Glomerular Diseases in Children

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Unique challenges exist in the diagnosis and treatment of glomerular diseases with their onset during childhood. Mounting evidence supports the notion that earlier onset cases occur due to larger numbers of genetic risk alleles. Nearly all causes of adult-onset glomerulonephritis, nephrotic syndrome, and thrombotic microangiopathy have also been described in children, although the prevalence of specific causes differs. Postinfectious glomerulonephritis, Henoch-Schönlein purpura nephritis, and minimal change disease remain the most common causes of glomerular disease in younger children in the United States and can be diagnosed clinically without need for biopsy. IgA nephropathy is the most common pediatric glomerular disease diagnosed by kidney biopsy and is considered the most common chronic glomerulopathy worldwide. In both developing and developed countries, there is a strong relationship between infectious diseases and nephritis onset or relapse. Although research has led to a better understanding of how to classify and manage glomerular diseases in children, the need for disease-specific biomarkers of activity and chronicity remains a hurdle. The strength of the immune system and the growth and maturation that occurs during adolescence are unique and require age-specific approaches to disease management.

Key Words: Glomerulonephritis, Hematuria, Proteinuria, Nephrotic syndrome, Pediatric

INTRODUCTION

In children as in adults, glomerular diseases present clinically in several different ways. Depending on both the nature and severity of the primary disease and the extent to which the normal physiological functions of the glomerulus are perturbed,[1] children may be identified incidentally or may become critically ill with oligoanuric rapidly progressive kidney injury in need of urgent dialysis. A few glomerular diseases are inherited, but most forms are acquired and are generally considered to be immunologically mediated. There are 3 classical clinical syndromes that develop from glomerular injury: acute and chronic glomerulonephritis (GN), defined by the triad of hematuria, hypertension, and acute kidney injury (AKI); nephrotic syndrome (NS), defined by proteinuria and hypoalbuminemia; and hemolytic uremic syndrome (HUS), defined by microangiopathic hemolytic anemia, thrombocytopenia, and AKI.

In GN, glomerular proliferation and inflammation lead to decreased glomerular perfusion, resulting in compromised kidney function and retention of salt and water with potential development of hypertension and edema. In isolated NS, glomerular injury occurs in the absence of inflammation and often proliferation, and an increase in the permeability of the glomerular capillary loops drives a sequence of events leading to the classical clinical features: proteinuria, hypoalbuminemia, decreased plasma oncotic pressure, and edema. However, NS can also occur secondarily to GN in many cases.

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APPROACH TO CLASSIFICATION

The patient with glomerular disease presents clinically with a constellation of features that may include hematuria, proteinuria, edema, hypertension, and AKI.[2] In GN, the urinary sediment is characterized as active when dysmorphic erythrocytes and cellular casts are present. A series of questions guide the initial diagnostic and management plan (Table 1). NS is not a diagnosis but a constellation of clinical findings. By definition, in children, it comprises proteinuria greater than 50 mg/kg per 24 hour (or >40 mg/m^2 per hour or a urinary protein-to-creatinine ratio greater than 2.0 mg/mg), hypoalbuminemia (serum albumin < 3.0 g/dL), and hyperlipidemia. NS may manifest in any of the proliferative glomerular diseases, but in children, it more commonly occurs as in isolation without nephritis. Table 2 guides the initial diagnostic and management plan for isolated NS.

Various classification systems have been proposed to understand and manage glomerular diseases. As advances in kidney research have revealed more about the molecular and cellular pathways,[3-6] disease classification has evolved to reflect these findings (Table 3).[1] GN classification starts by establishing whether disease is kidney limited or systematic, followed by pathologic classification and genetic evaluation in appropriate cases. Most acute GN episodes in children are postinfectious, isolated to the kidney, and prone to spontaneous resolution.[7] A history of antecedent illness with hypocomplementemia precludes the need for kidney biopsy and intensive pharmacologic therapy. Diagnosing pulmonary edema and hypertension secondary to oliguria and volume overload is important to distinguish from the pulmonary-kidney syndrome as seen in vasculitis, lupus, or Goodpasture syndrome.[8,9]

Evaluation of the urine sediment is the key to distinguishing between GN and primarily proteinuric diseases. In the absence of red blood cell casts and proliferative urinary sediment, suspicion should shift away from GN. Diagnosis of proteinuric kidney diseases proceeds with ruling out secondary causes (Table 4). Only then should kidney biopsy or genetic testing be considered to identify

primary podocytopathies[10] or idiopathic forms of minimal change disease (MCD),[11] focal segmental glomerulosclerosis (FSGS),[12] or membranous glomerulopathy.[13] In the near future, our understanding of genetics, autoimmunity, and infectious diseases will most certainly necessitate further refinements.

Finally, the clinical triad of glomerular disease, thrombocytopenia, and microangiopathic hemolytic anemia points toward the thrombotic microangiopathies (TMAs).[14] Whereas diarrhea-positive hemolytic uremic syndrome (D+ HUS) remains the most common TMA in children and Shiga toxin-producing *E. coli* (STEC-HUS) the most common cause of D + HUS cases, there is increasing recognition and diagnosis of many atypical causes for HUS (Table 5). Again, further classification involves ruling out secondary causes before embarking on complement profiling and genetic testing.

APPROACH TO PATHOLOGIC EXAMINATION

Examination of the biopsy material should include light, immunofluorescence, and electron microscopy performed using standard techniques. Routine stains performed for light microscopy include hematoxylin and eosin, periodic acid-Schiff, Jones' methenamine silver, and Masson's trichrome. Immunofluorescence staining for IgG, IgA, IgM, C3, and C1q (and at some centers for C4, fibrinogen, albumin, kappa light chain, and lambda light chain) is performed for all native biopsies. Kidney pathologic findings may be grouped by the pathologic patterns observed on light microscopy. Since the kidney responds to injury in a limited number of ways, incorporation of the pathologic pattern of injury with the clinical presentation is critical to arrive at an accurate diagnosis.

CLINICAL SUMMARY

- Diagnosis of glomerular diseases in children should incorporate relevant genetic information and tissue histopathology, in addition to serologic and urine analyses.
- Care is warranted to distinguish between a primary pediatric disorder and acquired glomerulonephritis.
- Management should involve ongoing monitoring for pediatric-specific measures of therapeutic responsiveness, including systemic and kidney-specific assessment of both disease activity and damage.

Scoring of histopathology can also be of great utility. Determination of activity and chronicity indices in patients with lupus nephritis can be performed on permanent sections.[8,15] Similarly, applying the recently revised Oxford classification for IgA nephropathy may assist in personalized management of these patients.[16]

Minimal Changes

It is not uncommon to observe minimal glomerular findings on a pediatric kidney biopsy (Fig. 1A). The differential diagnosis depends on the adequacy of the sample: if < 10 glomeruli are present and the corticomedullary junction is not available, a diagnosis of FSGS cannot be excluded with confidence. Both FSGS and MCD will show diffuse podocyte foot process effacement in nonsclerotic glomeruli in the absence of immune-complex deposits. In contrast, patients with membranous glomerulopathy will show subepithelial IgG deposits with or without codeposition of C3. Although patients with membranous glomerulopathy will more commonly show thickened glomerular capillary loops with associated spike formation on the silver stain, patients with Ehrenreich and Churg stage I disease may show only minimal changes.[17] Further staining for target antigens for membranous glomerulopathy, such as phospholipase A_2 receptor 1 (PLA_2R) and thrombospondin type 1 domain-containing 7A, can be helpful in discriminating primary vs secondary causes.[18,19] In a pediatric study, positive PLA_2R staining was detected in 2 patients' ages of 11 and 12 years from a cohort of 34 with idiopathic membranous glomerulopathy.[20] In adults, thrombospondin type 1 domain-containing 7A membranous patients have a higher incidence of malignancy.[18] In neonates, membranous glomerulopathy may have developed from maternal transfer of antineutral endopeptidase antibodies,[21] and antibodies directed against cationic bovine serum albumin have also been implicated in children.[22]

If the patient presents with hematuria and shows minimal changes on light microscopy, the differential diagnosis includes IgA nephropathy, lupus nephritis, thin basement membrane nephropathy, and Alport syndrome. Whereas IgA nephropathy and lupus may be readily distinguished by immunostaining, electron microscopy is required to diagnose thin basement membrane nephropathy and Alport syndrome. Various cutoffs of glomerular basement membrane (GBM) thickness have been proposed to qualify as thin (between 200 and 270 nm or between 1.5 and 2 standard deviations below the mean thickness for age and gender).[23,24] Thinning of the GBM may also be seen in heterozygous women with Alport syndrome. Given the significant overlap between thin basement nephropathy and Alport syndrome, genetic testing for variants in the *COL4A3*, *COL4A4*, and *COL4A5* genes may be indicated.[24]

Mesangial Hypercellularity

Mesangial hypercellularity is a common finding in pediatric kidney biopsies and is typically encountered in the clinical setting of hematuria (Fig. 1B). The differential diagnosis is IgA nephropathy and class II lupus nephritis.[15] The Oxford classification of IgA nephropathy has been demonstrated to predict kidney outcome.[16] Since IgA nephropathy may have variable pathology,[25] similar to lupus nephritis, the various pathologic lesions are enumerated and used to determine an overall score (MEST-C). The lesions include mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and crescents (C). The MEST-C score is generated and may provide additional information to the clinician useful for predicting the clinical course of disease.