

The Spectrum of Kidney Diseases in Children Associated with Low Molecular Weight Proteinuria

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Abstract

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BACKGROUND: Proteinuria, in addition to haematuria, is the most important laboratory parameter in patients with nephro-urological diseases. Low molecular weight proteinuria (LMWP) is of particular importance because some diseases genetic and tubulointerstitial are diagnosed based on its presence.

AIM: The purpose of this study is to describe the clinical features, the course and outcome of pediatric patients with a renal disease associated with LMWP.

MATERIAL AND METHODS: This retrospective observational study included 250 pediatric patients with various kidney diseases in which the type of proteinuria was defined by 4-20% gradient gel sodium dodecyl sulphate polyacrylamide gel (SDS-PAG) electrophoresis.

RESULTS: Isolated LMWP was detected in 12% of patients, while mixed glomerulotubular proteinuria was detected in 18% of patients. It was detected in all patients with the Dent-1/2 disease, Lowe's syndrome and secondary Fanconi syndrome. Transient LMWP was also detected in a series of 12 patients with distal renal tubular acidosis. In patients with nephrotic syndrome, it was associated with corticoresistance and unfavourable clinical course.

CONCLUSION: This study contributes to the understanding of the clinical spectrum of various kidney diseases associated with LMWP, their natural course, and the effect of therapy.

Introduction

Proteinuria in addition to haematuria is the most important laboratory parameter in patients with nephro-urological diseases. It is of paramount importance in the diagnosis, monitoring of the effect of therapy and follows up of these patients. It is defined as excretion of proteins in the urine above the upper limit of normal. Because most of the excrement is due to albumin, values above 30mg/L are taken for an upper limit of normal [1]. The remainder belongs to the Tamm-Horsfall protein, whose function is not completely clarified and is conceived in the distal tubule.

A problem in younger children who are not toilet trained is the inability to determine proteinuria in a 24-hour sample. The protein/creatinine index is then determined in a single urine sample. This mg/mmol ratio is normally < 20. In everyday work, proteinuria is tested with urinary sticks and is graded as negative, trace (+/-), 1+, 2+, and 3+. The sticks primarily detect albumin and are less sensitive to low molecular weight proteins, Bence Jones proteins or gamma globulins.

A false positive finding is when the urine is extremely concentrated, while a false negative finding is when the urine is maximally diluted. But the ideal way is to determine proteinuria with a more precise method, such as, for example, with sulphosalicylic acid.

Before the treatment of a child with proteinuria, functional (orthostatic) proteinuria should be excluded [2] [3] [4] [5]. It is characterised by excretion of proteins only in postural position. It is typical for older children, usually occurs in puberty and tends to resolve itself. Renal biopsy does not show specific signs and is not indicated in this condition. Some patients have "nutcracker phenomenon" or so-called aortomesenteric plicae, with the left renal vein entrapped between the aorta and the upper mesenteric artery in an upright position.

In the treatment of a child with orthostatic proteinuria, it is necessary to measure blood pressure, examine the sediment for the presence of haematuria, quantify proteinuria (allowed up to 1.0 g/day) and measure the C3 complement. If this processing shows normal results, only annual audits are sufficient. SDS-PAGE electrophoresis is an elegant method where the presence of Apolipoprotein A1 fraction (APO-A1) with a molecular mass of 28 KD is a pathognomonic sign for orthostatic proteinuria [2] [3].

The next step in treating a child with proteinuria is the classification of the same. The following classification is the most common: (i) Glomerular proteinuria: proteinuria with a molecular weight greater than 60 KD, with the presence of albumin, haptoglobin, IgG and transferrin (ii) Tubular proteinuria-proteins with a mass lower than 60 KD, which are alpha-1-microglobulin, beta-2-microglobulin, retinol binding protein (RBP), light chains, and post-gamma globulin (iii) Mixed proteinuria - a combination of glomerular and nonglomerular fractions. Glomerular proteinuria can then be divided into selective (albumin with or without transferrin) and non-selective (albumin, transferrin, and IgG). Tubular proteinuria can be classified into incomplete and complete tubular proteinuria according to the size of the fractions.

Low molecular weight proteinuria (LMWP, i.e., tubular proteinuria) is the subject of this study. Many diseases as primary (hereditary) are characterized by the presence of tubular, ie, low molecular weight proteins [6] [7] [8] [9] [10] [11] [12] [13] [14] [15]. As already mentioned in healthy individuals, the intact proximal tubular cell completely absorbs proteins with a small molecular mass. If transport systems are damaged as a result of a genetic defect (recycling of cubilin and megalin, defect in endosomal acidification), as in the case of Fanconi syndrome or Dent's disease, then LMWP is present [16].

It can be isolated as in Imlerslund Grasbeck syndrome [14] or be accompanied by outbursts in other tubular functions (electrolyte, phosphate, bicarbonate, glucose, and amino acid loss). Low molecular weight proteinuria is often also found in other metabolic diseases with the affection of the proximal tubular cell such as tyrosinaemia, fructosemia, galactosaemia, Wilson's disease.

For the detection of tubular (low molecular weight proteinuria, single markers such as alpha-1-

microglobulin, beta-2-microglobulin or retinol binding protein alone or in combination may be used [17] [18] [19] [20]. Beta-2-microglobulin, which is one of the first and most popular markers, is unstable in an acidic environment so that one can gain unreliable results by using it.

Sometimes the interpretation of these markers can be problematic and hence the so-called urinary protein expert system has been introduced in clinical practice [21]. This system is computerised and allows to doctors without experience in this field to interpret the findings from determining urinary protein markers.

In this study, low molecular weight proteinuria was determined by SDS-PAGE (sodium dodecyl sulphate polyacrylamide gel electrophoresis). It is a method that was developed during the 90s of the last century. The advantage is that a panoramic view of all proteins is obtained, so a clear classification of the type of proteinuria is possible [1] [2] [3] [17] [18] [19] [20]. It is relatively fast and inexpensive method; it is possible to analyse multiple samples, especially using the Phast system [21]. The method is refined, by providing a computerised analysis of the resulting fractions and their relative estimation using laser densitometry.

This study aimed to describe the clinical features, the course and outcome of pediatric patients with renal disease in whom the LMWP has been diagnosed.

Material and Methods

The study was designed as a retrospective-prospective study. Pediatric patients aged 1-18 years who have been treated as out- or in-patients at University Children's Hospital Skopje were included in the study. In all patients, standard clinical and laboratory workup was performed. It included a detailed personal and family history of renal disease, as well as a physical examination including measurement of the blood pressure.

Proteinuria was determined by urinary stix and sulphosalicylic acid qualitatively and quantitatively. The glomerular function was assessed through the values of degradation products (urea, creatinine and uric acid depending on the reference values). Glomerular filtration rate was calculated according to the new Schwartz formula. Tubular functions have been investigated by determining low molecular weight proteinuria, glucosuria, phosphaturia, uricosuria, aminoaciduria, the presence of tubular acidosis (proximal, distal, mixed).

The serum values of bicarbonate, sodium, potassium, calcium, phosphorus, magnesium,

chloride, uric acid, total proteins and albumin, hepatic enzymes, alkaline phosphatase, and creatinine phosphokinase were also determined. Tubular reabsorption of phosphate (TRP) and fractional excretion of urate was calculated according to the reference formulas. Depending on the clinical picture, other studies have been performed-e.g. imaging of the kidneys and urinary tract to assess the gross morphology. In some patients, especially those with glomerulonephritis, the biopsy findings obtained with a punctured renal biopsy were also analysed.

Determination of low molecular weight (tubular proteinuria) with Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis (SDS-PAGE) was performed at the Laboratory for Protein Chemistry at the Institute for Clinical and Experimental Biochemistry at the Faculty of Medicine in Skopje, with the procedure for separation and identification performed in several stages: linear gel preparation (4-22%), treatment of urinary samples before their application on the gel, electrophoresis, gel fixation, coloring with Coomassie blue, and identification of the separated protein fractions based on standards with exactly known molecular weight.

This study was approved by the Ethical Committee at Medical School Skopje. Informed consent was obtained from the participants' parents/legal guardians.

Results

This study included 250 pediatric patients with the various nephro-urological disorders in whom the type of proteinuria was defined by 4-20% gradient gel sodium dodecyl sulphate polyacrylamide gel (SDS-PAGE) electrophoresis. There was a mild predominance of the female sex ($n = 132, 52.8\%$). The average age of the patients was 7.6 years (ranging from 2 to 23 years). Regarding the ethnicity, subjects from the Macedonian nationality predominate, which corresponds to the national level in the Republic of Macedonia ($n=158, 63.2\%$).

The most common indications for performing SDS-PAGE electrophoresis were following: haematuria, urinary infection, proteinuria, nephrolithiasis, and congenital anomalies of the urinary tract.

Isolated LMWP was detected in 12% of patients, while mixed glomerulotubular proteinuria was detected in 18% of patients (Figure 1). It has been detected in all patients with Dent-1 and Dent-2 disease, Lowe's oculocerebrorenal syndrome and secondary Fanconi syndrome. LMWP was also detected in a series of 12 patients with distal renal tubular acidosis, and it was transient. The presence of LMWP in patients with nephrotic syndrome was

associated with corticoreistance and unfavourable clinical course.

The value of SDS-PAGE electrophoresis in children with OCRL mutations was also evaluated. Three children were phenotypically characterised as Lowe's oculocerebrorenal syndrome and 3 children as Dent-2 disease. Low-molecular-weight proteinuria was detected in all 6 children with SDS-PAGE. It is noteworthy that only one child with Lowe syndrome had a complete Fanconi syndrome and this patient had a fatal outcome.

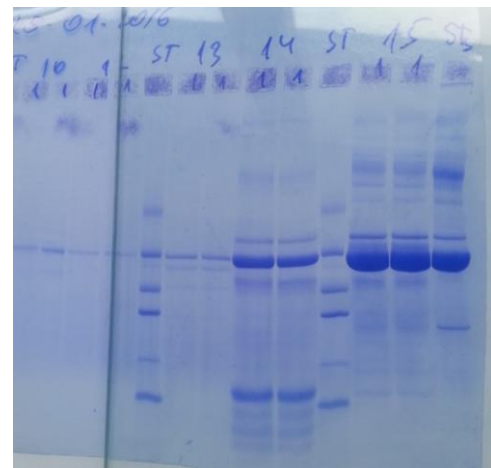


Figure 1: St-standard; Track 13, incomplete tubular proteinuria; Track 14, complete tubular proteinuria; Track 15, Mixed glomerulotubular proteinuria

An interesting case is a 12-year-old boy who presented with nephrotic range proteinuria at the age of 3 years. Because serum biochemistry was normal, as well as the values of C3 complement, the biopsy was postponed, but the child was lost to follow up. At the age of 13, he was hospitalised for persistent proteinuria of nephrotic range but without oedema. The biopsy did not show abnormalities on light-microscopic and immunofluorescent examination. SDS-PAGE electrophoresis was then performed showing the presence of complete tubular proteinuria (Figure 2). Finally, 24-hour urinary excretion of calcium was determined (11.0 mg/kg/d) leading to the establishment of a clinical diagnosis of Dent's disease. The diagnosis of the Dent-2 disease was confirmed by genetic analysis which showed the presence of a pathogenic OCRL mutation.

The outcome of patients with LMWP: in children with acute tubular-intestinal nephritis (drugs in three cases), complete normalisation of renal function has occurred. Two children had the fatal outcome (one with Lowe syndrome and one with a secondary Fanconi syndrome- eczema, enteropathy, IPEX syndrome). A complete resolution of the Fanconi syndrome ensued in two children (one cisplatin nephrotoxicity and one with Fanconi anaemia treated with a chelating agent)

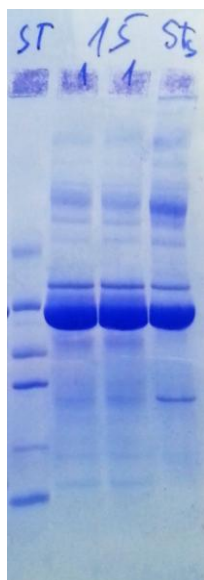


Figure 2: Patient with the Dent-2 disease, Eleferogram shows massive proteinuria, mixed (glomerulo-tubular)

Discussion

In clinical practice, LMWP is detected in patients with acute tubulointerstitial nephritis. In addition to tubular proteinuria, glycosuria, acidosis and various degrees of reduction of glomerular filtration rate are present. Typically it is a non-oliguric acute renal failure. TINU syndrome is tubulointerstitial nephritis with uveitis. LMWP can be the first sign of toxic damage to the tubular cell (antibiotics in particular tetracyclines, heavy metals, mercury, cadmium, lead, etc.).

Some drugs such as cisplatin, ifosfamide, valproic acid can also lead to tubular cell damage with a consecutive occurrence of tubular proteinuria [22] [23]. In this study, in two children the incriminated agent was cisplatin, while the other was a chelating agent for the treatment of Fanconi anaemia (Fanconi in Fanconi). Low molecular weight proteinuria may be the first sign of diabetic nephropathy [24] [25]. Patients with long-standing cystic fibrosis may also have proteinuria [26]. Tubular proteinuria may also be the first sign of nephropathy in Henoch Schonlein disease [22].

There are many studies that indicate the presence of tubular proteinuria in patients with glomerular disease and may be a poor prognostic marker (steroid-resistant nephrotic syndrome, focal segment glomerulosclerosis, IgA nephropathy) [27] [28] [29] [30] [31] [32] [33] [34]. In our study, the unfavourable course of focal glomerulosclerosis and steroid-resistant nephrotic syndrome was also associated with LMWP.

In addition to the acquired diseases, LMWP is found in a number of genetic tubulointerstitial diseases (nephronophthisis, Dent-1, Dent-2 disease, Lowe syndrome, cystinosis, tyrosinaemia, fructosamine, Wilson's disease) [35] [36] [37] [38] [39] [40]. We had an interesting observation for the presence of LMWP in patients with distal renal tubular acidosis [41]. This can lead to differential diagnostic difficulties with the Fanconi syndrome. Tubular proteinuria was present only at the onset of the disease, while the children were decompensated. With metabolic compensation, a complete resolution of proteinuria ensued.

In conclusion, this study contributes to the understanding of the clinical spectrum of various diseases associated with LMWP, their natural course, and the effect of therapy. SDS-PAGE electrophoresis is a sensitive, inexpensive and well-established method for the detection of LMWP in children with renal disease.

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