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EDITORIAL COMMENTARY

Management of focal segmental glomerulosclerosis in resource-limited regions

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Introduction

The management of focal segmental glomerulosclerosis (FSGS) is challenging, and a definitive long-term cure remains elusive. It is associated with poor outcomes due to underlying irreversible glomerular fibrosis, scarring, different degrees of interstitial injury, and a variable rate of chronic kidney disease (CKD) progression [1, 2]. In non-genetic primary FSGS, complete or partial remission (CR or PR) of proteinuria is associated with a better prognosis, with 90% kidney survival at 5 years follow-up. Conversely, approximately 50% of non-responders have kidney failure (KF) by 5 years [1]. Thus, the challenge is to provide optimal therapy to all affected children with the aim of achieving proteinuria remission and thereby improving short-term morbidities and long-term outcomes.

SRNS is a clinical problem for all pediatric nephrologists, with FSGS constituting up to 20% of children presenting with nephrotic syndrome (NS) and 10 to 15% of pediatric KF [3]. There is significant ethnic and geographic variability in the pattern of steroid responsiveness in NS, with higher steroid resistance in African Americans in the USA and in resource-limited regions such as South Africa and Pakistan [4]. An increased prevalence of familial FSGS was reported in a Jordanian cohort with a high rate of progression to KF [5]. Whether the higher steroid resistance reported in many low-resource regions is secondary to a higher prevalence of genetic causes is unclear as there is limited accessibility to genetic studies in most low- and lower-middle-income (LLMIC) countries [6].

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Roughly, 1/3 of patients with primary FSGS may have proteinuria remission with steroid courses and renin-angiotensin system inhibitors (RASi), without the addition of other immunosuppressives (IS) [1, 7]. The recent IPNA evidence-based guidelines for steroid-resistant (SR) NS recommend that, if available, genetic testing should be performed in all children diagnosed with primary SRNS, even before a kidney biopsy. In addition, secondary causes should be excluded, and a renal biopsy is indicated, except in known infection or malignancy-associated secondary disease or if a genetic cause is identified. After diagnostic evaluation, it is recommended to initiate RASi therapy and treatment with calcineurin inhibitor (CNI) for at least 6 months. Cyclophosphamide (CP) is suggested as an alternative first-line IS in low-resource settings if CNI is unavailable [8]. Other IS agents used in non-responders include mycophenolate mofetil (MMF) and rituximab (RTX).

Despite multiple trials and guidelines, several challenges in managing primary FSGS remain. At onset, it is difficult to predict response to IS, and the best options for long-term therapy and benefits for kidney survival remain unknown for the individual patient [9]. In addition, many of the drugs used and their monitoring are expensive, associated with adverse effects, and unavailable in many resource-challenged settings.

The setting of the study by Priyanka et al.

This retrospective study [10] was performed in a tertiary care center in India, an LMIC as per World Bank classification [11]. The country has significant diversity in per family income, with a Gini (inequality) coefficient of 34.2 in 2024 [12]. Families from higher socio-economic groups have access to private health care and are often supported by employers or subscribe to health insurance. For patients of lower socio-economic groups, government hospitals, trust-run charitable institutions, and several national and state

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government schemes are available that subsidize or fund several aspects of management and medications. However, pediatric nephrology facilities usually exist only in tertiary-level institutes based in metro cities. Lack of awareness and inability to avail existing support options, distances and expenses associated with travel to the medical unit, and the loss of caregiver work hours and income for clinic attendance and monitoring requirements, all remain barriers to optimal care.

In this study, Priyanka et al. report on outcomes in patients with biopsy-proven FSGS, biopsy material being screened by light microscopy (LM), and immunofluorescence (IF). While LM and IF are readily available in Indian pediatric nephrology units, only a few centers nationwide have electron microscopy facilities, and therefore the latter are used sparingly. Genetic tests similarly are available, but due to cost implications, were only performed in selected patients with high risk in this study, i.e., those in whom the disease was familial, associated with extra-renal features, and if there was steroid plus CNI-resistance, as per the Indian SRNS guidelines [13]. Approximately 14% of patients were initially treated with intravenous CP rather than CNI due to its unavailability or financial issues. The clinicians were able to perform and maintain adequate CNI levels in those that did receive them. Drug level monitoring was funded by the institute in this case, and otherwise, is often funded by the drug manufacturers/suppliers. The easy availability of good quality generic agents also reduces costs to some extent [14, 15]. With these limitations, the authors achieved CR/PR rates similar to those from other regions, while CKD rates at 4 years were higher than high-income group countries (HIC).

Relevance and generalizability to other under-resourced regions

The management of FSGS in LLMIC may face several limitations, even exceeding those faced by Priyanka et al. A recent survey revealed that, while 88% of the pediatric nephrology centers in under-resourced areas have kidney pathology services available, the analysis of the biopsy is often restricted to just LM, which significantly limits its value for excluding several primary kidney diseases [6, 16].

In the same survey, genetic studies were available to only 26% of centers [6]. The underlying logic of controlling expense by restricting genetic studies to high-risk patients is that monogenic NS is unlikely to respond to IS [13]. Whether PR may also be considered exempt from need for genetic assessment is unclear since medications like CNIs, RTX, and RASi may act by non-immune mechanisms to reduce proteinuria to some extent [7, 17]. The unavoidable problem here is of potential months of unindicated toxic IS use in undetected monogenic disease. Furthermore, in patients who do not respond and progress to KF, genetic testing provides valuable guidance to the transplant team and the family in the process of decision making [18].

With a gross national income per capita below $4465 USD in LLMICs [11], even medications such as prednisone, generally considered low-cost, may be inaccessible where governmental support is limited or absent. Medications used in SDNS and SRNS, like CNIs, MMF, and RTX, are even more expensive, and guidelines for frequency of monitoring and drug levels may be difficult to follow. Successful strategies that have been used to decrease costs include adding an inexpensive drug like ketoconazole to inhibit the metabolism of cyclosporine. This has been shown to reduce the cost of treatment by more than 50% without increasing adverse events or the need for drug monitoring [19, 20]. Guidelines have suggested the use of CP as an alternative to CNI as the first line in SRNS [8, 13]; however, previous reports as well as the current study show lower rates of response compared to CNI [10, 21, 22]. Delaying or not being able to provide optimum IS may worsen outcomes in regions where the options of effectively managing complications of persistent proteinuria, CKD, and KF are limited.

Future directions

Primary non-genetic FSGS is a heterogeneous disease as is clinically evidenced by different responses to IS and recurrence after kidney transplantation in some patients but not all. Ongoing research may help to differentiate between clinico-pathological entities and allow better tailoring of management, thereby avoiding toxic medications in cases where they are unlikely to be effective, and streamlining resources to target cases where there is a good chance of response [2, 23]. A host of therapies ranging from new IS agents, biological therapies, and extracorporeal treatments to non-specific anti-proteinuric, anti-inflammatory and anti-fibrotic agents are under investigation and may in the future contribute to improving the long-term kidney survival and effect a cure [23]. In parallel, increased manufacture and availability of quality-controlled generics and biosimilars may reduce costs [24].

Unfortunately, to date, many therapeutic agents and diagnostic tools are not available to children living in non-HIC, or are too expensive, necessitating adaptations in their use which may lead to sub-optimal interventions and outcomes. Access to medications is lowest in non-tertiary community settings where close to 70% report poor access to all medications [25]. Lack of government funding is identified as the major barrier to medication access. Publicly funded treatment for non-dialysis CKD is much lower in LLMIC, with exclusive use of private and out-of-pocket payment methods

in 20% of LICs and 9% of LMICs [26]. Moreover, the WHO Model List of Essential Medicines for Children published in 2023 does not have a section on drugs for kidney disease. Of the drugs frequently used to treat FSGS, cyclosporine, and tacrolimus only are included in Sect. 8.1 as immunomodulators for non-malignant disease. Cyclophosphamide and RTX are listed but with cancer as the only indication. The international pediatric nephrology community needs to keep raising awareness of these deficiencies at global, regional, and national levels. FSGS management should be a particular area of interest for advocacy as a response to effective treatment is associated with significantly improved outcomes.

Conclusions

In the last three decades, the increasing availability of a large number of IS and biological agents has improved the prognosis of patients with primary non-genetic FSGS. Further research into more precise phenotyping to guide therapy, as well as less expensive and less toxic therapeutic agents will hopefully continue to improve outcomes in this difficult condition. However, we cannot ignore the fact many children with primary FSGS living in non-HIC are unable to receive what is considered current optimal therapy. It is our responsibility to develop strategies that will ensure that all children can benefit from recent scientific advances. Although efforts have been made to raise awareness of kidney disease, the fact that most medications used for the treatment of glomerular diseases, including FSGS, are not included in the WHO list of essential medicines is evidence that we need to continue increasing our advocacy efforts [27].

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