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Clinicopathological Findings in Pediatric Tubulointerstitial Nephritis: Iranian Experience

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Introduction: Tubulointerstitial disorders are characterized by diseases that affect the vascular and interstitial compartments of the kidney with relative sparing of the glomeruli. They might be either acute or chronic. Acute tubulointerstitial nephritis (TIN) is associated with acute renal failure due to either acute infection of the kidneys or reaction to medication. Chronicinterstitial nephritis is characterized by many syndromes of renal tubular dysfunction that may be primary or secondary due to renal tubular damage from a wide variety of causes. The aim of this study was to evaluate the pathologic characteristics of acute and chronic TIN and their probable causes.
Materials and Methods: All native kidney biopsy specimens with a diagnosis of tubulointerstitial nephritis admitted to Ali-Asghar Hospital, a pediatric referral center in Tehran, from 1983 to 2013 were retrospectively re-evaluated. The demographic data of the patients were collected and pathologic findings were reviewed.
Results: Forty-four patients, 18 males and 26 females with a mean age of 8.8 years (SD=4), were enrolled in this study. Thirty-seven (84%) patients had chronic and 7 (16%) had acute TIN. The disease was primary in 32 (72%) patients with a diagnosis of familial nephronophthisis and medullary cystic disease and 12 (28%) had other diseases. Kidney biopsy showed similar pathologic findings including periglomerular fibrosis (72%), different scores of interstitial fibrosis/tubular atrophy (91%), infiltration of inflammatory cells, and segmental and global glomerular sclerosis (89%).
Conclusions: Acute and chronic tubulointerstitial nephritis with different etiologies has similar pathologic findings. The patients mostly present in the late stages of the disease; therefore, determining the etiology is impossible. Many cases are congenital.

Keywords: Nephritis, Interstitial, Child, Renal Insufficiency.

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Running Title: Clinicopathological Findings in Pediatric TIN

Introduction

Tubulointerstitial nephritis (TIN) is a rare event in children. It usually presents with nonspecific symptoms, so the diagnosis may be delayed [1-3]. The most common underlying causes are drugs and infection, but no definite etiology is identified in some cases. Pathologic findings may vary in different cases but common findings are interstitial inflammation, edema, and tubulitis. In fact, tubulointerstitial disorders are characterized by diseases that affect the vascular and interstitial compartments of the kidney with sparing of the

glomeruli [4-6]. The aim of this study was to identify the clinicopathologic findings of tubulointerstitial nephritis in children over a period of 30 years in Iranian children.

Materials and Methods

All native kidney biopsy specimens evaluated in Ali-Asghar Children's Hospital, A pediatric referral center in Tehran, from 1983 to 2013 with a diagnosis of tubulointerstitial nephritis were retrospectively analyzed. The demographic data of the patients were collected and pathologic findings were reviewed. A pathologic diagnosis of TIN was made by the presence of prominent interstitial inflammation in the non fibrotic cortex and tubulitis using light microscopy and immunofluorescence. For light microscopy, all cases were stained with H&E, periodic Acid-Schiff, Masson Trichrome and Jones methenamine silver. Tubular atrophy and interstitial inflammation were scored from 0 to 3+. The patients were divided into three age groups to evaluate whether the correlation of clinical and pathologic findings were similar in different age groups. Data was analyzed using SPSS version 16. P values less than 0.05 were considered significant.

Results

Between 1983 and 2013, a total of 44 patients with a biopsy proven diagnosis of TIN were enrolled in the study. Of 44 children, 26 were male and 18 were female with a mean age of 8.8 years (ranging from 9 months to 16 years). The majority of the patients (n=37, 84%) had chronic and 16% had acute tubulointerstitial nephritis.

Clinical presentation

In evaluating the etiology, most of them (n=32, 72%) were primary with a diagnosis of familial nephronophthisis and 28% were secondary to other disease such as Alport syndrome, glomerulonephritis, hyperoxaluria, congenital nephrotic syndrome, and amyloidosis (Table 1). Secondary forms were seen in seven patients due to secondary FSGS presenting with nephrotic syndrome and in 11 patients due to chronic pyelonephritis or reflux disease. The dominant clinical presentation was chronic renal failure (27 out of 44) but it was more prevalent in children aged 5-10 years. Common manifestations were failure to thrive, elevated serum creatinine, and anemia in children.

Nephrotic syndrome and acute renal failure were the least prevalent manifestations with no significant difference in prevalence at different ages. The number of children with nephrotic syndromes was also similar in different groups (3 patients in each group).

Table 1. Distribution of different etiologies in secondary TIN

	Number	Frequency (Percent)
Alport syndrome	2	17
Glomerulonephritis	6	50
Hyperoxaluria	1	8
CNS	2	17
Amyloidosis	1	8
Total	12	100

Pathologic findings

In reviewing microscopic slides, all shared similar findings including periglomerular fibrosis (72%), interstitial fibrosis/tubular atrophy with different scores (90%), acute or chronic inflammatory cells infiltrates (100%), and glomerular sclerosis (segmental & global) 89% (Table 2).

Table 2. Pathologic findings in chronic tubulointerstitial nephritis

	Number	Frequency (Percent)
Periglomerular fibrosis	32	72
Interstitial fibrosis/tubular atrophy	40	90
Inflammation	44	100
Glomerular sclerosis	39	89

In acute disease, tubulitis was the most common pathologic finding (Figure 1 and 2). In pathologic finding, inflammation and periglomerular fibrosis showed statistically significant correlation with atrophy (p-value= 0.01 and 0.001 respectively),

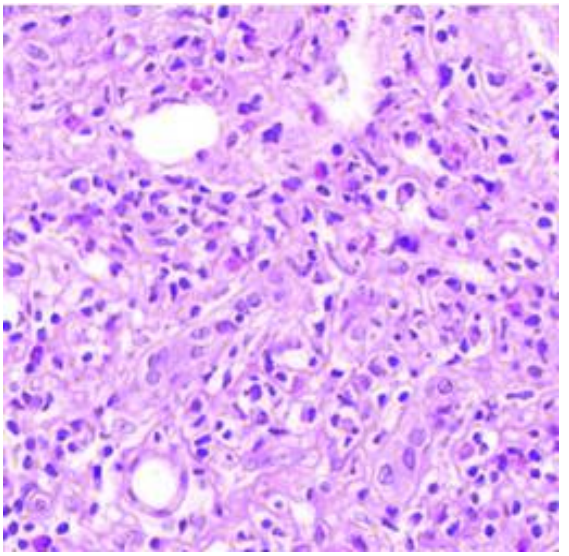

Figure 1. Acute tubulointerstitial nephritis with foci of tubulitis (H&E, x40)

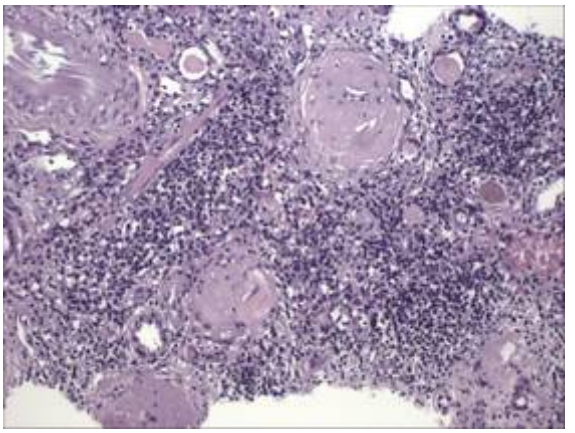

Figure 2. Chronic tubulointerstitial nephritis with global sclerosis of glomeruli and extensive loss of parenchyma (H&E, x40)

and inflammation showed significant correlation with periglomerular fibrosis (p-value=0.001) too. However, atrophy and inflammation showed no significant correlation with global sclerosis, and atrophy had no correlation with types of inflammatory cells (p- value>0.05).

Discussion

Tubulointerstitial nephritis is defined by the presence of edema and inflammatory cells in the interstitium, which are both usually associated with a decline in the kidney function. It may be acute or chronic. Acute tubulointerstitial nephritis (AIN) is usually associated with acute renal failure which occurs in a period of days to several weeks either due to infection or a hypersensitivity reaction to medication [7.8]. Chronic tubulointerstitial nephritis (CIN) develops over months and years because of many underlying etiologies (e.g. toxins, hematologic or neoplastic diseases, immune mediated diseases, metabolic or genetic diseases, etc. [4, 7, 8]. History and physical examination of older patients may be a clue to diagnosis (e.g. fever, rash, and eosinophiluria but TIN has vague clinical symptoms mostly in children, so considering it as a differential diagnosis in children with rapid onset kidney function failure is logical. Although NSAIDS are more consumed in the elderly because of the higher incidence of arthritis in this population, children with juvenile arthritis may also suffer from its usage and present with nephrotic syndrome [9-11].

In reviewing the etiology, lead nephropathy in children may be presented with encephalopathy and acute renal failure. In addition obstructive uropathy due to congenital diseases is a very important condition that should guide us to a probable AIN in children with this history [11-13]. Contrary to AIN, chronic interstitial nephritis is an insidious disease and may be a final response. It is often diagnosed incidentally in kidney biopsy evaluating for decline of kidney function [14,15].

In 2013, Goicoechea et al [4] investigated the prevalence of AIN and reported that nearly all cases were due to antibiotics and drugs. In 2014, Murithi et al [5] studied 133 patients to evaluate the causes of AIN and showed that drugs and autoimmune disease were the most common etiologies followed by infections. In this study, we evaluated the clinicopathologic findings of TIN in children, which has not been evaluated so far. As predicted, the majority of the patients were diagnosed with CIN because AIN has an abrupt onset and a through history and physical examination may result in a correct diagnosis leading to treatment; therefore, the need for kidney biopsy is decreased for evaluating the case. In reviewing the clinical presentation in three consecutive decades, the prevalence of chronic renal failure did not change very much but the number of patients presenting with acute renal failure and nephrotic syndrome increased, which may be due to rapid diagnosis and better access to the necessary equipment and pathology ward. In biopsy proven CIN patients, similar pathologic findings, e.g. peri glomerular fibrosis, interstitial and tubular atrophy, infiltration of inflammatory cells and glomerular sclerosis are seen. The most etiologies which play a crucial role in children are

primary familial nephronophthisis and secondary changes due to metabolic and congenital nephrotic syndrome which is not important in older patients. Acute and chronic tubulointerstitial nephritis with different etiologies has similar pathologic findings. The patients mostly present in the late stages of the disease, therefore differentiating the etiology is impossible. Many cases are congenital.

Conclusions

As TIN in children has a better prognosis the chances of progression to ESRD are very low upon early treatment, it should be considered as a differential diagnosis in children with a decline in the kidney function despite its nonspecific symptoms.

Conflict of Interest

The authors declare that they have no conflict of interest.

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