Nephrotic Syndrome in Children – A Tale of 50 Years

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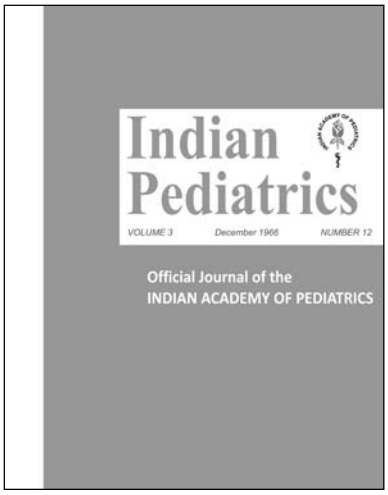
An original research paper on 'nephrotic syndrome in children' was published in the December 1966 issue of *Indian Pediatrics,* from the department of Pediatrics MGM Medical College, Indore. We decided to review this article to trace the evolution in the diagnosis and management stra-tegies for this condition since that era.



THE PAST

The study by Bhandari, *et al.* [1], was amongst the early published original articles on nephrotic syndrome from India. This study, conducted on 75 children with nephrotic syndrome, compares the effect of treatment with long- and short-term regimes of oral steroid therapy.

Nephrotic syndrome was defined by the authors as the presence of edema, hypoproteinemia, hyperlipidemia and proteinuria, and an absence of persistent hypertension, azotemia and gross hematuria. More than half (52%) of included children were aged between 2 and 5 years at first presentation, with male preponderance (62%). Generalized edema was the commonest (73%) presenting complaint. While azotemia and hypertension were found in less than 30% of the patients, nearly half had microscopic hematuria. Kidney biopsy performed in four patients revealed subacute nephritis in two and hypercellular glomeruli with degenerative changes in tubular epithelium in the other two patients.

All the patients received a general treatment comprising of antibiotics, diuretics, and a high protein and salt-free diet. To study the effect of different treatment regimens, the patients were divided into three groups: Group I (20 patients) received general treatment alone, Group II (35 patients) received short-term steroids (10-21) days in addition to general treatment, and Group III (20 patients) received long intermittent steroid therapy ranging from 6 weeks to 30 months. Resolution of edema and albuminuria, and onset of diuresis were considered as indicators of improvement. The most favourable response to treatment was observed in patients in group III; 65% subjects in this group had complete resolution of edema as opposed to 30% in group I and 51% in group II. Children in group III also showed the least recurrence of edema. The authors concluded that the patients who received steroids for longer periods, especially those who were treated for more than one year, showed better clinical response and had longer periods of remission.

Historical background and past knowledge: The earliest mention of nephrotic syndrome dates back to Hippocrates who made an important observation about the disease that '*when bubbles settle on the surface of the urine, it indicates disease of the kidneys, and that the complaint will be protracted*' [2]. In 1827, Richard Bright described the triad of generalized edema, proteinuria, and kidney disease [3], and in 1905, Müller coined the term 'nephrosis' to describe all non-inflammatory diseases of the kidney [4].

The understanding of this disease at the time of publication of the study by Bhandari, *et.al* [1] is reflected in the review by Derow in New England Journal of Medicine in the year 1958 [5]. The patients with nephrotic syndrome were classified as: (*i*) those with known etiologic associations (*e.g.* syphilis, malaria, SLE, poisoning with heavy metal, poison-oak, bee-sting and trimethadione or paramethadione), and (*ii*) those where etiology was unknown – referred to as idiopathic nephrotic syndrome or 'lipoid nephrosis.' The pathogenesis in the latter was believed to be complement-mediated antigen-antibody reaction that produced tissue damage [6].

Renal biopsy – introduced in the routine clinical nephrology practice in late 1950s – transformed the

understanding of pathogenesis of this disorder. With the advent of electron microscopy, characteristic histopathological findings in idiopathic disease were described [7]. During that time, ACTH and the adrenocortical steroids were the agents of choice for specific treatment for nephrotic syndrome. Sometime later, in 1965, International Study for Kidney Disease in Children (ISKDC), a multinational group, defined heavy proteinuria, dose regimen of prednisolone and response to prednisolone therapy. The criteria defining relapses and steroid-dependence and steroid-resistance were also laid down [8].

THE PRESENT

Over the last three or four decades, ISKDC, through multi-centre prospective trials, established treatment-oriented classifications and standardised management guidelines for nephrotic syndrome. In the current era, advanced genetic and molecular studies promise an opportunity to provide individualised care to children with nephrotic syndrome.

The Indian Pediatric Nephrology Group formulated guidelines for treatment of steroid sensitive nephrotic syndrome in 2001 which were subsequently revised in 2008 [9]. The guidelines provide recommendations on investigations and treatment of the initial episode of nephrotic syndrome, indications of alternative medications (mycophenolate mofetil, cyclosporin and tacrolimus) in patients with frequent relapses and steroid dependence and management of complications. The same group described management guidelines of steroid-resistant nephrotic syndrome in early 2009 [10]. More recently, evidence-based clinical practice guidelines were published by the Kidney Disease: Improving Global Outcomes (KDIGO) working group for management of nephrotic syndrome and glomerulonephritis [11].

Various randomized trials from India have, since then, examined the effect of long (5-6 months) *versus* short (2-3 months) duration prednisolone therapy in treatment of first episode of nephrotic syndrome, on frequency of subsequent relapses [12,13]. A recent Cochrane review found that there was no significant difference in the risk for relapse between the two regimens, indicating that there is no benefit of increasing the duration of prednisone in the first episode beyond two or three months [14].

For treatment of steroid-resistant nephrotic syndrome, calcineurin inhibitors are found to be better in inducing remission as compared to cyclophosphamide [15]. Rituximab, a monoclonal antibody against CD20 antigen on B-lymphocyte, is now an established steroid sparing agent used in frequently-relapsing and steroid-dependent nephrotic syndrome. The introduction of next-generation sequencing techniques has helped in exploring the genetic mutations causing nephrotic syndrome, especially the congenital, familial and steroid-resistant varieties. It has led to a better understanding of the pathophysiologic mechanisms altering glomerular filtration barrier, and holds promise for future research.

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