Assessment and management of non-nephrotic range proteinuria in children

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Introduction

Proteinuria is a common incidental finding in children. Fortunately it is often transient and benign. However, when persistent, it can be serious as it may then represent the early stages of chronic kidney disease, which can progress to renal failure, and is, by its own right, an effector mechanism in the development of progressive renal injury regardless of the initial nephropathy[1,2]. Furthermore, it is also a marker of and probably an independent risk factor for atherosclerotic diseases, such as coronary artery disease or stroke, and is associated with increased mortality.

This article focuses on mild to moderate proteinuria discovered in an asymptomatic child (usually by Dipstick), in the non-nephrotic range (<40 mg/m²/hour). We deliberately exclude from the discussion children presenting with overt nephropathy (nephrotic syndrome, glomerular nephropathy, diabetes, etc.). We will define proteinuria, its type and range, review the mechanisms and causes of such proteinuria and its clinical importance, and recommend a practical approach to investigations and a management strategy[3].

Epidemiology

In large series, the prevalence of isolated asymptomatic proteinuria in children has been estimated to be between 0.6 and 6.3 percent. This wide range reflects the transient and intermittent nature of this condition, explaining the higher prevalence observed when a single urine specimen is tested; although it can be found in 5-15% of children, its prevalence declines when testing is repeated. When testing 4 times in children for proteinuria, 10.7% are found to have proteinuria in 1 of 4

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specimens, 2.5% in 2 of 4 specimens and only 0.1-1% have proteinuria in all 4 specimens. In addition, most children with proteinuria on initial evaluation "lose" the proteinuria at follow-up, with only about 10 percent of children having persistent proteinuria after 6 to 12 months. In both sexes, the prevalence of proteinuria increased with age.

Morbidity associated with proteinuria

Proteinuria may not only be a marker of renal disease, but when persistent it can also be a cause of progressive renal injury[1,2]. Increasing levels of proteinuria are the best predictor of progressive renal damage.

The mechanisms by which proteinuria may induce renal injury include:

- renal tubules obstruction by proteinaceous casts,

- damage caused by the release of lysosomal enzymes into the cytoplasm of protein-reabsorbing tubules,

- cytotoxic effect of iron filtered into the tubular fluid and bound to transferrin,

- consequence of iron-catalyzed synthesis of reactive oxygen metabolites,

- activation of the alternative complement cascade by proximal tubules,

- ischaemic tubular injury following the release of vasoconstricting molecules,

- release of fibrosis-promoting factors from renal cells activated/injured by proteinuria resulting in interstitial fibrosis,

- filtration of lipoproteins and absorption by proximal tubules activating inflammatory pathways,

- filtration of cytokines/chemokines provoking cell proliferation, inflammatory cell infiltration, and activation of infiltrating cells, and possibly

- filtration/ generation of novel antigens functioning as antigen-presenting cells and initiating a cellular immune response.

While proteinuria of any magnitude is a risk factor for cardiovascular disease in adults, severe persistent proteinuria may also be a long term risk factor for atherosclerosis and hypertension in children[4-6]. Increasing proteinuria is associated with metabolic disturbances that contribute to cardiovascular disease, such as obesity, hypercholesterolaemia, hypertriglyceridaemia, and hypercoagulability[7,8]. In addition, factors such as hypertension, renal insufficiency, and steroid therapy associated with the underlying renal disease may also increase that risk.

Mechanisms of proteinuria

The normal rate of protein excretion in the urine is less than 4 $mg/m^2/hour$ (less than 100 $mg/m^2/day$) throughout childhood, in both genders, and is usually not detected on routine dipstick testing. Approximately 50% of this small amount of protein consists of Tamm-Horsfall protein, a glycoprotein secreted by the ascending limb of the loop of Henle. The rest consists of small quantities of plasma proteins filtered by the glomeruli (e.g. albumin, immunoglobulins, transferrin, and $ß_2$-microglobulin), with albumin comprising 30% of the total urinary protein in normal individuals.

The glomerular capillary wall and its adjacent structures constitute the main barriers to the passage of macromolecules, including globulins and albumin. The passage of macromolecules across the glomerular capillary wall is inversely proportional to their size. Most glomerular diseases result in alterations of the size barrier and loss of anionic charges, leading to proteinuria.

Low-molecular-weight proteins (molecular weight less than 40,000 Daltons) are freely filtered through the glomerulus and 99% are subsequently absorbed and catabolized by the proximal tubule. They include $ß_2$ microglobulin, retinol binding protein, $alpha_1$ microglobulin and hormones such as vasopressin, insulin and parathyroid hormone.

There are several mechanisms of excessive protein excretion:

1. *Increased glomerular filtration* of normal plasma proteins is due to altered glomerular permeability (glomerular proteinuria).

2. *Inadequate tubular reabsorption* of the small amounts of normally filtered proteins occurs in tubulointerstitial diseases. Injury to the proximal tubular epithelium leads to inability of the tubule to reabsorb low-molecular-weight proteins and thus to their loss in urine (tubular proteinuria).

3. *Hemodynamic alterations* in glomerular blood flow can also result in proteinuria. A reduced number of functioning nephrons, as occurs in chronic renal failure, reflux nephropathy, unilateral kidney agenesis, leads to increased filtration of proteins in the remaining nephrons and to proteinuria[9-12]. Other conditions that cause proteinuria by altering glomerular haemodynamics include exercise, fever, seizures, epinephrine use and emotional stress[13].

4. *Overflow* of elevated normal or abnormal plasma protein*s* occurs in plasma cell dyscrasias when there is an excessive amount of protein and the tubular cells cannot reabsorb all that is filtered. If this condition persists, the tubular cells may be damaged by precipitation of microproteins, leading to further proteinuria. Overflow proteinuria occurs when the plasma concentration of certain small proteins exceeds the capacity of the tubules to reabsorb the filtered protein. Examples include the presence of immunoglobulin light chains in the urine in multiple myeloma, haemoglobinuria in intravascular haemolysis, myoglobulinuria in rhabdomyolysis and amylasuria in acute pancreatitis.

5. *Increased secretion* of tissue proteins from the epithelial cells of the loop of Henle occurs in Tamm-Horsfall proteinuria. It forms the backbone of urine casts as it takes the shape of the tubule and traps other components such as red blood cells, white blood cells, and epithelial cells. Tamm-Horsfall protein leaks into the interstitium in human and experimental reflux nephropathy, obstructive uropathy, and some other tubulointerstitial disorders.

Clinical testing for proteinuria[3,14]

Qualitative or screening methods

Dipstick testing

It is the most frequently used screening method for proteinuria. It primarily detects albumin (rich in amino groups), leaving low molecular weight (LMW) proteins undetected. The dipstick carries a reagent strip impregnated with a pH indicator (usually tetrabromophenol blue) and a buffer to maintain a pH of 3.0. A colour reaction between urinary albumin and tetrabromophenol blue produces various green hues based on the concentration of albumin in the sample. This change is independent of the urine pH.

Urine dipstick testing is usually highly specific, although it can give false-positive results in some situations, such as with very alkaline (pH>8) or concentrated urine specimens (specific gravity >1.025), gross haematuria, or in the presence of contaminating antiseptics, such as chlorhexidine and benzalkonium chloride, or after the administration of radiographic contrast such as an intravenous pyelogram (IVP). On the other hand, it is not as sensitive as quantitative methods. It is sensitive for albumin (containing many amino groups) at a concentration above 15 mg/dl but cannot detect microalbuminuria, showing only "trace" at threshold to frank albuminuria (15 mg/dl) Using 20 to 25 mg/dl of total protein as the limit of detection in clinical specimens, the sensitivity of reagent strips is only 32% to 46%, with a specificity of 97% to 100%. False-negative results can occur if the urine is dilute (SG<1.005), or protein loss is mild or in case of non-albumin proteinuria or high urinary concentration of penicillin, sulphonamides.

Therefore, dipstick testing is useful only when urinary protein exceeds 300 to 500 mg/day (or albumin >10–20 mg/day). Moreover, the dipstick is essentially specific for albumin, so it may miss other, positively charged proteins. It is insensitive for detecting low-molecular weight proteins such as immunoglobulin light chains and β_2 microglobulin. The dipstick is difficult to read in case of abnormal urine colour (nitrofurantoin, some sulfonamides)

Turbidometric tests

If a protein other than albumin is suspected to be present in elevated amounts in the urine, a turbidometric test should be done. The two most commonly used are the sulfosalicylic acid test and the heat (Putnam) test.

Protein precipitation with sulfosalicylic acid provides a more quantitative estimate of all the urinary proteins including LMW proteins. Eight drops of 20% solution of sulfosalicylic acid are added to 10 ml of the urine. The results range from "clear" to "flocculent precipitate," suggesting protein levels of 0 to greater than 500 mg/dl, respectively. This test can give false-positive results in the presence of gross haematuria, highly concentrated urine, iodinated contrast agent, tolbutamide metabolites, high levels of cephalosporin or penicillin analogs, or sulfonamide metabolites. It can be falsely negative with highly alkaline urine.

In the *heat test* 5 ml of urine is centrifuged, 2 ml of acetate buffer is added to the supernatant, and this solution is incubated at 56°C for 15 minutes. A precipitate indicates Bence-Jones proteins. These can be dissolved by heating the mixture to 100°C for 3 minutes. This test is not widely used. Radiocontrast agents can cause false-positive results in both dipstick testing and the sulfosalicylic acid test therefore, testing should not be done until 24 hours after a contrast study.

Quantitative methods

24-hour protein measurement

Quantitative measurement of protein in a 24-hour urine collection remains the gold standard, especially since protein excretion may vary with the circadian rhythm. Patients should be told to begin the collection at a fixed time by voiding into the toilet and then saving all of the urine they pass thereafter, including urine collected 24 hours later at the same time. One must also measure the creatinine in the collected urine to ascertain collection completion. Men usually excrete 19 to 26 mg of creatinine/kg/day, and women 14 to 21 mg/kg/day. Creatinine excretion increases with muscle mass and weight. It decreases in old age. However, in young children, accurately timed urine collections are difficult to obtain and other methods (spot or untimed urine collection) are used.

Spot urine sampling

It is another reliable method of screening for proteinuria, it does not have the compliance problems associated with 24-hour urine collection and is not affected by hydration status. The protein and creatinine concentrations are measured, and the protein-creatinine ratio calculated.

The *protein/creatinine (Pr/Cr) ratio* of an untimed (spot) urine specimen (preferably a first morning specimen, because urine protein concentrations can vary significantly during the day) is used to estimate protein excretion in children and has been shown to correlate very well (R=0.8-0.99) with the 24-hour urine protein excretion, particularly since first morning specimens eliminate the possibility of postural proteinuria[15,16]. A milligram-per-milligram protein-to-creatinine ratio of 0.2 or less is normal. Its sensitivity is 87.8%, specificity 89.3%, positive predictive value 29.3%, and negative predictive value 96.2%.

The *albumin-creatinine ratio* likewise correlates well with 24-hour albumin excretion. Normal values are <30 mg albumin/g creatinine on 1st morning urine or <0.03 mg albumin/mg creatinine on first morning urine. On a milligram-per-gram basis, an albumin-creatinine ratio of less than 30 is normal, 30 to 300 is considered microalbuminuria, and greater than 300 is overt nephropathy. The finding of microalbuminuria in a spot sample had a sensitivity of 91%, specificity 84%, positive predictive value 44.2%, and negative predictive value 97.9% for predicting microalbuminuria in a 24-hour sample. Microalbuminuria is a marker for early renal involvement due to hyperfiltration injury (diabetes, hypertension, any kidney disease with reduced nephron mass such as reflux nephropathy, etc.).

Urine protein electrophoresis

Qualitative evaluation of proteinuria can be done using immunoelectrophoresis. In Bence-Jones proteinuria there is a monoclonal peak in the gamma region, whereas a broad heterogeneous peak in the gamma region indicates tubular proteinuria, in which the protein molecules are usually smaller than albumin.

Approach to proteinuria[3,14]

When proteinuria is detected, the first thing is to make sure that it is not a false-positive result. Once confirmed, the initial evaluation should include a complete history, including a family history of renal disease, recent upper respiratory infections, gross haematuria, changes in weight and in urine output. The physical examination should include measurements of height, weight and blood pressure, identification of oedema, ascites and skin pallor, and palpation of the kidneys.

The next step is to define its quantity (non-nephrotic/ nephrotic), its character (intermittent/ constant) and

its relation if any to posture (orthostatic/ non–orthostatic). Having established proteinuria in the non-nephrotic range, the next step is to obtain a complete urinalysis and a first morning spot urine specimen over a few days to determine the Pr/Cr ratio[16]. It is important to have the child void before going to bed and remain recumbent until just before obtaining this specimen.

If the proteinuria is transient

Transient proteinuria is common in children and adolescents. It is benign and usually mild ($\leq$ 2+ on dipstick, urine Pr/Cr 0.5-1.0 or < 1 g/day). In most patients, it is asymptomatic and discovered incidentally during screening. The urinary sediment is normal. It may be seen in patients with a recent history of fever, dehydration, cold exposure, emotional stress, strenuous exercise, heart failure or seizures[13]. This type of proteinuria usually resolves spontaneously within several days after the precipitating factor disappears and does not progress to renal failure. Repeat sample 2 -3 times after a few days (to document its transient nature) before investigating and discharge if all clear.

If the proteinuria is persistent

Three possibilities exist:

1. *Orthostatic (postural) proteinuria*: the urinalysis is normal and the urine Pr/Cr ratio on the first morning urine sample is <0.2 and no additional studies are necessary. It is common, occurring in 60% of asymptomatic persistent proteinuria in childhood and 75% in adolescents. It commonly occurs in tall physically active adolescent, with a slender body habitus, normal renal function and blood pressure. It occurs only in the upright position, completely normalizes in the recumbent position or when awakening. Although it may be persistent, it is benign. It is seen primarily in young adults, usually is less than 1 $g/m^2/24$ hours (protein/creatinine < 0.2 mg/mg). Although 24 hour urine may show large proteinuria, only the 1st morning specimen should be tested. It is thought to be due to an alteration in glomerular haemodynamics, with the upright position resulting in venous pooling in the legs, renal vein congestion, decreased renal blood flow (with increase angiotensinogen II) and increased efferent arteriolar resistance. The renal histology is generally normal or nonspecific, and the long-term prognosis is excellent. After 20-50-year follow up, resolution of proteinuria has been shown in >85% of individuals, with normal renal

function. It is considered to be benign but follow up is prudent, with intermittent review (perhaps yearly) with early morning urine Pr/Cr.

2. *Persistent proteinuria* is defined as being present (≥1+ by dipstick) on two or more occasions both in upright and recumbent position. It is believed to reflect structural renal disease and may progress to chronic renal insufficiency. While it can be seen in tubulointerstitial diseases and in mild degrees of glomerulopathies, persistent proteinuria usually indicates glomerular disease. It can also be a part of a systemic disease and is a forerunner of renal disease in its own right. Once systemic diseases that cause nephrotic syndrome, such as diabetes mellitus, heavy metal poisoning, collagen vascular disease, nephrotoxic drugs, amyloidosis, and plasma cell dyscrasia have been excluded, the likely cause is primary glomerular disease (early glomerular disease, focal segmental glomerulosclerosis, IgA nephropathy, essential hypertension, early diabetic nephropathy, membranous glomerulonephritis, etc.). It requires investigations to define disease and renal function, proteinuria, and blood pressure monitoring[17].

3. *Idiopathic intermittent proteinuria*. Proteinuria independent of body posture in most (>50%) but not all random urine samples. Renal biopsy studies have shown 40% with normal or with minimal histological change, 60% with a variety of lesions including glomerular hypercellularity and sclerosis[18]. However, no electron microscopy studies were done and no clinicopathological correlations were studied. The prognosis is thought to be benign if proteinuria resolves over a few years.

Investigation of persistent proteinuria[3,14]

Urine microscopy: Examine a freshly spun urine sample under the microscope. Glomerular disease usually presents with abnormal urinary findings such as red blood cell casts and dysmorphic red blood cells. White blood cell casts may indicate glomerular or interstitial disease. Oval fat bodies are usually seen in nephrotic-range proteinuria. A quantitative assessment of urinary protein excretion should be made, using either a 24-hour collection or a random urine sample for the UPr/Cr ratio.

Blood tests: The serum creatinine concentration, electrolyte, blood urea nitrogen, total protein and albumin levels, as well as a complete blood cell count and C3 complement. As slight changes in GFR, as in early stages of renal disease, may not be reflected in serum creatinine levels, a more comprehensive evaluation of GFR might be needed.

Immune system tests: The workup should also include measurements of antinuclear antibodies, antineutrophil cytoplasmic antibodies (C-ANCA and P-ANCA), complement levels, and the erythrocyte sedimentation rate to evaluate for rheumatologic diseases (eg, systemic lupus erythematosus, Wegener granulomatosis, Goodpasture syndrome, cryoglobulinaemia), lymphoproliferative diseases, and solid organ cancers.

Screening for infections such as human immunodeficiency virus, hepatitis B and C, and syphilis should also be performed.

Urinary protein immune electrophoresis should be ordered if there is a suspicion of multiple myeloma (primarily in adults) or if there is discrepancy between the urine dipstick test and the sulfosalicylic acid test.

Ultrasonography of the kidney is important to rule out structural urinary lesions, especially in young children under six years of age, where anatomic or congenital abnormalities such as polycystic kidneys can be diagnosed. It also provides information on renal size, scarring, and possible obstruction. It also helps in planning for biopsy, as biopsy of a small, scarred kidney might not be useful and might cause bleeding. Similarly, the presence of a solitary kidney may also be a contraindication for performing a biopsy.

If fixed isolated proteinuria is ascertained, the work-up depends on the degree of proteinuria. If total protein excretion is less than 1 g per 24 hours (or the UPr/Cr is less than 1.0), twice-yearly visits, later extended to annual visits, with determination of the UPr/Cr ratio are sufficient. A referral to a nephrologist is appropriate for definitive diagnosis and further management in case of heavier proteinuria, persistence beyond one year, or abnormalities on the above investigations such as increased creatinine levels or hypocomplementaemia or haematuria, for consideration of renal biopsy .A close follow up and liaison with the nephrologist is very important.

Renal biopsy is indicated in all cases of nephrotic-range proteinuria (except in obvious diabetic nephropathy or drug-induced proteinuria that resolves when the drug is stopped), when proteinuria > 1 g/day, urine Pr/Cr >1.0 or proteinuria lasting over 1

year, presence of haematuria, or decreased renal function, or hypertension[17]. It is usually not indicated in mild proteinuria (<1 g/day) with normal renal function and negative urine sediment[19].

Prognosis

While patients with orthostatic proteinuria have an excellent prognosis, the long-term prognosis for children with isolated fixed proteinuria remains unknown. The prognosis of patients with proteinuria is related to the quantity of protein excreted[20]. Non-nephrotic proteinuria is associated with a lower risk of progression to renal insufficiency than nephrotic-range proteinuria. It is generally believed that children with isolated proteinuria not exceeding 1 g per 24 hours have a better prognosis than those with higher amounts of protein in their urine. Patients with persistent proteinuria of more than 1 g/day are more likely to progress to renal insufficiency.

Treatment

Specific treatment of the underlying nephropathy

When a specific nephropathy is found to be the cause of the proteinuria, it will obviously warrant a specific therapy (corticosteroids, immunosuppressants, etc.)

Non-specific treatment

In addition, nephroprotective therapy measures need always to be initiated regardless of the underlying cause of the persistent proteinuria.

1. **Dietary Recommendations**

   a. *Avoid excessive sodium intake[3]*.

   b. *Avoid excessive protein intake*. Although some benefit from dietary protein restriction has been described in a small series of children with chronic renal insufficiency, there was no significant impact of protein restriction on the rate of progression of renal disease. However, it seems reasonable to avoid an excess of dietary protein in children with proteinuric renal diseases, because high dietary protein intake may worsen proteinuria, at least in some patients with nephrotic syndrome (NS), without achieving higher serum albumin level. Thus, it is recommended that children with proteinuria receive the recommended daily allowance of protein for age (2 g/110 kcal/day)[3].

2. **Medications that lower BP and decrease proteinuria**

Renal function is better preserved when lower systolic blood pressures are achieved. The choice of antihypertensive agent should be determined in consultation with a paediatric nephrologist. Certain classes of antihypertensive agents, eg, the angiotensin converting enzyme inhibitors (ACEi) and the angiotensin II receptor blockers may, in addition to reducing systemic blood pressure, exert other beneficial effects, such as reducing urinary protein excretion and decreasing the risk of renal fibrosis[3,21,22].

   a. *Angiotensin Converting Enzyme Inhibitors (ACEi)*: they reduce proteinuria, delay progression of chronic renal failure in adults with chronic nephropathies, proteinuria and/or hypertension. However, their long-term benefit in children and adolescents with proteinuria remains to be established, and there are some concerns with the use of these agents in infants. Infants born to mothers receiving ACEi during the second and third trimesters of pregnancy may develop oligohydramnios, pulmonary hypoplasia, hypocalvaria, postnatal hypertension, anaemia and on postmortem examination severe glomerular and tubular malformations. ACEi are therefore contraindicated during pregnancy and their risks in young infants are unknown.

   b. *Angiotensin II Receptor Blockers*: reduce systemic BP, reduce proteinuria, decreased risk of renal fibrosis. Their risks in young infants are unknown

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