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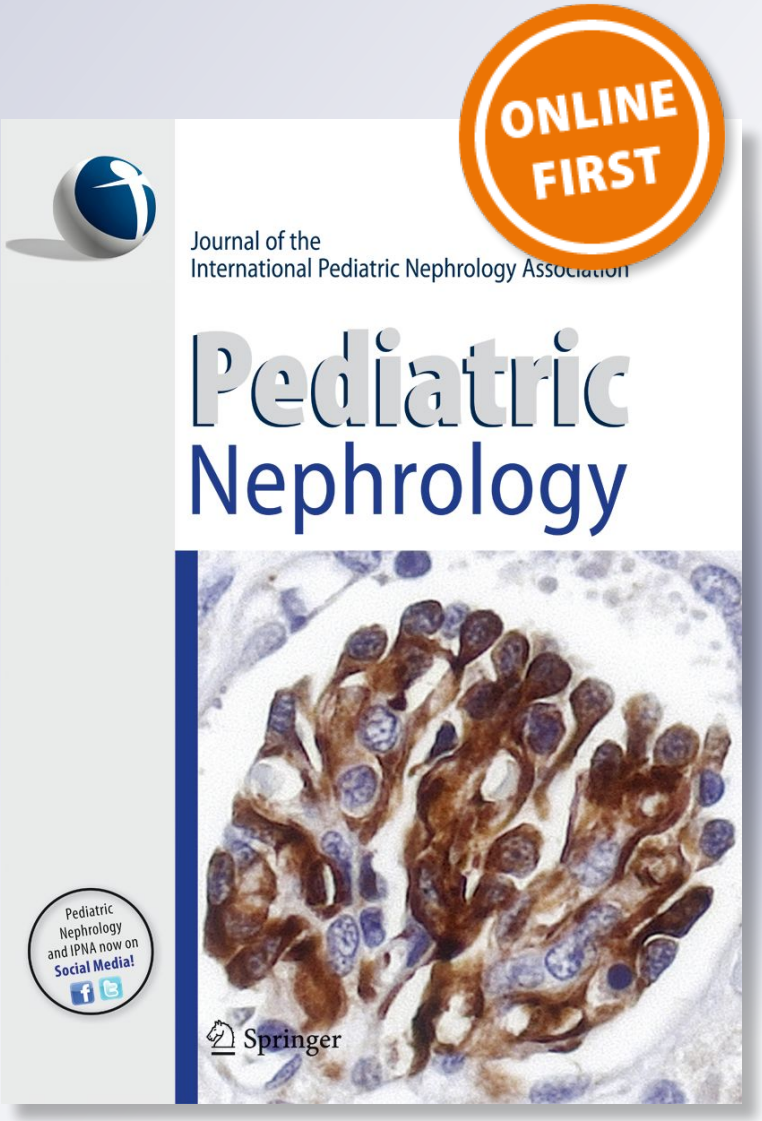

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REVIEW

The implications of focal segmental glomerulosclerosis in children with IgA nephropathy

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Abstract

Focal segmental glomerular sclerotic lesions in IgA nephropathy (IgAN), considered for years a chronic histologic feature related to proteinuria in remnant nephrons without any active role in the pathogenesis and progression of glomerular damage of IgAN, have been recently reconsidered. The Oxford classification of IgAN reported it as the "S" score and found it to be an independent risk factor for progression of IgAN. Its prognostic value was confirmed also in children. The identification of some histologic subvariants of the S lesion has produced interesting insights into different pathogenetic mechanisms of glomerular damage in IgAN. Tip lesion and podocyte hypertrophy are considered secondary to active podocytopathy and are correlated with higher levels of proteinuria and a faster decline in glomerular filtration rate. Moreover, endocapillary and mesangial hypercellularity might contribute in children with IgAN to formation and progression of S lesions. Considering the pathophysiology of these processes, children with some S features may benefit not only from nephroprotective measures but also from immunosuppression.

Keywords IgA nephropathy · Proteinuria · Glomerulosclerosis · Hypertension · Chronic kidney disease · Endocapillary hypercellularity · Mesangial hypercellularity

Introduction

IgAN is a glomerular disease which usually presents in children with episodes of macroscopic hematuria in coincidence with upper respiratory tract infections or persistent mild microscopic hematuria [1]. The clinical course is mostly benign within the pediatric age; hence, pediatricians have for years given little importance to these clinical features, without performing diagnostic renal biopsies and/or treating these children. Over the last decades, it has become clear that, even in childhood, several cases still progress to end-stage kidney disease (ESKD), while others experience it in young adult age.

Hernán Trimarchi and Rosanna Coppo have contributed equally to the development of the manuscript

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In the long-term follow-up of the European Validation study of IgAN classification (VALIGA), the combined end point of 50% decline in eGFR or ESKD at 10 years was 9% versus 30% in adults [2], while at 20 years, it was estimated by Kaplan-Meier curve to be 18% in children versus 53% in adults (unpublished data from VALIGA follow-up report) [3]. The median follow-up of VALIGA subjects was prolonged from 4.9 (IQR 2.4–7.9) years to 7.0 (IQR 4.1–10.8) years. According to this criticism, we reported in R1 the estimate calculated by Kaplan-Meier curve at 20 years [3]. A single-center child cohort long-term study showed that up to 13% of subjects eventually reached ESKD within 10 years, and up to 30% within 20 years, similar to what has been found in adult patients [3–6]. In this respect, it is critical to better understand the factors affecting progression that have originated back in childhood, particularly when these patients have already finished pediatric care.

The development of proteinuria is crucial for increasing the risk of progression in children with IgAN, as well as in adults [7, 8]. To date, persistent proteinuria is the only recognized risk factor by Kidney Disease Improving Global Outcomes (KDIGO) guidelines to target therapy in IgAN [9]. The Oxford clinico-pathological classification of IgAN and

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subsequent update detected in cohorts including children and adults the predictive value on outcome of histologic lesions, addressed by the MEST-C score [10]. This study assessed the correlation of each lesion with proteinuria at renal biopsy. These pathology features had independent prognostic value added to the risk based on clinical data, including proteinuria, mean arterial blood pressure, and estimated glomerular filtration rate (e-GFR) at renal biopsy. The MEST-C score included not only signs of mesangial and capillary loop inflammation or tubulointerstitial damage but also segmental glomerulosclerosis (S1). The presence of glomeruli showing segmental adhesions between visceral and parietal Bowman's capsule components and/or glomerulosclerosis was detected in 76% of renal biopsy specimens of the Oxford study including adults and children [11].

Segmental glomerulosclerosis (S1) in IgAN develops from different processes and displays different clinical expressions and dissimilar susceptibility to treatments. We have recently reviewed the pathogenesis of these lesions in IgAN and their impact on the clinical course and prognosis in general cohorts of patients with IgAN enrolled in large studies [12]. In the present review, we shortly summarize the major advancements in this area and discuss whether the S1 lesions encountered in kidney biopsies of children with IgAN have any peculiar value in comparison with similar lesions in adults.

Classification of subtypes of glomerulosclerosis in IgAN

Segmental glomerulosclerosis is defined by a segmental increase in matrix and obliteration of glomerular capillary lumen, and can be the only sign of glomerular damage as in idiopathic focal segmental glomerulosclerosis (FSGS) or in association with other glomerular diseases [13]. This is the case in IgAN, in which the predominant damage is mesangial cell proliferation with increase in mesangial matrix. At this histological stage, an irreversible podocyte loss of approximately 20% has already occurred [14].

Idiopathic FSGS is defined as a podocytopathy since podocyte injury with cytoskeleton disorganization and foot process effacement is the initiating mechanism leading to loss of adaptation and detachment from the glomerular basement membrane. Large podocyte loss results in focal adherence to parietal epithelial cells and scarring. At this point, an absolute 40 to 50% podocyte loss has already taken place [14, 15]. In animal models, activated parietal epithelial cells start to synthetize extracellular matrix and then migrate to a segment of the glomerular tuft where denuded podocyte-depleted glomerular basement membrane (GBM) exists. It is from this entry site wherein podocytes had detached that matrix is deposited and typical FSGS develops [16, 17].

In IgAN, the S1 lesion is defined as the presence of segmental sclerosis or adhesion in at least one glomerulus [7]. This lesion may be due to several mechanisms, including (a) podocyte damage with "podocytopathy" similar to primary FSGS due to mediators produced by activated mesangial cells, (b) podocyte maladaptation to hemodynamic changes induced by expansion of mesangial area or reduction in filtering glomerular capillary surface, and (c) organization and scarring resulting from segmental endocapillary inflammatory lesions with necrosis [17].

Glomerular sclerosis and podocytopathy secondary to inflammation in IgAN

Podocytopathy in IgAN can result from inflammatory mediators including complement activation products, reactive oxygen species, and cytokines released onto the circulation or most likely in the glomerular area during the inflammatory process following the deposition of IgA-containing immune complexes. This can result from an acute condition, driven by endocapillary hypercellularity, or as a continuous cross talk between mesangial cells and podocytes [12]. In the first case, proteinuria can develop suddenly and disappear after quick reversal of acute endocapillary lesions. The second mechanism is likely to operate more chronically, being dependent mostly on mesangial cell reactivity, and induce the clinically evident functional damage as proteinuria. In cultured mesangial cells, aberrantly glycosylated IgA1, defective in galactose (Gd-IgA1) and macromolecular IgA isolated from patients with IgAN, was found to trigger the production of tumor necrosis factor alpha (TNF-α) and other cytokines which synergistically act on podocytes, activating the nuclear translocation of nuclear factor kappa B (NF-kB) and reducing the expression of nephrin and ezrin, pivotal proteins in the podocyte-regulated slit diaphragm physiology [18, 19].

Glomerular sclerosis secondary to hyperfiltration in IgAN

Hemodynamic changes with podocyte hypertrophy and foot process effacement are a common consequence of hyperfiltration of residual glomeruli in advanced stages of glomerular damage, proteinuria being a common marker of chronic kidney damage. However, in IgAN podocytopathy, proteinuria can develop in early stages of the disease [20]. Indeed, podocyte damage can follow expansion of the mesangial area, with lengthening of the mesangial axis due to accumulation of IgA immune deposits which induces podocyte detachment and loss [21]. This is due to podocytopathy as a result of mesangial inflammation plus hemodynamic disturbances.

Glomerular sclerosis secondary to scarring in IgAN

In several glomerulonephritides, organization and scarring result from segmental endocapillary inflammatory lesions with necrosis. This mechanism is associated with acute inflammatory influx of cells in a mechanism mimicking vasculitic complement-mediated damage. This mechanism is likely to be operating in IgAN [17].

Different pathology features of S1 in IgAN

The histological Columbia classification of FSGS identified five morphological variants of primary and secondary forms with dissimilar frequencies of diagnosis: (a) not otherwise specified form (NOS) or "classic FSGS" (68% of cases); (b) tip variant or tip lesion, with the sclerotic lesion next to the proximal tubule (10% of cases); (c) cellular variant with segmental endocapillary hypercellularity (3%); (d) perihilar variant, with perihilar hyalinosis and sclerosis in > 50% of the glomeruli with segmental lesions (7%); and (e) collapsing variant, which requires at least a single glomerulus with a collapsing lesion, defined as segmental or global collapse of the tuft with overlying visceral epithelial cell hyperplasia (12%) [13].

Segmental sclerosis lesions are consequently heterogeneous, and the different morphological variants may shed some light onto the pathogenesis of FSGS, underscoring the fact that it is not a disease but a morphological pattern of injury. In this respect, the broad-based scars suggest previously healed necrotizing lesions; perihilar segmental sclerosis and hyalinosis are hallmarks of adaptive haemodynamic changes; visceral epithelial hyperplasia and hypertrophy and tip lesions are markers of podocyte injury, known as podocytopathies [22].

Rapid loss of renal function has been reported to be associated with cellular and collapsing variants, while a higher level of proteinuria was associated with the podocytopathic features, as tip lesions and visceral epithelial hyperplasia [23].

Prevalence and prognostic value of histological features associated with S1 in IgAN subtypes was investigated in a focused study on 137 cases (adults and children) with segmental glomerulosclerosis (S1) or adhesion enrolled in the original Oxford classification [23]. Tip lesions were observed in 7% of the cases, while the perihilar variant was observed in 3% and no collapsing variants were reported. Podocyte hypertrophy was detected in 38% of the cases, hyalinosis in 10%, and reabsorption of protein droplets within podocytes in 9% of biopsies. Tip lesions, podocyte hypertrophy, and adhesions (detected in 45% of patients with S1) presented podocytopathic features associated with greater initial proteinuria independently from other lesions. Over a follow-up of 5 years S1 with podocyte hypertrophy and adhesions had a more rapid renal functional decline and a worse kidney survival from the combined end point compared with patients with S1 without these features. In this S1 subgroup with podocytopathic features, corticosteroid-immunosuppressive (CS-IS) therapy was associated with a better renal survival. These patients who received CS-IS treatment tended to be younger (31 ± 17 years), with greater proteinuria (median 2.4 g/day), and had more E1 lesions (co-detected in 92% of the cases versus S1 with podocytopathy not treated with CS-IS drugs) [23].

Segmental glomerulosclerosis S1 lesions in children with IgAN: value over long-term follow-up

The European collaborative study VALIGA enrolled 174 children from 13 different European countries aged < 18 years at biopsy (40% were < 12 years old) followed for a median of 4.6 years [2, 24, 25]. At renal biopsy, most children presented with normal eGFR and median proteinuria 0.84 g/day (in 1% only of nephrotic range). Twenty percent of children were hypertensive and/or were receiving anti-hypertensive medications. During the follow-up period, renin-angiotensin system blockers (RASB) were prescribed in 66.6% of the cases and 50% of the children received CS-IS treatment.

S1 lesions were found in 42.5% of the pediatric cases, versus 70% in adults. The frequency of S1 increased to 62% in the group aged between 18 and 23 years. In the cohort of young subjects aged less than 23 years, the S1 features were found to be independent predictors of the combined event [4]. The long-term outcome of pediatric IgAN in the VALIGA cohort was investigated in a recent study updating the database and prolonging the follow-up from 4.7 to 7.0 years [26]. Over this long follow-up, the prognostic value of S1 (and M1 and T1) was confirmed decades after the renal biopsy and was independent of age, suggesting it as a valid prognostic factor both in children and in adults.

As mentioned above, the S1 lesions were predictive of the combined outcome only in the group of young subjects aged < 23 years. The few end points of 50% reduction in eGFR or ESKD in younger age may account for the difficulty to find significant results (using this hard end point) in the cohort aged < 18 years. When considering the yearly rate of eGFR loss, children with all negative MEST-C scores had an eGFR slope of 0 (− 1.9 + 2) ml/min/1.73 m^2/year, which was not significantly different when S1 or E1 or M1 were investigated separately. However, when S1 lesions were associated with E1 or M1, the rate of eGFR loss tended to be faster, being from − 0.6 mL/min/1.73 m^2/year for S1E1 to − 2 mL/min/1.73 m^2/year for S1M1 (unpublished data from VALIGA young cohort) [3]. These data suggest that in children, the S1 lesions are

a risk factor for progression when associated with inflammatory and proliferative lesions as mesangial or endocapillary hypercellularity.

The whole cohort of VALIGA patients with S1 alone had significant benefits from CS-IS therapy in terms of eGFR decline (− 3.7 mL/min/1.73 m^2/year in patients treated with RASB alone versus 1.1 mL/min/1.73 m^2/year in those receiving CS-IS in addition to RASB). The percentage of patients with S1 lesions with initial proteinuria > 1 g/day reaching follow-up proteinuria < 1 g/day was 52% in patients receiving RASB alone versus 84% in those with additional CS-IS treatment ($p < 0:001$). In S1 cases treated with CS plus RASB and RASB alone, the difference of progression of eGFR loss was 2.6 mL/min/year, while in S0 cases, this difference was 1.7 mL/min/year [27].

Segmental glomerulosclerosis S1 lesions in children with IgAN: value over short-term follow-up

Podocytopathic lesions were found to be a risk of progression over a short-term 6-month follow-up in children with IgAN. In a French study including 49 children with S1 lesions from a cohort of 82 pediatric patients, podocytopathic features (P1) consisting of tip lesions and podocyte hypertrophy were detected in 12 cases (24% of the total S1 cases). The 12 cases with S1 did not show values of baseline proteinuria different from children with S0, but the short-term outcome was significantly worse in S1 with podocytopathy (S1P1) in comparison with S1P0. The follow-up after CS-IS therapy or not was 6 months in all cases. The end point was a 10% reduction in eGFR from baseline or CKD stage 3. Over this short follow-up time, S1P1 lesions were the only histological variables predictive of the decline of renal function, independent of clinical data at the time of renal biopsy and CS-IS treatment [28].

Conclusion

In conclusion, both long-term and short-term studies on subjects with IgAN and S1 lesions indicate that the presence of podocytopathic features are associated with worse outcome. The association of S1 lesions with M1 and/or E1 deserves particular interest in the young due to the frequent presentation of active glomerular damage. The benefits of CS-IS may be only inferred from the retrospective uncontrolled reports; however, the present studies report that no benefit of CS-IS drugs can be observed in follow-up studies shorter than 1 year [26], as confirmed in children after 6 months of observation [28]. This suggests the hypothesis that there exists a podocytopathy, mostly driven by mesangial activation. As such, it takes time to be reversed, in contrast to the rapid effects of CS-IS drugs in primary podocytopathies like minimal change disease. S1 lesions must be carefully assessed in renal biopsies of children with IgAN.

Compliance with ethical standards

Conflict of interest Hernán Trimarchi has received honoraria from Calliditas and Retrophin. Rosanna Coppo has received honoraria from Calliditas, Retrophin, and Omeros.

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