with only mesangial deposits. In addition, three of five children with capillary loop deposits progressed to CRI or ESRD as compared with only one of nine with no such deposits. In a larger Japanese study, the presence of subepithelial deposits demonstrated by electron microscopy associated significantly with outcome defined mostly by surrogate markers for ESRD.[47] The 1994 SPNSG[19] report failed to find a significant association between capillary loop deposits by immunofluorescence or by electron microscopy and the outcome of ESRD. One possible explanation for the differences in these reports is that individuals with capillary loop deposits could have a tendency to progress to ESRD earlier than those with only mesangial deposits, and the length of follow up for patients in the latter study was longer than that of the other two studies.

Pediatric studies have documented associations with CRI and/or ESRD and glomerular hypertrophy[48] and CD8+ interstitial cells.[49] Another pediatric study showed an association between hematuria and leukocyturia and macrophage infiltration of the glomeruli.[50] These macrophages were felt to participate in paramesangial, glomerular basement membrane and podocyte injury that could predispose to crescent formation.[50]

Serologic or Genetic Markers of Outcome

ACE genotype as a prognostic factor has been extensively examined in adult patients with IgAN.[51] That ACE genotype is associated with

progression in IgAN makes an attractive hypothesis, because serum ACE level is partly determined by ACE genotype.[52] Several pediatric studies from Japan showed an association between ACE genotype and increased urinary protein excretion and/or histologic changes.[53-55] One Japanese study showed a significantly higher mean level of proteinuria at the time of biopsy in patients with the ID or DD genotypes as compared with those having the II genotype.[53] Renal biopsies did not show differences between these two groups with respect to mesangial proliferation or crescents, although ID/DD genotypes were associated with a higher mean percentage of glomeruli with sclerosis or capsular adhesions.[53] Another Japanese group found that patients with either the DD or ID genotype had significantly greater urinary protein excretion at biopsy and significantly more biopsy specimens with changes such as capsular adhesions and sclerosis as compared with those with the II genotype.[54] In a follow-up study, the latter group examined angiotensinogen (AGT) and angiotensin II type 1 receptor (ATR1) genotype in the same cohort of patients.[55] Urinary protein excretion was significantly greater for patients with the TT genotype of the AGT gene as compared with those with MM or MT genotypes. The highest urinary protein excretion was found in those having AGT TT and ACE ID or DD genotypes, whereas the lowest was for the AGT MM or MT genotypes and the ACE II genotype, 1.5 versus 0.3 g/m^2 per day, respectively.

We are the only pediatric group to examine ACE genotype in IgAN using progression to ESRD as the primary outcome measure.[33] We studied 79 patients with IgAN diagnosed before age 18 years who had either progressed to ESRD or were more than 5 years postbiopsy. Kaplan-Meier survival curves for progression to ESRD did not differ significantly for the ACE DD, ID, and II genotype groups ($P = 0.095$, log-rank test). By univariate analysis, presence of hypertension and degree of proteinuria at diagnosis, and grade 3 SPNSG histology, but not ACE genotype, significantly associated with progression to ESRD. In the Cox proportional hazards model that included grade of proteinuria, the ACE D allele was a significant independent predictor of outcome with a hazard ratio of 2.37 ($P = 0.031$), although when this model included hypertension or SPNSG, biopsy-grade ACE genotype was not a significant independent predictor of progression to ESRD ($P = 0.067$ and $P = 0.199$, respectively). Still, the results of this study and the Japanese studies suggest that the ACE D allele could associate with poor outcome in pediatric IgAN.

The frequency for the 2.6/2.1 kb S mu heterozygous genotype for the IgM heavy chain switch region gene was significantly decreased in pediatric patients with IgAN and diffuse mesangial proliferation as compared with those with minimal or focal mesangial proliferation.[56] Pediatric patients with IgAN and the GT/TT genotypes for the platelet activation factor (PAF) acetylhydrolase gene had significantly higher urinary protein excretion and more glomeruli with severe to moderate mesangial proliferation than those with the GG genotype.[57] The former children had lower plasma levels of PAF acetylhydrolase activity and presumably the ability to generate more PAF than those with the GG genotype. In addition, patients who had the PAF T allele and the ACE D allele had a much higher urinary protein excretion than those without either of these alleles.[57]

TREATMENT

The evaluation of approaches to the treatment of pediatric IgAN is quite problematic. Foremost is the lack of well-designed randomized, controlled trials (RCTs) that use appropriate outcome measures.[30] The highest level of evidence (LOE 1) warranting a grade A recommendation must be based on a well-designed RCT that demonstrates statistical significance for the primary outcome measure.[58] The primary outcome measure must be chosen before the initiation of the study, and a surrogate outcome measure should correlate highly and unequivocally with the true outcome of progression to ESRD.[30] Progression to ESRD is not useful for pediatric trials because over half of the children who progress will do so as adults, often over 10 years from onset of clinical signs of IgAN.[20] Similarly, measures such as doubling of the serum creatinine or 50% to 100% reduction in creatinine clearance, while useful in adult studies, are impractical for pediatric trials. Some pediatric studies have the selected very weak surrogate markers for outcome such as reduction in hematuria or reversible histologic features. The inclusion of subjects with such mild clinical and histologic features that eventually resolve without intervention is the expected outcome brings the conclu-

sions from such studies into question. This is particularly true if one accepts the premise that almost all of those with normal histology and mild proteinuria at onset will be among the children that who a normal urinalysis a decade later. Such subjects should not be subjected to RCTs that use agents with significant potential side effects and possibly not even be subjected to less harmful agents.

In recent years, change in urinary protein excretion has gained acceptance as a good surrogate marker of outcome for adults with nondiabetic kidney disease.[59-61] Reduction in urinary protein has not yet been proven to be the best surrogate marker for outcome. However, many investigators now make the assumption that a significant and persistent reduction in proteinuria results in the preservation of kidney function. Using urinary protein excretion rather than progression to ESRD has the study outcome measure allows a RCT to be performed in a relatively short timeframe of several years rather than a decade.

Nolin and Courteau proposed the first evidence-based recommendations for treatment of IgAN in adults in 1999.[62] They concluded that patients with heavy proteinuria (over 3 g/day) and normal or near-normal kidney function (creatinine clearance) would benefit from treatment with corticosteroids. Floege[63] reviewed studies in adults with IgAN published after that review and made the observation that virtually all trials were performed before the routine use of angiotensin-converting enzyme inhibitors (ACEi) for treatment of hypertension or proteinuria alone in nonhypertensive subjects. Many nephrologists now follow the principle of renoprotection in which all patients with chronic glomerular disease are treated with ACEi or ARB before the development of progressive renal insufficiency.[64]

Angiotensin-Converting Enzyme Inhibitors

Several investigators now advocate the use of an ACEi or angiotensin receptor blocker (ARB) as initial therapy for adults with IgAN.[65,66] Very little data are available on the use of such an approach to pediatric IgAN.[67] Except for rare presentation of crescentic or rapidly progressive disease, we are treating most children diagnosed with IgAN and having urinary protein excretion above 1 g/1.73 m^2 per day or a urinary protein to creatinine ratio above 1.0 with an ACEi. We have used this approach for both hypertensive and normotensive children. We observe the response of urinary protein excretion to ACEi for several months before considering additional therapeutic modalities. This approach is incorporated into the protocol for the ongoing North American IgAN study RCT of mycophenolate mofetil (MMF) in children and adults with IgAN in which only subjects with a urinary protein to creatinine ratio ≥ 0.8 for males and ≥ 0.6 for females after 3 months of ACEi and fish oil supplements are eligible for randomization to MMF or placebo.[68] A European RCT of benazepril versus placebo for patients with IgAN who are under age 35 will be completed by the end of 2004.[69]

Corticosteroids

Fortunately, only a small percentage of children with IgAN will present with rapidly progressive GN associated with significant crescentic involvement.[16,34] The published experience on treatment of children with crescentic IgAN is based on early aggressive treatment with intravenous methylprednisolone,[34,70-73] sometimes in combination with cyclophosphamide and/or plasma exchange.[71-73] Although these studies are not sufficient to support an evidence-based recommendation for treatment,[56] we feel that such children should be treated aggressively if the biopsy findings are not too advanced or chronic.

Treatment with oral corticosteroids alone is the earliest and most widely used therapeutic approach for children with moderately severe IgAN.[37,74-76] However, the experience that supports such therapy is from small case series with either no controls[37,75] or concurrent untreated controls from another center.[74,75] Surrogate measures of outcome were used for all of these studies, except for the second report by Waldo et al.[75] that found a significant difference with respect to progression to ESRD for patients followed in Birmingham, Alabama, treated for at least 2 years with prednisone on alternate days (60 mg/m^2 for 12 months, 30 mg/m^2 for 12 months, then 15 mg/m^2 for a variable period), as compared with untreated patients followed in Lexington, KY. The subjects had either proteinuria over 1 g/m^2 per day, or interstitial fibrosis or tubular atrophy and/or glomerular sclerosis. This study provides level 3 evidence that at best supports a grade C recommendation for such therapy.[59]

A RCT with a crossover design showed that 2 weeks of treatment with daily prednisone in a dose of 2 mg/kg per day (80 mg maximum) had no effect on hematuria as assessed quantitatively by Addis counts.[77] The subjects for this trial tended to have mild histologic findings and proteinuria in the range of 500 mg per day. The results of this trial are not useful in helping to determine the best therapeutic approach for moderately severe IgAN in children.

The North American IgAN Study Group has just completed a RCT of alternate-day prednisone, fish oil therapy, and placebo for children and adults under age 40 with IgAN.[78] This study failed to show that alternate-day prednisone was superior to placebo in slowing disease progression.[79]

Corticosteroids and Azathioprine

Two studies have examined a more aggressive approach to treatment of pediatric IgAN with corticosteroids and azathioprine.[80,81] Both incorporated histologic features from repeat renal biopsies and change in urinary protein excretion as outcome measures. Andreoli et al.[80] reported results of treatment for 10 children with severe IgAN (defined as proteinuria over 1 g/day, hypertension, renal insufficiency, segmental sclerosis, crescent formation, and/or glomerular basement membrane deposition of IgA). Treatment consisted of azathioprine 2 to 3 mg/kg per day combined with daily prednisone (60 mg/m^2 per day, maximum 60 mg) for 8 weeks followed by 60 mg/m^2 on alternate days for 10 months. Mean urinary protein excretion decreased from 4.1 g per day at entry to 1.6 g per day at the end of the treatment period ($P < 0.01$). For the seven patients having repeat biopsies at 1 year, the chronicity index was unchanged but the activity index improved significantly ($P < 0.01$). Because this study was performed before the use of ACEi, it provides quite useful data with respect to the effect of prednisone and azathioprine alone on urinary protein excretion in pediatric patients with relatively severe disease.

The Japanese Pediatric IgAN Study performed a RCT in which all subjects were treated with heparin–warfarin and dipyridamole; half of the subjects were treated with prednisone and azathioprine for 2 years.[81] Prednisone was given in a dose of 2.0 mg/kg (maximum 80 mg) daily for 8 weeks, followed by an alternate-day dose of 2.0 mg/kg for 4 weeks, 1.5 mg/kg for 4 weeks, and 1.0 mg/kg for 21 months. Azathioprine was given in a dose of 2 mg/kg per day. No placebo was used for the comparison group. The mean urinary protein excretion at entry was 1.35 and 0.98 g per day for the treatment and control groups, respectively. The urinary protein excretion was not corrected for body surface area making comparison with other pediatric reports problematic. However, this study clearly included patients with much milder disease than those in the study by Andreoli et al.[81] The study could also have included a substantial number of subjects with urinary protein excretion under 1 g/m^2 per day at entry, because entry criteria did not include a lower limit for urinary protein excretion. Apparently, few if any of the subjects were treated with ACEi, because none of those in the treatment group and one in the comparison group became hypertensive during the course of the study.

The primary outcome of this Japanese study was not clearly stated, but mean creatinine clearance remained normal and did not significantly change for the treatment and comparison groups during the course of the study. A number of surrogate markers of outcome differed significantly between the treatment and comparison groups. The urinary protein excretion dropped to 0.22 g per day in the treatment group while remaining virtually unchanged in the comparison group. The percentage of glomeruli showing sclerosis increased fourfold on repeat biopsy for the comparison group (3.9-16.4%) but was unchanged in the treatment group. A very interesting finding was that mesangial IgA deposition was absent in seven of 33 follow-up biopsies for the treatment group but none of 33 for the comparison group.

Although the study by Yoshikawa et al.[81] is the largest RCT and was well conducted, it poses a number of problems with respect to their therapeutic regimen being widely used outside of Japan. Many of the subjects that were enrolled in this study could have had a significant reduction in urinary protein excretion in response to ACEi alone. Also, most North American and European pediatric nephrologists would not use the anticoagulation and antiplatelet regimen given to all subjects in the study, even for children with moderately severe disease. Finally, follow up for another decade could be required to see if subjects in the treatment group have a significantly lower rate of

progression to ESRD than those in the comparison group.

Fish Oil Supplements

All studies reported to date on fish oil supplements (FOS) in patients with IgAN have been conducted in adults. However, pediatric patients are currently enrolled in the North American IgAN study in which subjects under age 40 are randomized to 2 years of treatment with FOS, alternate-day prednisone, or placebo.[78] This study failed to show that omega-3 fatty acid therapy was superior to placebo in slowing disease progression.[79]

Tonsillectomy

The studies that advocate tonsillectomy for treatment of IgAN come from predominantly adult populations (reviewed in reference 30). In addition, many of the studies used tonsillectomy in conjunction with immunosuppressive medications and most used weak surrogate end points. Two nonrandomized cohort comparison studies used ESRD as the outcome measure: a German study showed no difference,[82] whereas a Japanese study that had a longer follow-up period showed significantly better kidney survival for patients undergoing tonsillectomy.[83] One cannot determine if patients diagnosed in childhood were included in the latter study.[30] Based on the available data, an evidence-based recommendation for tonsillectomy in children cannot be made.

Vitamin E

A multicenter study of children with very mild IgAN examined patients treated with vitamin E (400 units per day for body weight <30 kg, 800 units per day for body weight ≥ 30 kg).[84] ACEi therapy before or after study entry was one of the exclusion criteria. Of the 38 subjects who completed 1 year on the study, 21 in the treatment group had urinary protein to creatinine ratio of 0.31 at entry and 0.24 after 1 year. In contrast, the 18 who received placebo had urinary protein to creatinine ratio of 0.52 at entry and 0.64 after 1 year. The end of treatment urinary protein to creatinine ratio was significantly lower for the treatment group. The authors suggest that vitamin E could be useful for treatment with or without other agents in children with mild IgAN.

Summary and Future Directions

Multicenter RCTs for moderately severe pediatric IgAN have been difficult to organize in North America. Thus, even more reliance will be placed in the future on data from adult studies or studies that contain both children and adults. This approach appears sound, because the outcome for patients diagnosed in childhood is not different than that of adult patients having normal renal function at diagnosis.[20,22,24,85] The benefit of renoprotection with ACEi and/or ARB treatment before the use of corticosteroids for most children with moderately severe IgAN will be investigated and could become the standard of care. Thus, much of the old experience with long courses of corticosteroids in children with IgAN could become irrelevant. More rational approaches to treatment might include immunosuppressive drugs alone or in combination with more limited use of corticosteroids after the maximum benefit from renoprotection is documented.

Despite the limited data from RCT in pediatric IgAN, children with moderately severe disease are the perfect group for such studies, because children are often diagnosed earlier in the course of the disease than adults. For this reason well-designed RCTs in pediatric patients with IgAN should be a high priority for the future.

HENOCH-SCHÖNLEIN PURPURA NEPHRITIS

Much of the evidence on the common pathogenetic features of IgAN and Henoch-Schönlein purpura (HSP) are derived from pediatric studies. Berger noted the mesangial deposition of IgA in patients with HSP in his original report.[12] Some children being followed for HSP nephritis (HSPN) will experience one or more episodes of macroscopic hematuria at the time of an upper respiratory illness in the absence of rash, joint or abdominal symptoms.[86-88] Meadow and Scott reported previously well identical twins who had adenovirus infection with one having the clinical phenotype of HSP and the other having only macroscopic hematuria but both having mesangial IgA deposits.[89] A number of reports have documented the development of HSP in a child previously proven or suspected to have IgAN based on episodes of isolated macroscopic hematuria[90-92] with the longest interval between the respective conditions being 12 years.[92]

Epidemiology

Case-series from tertiary centers include a disproportionate number of patients with renal and/or significant gastrointestinal involvement. However, a number of studies are based on unselected series of children and yield reliable incidence data.[93-99] These studies include children with HSP regardless of whether or not clinical evidence for HSPN was present.

The incidence of HSP in Northern Ireland for the period 1970 to 1982 was 135 cases per MPPY.[93] In Denmark for the period 1977 to 1987, the incidence was 180 cases per MPPY for children under age 14 in the county of Copenhagen and 140 cases per MPPY for the entire country.[94] In an ethnically homogenous Spanish population of Celtic descent, the incidence for the period 1980 to 1999 was 105 cases per MPPY for children <14 years.[95] In the northern midlands of the United Kingdom, incidence of HSP was 204 cases per MPPY for children aged <17 years during the period 1996 through 1999.[96] In addition, in that study, the incidence was 240, 178, and 62 cases per MPPY for Asians, whites, and blacks, respectively.[96]

Two reports documented the incidence of HSP in Arab children.[97,98] The incidence in Kuwait for children under 12 for the period 1981 through 1987 was 67 cases per MPPY.[97] In Jordan, during the period 1991 through 1994, the incidence of HSP for children under age 13 was 85 cases per MPPY and 49% of the children with HSP had evidence of a recent group A streptococcal infection as compared with 16% of controls.[98]

Farley et al.[99] documented an outbreak of HSP in Hartford County, Connecticut, during the fall and winter of 1987 to 1988. During this 7-month period, the incidence was 170 cases per MPPY, as compared with 30 cases per MPPY for the previous 7-month period. During this "outbreak," the incidence was higher among urban (480 cases per MPPY), Hispanic (860 cases per MPPY), and children of lower socioeconomic status (690 cases per MPPY). The results of this study should be interpreted with caution because the "outbreak" involved a total of only 17 cases and the incidence during the "outbreak" is not different from incidence data from other reports generated over long periods of time.[90-96]

The male to female ratio from unselected series of children with HSP is close to 1:1.[95,96,100] The mean age at presentation for the same studies is 6 years.[95-97,100]

CLINICAL FEATURES

HSP is a systemic vasculitis that affects the skin, gastrointestinal tract, joints, and kidneys. The first description is credited to Heberden who reported abdominal colic, bloody stools, arthralgia, purpuric rash, and macroscopic hematuria in a young child.[101] Schönlein described arthralgia in association with a purpuric rash in 1837.[102] Henoch described purpura, abdominal colic, bloody diarrhea, and arthralgia in four children in 1874[103] and subsequently included nephritis as an associated feature in 1899.[104] In 1900, Sir William Osler noted that nephritis associated HSP resulted in the death of five patients.[105]

Diagnosis of IgAN depends on performance of a renal biopsy that demonstrates typical mesangial deposition of IgA. In contrast, the diagnosis of HSP is made without a renal biopsy and the biopsy is usually reserved for patients with severe or persistent nephritis. Diagnosis of HSP relies on the demonstration of typical clinical features based on criteria established by the American College of Rheumatology.[106,107] Renal biopsy findings in HSPN and IgAN are essentially indistinguishable.[86,108] Like in IgAN, mesangial IgA deposits are typically present in HSPN and can be accompanied by IgG, C3, and properdin.[86] In the rare instances that mesangial IgA is absent in HSPN, capillary loop deposition of IgA could be present.[86,109-112]

Presentation

Many children with HSP will never develop clinical evidence of nephritis. The earliest case series documented nephritis in as low as 6% of cases[113] and as high as 40%.[114,115] This wide variation in percentage of children with HSP who develop HSPN is also present in more recent series from 20% to 54%.[93,100,116-119] However, nephritis is clearly the most important cause of morbidity for children with HSP and should always be excluded by the primary care physician and, when present, evaluated by a pediatric nephrologist. Although a child could have abdominal pain, arthritis, typical rash, and nephritis at the time of presentation, the more common presentation is of sequential mani-

festations with abdominal pain and arthritis preceding the typical rash by several days.[100] Nephritis usually develops within 3 months after presentation.[86,100,120] Nephritis can even develop after the other manifestations of HSP have subsided.[121] The most severe renal manifestation of HSP is rapidly progressive nephritis (usually with >50% glomeruli with crescents) and/or nephrotic syndrome. Although nephrotic syndrome was present in almost 40% of children with HSPN in an early report from the United Kingdom[122] and 64% from Poland,[117] more recent, less selected series show a rate for nephrotic syndrome of 10% to 20%.[93,95,100] Hypertension at presentation is related to the severity of the renal involvement[100] and occurs in 15% to 25% of children with HSPN.[100,115,119,123]

The percentage of children with HSPN having macroscopic hematuria is difficult to determine in many of the reports, but probably is approximately 25%. In the recent Spanish report, 24% of those with HSPN had macroscopic hematuria.[95] An early series of nonbiopsied children showed the rate to be 40%, and the initial report from Guy's Hospital of biopsed children found 64% to have macroscopic hematuria.[120] Another, more recent Italian biopsy series found the percentage with macroscopic hematuria to only be 11%.[123]

Rarely, a child will present with the typical rash, abdominal and joint symptoms of HSP and have renal biopsy findings diagnostic for poststreptococcal acute glomerulonephritis (PSAGN) rather than HSPN.[124,125] In a child with the clinical phenotype of HSP, but hypertension and reduced serum C3 concentration, the diagnosis of PSAGN should be strongly considered. It was recently reported that 30% of biopsies from children with HSPN showed mesangial deposition of the group A streptococcal antigen, nephritis-associated plasmin receptor as compared with less than 3% for other glomerular diseases, including IgAN.[126] In addition, patients with HSPN had significantly higher ASO titers than those with other chronic glomerular diseases.[126] These findings suggest a potential role for the group A streptococcus in the pathogenesis of some cases of HSPN.

Outcome

Because most outcome data for HSPN are from nephrology units in tertiary centers, the true outcome of HSPN is difficult to determine. Such clinical series are clearly influenced by selection bias toward patients with significant glomerular disease and children with mild findings might not be referred. In addition, some reports analyze data for all children with HSPN regardless of whether or not a biopsy was performed,[92,99] whereas other reports are biopsy series.[47,123,127-129] Obviously, the biopsy-based series will yield the poorest outcome for HSPN.

In an unselected series of 141 Finnish children, only 28% had abnormal urinary sediment that persisted longer than 4 weeks.[116] Of these 39 children with HSPN, eight showed resolution within 3 months. Only one child in this case series progressed to ESRD. Of 270 cases of HSP diagnosed in three pediatric hospitals in greater Belfast, Northern Ireland, 20% developed HSPN.[93] Of those with HSPN, one child progressed to ESRD and one had a renal-related death. HSPN occurred in 58% of children with HSP in a Spanish series.[95] After 7 years of follow up, over 20% of the children in this study with HSPN continued to have microscopic hematuria and proteinuria, but none progressed to ESRD. From these unselected studies, it appears that the risk of progression to ESRD for all children with HSPN is approximately 3%.

In contrast, the risk for progression to CRI/ESRD in children with HSPN followed at tertiary centers is much greater. CRI, ESRD, or death occurred in 23% of 88 children with HSPN who were followed for more than 1 year at the Hôpital des Enfants-Malades in Paris.[86] Sixteen percent of 100 children biopsied for HSPN at the University of Minnesota during the period 1955 through 1981 progressed to ESRD.[127] Similarly, 16% of 128 Japanese children with HSPN progressed to chronic renal failure.[47] Long-term follow up of patients having a renal biopsy for HSPN at Guy's Hospital, London, between 1962 and 1969 found 14% with CRI, ESRD, or death.[128] Some of the patients in the study progressed to ESRD more than a decade after initial presentation. A recent report from Finland examined the outcome in adults who were treated for HSP between 1964 and 1983.[130] Patients with severe HSPN at onset were significantly more likely to have renal impairment, defined as hypertension and constant proteinuria or ESRD. Seventy percent of 23 pregnancies were complicated by hypertension, but none of the five women with uncomplicated pregnancies had a poor outcome.

Most of the children in these studies presented long before the time of renoprotection with ACEi and/or ARB and aggressive therapy with pulse intravenous methylprednisolone or plasmapheresis. Some were treated with prednisone and immunosuppressive or cytotoxic agents. Thus, like with pediatric IgAN, one would expect the outcome for similar patients to be better today.

Limited data from more recent studies have used Kaplan-Meier survival analysis to predict kidney survival in children with HSPN. An Italian study found that only 7% of children with HSPN progressed to ESRD, and the kidney survival 5 years from onset was 90%.[123] A German report of 64 children biopsied for HSPN showed a 10-year kidney survival of 73%.[129]

In a recent study, kidney biopsies were performed 2 to 9 years after presentation in 12 children with a history of HSPN.[131] Four of the subjects with normal urinalyses or only microscopic hematuria no longer had mesangial IgA deposition. The other eight all had mesangial IgA deposition and a clinical course consistent with IgAN. The authors speculate that for some patients after the acute HSP "storm," mesangial deposition of IgA continues with the patient now having IgAN. However, this hypothesis does not completely explain the clinical observations of HSPN occurring 6 to 17 months after the onset of HSP without nephritis[120,132] unless one postulates that a child having HSP is at risk to later develop IgAN.

Prognosis

Two types of prognostic studies have been done for children with HSP. The first type relates to prognostic factors for a child with HSP to develop HSPN, whereas the second type of study is about prognostic factors in children with HSPN that are related to the outcome of progression to ESRD.

Development of Henoch-Schönlein purpura Nephritis

Kaku et al.[118] examined a series of 194 patients $<$15 years of age who developed HSP but did not have urinary abnormalities at the initial evaluation. Many of the children developed HSPN within days of that evaluation, but the study was designed to exclude those referred for evaluation of HSPN or with HSPN as a major presenting feature. Patients with renal involvement at disease onset were excluded from the study. Significant risk factors for development of HSPN by univariate analysis were age of onset $>$7 years, persistent purpura, and decreased factor XIII. Significant independent risk factors for developing renal involvement were determined by Cox regression analysis to include severe abdominal symptoms (hazard ratio [HR] = 3.26), persistent purpura (HR = 11.53), and decreased factor XIII (HR = 2.27). In addition, although steroid treatment decreased the risk of renal involvement by Cox regression model (HR = 0.36), univariate analysis was not able to show that steroids had any effect on renal involvement.[118] Similar results were reported in a subsequent Japanese study.[119] Forty-nine percent of 134 children with HSP developed HSPN within 3 months of onset. By univariate analysis, age of onset $>$4 years, severe abdominal symptoms, gastrointestinal bleeding, persistent purpura, and decreased factor XIII levels were significantly associated with development of HSPN. In addition, age of onset $>$4 years, severe abdominal symptoms, and persistent purpura remained significant risk factors by multivariate analysis.

Mestecky et al.[133] first demonstrated deficient galactosylation of the side chain of IgA1 in patients with IgAN. This defect is detected in serum samples using lectin-binding assays with some lectins showing better sensitivity than others.[134] Saulsbury[135] found no difference between children with HSP and controls for jacalin binding to IgA1, but did show that peanut lectin binding was significantly greater for the HSP group. However, no difference in peanut lectin binding could be demonstrated for HSPN as compared with HSP without nephritis. However, Allen et al.[136] clearly demonstrated a significant difference in binding of the *Vicia villosa* lectin to IgA1 from the serum of children with HSPN as compared with those without nephritis. In addition, the HSP without nephritis and control groups demonstrated similar binding of this lectin to IgA1. If substantiated, this observation is potentially of great importance for understanding the pathogenesis of HSPN in that it provides a means of detecting which children with HSP are at risk for the development of HSPN.

The tubular marker proteins, n-acetyl-β-D-glucosamindase and α_1-microglobulin were significantly elevated in children that developed HSPN, but normal in HSP without nephritis.[137] Eosinophilic cationic protein levels were significantly higher for children with HSP as compared with

those with IgAN and for those with HSPN as compared with HSP patients with a normal urinalysis.[138] IgA antiendothelial cell antibodies (AECA) were detected in seven of 15 patients with HSPN, but were not in patients without nephritis or in controls.[139] In the same study, children with HSPN had elevated serum thrombomodulin levels.[139] Serum tumor necrosis factor concentrations were significantly higher in children with HSPN as compared with those without nephritis.[140] In contrast, mean serum endothelin level was significantly elevated in the acute phase of HSP, but was not different for children with and without HSPN.[141]

Clinical Markers of Outcome

Data on clinical markers of prognosis for HSPN are limited. Logistic regression analysis in the German cohort identified renal insufficiency at presentation ($P = 0.004$) and nephrotic syndrome ($P = 0.037$) as significant independent predictors of outcome.[129] Age at presentation of HSP, number of recurrences, and initial hypertension did not predict outcome. The studies by Ronkainen et al.[130] and Counahan et al.[122] showed no significant association between age at onset and clinical severity at follow up, although children presenting with more serious renal symptoms at onset tended to be older than those whose symptoms were not serious. Coppo found no relationship between age at presentation and outcome by both univariate and multivariate analysis.[123]

Histologic Markers of Outcome

The most commonly used histologic classification system for HSPN was initially developed by Meadow et al.,[120] but was modified for use by the International Study of Kidney Disease in Childhood (ISKDC).[142] Grade I denotes normal histology or only minor abnormalities; grade II is pure mesangial proliferation with IIa focal and IIb diffuse; grade III indicates crescentic involvement in <50% of glomeruli with associated focal (IIIa) or diffuse (IIIb) mesangial proliferation; grade IV is same as III but with crescents in 50% to 75% of glomeruli; grade V is same as III but with crescents in >75% of glomeruli; and grade VI has membranoproliferative-like lesions. Using this grading system, studies from the United Kingdom[128,140] and Japan[47] showed progressively higher fractions of patients with poor outcomes (defined in the latter study ad proteinuria >1.0 g/m^2 per day, hypertension, or glomerular filtration rate <60 mL/min/1.73 m^2) with increasing histologic grade from I to V.

Logistic regression analysis in the German cohort showed percent of glomeruli with crescents ($P = 0.051$) to be a significant independent predictor of outcome.[129] Several studies appear to indicate that >50% of glomeruli with crescents is associated with a poor outcome.[86,128] Yoshikawa et al.[47] found the presence of subepithelial dense deposits to be significantly associated with a poor outcome in HSPN. Ten of 39 patients with HSPN with subepithelial deposits had active nephritis or developed renal failure as compared with six of the 63 without such deposits ($P < 0.05$). However, several studies concluded that severity of biopsy findings is not related to long-term outcome.[123,130]

Kumada et al.[143] evaluated the histologic importance of C3c deposits in pediatric HSPN. Twenty-two of the 51 patients yielded C3c-positive biopsies in this study. Although subepithelial deposits and crescents were associated with the degree of proteinuria and duration of hematuria and/or proteinuria, they were not associated with the presence of C3c. The presence of C3c differed significantly different those with heavy and mild proteinuria.

Serologic or Genetic Markers of Outcome

A number of studies have examined ACE I/D genotype in HSPN and failed to find an association between ACE genotype and outcome or severity.[144-146] Yoshioka et al.[147] determined the ACE DD genotype to be predictive of persistent proteinuria above 500 mg/m^2 per day in children with HSPN. In this Japanese report, the DD genotype did not associate with proteinuria at onset, but was significantly associated with proteinuria at 4 and 8 years after onset in children with HSPN, but not those with IgAN.[147]

In a predominately pediatric HSPN population, the interleukin-1 receptor antagonist *2 allele associated with the development of nephrotic syndrome and renal insufficiency.[148] Ault et al.[149] found a significant association between HSPN and complement C4B deficiency and a significant association between C4A deficiency and severity of HSPN.

TREATMENT

Very few RCTs have been done for treatment of HSPN. Virtually all data for treatment come from

case series. Approaches to treatment can be grouped into the following three categories or stages of disease: (1) prevention of HSPN in a child presenting with HSP, (2) treatment of rapidly progressive or severe crescentic HSPN, and (3) treatment of chronic or persistent HSPN.

Prevention of Henoch-Schönlein Purpura Nephritis

Three studies found that treatment with prednisone for 2 to 3 weeks lowered the risk of a child with HSP and a normal urinalysis developing HSPN.[116,150,151] One of these studies was a RCT of 168 children. One retrospective study found no decreased risk of HSPN in children treated with prednisone.[152] In all of these prevention studies, nephropathy is broadly defined to include any amount of microscopic hematuria. Very small amounts of microscopic hematuria are unlikely to put a child with HSP at risk for progression to ESRD, and treatment of such children with corticosteroids could have little effect on the ultimate outcome.

Treatment of Rapidly Progressive or Cresentic Henoch-Schönlein Purpura Nephritis

Studies on treatment of severe HSPN in children are case series of children presenting with prognostic features that suggest probable progression to ESRD.[128,153-157] These prognostic features are usually heavy proteinuria and/or nephrotic syndrome and/or significant crescentic nephritis (usually >50% of glomerular involvement). Two of these studies began with 3 days of treatment with high-dose methylprednisolone, followed by oral prednisone with the addition of cyclophosphamide and dipyridamole in one study[153] and cyclophosphamide for some patients in the other.[154] Only four of 50 patients from these two studies progressed to ESRD and 76% had normal renal function at the time of the reports.[149,150] Bergstein et al.[155] treated 21 children who had severe crescentic HSPN either with azathioprine and methylprednisolone followed by oral prednisone or with azathioprine and oral prednisone alone. Most of these children had a marked reduction in proteinuria and only two progressed to ESRD. The authors concluded that response to treatment that began with high-dose methylprednisolone was no different than that with oral prednisone alone.

Another Japanese study used daily followed by alternate-day prednisone in combination with oral cyclophosphamide and warfarin followed by dipyridamole to treat 14 children with severe HSPN.[156] After a mean follow up of 7.5 years, nine children had normal renal function and a normal urinalysis, four had minor urinary abnormalities, and one had heavy proteinuria.

Two studies of treatment with plasma exchange showed less dramatic results.[129,157] In a Japanese report of nine children, four eventually had normal renal function and normal urinalysis with two progressing to ESRD,[157] whereas seven of eight German children progressed to CRI or ESRD.[129] Analysis of the data from studies on treatment of rapidly progressive or crescentic HSPN using evidence-based criteria finds that the studies at best are at a level of evidence of 5 and 6 and can only support a grade D recommendation.[30] Nevertheless, we and most other most pediatric nephrologists will attempt aggressive treatment of such children and will not accept RCTs with placebo or untreated patients. The best approach to this dilemma should be the organization of a large RCT comparing pulse methylprednisolone followed by oral corticosteroids alone with the same regimen plus another agent such as cyclophosphamide or mycophenolate mofetil.

Treatment of Chronic Henoch-Schönlein Purpura Nephritis

Nine Japanese children with HSPN (8 ISKDC histologic grade IIb, one grade IVb) and with proteinuria from 3.2 to 6.8 g per day were treated early in the course of the disease with oral prednisolone (1.5 mg/kg per day) combined with an 8-week course of cyclophosphamide (2 mg/kg per day).[158] Proteinuria and activity index on repeat biopsy decreased significantly for all nine, with seven of the repeat biopsies showing grade III histology and two grade IIIa. All had normal renal function at last follow up.

In a follow-up study of the Guy's Hospital cohort, for 88 children with HSPN, no association was found between treatment with prednisone and/or immunosuppressive agents and outcome.[122] However, the authors state that severity of disease was a major determinant in the decision to treat a child with HSPN. Thus, the results could be explained by selection bias favoring treatment of the more severe cases rather than failure of such ther-

apy. Foster et al.[159] compared the clinical course of 17 patients with HSPN treated with prednisone and azathioprine with historical controls reported over 2 decades earlier by Lévy et al.[86] Although the 15 of the 17 had a favorable outcome, the historical controls could well have had much more severe disease. However, repeat biopsies in 13 of the patients showed a significant improvement in activity index.

Watanabe et al.[160] reported improvement in activity index and no change in chronicity index in repeat biopsies of 13 children with IgAN or HSPN treated with urokinase infusion. The results of this study suggested that urokinase might prevent mesangial proliferation associated with IgAN and HSPN by either its fibrinolytic action or other mechanisms such as digestion of the mesangial matrices. Kawasaki et al.[161] treated 56 children with HSPN who had at least ISKD grade IIIb histology with intravenous methylprednisolone (3 days) and urokinase (7 days) pulse therapy. The pulse therapy was followed by daily oral prednisone, dipyridamole, and warfarin for at least 6 months. The mean urinary protein excretion decreased from 146 mg/m^2 per hour to 33 mg/m^2 per hour at 6 months and 14 mg/m^2 per hour after 2 years. After a mean follow up of almost 10 years, only one subject progressed to CRI.

SUMMARY

At the present time, there are no RCTs that can be used to guide the therapy of HSPN in children. Thus, reliance has to be placed on the use of clinical case series as well as the experience with treatment of IgAN. In the past, pediatric nephrologists have had the impression that in some instances HSPN could be more aggressive than IgAN. Thus, children with moderately severe HSPN are more likely than children with IgAN to receive treatment with immunosuppressive or cytotoxic agents in addition to corticosteroids. Large, well-designed RCTs are urgently needed for determination of the best treatment for HSPN.

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