Henoch-Schoenlein purpura: The most common vasculitis in children with severe renal involvement

Rosanna Coppo
Director Nephrology, Dialysis and Transplantation Department
Regina Margherita University Hospital, Turin, Italy.

Henoch-Schoenlein purpura (HSP) is a vasculitis of the small blood vessels with clinical presentation of a multi-organ involvement syndrome at variable expression in derma, intestine, articulations and kidney. Firstly identified by Heberden, Schoenlein described the purpuric and articular manifestations and Henoch the gastrointestinal and renal features. The combination of various systemic and renal symptoms leads to apparently different clinical entities and often overlaps the autoimmune diseases. The difficulty of correctly interpreting the frequent concomitant cutaneous allergic reactions to drugs and infective agents were matters of further confusion, leading in the past to some ambiguous definitions of HSP, including hypersensitivity angiitis or anaphylactoid purpura or streptococcal rheumatic peliosis.

DIAGNOSTIC CRITERIA AND CLINICAL FINDINGS

Basing on the 1990 American College of Rheumatology diagnostic criteria of HSP and the following 1994 Consensus Conference, HSP has been defined as a small vessels vasculitis (involving capillary vessels, arterioles, venules) with immune-deposits prevalently formed by IgA.
EPIDEMIOLOGY AND ENHANCING FACTORS

HSP is a relatively uncommon disease particularly in adults, whereas in children its incidence accounts for about 14/100,000 cases/year. In children, HSP is the most frequent vasculitis. The median age at onset is about 4 years although it can also affect old people. The male sex is most represented (M/F 1.3-2.5).

The renal involvement is particularly frequently in the first and second decade of life. In unselected cohorts of children, the prevalence of the renal involvement during the course of HSP varies from 20% to 54% (mean 33%), whereas in adults this frequency is much higher (meanly 63%)\(^2\).\(^4\).\(^7\).\(^2\).\(^4\).\(^7\). Even taking into account that the mildest cases of renal involvement among children could be under-diagnosed and that some adult patients could be misdiagnosed as primitive vasculitis, the most frequent development of renal disease in older cases remains unquestionable and unexplained. In comparison to other renal diseases severe enough to warrant renal biopsy, a glomerulonephritis (GN) secondary to HSP was more frequent in children (11.6% of all biopsies) than in the whole cohort (3.5% of renal biopsies) as reported by the General and the Pediatric Registers of the Renal Biopsies in Italy.

The geographical distribution is similar to that of primary IgAN. Triggering factors are reported in about two third of the cases, mostly infections and particularly in children. Streptococcus b, Yersina enterocolitis, mycoplasma, toxoplasma, varicella, measles, rubella, adenovirus, HIV and several other agents have been sporadically recorded among the enhancing factors.

A coincident role of allergic reactions to vaccination against smallpox or influenza, drugs (including ciprofloxacin, angiotensin converting enzyme inhibitors and angiotension II receptor antagonists, vancomycin, minocycline, carba-zepine, caridopa/levodopa and others) or other allergens has been strongly suspected in some cases also. Cancer, monoclonal IgA gamopathy, chronic alcoholic liver disease, trauma and a number of other miscellaneous factors have been reported to be associated to HSP.

Some familial cases and restricted epidemic clusters of HSP have been observed.\(^5\).

SYSTEMIC EXTRA-RENAL FEATURES

Skin lesions

The skin lesions are characteristic and consist of slightly raised “palpable” purpuric macules that do not disappear on pressure and are not related to thrombocytopenia. Typically the skin lesions begin with erythematous macules, some of which develop into slightly raised urticarial papules, which soon become purpuric and eventually take a fawn color as they fade. The purpuric rash is symmetrically distributed over the extensor surfaces of the lower limbs and forearms and over the sides of buttocks. Fever and general malaise may accompany the rash. At the beginning the picture is hardly distinguishable from infectious purpuras or allergic reactions.

At microscopic examination, the lesions consist of leukocytoclastic vasculitis of dermal vessels with IgA deposits in the vascular walls. The purpura lasts for a few days and often relapses in new crops of lesions when the first eruption ceases. It recurs in almost one third of cases, but this is generally unrelated to the severity of renal lesions.
Gastrointestinal tract

The abdominal manifestations include diffuse abdominal pain, increasing after meals, referred to as “bowel angina” often accompanied by vomiting, haematemesis and haematochezia/melena. In some cases, the pain is so severe as to mimic an acute surgical emergency, even if intussusception, intestinal infarction, bowel perforation are very rare events. In these cases laparotomy is often necessary; however a spontaneous reduction may be induced by relieving bowel-wall oedema using antihistamine and steroid therapy.

The gastro-intestinal symptoms are reported in 50-70% of all cases, more frequently in children (62%) than adults (47%) and incidence rises to 90% in patients with renal involvement when mucosal purpura is checked by gastroscopy or colonscopy.

Joints

Transient arthralgias due to oligoarticular synovitis, mostly involving lower limb articulations, ankles and knees, are reported in 50-70% of all cases. These lesions do not evolve into joint erosions or deformities.

OTHER EXTRARENAL MANIFESTATIONS

Convulsions, encephalopathy, chorea or blindness occasionally occur due to cerebral vasculitis. Other rare manifestations include pulmonary-renal syndrome, cardio-pulmonary syndrome, pancreatitis, adrenal bleeding or testicular, rather than ovarian involvement mimicking torsion.

Haemorrhagic ureteritis is a clinical feature sometimes occurring in children, usually under the age of 5 years. The clinical presentation is haematuria, associated with loin pain and renal colic. The necrotizing vasculitis and ureteritis may lead to ureteral obstruction, occasionally bilateral. Ureteric lesions, when healed in fibrosis, may progress to ureteral stenosis often requiring surgical correction.

Kidney

The proportion of childhood patients with renal involvement has been reported to range from 20 to 100%, according to the pre-selection of the cohorts investigated. Renal lesions may occur without clinical signs, or be evident only after some careful follow-up. Indeed the percentage of renal involvement increases progressively to 35% after one year and continues to increase thereafter. Hence, late renal involvement can be missed in mild cases not sequentially investigated.

In unselected cohorts of children, the prevalence of the renal involvement during the course of HSP is a mean of 33%, whereas in adults it is much more frequent (mean 63%).

In cohorts of patients selected for a kidney disease severe enough to warrant renal biopsy, the prevalence of the glomerulonephritis secondary to HSP of all renal diseases is higher in children, 11.6% versus 3.5% in the whole cohort in the Italian register of renal biopsies, data comparable to the French series (10-15% of glomerulonephritis in children versus 2% in adults).

General paediatricians often report a systemic disease with modest and transient urinary abnormalities, whereas paediatric nephrologists and nephrologists describe much more severe and often chronic renal involvement both in children and in adults. The HSP manifestations range from isolated microscopic haematuria, gross haematuria, proteinuria to nephrotic syndrome. When analysis is made...
of HSP patients with a renal disease severe enough to warrant renal biopsy, the severity of the clinical presentation is similar in adults and children except for a higher frequency of nephrotic syndrome in children.\textsuperscript{21,22} Haematuria is detected within 4 weeks of onset of illness in 80\% of cases. It is often transient, detectable only by routine urinalysis during the acute illness, giving place to a complete and lasting remission. Instead, when haematuria persists, the nephritis become chronic, and proteinuria often develops. In non selected series of children, nephrotic syndrome is detected less frequently than in adults. Renal function is often normal at the beginning, particularly in children, but sometimes there is a functional impairment at onset. Acute nephritic syndrome, often with hypertension is observed in about half of the cases. In rare cases the disease rapidly progress to renal insufficiency. Palpable purpura often precedes or is coincident with the nephritis onset, nevertheless in 10\% of the cases purpura follows renal symptoms by weeks or months, leading to initial diagnosis of idiopathic IgAN.\textsuperscript{21} These observations confirm the weak distinction between idiopathic IgAN and HSP nephritis discussed further below. However, it is interesting that macroscopic haematuria coincident with upper respiratory tract infections, so common in IgAN patients, was reported in only 7\% of patients needing renal biopsy (4\% of adults and 19\% of children).\textsuperscript{24}

**Serum abnormalities**

Mean levels of serum IgA are increased, as in the idiopathic IgAN, but the increase is often limited to the acute illness, and serum IgA returns to within normal values as the disease heals. The increase mainly involves polymeric IgA\textsuperscript{10}, IgA immune complexes (IC), and IgA/\textgreek{I}gA1Cor IgA/fibronectin aggregates have been detected mostly during the acute phases or during relapses\textsuperscript{16,17,49}. IgA1IC, mixed IgA/IgGIC and high molecular weight complexes (> 19S) have been reported to be more frequent and significantly higher in HSP than in IgAN\textsuperscript{17}.

Aberrantly glycosylated IgA showing signs of truncation of GalNAc-Gal sequence in O-linked carbohydrate chains have been detected in patients with HSP, particularly children with renal involvement.\textsuperscript{77,22,1} IgA antibodies with specific binding to endogenous or exogenous antigens have been reported, including IgA rheumatoid factor\textsuperscript{77} anti \textgreek{a} galactosyl antibodies,\textsuperscript{28} IgA binding to mesangial cell antigens and mesangial matrix\textsuperscript{20}. These reactivities might be due to lectin-lectin interactions consequent to IgA aberrant glycosylation more than to true antigen-antibody reactions.

In HSP with renal involvement increased levels of IgA reacting with sonicated neutrophil extracts (IgA-ANCA) and with purified cytoplasmatic antigens (myeloperoxidase) have been detected\textsuperscript{74,22}. The presence and the meaning of IgA-ANCA is still debated, and lectin-like interactions are likely to play a role in this reactivity as discussed above.

IgA-producing T cells are increased in circulation during acute phase of the disease.\textsuperscript{14} Transforming growth factor (TGF) \textbeta-secreting T cells have been detected in circulation during the phases of clinical activity of HSP, while resolved during recovery.\textsuperscript{30} Plasma IgE levels are increased in HSP, and significantly higher than in IgAN\textsuperscript{29} as well as eosinophil cationic protein levels. Serum C3 and C4 values are within the normal ranges, even though CH50 and properdin levels are often reduced. These data, together with the frequent increase in C3d detected in adults and children\textsuperscript{16,80}, suggest C3 activation, possibly via the alternative pathway, balanced by enhanced factor synthesis.

Platelet count, as well as the activity of the
HENOCH-SCHOENLEIN PURPURA: THE MOST COMMON VASCULITIS IN CHILDREN WITH SEVERE RENAL INVOLVEMENT

clotting factors is normal. Conversely abnormalities in fibrin-stabilizing factor (factor XIII) have been reported as well as increased von Willebrand factor plasma levels\textsuperscript{32}, which may favour fibrin deposition in glomerular structures and crescent formation.

**Genetics**

A positive association with DRB1*01 and DRB1*11 as well as a negative association with HLA-DRB1*07 was firstly reported by our group in an Italian cohort\textsuperscript{5} and confirmed in a Hispanic one\textsuperscript{2}. In Japanese patients there is an increase in DQA1*0301\textsuperscript{50}. Genetic studies on Class III region have shown an increased frequency of homozygous C4A or C4B null phenotype in Caucasians\textsuperscript{60} and in Japanese patients\textsuperscript{50}.

**HISTO-PATHOLOGY**

**Light microscopy**

HSP nephritis is characterized by mesangial damage with different degrees of hyper-cellularity, ranging from focal-segmental endo-capillary proliferation to crescent formations.

The classification of renal damage considered the severity of the proliferative intra and extra-capillary lesions\textsuperscript{56, 34} (Figure 1). Six histologic classes are distinguished according to presence/absence and extension of extra-capillary proliferation, with subclasses defining the characteristics of the endo-capillary lesions.

- **Class I:** minimal glomerular lesions and absence of crescents
- **Class II:** no crescents
  - Ila: mesangial proliferation only
  - Ilib: focal-segmental endo-capillary proliferation
- **Class III:** presence of extra-capillary florid proliferation in less than 50% of glomeruli
  - IIIa: in association with focal and segmental endo-capillary proliferation
  - IIIb: with diffuse endo-capillary proliferation
- **Class IV:** florid extra-capillary proliferation in 50-75% of glomeruli
  - IVa: in association with focal and segmental endo-capillary proliferation
  - IVb: with diffuse endo-capillary proliferation
- **Class V:** florid extra-capillary proliferation in more than 75% of glomeruli
  - Va: in association with focal and segmental endo-capillary proliferation
  - Vb: with diffuse endo-capillary proliferation
- **Class VI:** absence of crescentic lesions, simultaneous presence of mesangial and endo-capillary proliferation with diffuse aspects of double border of the capillary walls, with such cellular interposition to shape a picture of pseudo-membrane-proliferative glomerulonephritis.

Lobules with extensive intracapillary and extracapillary proliferation may undergo necrosis, or rarely mesangiolysis, with aneurismatic capillary dilation. Focal fibrinoid necrosis is often present at onset, which corresponds, at a later time, to disorganized sclerosis. Intracapillary glomerular through adhesions between visceral and parietal epithelium may occur, leading to obliteration of the urinary space. The most common histological feature is a predominance of small crescents, with some large ones and
only rarely and repair without fibrosis, the latter indicate more severe cases and the fibrous evolution is common. In patients, either adults or children, having a disease so severe to warrant renal biopsy, extra-capillary proliferation is detected in half or more of the cases. When present, proliferative extra-capillary lesions often involve less than 50% of glomeruli (class III) and are associated with polymorphonuclear glomerular infiltration.

Blood vessels may show medial hypertrophy and intimal fibroelastosis. Hyalin change and/or accumulation of fibrinoid material, or necrosis with inflammatory infiltration and clear findings of vasculitis can be present. In the past, these lesions were considered of diagnostic value, nevertheless the presence of capillary necrosis even in idiopathic IgAN invalidates this putative criterion.

Degenerative tubular alterations are often detected, focally, in the cortical tubuli and they are more frequent than in the idiopathic IgAN. A severe lymphomonocytic interstitial infiltration characterizes the progressive cases.

Immunohistochemistry

The characteristic feature is granular mesangial IgA deposition which, in contrast with the frequent focal and segmental proliferative changes, is always diffuse as in primary IgAN.

IgA1 is the dominant subclass with equal distribution of light chains. As for idiopathic IgAN, C3 is co-deposited in most cases (80%). The membrane attack complex C5-C9 and the alternative complement pathway components are regularly detected. IgG and IgM co-deposits are present in the 40% of the cases. Glomerular fibrin related deposits are much more frequently present in HSP nephritis than in IgAN and are often related to active disease with extracapillary
proliferation. In cases with severe glomerular changes, deposits of IgA and C3 can be found in arterioles and/or cortical peritubular capillaries.

**Electron microscopy**

Mesangial matrix expansion and variable degree of cellular hyperplasia are evident together with electron-dense deposits. Mostly the deposits have a mesangial site with parietal extensions and only in 30% of the cases are they purely mesangial. The presence of parietal deposits modifies the capillary basal membrane profile because of the widening of the rara interna and external lamina, with neo-formed layers, as a possible consequence of the membrane reactivity to immune deposits.

**EXTRA-RENAL LESIONS**

The typical leukocytoclastic vasculitis - with fragmented nuclei of leukocytes in and around arterioles, capillaries and venules, surrounded by infiltrating neutrophils and monocyte cells in presence of nuclear residues (nuclear dust) in the wall of arterioles - is detectable in the kidneys and in other areas, particularly in the skin and gut. Fibrinoid accumulations and arteriolar and venular necrosis can be found. Deposits of IgA and C3 are present in the capillary derma in purpuric lesions and uninvolved skin and are considered a valid diagnostic criteria, with 100% specificity in combination with leukocytoclastic vasculitis.

**CLINICO-PATHOLOGICAL CORRELATIONS AT ONSET**

In the Italian series of 219 renal biopsies patients with minimal proteinuria had higher prevalence of classes I and II lesions, without crescents. In patients with significant proteinuria more severe renal lesions were frequently found, nevertheless with low predictive value for the single case. In children, particularly, cases with non nephrotic proteinuria had often extracapillary proliferation. Gross haematuria at presentation was associated with crescent formations in the 22% of the cases, independently from the patient's age. Renal functional impairment at onset had a predictive value of severe histologic lesions. Similar figures have been reported in other cohorts of either children and adults.

**CLINICAL COURSE AND PROGNOSIS**

The proportion of HSP nephritis in comparison of other renal diseases as a cause of ESRF is minimal - 0.05% - in adults, while it is up to 5.1% in children. The long-term outcome in chronic renal failure varies according to the cohorts examined, being in general worse in adults then in children, particularly in unselected cases. When patients having had renal biopsy are compared, the difference is less evident. In unselected settings HSP is a mild disease, with renal involvement in a minority of cases, mostly presenting isolated haematuria and/or minimal proteinuria and a long-term morbility is reported to involve no more than 1% of patients.

When considering hospital series of non-selected children admitted into General Paediatric Hospitals, the reports indicate that 20-28% had urinary sediment that was abnormal for more than 1 month. After a decade follow-up about 2-3% of the children with initial signs of renal involvement progressed to end stage renal failure (ESRF). Tertiary Reference Centres report remission...
rates below 50% and a poor outcome in 10-25% of children\textsuperscript{36,41}. The outcome of patients selected on the need for renal biopsy is much more severe and long-term analyses show that 15-30% of patients progress to renal failure with wide variability depending on the initial selection criteria and follow-up duration\textsuperscript{72}.

In a long-term follow-up study over about 25 years late progression was observed in 25% of children admitted to a Paediatric Nephrology Reference Centre, even after initial clinical improvement\textsuperscript{41}. It reported that 15% of patients with a nephritic onset or persistent heavy proteinuria, 40% of those with a nephritic presentation and 50% of those with mixed nephritic-nephrotic syndrome at onset have ongoing urinary abnormalities and that many of these patients end in chronic renal failure. This progression can occur more than a decade after the initial presentation. The disease is more severe in adults, where the progression to renal failure is reported in 8%-68% of the cases\textsuperscript{38,72}.

It is generally thought that an important factor for individual prognosis is the presence and extent of extracapillary proliferation. The relationship is particularly strict for Class IV and V, showing extensive glomerular involvement by crescents. In a Japanese series, 33% of Class IV and 83% of Class V, displaying respectively > 50 % and >75 % of crescents ended in chronic renal failure\textsuperscript{86}.

In the Italian multicentre study on patients with a renal disease severe enough to warrant kidney biopsy\textsuperscript{21}, after 1-20 (mean 5) years one third of the cases were in remission, often complete and without significant urinary anomalies. In another third of patients only minimal or moderate proteinuria was left. The outcome was substantially similar in adults and in children. The progression to dialysis varied from a few days to 20 years, with an average of 3 years in the adults and 10 years in children. The actuarial renal survival of HSP nephritis in patients with indication for renal biopsy resulted similar in adults and children, with loss of renal function in 26% of adults and in 27% of children after 10 years\textsuperscript{21}. The comparison of the progression rate in HSP and IgAN is difficult due to the different indications to renal biopsy in IgAN, ranging from isolated microscopic haematuria to severe renal function impairment, however no significant difference in progression rate can be envisaged, since IgAN is reported to have a 10 year progression rate of 15-25% according to the biopsy criteria adopted\textsuperscript{86}.

**RISK FACTORS FOR PROGRESSION**

As reported above, in non-selected series of HSP nephritis greater age is associated with a higher risk of progression, but in biopsied patients this correlation is not evident. A good correlation between the clinical presentation and the long-term outcome is reported in paediatric series\textsuperscript{9}. In some reports nephrotic syndrome and/or renal insufficiency at onset were risk factors (44%) for renal failure after two decades of follow-up\textsuperscript{41}.

In the cohorts of children and adults having had renal biopsy\textsuperscript{21} the most unfavorable prognostic factor was renal function impairment at presentation: 45% of adults with severe renal failure and 18% of those with moderate functional impairment eventually required chronic dialysis, versus only 2% of adults with normal renal function at onset. This association was not found in children, who experienced progression to renal failure even in cases with normal renal function at onset.

Hypertension was a negative prognostic factor particularly in adults, in whom it was more constant and associated with renal function impairment.
The predictive value of proteinuria resulted differently in adults and children: in both cohorts absent or mild proteinuria or, at the opposite, a nephrotic-range levels, were respectively associated with high frequency of remission or functional deterioration. However, adult patients moderately proteinuric only seldom showed extra-capillary proliferation, while children with mild proteinuria frequently displayed severe histologic lesions, with extracapillary proliferation. Among adults, a proteinuria > 1.5 g/day resulted predictive for unfavorable outcome. On the contrary, nephrotic and non nephrotic children had similar outcomes.

Extent and activity of extracapillary proliferation are important risk factors when important. The predictive value of mild extracapillary proliferation was low when crescents involved less than 50% of glomeruli (Class III) (renal failure in 39% of adults and in 18% of children with crescents), since also cases without crescents experienced an unfavorable outcome (19% of adults and 23% of children).

**HSP NEPHRITIS AND RENAL TRANSPLANTATION**

In patients transplanted after ERSF from HSP nephritis, extra-renal systemic recurrence is rare, or very mild while IgA mesangial deposits may recur in allografts. The actuarial risk for histologic/immunofluorescent renal recurrence is 35% at 5 years, with loss of the graft in 11%. In most patients, no clinical manifestations or minimal haematuria accompanies histologic recurrence in grafted kidneys. Recurrence was more frequent in rapidly progressive cases, occurred even after a delay of one year between systemic signs and transplantation and was not prevented by triple therapy, including cyclosporine. The recurrence rate appears to be increased in recipients of living-related grafts, suggesting a role for genetic factors and arguing against the use of living donors for renal transplantation in HSP, even though this association is still controversial.

**THERAPY**

**Non-renal cases**

No treatment is required for mild cases, provided an efficient urine monitoring is ensured to detect modifications in the clinical follow-up, mostly during the first 2-3 months after the purpuric rash.

Corticosteroids are generally considered to be effective in controlling the extra-renal signs, particularly abdominal pain and arthritis, hastening resolution. Severe recurrent necrotizing purpura as well as abdominal pain have been successfully treated by immunoglobulin i.v. infusions.

An important issue is whether medium level doses of prednisone (1-2.5 mg/Kg/day for 1 to 3 weeks) in children with normal urinalysis are able to prevent the development of nephropathy. This preventive effect has been debated using retrospective data analysis, which compared treated versus untreated patients. However a selection bias may have influenced the treatment choice, often reserved to the more active cases. A prospective study (albeit not strictly randomized) has contradicted the previous negative conclusions, suggesting a protective effect of small doses of prednisone for two weeks. However, very small amounts of microscopic haematuria are not likely to be a risk for progression to renal failure. Thus, the prevention of mild nephropathy may not affect the risk of progression of HSP nephritis.
**Treatment of HSP nephritis of moderate severity**

For a long time steroids have been thought to be ineffective for treating established HSP nephritis, based on observations dating back decades. Indeed, no benefit of prednisone in the attempt to treat children with HSP nephritis was demonstrated in retrospective analysis\(^2\). However, the severity of the disease was a major determinant in the decision to treat, leading to a selection bias favouring treatment of more severe cases. More recently, positive results were reported by treating patients with moderately severe renal involvement for almost one year by means of oral prednisone and azathioprine\(^3\), when compared with historical untreated cases\(^5\). Since it is likely that the historical group included more severe cases, no recommendation for treatment of moderately severe HSP nephritis is presently made\(^8\).

Finally, also reports on tonsillectomy do not support a recommendation this intervention in the treatment of mild forms of this nephropathy\(^7\).

**Treatment of severe HSP nephritis with extensive crescents**

Great interest is focused on the possibility of lessening or stopping the progression to renal failure of HSP nephritis with severe endocapillary and extracapillary proliferation, clinical presentation of nephritic or nephritic syndrome with impaired renal function, which present with an evolutive course. A favorable clinical outcome was reported in 11/12 children with 60-90% glomeruli with crescent formations by using a triple therapy\(^6\) of 30 mg/Kg/iv pulses for 3 days followed by 6 months of prednisone and dipyridamole and cyclophosphamide for 3 months. More than 60% of these patients experienced a complete remission.

Larger series\(^7\) confirmed that a similar prednisone regimen, in some cases associated with a 2 month course of oral cyclophosphamide, induced a clinical recovery in 71% of children with nephritic syndrome and/or crescentic involvement of 50% of the glomeruli, versus 40% in untreated children. The most significant results have been obtained in paediatric patients with epithelial crescents involving more than 50% of glomeruli or with nephrotic syndrome. It is of interest to notice that in the same cohort, no effect of treatment was found when crescents involved less than 50% of glomeruli.

In children with HSP nephritis children having > 50% glomeruli involved in crescent formations, good results were reported by using oral prednisone treatment pursued for 4 months in association with 2 months of cyclophosphamide and 4 months of heparin or warfarin (Iijima et al. 1998). Positive results were obtained with a combination of prednisone, azathioprine or cyclophosphamide\(^7\).

Our group\(^8\) and more recently others\(^4\) successfully treated with plasma exchange, corticosteroids and cytotoxic drugs patients with rapidly progressive HSP nephritis. In the follow-up of our cases, even though some patients experienced a complete remission, most had subsequent renal relapses, and, in spite of a new cycle of plasma exchange, the renal function could not be improved again and patients had a final outcome in end-stage renal failure. The estimated progression was delayed by 1-4 years. In the Japanese experience after 10 years 60% of the treated patients had a complete remission of renal disease. The German series\(^7\) similarly showed that aggressive treatment including PE may delay the rate of progression, but not prevent chronic end-stage renal failure in the majority of severe crescentic HSP nephritis.
To sum up, uncontrolled studies of combined steroid (either intravenous pulses or oral therapy), immunosuppressive drugs (Cyclophosphamide or Azathioprine) sometimes in association with anticoagulation (Warfarin or Dipyridamole) in patients with nephrotic-range proteinuria and/or important extracapillary proliferation on biopsy can retard and sometimes halt the renal function deterioration, if the therapy is initiated early enough, before a non-return stage characterized by the establishment of fibrous crescents and glomerular or interstitial changes.

**Intravenous immunoglobulin therapy**

Besides steroid and cytotoxic therapy, favorable results with decrease in proteinuria and improvement of histological index of renal activity have been reported in potentially progressive patients with heavy proteinuria, using immunoglobulin i.v.infusions. However, a rebound was noticed shortly after the therapeutic cycles, which somehow banished the positive results obtained.

**PATHOGENESIS**

The histologic feature distinguishing HSP nephritis from other systemic vasculitides or collagen diseases with similar multiorgan involvement is mesangial IgA deposition. Hence, as for primary IgA nephropathy (IgAN), interest has been focused on this class of immunoglobulins. IgA is found in serum and mostly in external secretions, where it plays a major role in mucosal immunity. IgA exists as two distinct subclasses, IgA1 and IgA2, differing as an insertion of 19 aminoacids, peculiar to IgA1 and deleted in IgA2 subclass. Both subclasses are synthesized by plasma cells as a 155 kD protein consisting of two a chains and two light chains, or as dimers or polymers of the basic 4-chain immunoglobulin structure, with molecular weights multiple of 155kD. Dimers are joined by a J chain and can be transported from the basolateral to the luminal surface of secretory epithelium via a specialised glycoprotein receptor (secretory component). In humans, serum IgA is predominantly monomeric, of the IgA1 subclass, and it is derived from plasmocytes within the marrow and spleen. Mucosal-derived plasmocytes produce predominantly dimeric IgA containing J-chain. Glomerular deposits in HSP as well as in primary IgAN are made of polymeric IgA1, leaving open the possibility of either bone-marrow or mucosal origin, by a somehow disturbed synthetic pathway.

Since IgA is the major immunoglobulin in mucosal secretions working as a defence against viral and bacterial agents, and since HSP can be enhanced by mucosal infections, an extensive search for peculiar antigens was been carried out. Alimentary antigens or infectious organisms have been advocated. However, the search for an only eliciting antigen remained elusive.

HSP has been supposed to be an antigen-dependent process, on the basis of the cross-reactivity between eluted mesangial IgA with the mesangial area of other biopsy samples from different HPS patients. The concept of HSP as an antigen-dependent process was further emphasised by the experimental observation that most closely reproduces HSP: systemic vasculitis and nephritis was obtained by injecting animals with a complement activating carbohydrate antigen.

HSP nephritis has been ascribed to the accumulation of IgAIC within glomeruli, as has idiopathic IgAN. Many studies revealed high lev-
els of IgAIC during clinically active phases of HSP nephritis\textsuperscript{16,27,28} often coincidentally with the development of clinical signs of nephritis and in correlation with urinary activity. However, the correlation with renal involvement remained not completely satisfying and the search of eliciting antigens in humans remained elusive, lessening the support to the hypothesis of circulating IgAIC as the unique pathogenetic mechanism.

Several data accumulated evidence of a large spectrum of abnormal reactivities of circulating IgA in HSP patients, particularly those with nephritis, including anti-galactosyl antibodies\textsuperscript{28}, IgA binding to fibronectin\textsuperscript{48}, lectin-like molecules mostly gluten-derived\textsuperscript{19} or mesangial matrix glycoproteins\textsuperscript{20}. Hence we and others postulated that these reactions were not due to true antigen-antibody reactions but to some kind of affinity of circulating IgA to various molecules.

Attention has been focused on the carbohydrate moieties of IgA. Human IgA1, the predominant subclass deposited in both primary IgAN and HSP nephritis, is highly glycosylated. In addition to the N-linked oligosaccharides typically present in the carboxyl terminal portion of all classes of immunoglobulin heavy chain, IgA1 contains 5 short O-linked oligosaccharide chains composed of N-acetylgalactosamine, galactose and sialic acid. These oligosaccharides are coupled to serine and/or threonine residues which lie in the hinge region connecting the CH1 and CH2 domains, at the junction between the Fab and the Fc portions of the IgA molecule.

Several data support the hypothesis of a defective immunoregulation leading to aberrant IgA glycosylation not only in patients with primary IgAN but also in HSP patients\textsuperscript{78,22,1}. A genetic defect with inadequate activity of β1-3 galactosyltransferase in B-cells has been hypothesised as for primary IgAN but not yet proved. An imbalance in lymphocyte function, with a prevalence of Th2 over Th1 T cell subsets, can lead to altered IgA glycosylation in mice\textsuperscript{15}, similar abnormalities could derive from genetic conditioning, but the search is still now inconclusive, or from \textit{de novo} somatic mutations. Such aberrantly glycosylated IgA can circulate in monomeric form or participate in the formation of self-aggregates or true immune complexes.

Whether bound in IC or in self-aggregates, such aberrantly glycosylated IgA likely escapes clearance by hepatic receptors for asialoglycoproteins because of the lack of galactose and possibly because the size of the aggregates excludes them from the space of Disse.

In addition, by virtue of enhanced lectin-like reactivity with the fibronectin, laminin, and collagen within the mesangial matrix, abnormally glycosylated IgA deposits in glomeruli more readily than does normal IgA. Finally, mesangial catabolism of aberrantly glycosylated IgA may be diminished. In combination, these factors can lead to heightened accumulation and/or prolonged persistence of IgA deposits within the mesangium.

In turn, there is enhanced interaction with Fc\textsubscript{α} receptors on mesangial cells, resulting in cellular activation and phlogistic mediator synthesis. Our group has demonstrated that mesangial cells increase expression of integrin adhesion molecules\textsuperscript{4}, and of the inducible form of nitric oxide synthase (iNOS)\textsuperscript{4} in response to co-incubation with aggregated forms of desialylated or desialylated/degalactosylated IgA. The resultant increase in the production of intraglomerular nitric oxide may lead to peroxidative damage, apoptosis and sclerosis. The effect can be further enhanced by the concomitant depressed expression of vascular endothelial growth factor (VEGF) induced by aberrantly glycosylated IgA on mesangial cells, leading to an impaired repair process\textsuperscript{3}.

Aggregates of IgA also stimulate the synthe-
sis of a variety of cytokines (IL6, PDGF, IL1, TNF-α, TGFβ), vasoactive factors (prostaglandins, thromboxane, leukotrienes, endothelin, PAF, NO) or chemokines (MCP-1, IL-8, MIP-1, RANTES) by mesangial cells.

In the pathogenesis of HSP nephritis a particular role could be played by complement activation that shows some signs in circulation. It is of interest that aberrantly glycosylated IgA can activate complement more efficiently than normal IgA.

Antineutrophil cytoplasm antibodies of the IgA isotype (IgA-ANCA) have been reported in adults with active HSP, but other reports were negative. We demonstrated that IgA molecules from children and adults with HSP nephritis are provided either with reactivities due to abnormal glycosylation and increased binding to sonicated neutrophil extracts and to purified myeloperoxidase (MPO). No increased binding was found to serine protease 3. Of interest, this reactivity was never observed in sera of patients with primary IgAN, even though they have aberrantly glycosylated IgA. This binding was affected by electrical charge and carbohydrate interactions. The glycoprotein Fibronectin and the lectin Jacalin, which can bind IgA and the carbohydrate moieties of other glycoproteins, enhanced the binding of IgA to MPO. These data were consistent with a lectin-like binding of IgA to neutrophil cytoplasmic antigens.

We speculate that aberrantly glycosylated IgA in HSP patients- having among other reactivities also high affinity for ANCA antigens, may form circulating aggregates-, which, in presence of increased levels of eosinophilic cationic proteins as well as other phlogistic mediators, may favour the vascular deposition of IgA. The presence of IgA instead of IgG ANCA may avoid the precipitous and disastrous reactions which characterise IgG ANCA vasculitides.

Relationship between HSP and primary IgAN

The relationship between HSP nephritis and primary IgAN is complex, since the elements in common, such as the immunopathologic findings, are so strong to support the identity of the two nephropathies, while the peculiar clinical features, such as the recover capacity of HSP (even at histologic level) versus the persistence and progression of renal damage in primary IgAN, argue in favor of two different disease entities.

Paediatric nephrologists are so frequently facing an acute, benign illness, provided with a strong recovery potential, that they are more prone to conceiving of the two diseases as different entities, with different needs and clinical evolution. Besides the acute, mild and reversible form of HSP nephritis affecting children, which is typical of HSP only, the two entities become very similar when the disease is chronic and severe enough to warrant renal biopsy. The histologic lesions and the clinical outcome of this peculiar subset of HSP patients are identical to primary IgAN, supporting the hypothesis of only one nephrologic entity. For these reasons, most nephrologists working with adult patients consider primary IgAN a HSP nephritis without purpura.

Several reports support a common origin for the two diseases, such as the recurrence of IgAN in transplanted kidneys of patients on dialysis for HSP nephritis, or the development of HSP in twins of a primary IgAN patients. In several families the two diseases coexist in different members of the same family. In a French national survey of 40 families with two or more members affected by primary IgAN, 5 had members presenting with complete HSP syndrome, confirming a possible genetic link between the two diseases, and HSP as well as in primary...
IgAN has been reported an increased frequency of HLA-BW35\(^{30}\).

From an immunologic point of view the two diseases seem to share similar disturbances in IgA system. High levels of serum IgA are detectable in both HSP and primary IgAN, as well as high levels of circulating IgAIC, IgA1 IC and IgA/fibronectin aggregates, as discussed above, even though at higher levels in HSP (C17,48).

Aberrantly glycosylated IgA have been detected in children with HSP nephritis, more frequently than in subjects with extra-renal vasculitis only\(^{78,22,1}\).

The reason why some patients with IgAN develop a systemic vasculitis and present with the full expression of HSP is the clue of the problem of the different pathogenesis of these two entities.

A greater complement activation by aberrantly glycosylated IgA might represent the distinct pathogenetical mechanism inducing the vasculitic lesions that differentiate patients with HSP from those with primary IgAN\(^{16,80}\).

IgA-ANCA have been reported in active HSP only\(^{74,22}\), while they were never found in primary IgAN. Since this reaction is an indirect expression of altered glycosylation of the IgA molecule, it is tempting to speculate that the clue to the difference between HSP and IgAN is the quality and extent of aberrant glycosylation of IgA, which favours different reactivities and capacity of activating complement as well as other flogistic mediators. The involvement of a particular mediator pathway is suggested by the increase in IgE\(^{20}\) and eosiliphilic cationic proteins. This flogogenic potential in HSP is more time-limited than in primary IgAN, where it lasts life-long. In HSP there may be a clue role of a switch-on enhancing factor leading to an acute illness, often self-limiting and allowing a repair process. Genetic as well as acquired mechanisms might be responsible for this fine tuning.

References

16. Coppo, R. et al. (1982). Circulating immune complexes containing IgA, IgG and IgM in patients with primary IgA neph-


