

## Evaluation of Transient Proteinuria in Children

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### ABSTRACT

Proteinuria is a common laboratory finding in pediatric practice and can be found incidentally in children at school screening tests and during evaluation for other reasons. Usually only repeat urine testing is necessary to confirm transient nature of this phenomena. However, a small subset of these children may have persistent proteinuria but they are at highest risk for developing chronic kidney disease. Aggressive diagnostic procedures are usually not necessary at the beginning unless there is nephrotic range proteinuria or other parameters suggesting severe renal disease. Orthostatic proteinuria is one of the most common causes of proteinuria in children and has excellent prognosis with spontaneous resolution in most individuals.

**Key words:** Transient proteinuria; Orthostatic proteinuria; Children

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### INTRODUCTION

Proteinuria is a common laboratory finding in pediatric practice, detected in 5-15% of school-age children, and can be found

incidentally in asymptomatic children systematically at school screening tests and during evaluation for other reasons as well. Proteinuria was found in at least one urine sample in 10.7% of children but persisted in all four urine samples in only 0.1% of tested children where the interval between four urine sample analysis was up to 38 hours. Children who had proteinuria in two or more specimens and 11.6% of children who had proteinuria in one specimen were further evaluated. Among those, 34 (12.5%) had marked proteinuria, defined as proteinuria in at least eight of 14 consecutive urine samples, proteinuria in at least four of seven early morning urine samples, protein excretion rate of more than 6 mg/m<sup>2</sup>/h during the night or protein excretion rate of more than 20 mg/m<sup>2</sup>/h during the day. Only eight children (2.9%) had proteinuria over 300 mg/dL<sup>[1]</sup>.

Children with persistent proteinuria are at highest risk for developing chronic kidney disease. Persistent proteinuria can be either glomerular and primary (due to glomerular diseases, such as focal segmental glomerulosclerosis, IgA nephropathy etc.) or secondary (due to systemic lupus erythematosus, Henoch-Schönlein purpura etc.). On the other hand, persistent proteinuria can be tubular and primary (due to polycystic kidney disease, cystinosis etc.) or secondary (due to acute tubular necrosis, tubulointerstitial nephritis etc.)<sup>[2]</sup>.

One definition defines persistent asymptomatic isolated proteinuria as proteinuria that is present in > 80% of samples, including in recumbent specimens in an otherwise healthy child in whom clinical and laboratory work-up is normal<sup>[3]</sup>. But according to Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, a child has persistent proteinuria if present in two or more quantitative tests temporally spaced by 1 to 2 weeks<sup>[4]</sup>.

### EVALUATION OF CHILDREN WITH TRANSIENT PROTEINURIA

A big study on incidence of hematuria and proteinuria in Korean children revealed isolated proteinuria in 26.4% of children that were referred to further pediatric nephrology evaluation due to above mentioned urine abnormality, detected at mass school urine screening test. 74% of these children had transient proteinuria

(usually associated with fever, exercise, cold exposure or some other conditions, not related to urinary tract), 19% had orthostatic proteinuria (defined as elevated protein excretion in the upright and normal protein excretion in a supine position) and only 7% of them had persistent proteinuria. IgA nephropathy was the most common pathologic diagnosis in children who needed renal biopsy and most commonly presented with combined hematuria and proteinuria<sup>[5]</sup>.

A more recent study in a population of Korean children revealed isolated proteinuria in 10.8% of children that were evaluated by pediatric nephrologists on a basis of abnormal findings at a urine screening test. The most common renal biopsy finding in this group of patients was IgA nephropathy, followed by mesangial proliferative glomerulonephritis and focal segmental glomerulosclerosis (FSGS)<sup>[6]</sup>.

Renal biopsies in children with persistent asymptomatic isolated proteinuria most commonly revealed focal sclerosis, IgA nephropathy, membranous nephropathy and diffuse mesangial proliferation. Therefore it requires close follow-up and monitoring every 6 to 12 months. Persistent proteinuria, especially progressive one, that lasts for more than 1 year, requires a renal biopsy but its yield is poor when proteinuria is mild or moderate (less than 1g per day)<sup>[3]</sup>. According to results of studies in adults from different countries, IgA nephropathy accounts for 18-40% of all glomerulonephritis cases in Japan, France, Italy and Australia, but only 2-10% of glomerulonephritides in the United Kingdom and USA. This is probably a consequence of environmental and genetic factors as well as a consequence of different approaches to screening of asymptomatic patients<sup>[7]</sup>. Retrospective analysis of kidney biopsies in children in a single tertiary centre revealed minimal change disease to be the most common histopathologic diagnosis (present in 16.6%), followed by IgA nephropathy (12.8%), FSGS (12.2%), C1q nephropathy (8.9%), Henoch-Schönlein and lupus nephritis (both in 6.1%) but the indications for biopsy were nephrotic syndrome, renal failure and signs of glomerulonephritis, in addition to persistent proteinuria<sup>[8]</sup>.

These studies revealed some epidemiological aspects of proteinuria in children, the importance of screening programs for detecting chronic kidney diseases in an early stage and also emphasized that aggressive diagnostic procedures (such as renal biopsy) are usually not necessary at the beginning unless there is massive (nephrotic range) proteinuria or other parameters suggesting severe renal disease, such as abnormal renal function, hypertension or family history of chronic kidney disease.

A study in healthy children confirmed that orthostatic proteinuria is common, present in 20% of healthy children aged between 6 and 19 years. It was found to be more common in boys, in children above 10 years of age and with body mass index (BMI) above 85th percentile<sup>[9]</sup>. But another study of adolescents did not find a correlation between orthostatic proteinuria and obesity. Regarding pathogenesis, it is proposed that orthostatic proteinuria is due to at least one of the following reasons<sup>[10]</sup>: exaggeration of the normal response (increased protein excretion in the upright position), minute glomerular changes (focal mesangial hypercellularity, basement membrane changes)<sup>[11]</sup>, immoderate hemodynamic response to the upright position (increased glomerular permeability in some individuals due to increased angiotensin II and norepinephrine release in when upright)<sup>[12]</sup> and nutcracker syndrome (entrapment of the left renal vein by the aorta and superior mesenteric artery). The latter mechanism was confirmed in several small studies<sup>[13,14,15]</sup>. Overall, orthostatic proteinuria has excellent prognosis with spontaneous resolution in most individuals. Long-term follow-up showed normal renal function after several

decades, even in cases of persistent orthostatic proteinuria<sup>[16,17,18]</sup>. It is also worth mentioning that orthostatic proteinuria is rarely found in adults over 30 years of age. Regarding the benign nature of this condition additional investigations or treatment are not needed apart from occasional urine testing at follow-up visits until proteinuria resolves<sup>[19]</sup>.

On the basis of gathered data, a child with asymptomatic proteinuria needs a repeat testing for proteinuria to see whether it is transient, orthostatic (when repeat analysis of urine on a first morning void is necessary in one year) or persistent, when proteinuria is present on at least two additional occasions. In the latter case, further evaluation is necessary: renal function tests, serum electrolytes, cholesterol, total protein, albumin, renal ultrasound and additionally complement study (C3, C4), tests for systemic diseases (antinuclear antibodies) and hepatitis B, C and HIV testing, as needed according to clinical situation<sup>[20]</sup>.

In conclusion, proteinuria is a common finding in pediatric practice, often detected incidentally in asymptomatic children. Usually only repeat urine testing is necessary to confirm transient nature of this phenomena in majority of cases. However, we must keep in mind that a small subset of these children may have persistent proteinuria but they are at highest risk for developing chronic kidney disease. Therefore, aggressive diagnostic procedures (such as renal biopsy) are usually not necessary at the beginning unless there is massive (nephrotic range) proteinuria or other parameters suggesting severe renal disease, such as abnormal renal function, hypertension or family history of chronic kidney disease. Orthostatic proteinuria is one of the most common causes of proteinuria in children and has excellent prognosis with spontaneous resolution in most individuals.

## CONFLICT OF INTERESTS

There are no conflicts of interest.

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