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ORIGINAL ARTICLE

Reliability of different expert systems for profiling proteinuria in children with kidney diseases

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Abstract This study was designed to compare three urinary protein expert systems for profiling proteinuria in children with kidney diseases. Freshly voided urine specimens were collected from 61 children with glomerular diseases, 19 children with tubular diseases and 25 healthy children aged 3–16 years. The urinary protein expert systems were: (1) albumin/total protein ratio (APR), (2) α-1-microglobulin/α-1-microglobulin + albumin algorithm (AAA), and (3) the complex urine protein expert system (UPES, PROTIS) algorithm. APR correctly identified glomerular proteinuria in 47/61 children, tubular proteinuria in 16/19 children and normal proteinuria in 23/25 healthy children. AAA correctly identified glomerular proteinuria in 61/61 children and tubular proteinuria in 18/19 children, and 25/25 healthy children were characterized as having no abnormal proteinuria. AAA was not influenced by the stage of chronic kidney disease. UPES differentiated the type of proteinuria in children with glomerular diseases into glomerular (50/61 patients) and mixed glomerulo-tubular (6/61 patients). Tubular proteinuria was identified in 16/19 patients and described as mixed glomerulo-tubular proteinuria in 3/19 patients. Mixed glomerulo-tubular proteinuria was found only in children with chronic kidney disease stages 2–5 of glomerular and tubular diseases. In conclusion, the AAA and UPES had the highest accuracy levels.

Keywords Proteinuria · Expert system · Kidney diseases · Glomerular · Tubular · Diagnostics

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Introduction

Proteinuria is an indicator of kidney disease and a marker for site and severity of intra-renal lesions [1]. Urinary protein analysis is a non-invasive method for studying renal disease in children. The detection of marker protein/creatinine ratios has replaced time-consuming 24-hour urine collection without losing diagnostic sensitivity and specificity [2, 3]. Pre-analytical pitfalls, such as fever, vigorous exercise, haematuria and urinary tract infections, produce a transitory increase of urinary albumin excretion [4]. These pitfalls are rare and should be excluded by examination in a pitfall-free interval. The activity of proteases in the urine as an ex-vivo pre-analytical pitfall is moderate [5]. The urine can be kept for several hours if kept at temperatures below 8°C until processed [6–8]. The nephelometric measurement of marker proteins such as albumin (ALB) and alpha-1-microglobulin (AMG) allows a rapid differentiation between glomerular and tubular dysfunction in primary and secondary kidney diseases [9]. Urinary expert systems were used to standardize the procedure of profiling proteinurias for both paediatric nephrologists and general paediatricians [1, 10–13]. Software was developed that includes additional marker proteins in order to adapt the sodium dodecylsulphate-polyacrylamide gel (SDS-PAGE) classification [14–16] for indicating and locating renal damage. We undertook a

prospective study to test three different expert systems for profiling proteinuria in children with kidney diseases.

Patients

The study group of 105 children (aged 3–14 years) included 25 healthy children, 61 children with active glomerulopathies, and 19 children with tubular diseases such as a partial or complete DeToni–Debré–Fanconi syndrome (Table 1). Fifteen out of 61 children with glomerulopathies had a glomerular filtration rate (GFR) < 90 ml/min per 1.73m^2 body surface area [chronic kidney disease (CKD) stages 2–5 (stage 2, n=7 children, stage 3, n=7, stage 4, n=1)]. Eight out of 19 children with tubular disorders had CKD 2–5 (stage 2, n=3 children, stage 3, n=2, stage 4, n=1, stage 5, n=2). No patient had suffered from a urinary tract infection or extra-renal infections with fever 2 weeks prior to or during urine collection.

Methods

Serum and morning urine samples were analysed with a Hitachi 717 instrument (Roche Diagnostics, Germany) for creatinine (Crea) enzyme (creatininase), total protein (PROT) with pyrogallol-red, IgG, ALB and AMG by immunoturbidimetry with Tinaquant (Roche Diagnostics), and alpha-2-macroglobulin by immune nephelometry with the Behring nephelometer analyser (BNA) (Dade Behring, Germany), as well as urine strips with automated Clinitek Atlas (Bayer Diagnostics, Germany). GFR was calculated by the height index formula of Schwartz [17]. CKD was divided into five stages [18, 19].

Table 1 Underlying diseases in study patients (*NS* nephrotic syndrome, *FSGS* focal and segmental glomerulosclerosis, *GN* glomerulonephritis, *MPGN* membranoproliferative glomerulonephritis)

Glomerular diseases		Tubular diseases	
Diagnosis	Number	Diagnosis	Number
Steroid-sensitive NS	17	Dent's disease[b]	5
IgA nephropathy[a]	9	Cystinosis[b]	4
FSGS[a]	8	Ifosfamide toxicity	3
Post-streptococcal GN	6	Idiopathic renal Fanconi syndrome	4
MPGN[a]	2	Tubulointerstitial nephritis[a]	1
Mesangioproliferative GN[a]	3	Acute tubular necrosis	1
Membranous GN[a]	2	Fanconi syndrome and microvillus atrophy	1
Shunt GN[a]	1		
Alport syndrome[a]	3		
Schoenlein–Henoch GN	2		
Haemolytic uraemic syndrome	3		
Orthostatic proteinuria	5		
Total	61		19

[a] Biopsy proven
[b] Proven by molecular genetics

Algorithms of urinary protein expert systems

The algorithms of the urinary protein expert systems are depicted in Fig. 1.

The following algorithms were used for differentiation of glomerular proteinuria, tubular proteinuria, and other types of proteinuria:

1. Albumin–protein ratio (APR)

If the patient had a urinary protein–creatinine ratio <200 mg/g (< 22 mg/mmol), proteinuria was defined as normal. In children with a protein–creatinine ratio > 200 mg/g the type of proteinuria was analysed using the urinary albumin–protein ratio (% ALB/PROT = ALB × 100/PROT) [10]. Tubular proteinuria was defined as percent ALB/PROT lower than 50% and glomerular diseases as percent ALB/PROT higher than 50% [10].

2. Albumin–alpha-1-microglobulin algorithm (AAA)

If the patient had a urinary ratio of ALB/Crea < 20 mg/g and AMG/Crea <5 mg/g, the proteinuria was defined as normal. If ALB/Crea was >20 mg/g and AMG/Crea <5 mg/g, the proteinuria was defined as glomerular. If ALB/Crea was <20 mg/g and AMG/Crea >5 mg/g, the proteinuria was defined as tubular.

If both ratios were elevated (ALB/Crea > 20 mg/g and AMG/Crea > 5 mg/g), the following formula was used:

$$\mathrm{AMG} \times 100/(\mathrm{AMG}+\mathrm{ALB}) > 15\% = \text{glomerular proteinuria}$$
$$\mathrm{AMG} \times 100/(\mathrm{AMG}+\mathrm{ALB}) < 15\% = \text{tubular proteinuria.}$$

3. Urine protein expert system (UPES)

UPES is an example of a knowledge-based system designed for the interpretation of complex urine findings [12]. A diagnostic strategy of urine protein differentiation, based on dipstick screening (blood, leukocytes, protein) and the quantitative measurement of marker proteins in urine, has been developed to distinguish renal, pre-renal and post-renal causes of proteinuria, haematuria or leukocyturia. This urine protein differentiation, together with the assessment of the glomerular filtration rate by serum creatinine or cystatin C, provides a non-invasive diagnostic tool that reflects the quality of kidney function in a comprehensive and differentiated manner. The basis of interpretation of the

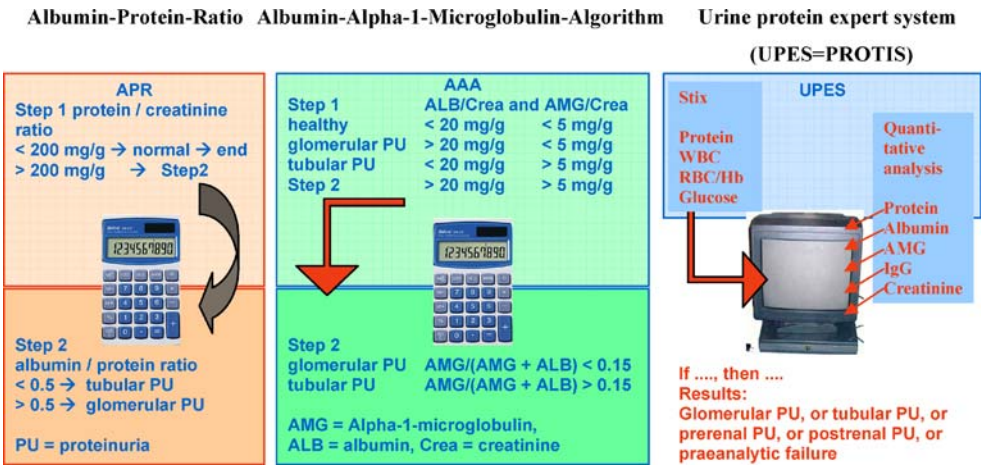

Fig. 1 Three expert systems for profiling proteinuria

analytes is not limited to a comparison with the reference ranges but includes various dependencies of both urinary and serum markers. The nonlinear relationships between the different urine proteins observed during the development of the knowledge base led to the implemented logical and mathematical algorithms. The knowledge base of UPES reflects a stepwise strategy that has been evaluated using a database of more than 500 urine protein patterns of adult patients with clinically and partly histopathologically proven diagnoses of nephrological or urological diseases. UPES was adapted for children [13]. Rules describe the knowledge in logical "if...then..." instructions that process the input data to find the matching text elements. The strategy of urine protein differentiation is briefly outlined and presented, with two examples: ALB serves as a marker protein for a glomerular lesion, AMG indicates a tubulointerstitial dysfunction. Total protein is used for plausibility control and the detection of a "protein gap" indicating prerenal proteinuria (Bence Jones proteins). These analytes, together with urinary creatinine as a marker for diuresis, are considered essential quantitative measurements in urine by UPES. The final report consists of the laboratory findings, with age-dependent reference ranges in a table and the knowledge-based interpretation result of the selected text items. The interpretative text covers not only underlying kidney disorders but also comments on pre-analytical and analytical problems [12]. A form of UPES is provided by Dade Behring under the trade name of PROTIS.

Statistical methods

The basis for profiling the types of proteinuria was the comprehensive clinical diagnosis in children with kidney diseases. This clinical diagnosis was based on the history, clinical examination, laboratory data (including molecular genetic testing) and renal histology with glomerular diseases (Table 1). Urine protein analysis was not included for differentiating the underlying renal diseases.

The Mann–Whitney non-parametric test was used to test the significance of differences between urinary protein excretions in the three study groups. The chi-square test and contingency coefficient were used to test whether the three tests differentiated between glomerular, tubular and normal proteinuria and whether the accuracy of the three tests differed significantly. The statistical post-hoc power analysis was made using G*POWER software package [13]. The chi-square test post-hoc analysis for contingency tables was applied. For the total sample size of 105 subjects, a 3 × 3 contingency table was analysed, having four degrees of freedom, with a level of hypothesis acceptance at 0.05; the calculated power at acceptable effect size (w) of 0.35 was 0.835. The statistical calculations were done with SPSS for Windows, version 11. The confidence intervals of binomial distribution were used to interpret percentage quotation [20].

Results

Mean urinary excretion of total protein, albumin and α-1-microglobulin in children with glomerular and tubular diseases were significantly higher than in healthy children ($P<0.001$) (Table 2). The mean protein–creatinine ratio was significantly higher in children with glomerular diseases than in children with tubular diseases, and the AMG/Crea ratio was significantly higher in children with tubular diseases than in children with glomerular diseases (Table 2).

The albumin–protein ratio identified glomerular proteinuria in 47/61 (77%) children; however, seven cases were attributed to tubular proteinuria and another seven to normal proteinuria. Tubular proteinuria was attributed by APR to 16/19 (84%) children with tubulopathies; three of 19 cases were falsely attributed to glomerular proteinuria. Twenty-three out of 25 (92%) healthy children were

Table 2 Urinary protein–creatinine ratios in healthy children and in children suffering from glomerulopathies and tubulopathies (mean ± standard error)

Parameter	Number	Total protein	Albumin	Alpha-1-microglobulin	
Glomerular diseases	61	4079±1230**	1570±342*	19±6***	mg/g creatinine
Tubular diseases	19	2067±454**	773±234*	532±182***	mg/g creatinine
Healthy children	25	82±16	6±1	1±0.3	mg/g creatinine

Glomerular versus tubular: *not significant, **$P<0.03$, ***$P<0.001$
Healthy versus diseased: all differences significant, $P<0.001$

identified as having normal proteinuria (Table 3), and two cases out of 25 were falsely attributed to tubular proteinuria.

The albumin–alpha-1-microglobulin algorithm identified glomerular proteinuria in all 61 (100%) children with glomerular diseases (Table 3). Tubular proteinuria was described in 18/19 (95%) children with tubular diseases. Glomerular and tubular proteinuria were correctly identified in all 23 children with CKD stages 2–5, and accuracy of AAA was not influenced by the stage of CKD (not shown in the tables). All 25 (100%) healthy children were characterised as having no abnormal proteinuria (Table 3).

UPES differentiated the type of proteinuria in children with glomerular diseases into glomerular (50/61 patients), mixed glomerulo-tubular (6/61 patients), tubular (1/61 patients) and pre- or post-glomerular (2/61 patients). In 2/61 patients with accompanying leukocyturia UPES asked for a repeat analysis after the disappearance of the leukocyturia. UPES identified the type of proteinuria in children with partial or complete renal Fanconi syndrome as tubular in 16/19 patients, and as mixed glomerulo-tubular proteinuria in 3/19 patients. All healthy children were identified by UPES as having normal proteinuria (Table 3). Mixed glomerulo-tubular proteinuria was found only in children with CKD stages 2–5, and not in stage 1.

Discussion

Diagnostic expert systems are useful tools to help general paediatricians come to firm conclusions by including the knowledge of specialists without having to contact the experts personally. Vice versa, they provide the experts with the surety of knowing that their decision-making processes are included in every day paediatric care in a standardized and conforming way. However, despite all the mathematical expertise, there is a risk that the expert systems may fail in individual cases. Therefore, a critical eye is mandatory when expert systems are used.

Three different urinary expert systems were analysed for their reliability in identifying glomerular and tubular proteinuria in children with different primary and secondary glomerular and tubular diseases. AAA and UPES had the highest accuracy when compared with the other expert system, APR. The accuracy of AAA was not negatively influenced by a decrease in GFR. AAA accurately identified all 61 patients with glomerulopathies and all 25 healthy children; however, statistically, this still means that up to 6% and 14%, respectively (confidence interval of binomial distribution), of cases in a larger study population have a risk of being falsely categorised by AAA.

Table 3 Reliability of three urine protein expert systems for profiling proteinuria in children with defined glomerular and tubular diseases and in healthy children (AAA vs APR, chi-square test $P < 0.001$; AAA vs UPES, chi-square test $P<0.001$). *NoD* no kidney disease, *GD* glomerular disease, *TD* tubular disease, *No* no proteinuria, *GP* glomerular proteinuria, *TP* tubular proteinuria, *Pre or post* pre-renal or post-renal proteinuria, *Unknown* expert system needs more information for a decision

Clinical classification		Classification of renal illness by the three expert systems											
Parameter		APR			AAA			UPES					
		No	GP	TP	No	GP	TP	No	GP	TP	GP +TP	Pre or post	Unknown
NoD	$n=25$	23	0	2	25	0	0	25	0	0	0	0	0
GD	$n=61$	7	47	7	0	61	0	0	50	1	6[b]	2	2[a]
TD	$n=19$	0	3	16	0	1	18	0	0	16	3[b]	0	0
Correct classification		86/105 (82%)			104/105 (99%)			100/105 (95%)					

[a] Comment of the expert system: ask for a repeat analysis after disappearance of leukocyturia
[b] Combined glomerulo-tubular proteinuria was interpreted as correct

Though slightly less accurate than AAA in attributing the underlying defect to either glomeruli or tubuli, UPES provided additional information on mixed glomerulo-tubular proteinuria in patients with a low GFR. UPES also identified cases of pre-renal and post-renal proteinuria [13]. In addition, it provides information on pre-analytical errors and a warning on implausible results.

Analytical or biological factors may be responsible for the failure of urinary protein expert systems in analysing the types of proteinurias. The lack of accuracy of APR in detecting glomerular proteinuria was found in those children with glomerular diseases having either normal PROT/Crea values or mildly elevated PROT/Crea values in relation to ALB/Crea. Therefore, those patients were either defined by APR as having normal proteinuria, or they were wrongly classified as having tubular proteinuria. In fact, almost all tests for total urinary protein lack accuracy when urinary protein concentrations are less than 200 mg/l [21], because protein staining is not stoichiometric for the different dyes [22, 23]. By contrast, turbidimetric and nephelometric tests for marker proteins show a high grade of reproducibility [8].

The variability of urinary albumin excretion is one of the most important limitations of assessment for clinical purposes [4, 21]. This variability is affected by a large number of factors, such as fever or exercise, which have to be excluded when patients with renal disease are investigated for proteinuria. The significance of urinary albumin excretion as a prognostic marker for renal, metabolic or cardio-vascular diseases in adults has been well described [24]. In children with a defined renal disease, albuminuria may indicate the progression of renal disease. For example, children with vesicoureteric reflux developing proteinuria run a high risk of developing reflux nephropathy, with scarring of the kidney, arterial hypertension and progression of kidney failure [4].

We conclude that the measurement of urinary marker proteins plays a central role in differentiating healthy children from sick children. The algorithm of AAA can serve as a first step in identifying renal patients and separating glomerular proteinuria from tubular proteinuria, whereas UPES may serve as a more complex system to differentiate further the origin of proteinuria. The need for either AAA or UPES may be seen differently by general paediatricians and by paediatric nephrologists (Table 4). General paediatricians may benefit more from the results of UPES, because it helps them to decide upon further diagnostic measures, whereas paediatric nephrologists do not depend on the additional information of UPES. UPES (PROTIS) includes more laboratory tests and the costs are approximately double that of AAA (approximately €35 and €20 in Germany) [25, 26].

In our study we tested the urinary protein expert systems in well-defined glomerular and tubular diseases. It is an open question whether these tests may play a role in characterizing the severity of renal involvement in children with other renal disturbances, such as congenital anomalies of the kidneys and urinary tract. AAA may serve in detecting tubular dysfunction after a variety of drug medication in all age groups, including preterm infants [27]. However, our reference data on urinary ratios for older children cannot be used for preterm, term neonates or older infants. Urinary substance/creatinine ratios are influenced in healthy and sick children by two factors; firstly, the amount of substances being excreted and, secondly, by the amount of creatinine being excreted. Owing to the lower muscle mass, lower amounts of creatinine are secreted in young children and higher amounts in older children [28, 29]. The younger the child, and the less they weigh, the more important is the influence of creatinine on the protein/creatinine ratio. Reference values for neonates can be obtained for healthy new-borns; however, these values may be influenced by differences in post-natal maturation of tubular function. Reference values for "healthy" premature babies are less easy to obtain, because the younger the child, the more the risk of developing extra-renal complications that may affect renal function. Therefore, great caution should be taken, when one is using published data on urinary proteins for reference [27], in concluding the risks of nephrotoxicity of a given drug.

Table 4 Comparison of three expert systems for classification of proteinuria (*UPES* urinary protein expert system, *APR* albumin–protein ratio, *AAA* albumin-alpha-1-microglobulin algorithm)

Parameter	UPES	APR	AAA
Number of correctly identified patients	76/80	63/80	79/80
Number of correctly identified healthy children	25/25	23/25	25/25
Warning on pre-analytical errors	Yes	No	No
Warning on analytical errors	Yes	No	No
Processing of results	Computer program	Pocket calculator	Pocket calculator
Identification of implausible results	Yes	No	No
Approximate costs in Germany	€35	€14	€20
Suitability	All paediatricians	Paediatric nephrologists	Paediatric nephrologists

In conclusion, urinary protein expert systems may be used to distinguish between glomerular and tubular proteinuria in children with acute or chronic renal diseases. The AAA had the highest accuracy when compared with the other two expert systems and the accuracy was not negatively influenced by a decrease in GFR. However, UPES provided additional information on mixed glomerulo-tubular proteinuria in patients with a low GFR. Profiling proteinuria in children with kidney diseases by urinary expert systems allows the rapid and accurate intrarenal location of the underlying abnormal processes, thus allowing the automated differentiation of glomerular and tubular manifestation of renal diseases within 4 hours.

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