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Proteinuria as a Signal of Nephropathy

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Abstract: ***Proteinuria prevalence varies by clinical symptoms in the pediatric population. It is found 1 out of every 10 school-aged children, if measured with reactive swabs (dipstick) which reach a value equal to or greater than 1. If this outcome is confirmed in four different samples, the percentage falls to 1 in 1000. The prevalence rises with age, with a peak in adolescence (16 years for males and 13 years for females) and a gradual decline in adulthood.***

Keywords: proteinuria, glomerular filtration

1.Introduction

The presence of protein in urine is a common laboratory finding in children. Although proteinuria is usually benign, it can be a marker of a serious underlying renal disease or systemic disorder (1-3). When proteinuria coexists with hematuria, the likelihood of clinically significant renal disease is higher (1, 2). Further, proteinuria represents an independent risk factor for the progression of nonglomerular or glomerular chronic kidney disease in children (4-9). The Chronic Kidney Disease in Children study demonstrated that persistent proteinuria with a high urine protein-to-creatinine (UPr/Cr) ratio (more than 2 in patients with nonglomerular disease and more than 0.5 in patients with glomerular disease) predicts significant chronic kidney disease progression (7). The challenge for the primary care physician is to separate benign forms of proteinuria from those with clinical significance.

Epidemiology: Proteinuria is present in up to 10% of routine urine testing in school-aged children, although this decreases to 0.1% with repeated testing (10). The prevalence increases with age, peaks during adolescence, and is higher in girls (11). Although proteinuria is usually benign in the form of transient or orthostatic proteinuria, persistent proteinuria may be associated with more serious renal diseases. Proteinuria may be an independent risk factor for the progression of chronic kidney disease in children. Mechanisms of proteinuria can be categorized as glomerular, tubular, secretory, or overflow. A history, a physical examination, and laboratory tests help determine the cause. Transient (functional) proteinuria is temporary. It can occur with fever, exercise, stress, or cold exposure, and it resolves when the inciting factor is removed. Orthostatic proteinuria is the most common type in children, especially in adolescent males. It is a benign condition without clinical significance. Persistent proteinuria can be glomerular or tubulointerstitial in origin. The urine dipstick test is the most widely used screening method. Although a 24-hour urine protein excretion test is usually recommended for quantitation of the amount of protein excreted in the urine, it may be impractical in children. A spot, first-morning urine test for a protein-to-creatinine or protein-to-osmolality ratio is a reliable substitute. Treatment of proteinuria should be directed at the underlying cause. Patients with active urinary sediments, hematuria, hypertension, hypocomplementemia, renal insufficiency with depressed glomerular filtration rate, or signs and symptoms suggestive of vasculitic disease may require referral to a pediatric nephrologist and a renal biopsy.

2.Material and Methods

This article provides an overview of proteinuria: its causes, methods of assessment, and algorithmic suggestions to differentiate benign from pathologic renal disease.

3.Results and Discussion

Mechanisms and causes of proteinuria

The amount of protein found in urine is determined by 3 processes: glomerular filtration, reabsorption and tubular secretion.

Glomerular filtration. Fluids, substances, and macromolecules should pass through the capillary glomerular wall, which is made up of three layers: the endothelial cell layer, the glomerular basement membrane and the epithelial cell layer. A substance's ability to cross glomerular capillaries is determined by its size and electrical charge. The basement membrane is the primary barrier to the pathway of large molecules like proteins. This is due to its permeability and the presence of negatively charged glycosaminoglycans, primarily in the basement membrane's bright lamina and the polyanions that mark the podocyte epithelial processes. When even hematic proteins have a negative charge at physiological pH, their route through the glomerular capillaries is blocked.

The glomerular capillary surface, convection and diffusion, as well as the shape and plasticity of the filtered molecule, all influence the amount of filtered proteins.

Proteinuria can be caused by any change in glomerular filtration factors. Acute or chronic glomerulonephritis is caused by increased pore size. The pore size remains normal in nephrotic syndrome with minimal damage, but there is a loss of glomerular anionic loads. Diseases that alter the chemical structure of the basement membrane, such as Alport syndrome, can also influence glomerular capillary absorbency (12). An increase in glomerular

hematic stream, as determined by decreasing renal mass by nephrectomy or scratching, increases transcapillary movement of molecules prior to convection and dissemination. Other causes of glomerular protein filtration are given in Table 1.

Reabsorption

Only a small percentage of proteins infiltrating the glomerular filter appear in urine under normal conditions. The majority is absorbed into the twisted proximal tubules via pinocytosis.

The lack of reabsorption by the proximal tubules causes a slight proteinuria of 1+ equal to 30mg / dl or an average of 2+ equal to 100mg / dl from the moment the amount of filtered protein is reduced (13).

However, because the glomerulus reduces the passage of albumin and other large proteins under normal conditions, proteinuria caused by a reabsorption defect is primarily related to low molecular weight proteins. Table 2 lists some of the most common diseases associated with decreased tubular reabsorption of proteins.

The most common is Fanconi syndrome, which is defined by a universal disorder of the proximal tubules, which are accountable for the presence of proteins and other substances in the urine such as glucose, potassium, calcium, phosphorus, and bicarbonate. Even acute tubular necrosis caused by an ischemic or toxic event can impair proximal tubular reabsorption (14).

Secretion

Proteins can reach the urine as it goes through the urinary tract. Some proteins are secreted as a consequence of normal cell exchange or as a result of tissue injury, while others are produced by urinary tract cells. Tamm-Horsfall mucoprotein, one of the major constituents of renal cylinders, is produced at a constant rate by the cells of the thick part of the Henle ounce. It increases during physical activity, acute renal failure, renal transplant rejection and kidney stones (15).

Examinations to determine the origin of proteinuria

Proteinuria is often an incidental finding on urine dipstick testing or urinalysis. Children with asymptomatic proteinuria usually have the transient or orthostatic form. If a urine dipstick test shows trace amounts of protein, the test should be repeated with first-morning urine. If the first-morning test shows a trace or negative amount of protein, it should be repeated in one year to ensure that the proteinuria does not recur (1-3). In children with a urine dipstick test showing a result of 1 or more, a first-morning urine dipstick test for UPr/Cr ratio and a urinalysis should be performed (urine bag collection is acceptable in younger children). If the UPr/Cr ratio is 0.2 or less (0.5 or less for children six to 24 months of age) and urinalysis results are normal, transient or orthostatic proteinuria is likely (2). A repeat first-morning urine dipstick test in one year should be considered. If the UPr/Cr ratio is more than 0.2 (more than 0.5 for children six to 24 months of age) or urinalysis results are abnormal (e. g., hematuria, leukocyturia, active urinary sediments), persistent proteinuria or proteinuria of clinical significance is more likely (2) and further evaluation with history, physical examination, and additional laboratory testing is recommended to rule out significant renal disease (1-3).

Determination of proteinuria is performed by quantitative, semi-quantitative and qualitative examinations.

Reactive swabs

The most common method in the clinical symptoms is reactive pad, which is based on the color alteration provoked by the reaction of tetrabromophenol with protein amino-groups. Reactive swab usually identifies albumin, while low molecular weight proteins react to specific mop for tubular proteins.

Protein determination depends on urinary pH, consequently alkaline urine will give false positive result. Other false positive causes are: leaving the swab for a long time immersed in urine, the presence of detergents, ammonium compounds, leukocytes or bacteria. Since swab determines the concentration of proteins the result is also influenced by the volume of urine. Highly concentrated urine may result in high protein values, whereas in highly dilute urine proteins may not be identified. Generally, a score of 1+ or more in a urine sample with a specific gravity of 1015 indicates an abnormal protein lack (16).

Urine analysis

The result of the swab should be confirmed by laboratory analysis using morning urine.

Urine collection at regular intervals

A 12-or 24-hour urine collection is required for accurate protein excretion measurement. The 24-hour collection has the disadvantage of not determining the amount of protein secreted on a daily basis. Protein excretion is higher during the day in healthy people and patients with mild or moderate insufficiency, and it increases during physical activity. The alteration in daily protein is minimal in children with advanced nephropathy.

Protein intake of less than 150 mg in 24 hours is considered normal in adults. This varies according to body length and age in children. As shown in Table 3, this can be corrected based on body surface area (17).

Less than 4 $mg/m^2/h$ are considered normal; 4-40 mg/m^2 is considered abnormal; and more than 40 mg/m^2 is considered nephrotic level.

These values do not apply to newborns: the large amount of protein excreted at this age is explained by a low tubular reabsorption capacity.

Protein/creatinine ratio

Urine collection is frequently difficult, particularly in young children. A protein / creatinine ratio measured in a random sample is an accepted alternative method. Values of 0.5 are considered normal for children aged 6 months to 2 years; 0.2-0.25 for children over 2 years old; and 0.2 for adults (18).

Because serum creatinine concentration and urinary excretion are both affected by muscle mass, the protein / creatinine ratio is unreliable in severely malnourished individuals. Even in children with low glomerular function, its reliability is debatable because a significant amount of urinary creatinine comes from tubular secretion rather than glomerular filtration. Finally, as in the case of orthostatic proteinuria, the protein/creatinine ratio is highly dependent on physical activity (19).

Electrophoresis of proteins

Tubular damage is linked to an increase in the excretion of low molecular weight proteins, which can be observed using protein electrophoresis. There are tests that measure the concentration of specific microproteins in the urine, such as Microglobulin (20).

Complete medical history and clinical examination

Assessment of a child with proteinuria begins with a detailed medical history and objective examination. Your doctor should evaluate the presence of signs and symptoms that indicate nephropathy. Hypertension, edema, stunted growth, and familial nephropathy are several indicators. The first test done is an analysis of the urine of a morning sample. This allows you to confirm the presence of proteinuria and evaluate for associated urinary abnormalities (blood, casts, etc.) that indicate glomerulopathy. Once proteinuria is identified, different samples should be analyzed at different time intervals. Two consecutive 12-hour samples are important for measuring benign orthostatic proteinuria (21).

Table 4 presents the guidelines for urine collection. If the daily sample taken in orthostatism contains abnormal amounts of protein, while the quiet night gathering is protein-free, chances are we are dealing with an orthostatic proteinuria that does not require further additional examinations. Abnormal amounts of protein in both samples indicate nephropathy and require further additional examinations. Blood electrolytes, BUN and creatinine are useful for assessing renal function, while renal ultrasound provides information on the structure of the kidney. Complementemy and anti-streptolysin titers should be measured if post infectious glomerulonephritis is suspected (22).

Generally, a positive result in one of the initial laboratory examinations justifies the request for consultation to the pediatric nephrologist. Other reasons for specialist visit are presented in Table 5. To determine the diagnosis, therapy and prognosis the specialist will perform more detailed examinations including kidney biopsy (23). .

4.Conclusion

The family can be reassured if the proteinuria is transient or orthostatic, and the child is asymptomatic, has no associated hematuria, and has normal blood pressure and glomerular filtration rate. Regular follow-up is important, however, as long as significant proteinuria persists. Although there are no formal guidelines for monitoring, a child with persistent proteinuria should initially receive a physical examination, blood pressure measurement, urinalysis, and blood tests for creatinine and urea nitrogen levels every six to 12 months. (29) There is no specific limitation on diet or physical activity. Once the child is stable, follow-up can be annual. The treatment of persistent proteinuria should be directed at the underlying cause. (2, 29) Patients with idiopathic nephrotic syndrome should receive a trial of prednisone (2 mg per kg per day, or 60 mg per m2 per day to a maximum of 80 mg per day) in up to three divided doses for four to six weeks, followed by treatment on alternate days for another four to six weeks.35 If steroid therapy fails or adverse effects are intolerable, second-line therapy may be required. In patients with renal dysfunction, an adjunctive angiotensin-converting enzyme inhibitor and/or angiotensin-II receptor blocker can be used to decrease proteinuria and slow progression of renal disease. Referral to a pediatric nephrologist may be needed for a definitive diagnosis or consideration of renal biopsy.

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Table 1: Causes of increased glomerular protein filtration development

Injury of the glomerular capillary wall	**Normal glomerular capillary walls**
Acute or chronic glomerulonephritis	Angiotensin-induced proteinuria
Hemolytic-uremic syndrome	Orthostatic proteins
Focal segmental glomerulosclerosis	Hypertension
Nephrotic syndrome with minimal damage	Increased plasma protein levels (plasma or albumin infusions)
Alport Syndrome	
Various inherited syndromes	

Table 2: Etiology of proteinuria of tubular origin

Transport disorders	Tubular toxins	Ischemic tubular damage	Acquired tubular nephritis	Different
Fanconi Syndrome	Aminoglycosides	Hypovolemic shock	Interstitial nephritis	Uropathy from obstruction
Cystinosis	Penicillin	Asphyxia	Pyelonephritis	Polycystic kidney disease
Hypercalciuria	6-mercaptopurina	Endotoxemia		Medullary cystic disease
	Azathioprine			
	Tetracycline			
	Heavy metals			
	Hemoglobin or free myoglobin			
	Uric acid			

Table 3: Protein excretion in children of various ages over the course of 24 hours

Age	**Proteine concentration (mg/L)**	**Proteine excretion (mg/24h)**	**Proteine excretion (mg/24/m^2)**
Preterm (5-30 days)	88-845	29 (14-60)	182 (88-377)
Term	94-455	32 (15-68)	145 (68-309)
2-12 month	70-315	38 (17-85)	109 (48-244)
2-4 year	45-217	49 (20-121)	91 (38-223)
4-10 year	50-223	71 (26-194)	85 (31-234)
10-16 year	45-391	83 (29-238)	63 (22-181)

Table 4: Guidelines for urine collection at regular intervals of 12 hours

1. Ask child to empty the bladder before bed and mark the time
2. Collect urine produced at night and the first morning sample. Mark the time of the first morning urine. Write in the container "night urine"
3. Collect all the urine of the day, including bedtime urine. Mark the start and end time in the container as well as the "urine of the day"

Table 5: When to visit a nephrologist

Persistent non-orthostatic proteinuria
Recurrent episodes of macroscopic hematuria
Family history of renal failure, glomerulonephritis, neurosensory hearing impairment, renal transplantation
Haematuria dhe proteinuria
High levels of BUN and creatinine
Hypertension
Cellullar casts
Edema
Systemic symptoms (joint pain, cutaneous eruptions, arthralgia)
Parenteral anxious and stress