A Modern Approach to the Diagnosis of Chronic Tubulointerstitial Nephritis in Children

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Abstract

The present study examined 120 children aged 4 to 15 years diagnosed with chronic tubulointerstitial nephritis (CTIN) to evaluate novel diagnostic approaches. Our findings indicate that metabolic disturbances leading to structural alterations at the nephron level, concomitant changes in renal functional parameters, and instability of tubular cell cytomembranes constitute critical pathophysiological mechanisms underlying interstitial tissue injury, clinical manifestation, and disease progression in CTIN. Comprehensive statistical analysis demonstrated that the diagnostic methodology proposed by the authors represents a highly accurate and reliable approach for CTIN detection, attributable to the integration of contemporary clinical and laboratory investigations. Implementation of this diagnostic strategy facilitates timely disease identification and contributes to a reduction in the duration of hospitalization.

Keywords: protein metabolism; chronic tubulointerstitial nephritis; endogenous intoxication; cytomembrane instability; kidney damage molecules; cystatin C

Introduction

Chronic tubulointerstitial nephritis (CTIN) is a progressive renal pathology characterized by a propensity for chronicity, recurrent exacerbations, and gradual progression, ultimately resulting in nephrosclerosis and the development of chronic kidney disease (CKD). These sequelae frequently lead to significant morbidity, functional disability, and the necessity for advanced therapeutic interventions. Current evidence from the literature has established that a fundamental component of CTIN pathogenesis involves abacterial, non-destructive, non-specific inflammatory alterations within the renal interstitial tissue [2, 6, 21, 24, 43, 51].

In the pathophysiological cascade of chronic CTIN in the pediatric population, injury extends beyond the tubular apparatus to encompass the entire vascular network of the renal interstitium. This widespread endothelial and parenchymal damage initiates an anti-destructive reparative response in the cortical layer, which progressively evolves into interstitial fibrosis with subsequent involvement of the entire nephron in the inflammatory process [36, 43, 48, 51]. Epidemiological observations from leading nephrology centers indicate that disease relapse is detected in approximately 30% of patients, with 50% of these individuals experiencing their first recurrence within three months following the initial episode [7, 26, 34, 54, 55].

Contemporary research conducted over recent decades has substantiated the pivotal role of kidney damage molecules (KDMs) in the initiation and perpetuation of tubulointerstitial injury. These biomolecules participate simultaneously in multiple pathological processes, including the formation of endotoxins and their accumulation within the internal homeostatic environment of the organism [14, 25, 33, 44, 53].

Several investigators have demonstrated that endotoxicosis progresses as a cascade phenomenon involving sequential activation of multiple inflammatory and metabolic pathways. Despite substantial advances achieved in the therapeutic management and preventive strategies for CTIN in children, the existing literature lacks a standardized, evidence-based algorithm for the comprehensive diagnosis of this pathological entity. Furthermore, comparative clinical and laboratory diagnostic criteria for the principal subtypes of tubulointerstitial nephritis remain inadequately developed. Notably, there exists a paucity of data regarding the pathogenetic interrelationship between tubular functional parameters and indicators of protein metabolism in both serum and urine specimens among pediatric patients with various CTIN phenotypes.

The primary objective of this investigation was to develop and validate an integrated diagnostic methodology for chronic tubulointerstitial nephritis in children, incorporating the pathogenetic significance of endogenous intoxication markers and tubular functional abnormalities into a comprehensive evaluative framework.

Materials and Methods

This investigation presents the findings from a prospective observational study of 120 pediatric patients diagnosed with CTIN in the active inflammatory phase, who received inpatient care at the Children's Nephrology Department of the Samarkand Regional Multidisciplinary Scientific Center during the period from 2019 to 2021. The study cohort comprised 71 males (59.2%) and 49 females (40.8%), with a mean age of 9.4 +/- 3.2 years. Additionally, 30 healthy children undergoing routine preventive medical examinations were enrolled as a control group.

All clinical investigations were conducted in strict adherence to the fundamental ethical principles governing human subjects research, including: recognition of the intrinsic value and dignity of human life, rigorous observance of the principle of non-maleficence (primum non nocere), obtainment of informed voluntary assent from all study participants and their legal guardians, complete disclosure of study procedures and potential risks, and assurance of confidentiality regarding all personal and medical information. The study protocol was conducted in accordance with the Convention on the Rights of the Child adopted by United Nations General Assembly Resolution 44/25 on 20 November 1989.

The biological specimens analyzed in this study included venous whole blood, serum, and urine samples, which were subjected to comprehensive clinical, biochemical, and instrumental evaluation. The following methodologies were employed: general clinical assessment, biochemical analysis, clinical-instrumental examination, and statistical analysis.

The following parameters of protein metabolism and renal function were quantified in all study participants: total serum protein concentration; serum albumin concentration; effective albumin concentration; serum protein fraction analysis; albumin binding capacity; altered albumin concentration; toxicity index; kidney damage molecule (KDM) concentrations in urine and serum; globulin fractions; serum cystatin C concentration; functional albumin status indicators; blood urea nitrogen level; and serum creatinine concentration.

Statistical Analysis

The laboratory data obtained were processed using parametric statistical methods and are presented in the International System of Units (SI) [12]. The statistical significance of intergroup differences was evaluated using Student-Fisher parametric tests, with calculation of arithmetic means (M), standard deviations (SD), and standard errors of the mean (m). Compliance with normal distribution within each sample was verified using the Shapiro-Wilk test. The probability (p) of type I error was determined from standard Student t-distribution tables. A p-value less than 0.05 was considered

statistically significant. All computations were performed using StatPlus version 7 software (AnalystSoft Inc., USA).

Results

Analysis of sex distribution within the CTIN patient cohort revealed no statistically significant predominance of either sex (Figure 1).

Figure 1. Distribution of the studied children by sex.

Comprehensive analysis of the CTIN patient population revealed a notably elevated morbidity prevalence among primary school-aged children (7-12 years), accounting for 55% (n=66) of the total cohort. An additional high-incidence group was identified among children aged 10-14 years, comprising 43.2% of all patients.

Among all CTIN patients, the glomerular filtration rate (GFR) calculated using the cystatin C-based formula demonstrated numerical differences both before and after therapeutic intervention; however, these differences did not achieve statistical significance ($p>0.1$). Glomerular function parameters in CTIN patients indicated preserved glomerular integrity without evidence of filtration impairment. Bacteriuria was not detected in any children with CTIN. Microhematuria (5-6 erythrocytes per high-power field) was identified in 90% of patients, whereas macrohematuria was observed in 10% of the examined children.

The active phase of CTIN was characterized by a reduction in effective albumin concentration to 30.04 +/- 0.26 g/L. This decrease in effective albumin concentration was accompanied by a concomitant reduction in albumin binding capacity to 64.8 +/- 0.65%.

A statistically significant positive correlation was established between the magnitude of kidney damage molecule excretion and the activity of the chronic inflammatory process. This association was characterized by the finding that increased KDM excretion in CTIN patients was accompanied by leukocyturia in 82% of cases: specifically, 87% of patients exhibited proteinuria, while 93% presented with hematuria.

A moderately strong positive correlation was additionally identified between the degree of daily proteinuria and urinary kidney damage molecule concentrations, indicating that higher levels of proteinuria corresponded to more active pathological processes and elevated urinary KDM levels ($r=0.50$; $r=0.51$). A strong positive correlation was observed between leukocyturia and urinary KDM concentrations ($r=0.70$; $r=0.72$).

Thus, increased inflammatory activity within the renal parenchyma was associated with elevated urinary KDM concentrations. A moderate inverse correlation was documented between glomerular filtration rate and urinary KDM levels ($r=-0.50$; $r=-0.51$).

Figure 2. Protein metabolism indicators in children with CTIN: albumin binding capacity (ABC), effective albumin concentration (EAC), toxicity index (TI), and coefficient of albumin utilization (CAU).

The observed increase in effective albumin concentration following treatment is presumably attributable to the antioxidant and nephroprotective properties of the therapeutic regimen employed. Post-treatment EAC levels were determined to be 30.74 +/- 0.58 g/L ($p>0.001$).

The albumin binding capacity (ABC) and toxicity index (TI) in CTIN patients were measured at 72.2 +/- 0.6% and 0.36 +/- 0.01 conventional units, respectively ($p=0.05$). In healthy control subjects, these parameters were 93 +/- 0.9% and 0.12 +/- 0.01 conventional units, respectively.

In the assessment of renal functional status based on the comparative dynamics of creatinine and cystatin C levels, cystatin C was found to be a demonstrably more reliable biomarker. Reductions in GFR as determined by cystatin C were detected earlier than those identified by creatinine measurement ($p=0.02$).

Table 1

Dynamics of Renal Function Parameters in Patients with Chronic Tubulointerstitial Nephritis Following Therapy (M +/- m)

Parameters	Healthy Subjects (n=30)	CTIN Patients (n=120)
Creatinine (micromol/L)	85.4 +/- 1.41	65.5 +/- 0.63 ($p=0.001$)
GFR (creatinine) (mL/min/1.73 m^2)	98.6 +/- 7.8	72.0 +/- 0.25 ($p=0.001$)

Parameters	Healthy Subjects (n=30)	CTIN Patients (n=120)
Cystatin C (mg/L)	0.62 +/- 0.1	1.0 +/- 0.2 (p=0.05)
GFR (cystatin C) (mL/min/1.73 m²)	93.5 +/- 6.5	67.4 +/- 10.3 (p=0.001)
Daily diuresis (L/day)	1.7 +/- 0.036	1.06 +/- 0.015 (p=0.05)
Minute diuresis (mL/min)	1.2 +/- 0.037	0.61 +/- 0.010 (p=0.05)
Oxaluria (mg/day)	25.0 +/- 2.4	46.8 +/- 1.14 (p=0.001)
Urinary ammonia (mmol/day)	46.8 +/- 1.2	30.3 +/- 0.55 (p=0.001)
Titratable urine acidity (mmol/day)	51.0 +/- 2.8	23.8 +/- 0.48 (p=0.001)

Note: p represents the statistical significance of differences between healthy controls and children with CTIN.

Discussion

Comprehensive analysis of the study findings demonstrates that the diagnostic methodology proposed by the authors represents the most accurate and reliable approach for CTIN diagnosis, attributable to the incorporation of contemporary clinical and laboratory investigations. This integrated diagnostic framework facilitates high-quality disease detection and contributes meaningfully to a reduction in the duration of hospitalization.

These findings underscore the imperative need for the development of effective therapeutic interventions for CTIN in the pediatric population, with the objective of restoring metabolic homeostasis, preserving residual renal function, mitigating endogenous intoxication, resolving the aseptic inflammatory focus within renal tissue, and preventing recurrent disease exacerbations.

Conclusion

In pediatric patients with CTIN, alterations in protein metabolism parameters were observed at earlier stages of disease evolution, preceding the emergence of characteristic laboratory abnormalities in standard blood and urine analyses. Specifically, reductions in albumin binding capacity, effective albumin concentration, and total serum albumin, coupled with sustained elevations in the toxicity index and coefficient of albumin utilization in plasma, as well as increased kidney damage molecule excretion in urine, were identified as early indicators of disease activity. These findings underscore the clinical significance of this diagnostic panel for the detection of aseptic inflammation within renal tissue.

The elevated urinary KDM levels observed in this study were positively correlated with the intensity of the aseptic inflammatory process within renal parenchyma, suggesting a predominant tubular pattern of renal dysfunction in CTIN patients. A significant positive correlation was established between endogenous intoxication markers and parameters of renal functional status, specifically a strong direct correlation between urinary KDM excretion and both proteinuria and leukocyturia. Additionally, a strong inverse correlation was documented between GFR and urinary KDM concentrations, further supporting the utility of these biomarkers in disease monitoring and prognostic assessment.

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