A renal biopsy-based clinicopathological study of primary tubulointerstitial nephritis in children

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ABSTRACT

Background: Inflammation of the tubular and interstitial compartment without involving the glomeruli and vessels is called as primary tubulointerstitial nephritis (TIN), which may be due to varied etiologies. This is relatively uncommon in children as compared to primary glomerular disorders. Infections and drugs are the most common causes of primary TIN worldwide. **Objectives:** The objectives of the study were to assess primary TIN in pediatric patients using findings from renal biopsies at a tertiary care center of Western India. **Materials and Methods:** All biopsy-proven cases of primary TIN in pediatric patients over a period of 10 years were included in the study. All cases with glomerular or vascular diseases, or where data were inadequate were excluded from the study. The cases were reviewed in detail for epidemiological data, clinical presentation, etiology, and histomorphological features. Depending on their clinical and morphological features, the cases were categorized into acute, chronic, and granulomatous TIN. **Results:** A total of 30 cases of primary TIN were assessed with a mean age of 12.4 years and range of 6–18 years. Pedal edema and facial puffiness were the most common symptoms followed by oliguria. The common causes of TIN were drugs, namely antibiotics and non-steroidal anti-inflammatory drugs and infections. Acute TIN was more common than chronic TIN. **Conclusion:** Primary TIN is an uncommon renal disease in pediatric patients with varied presentations and etiologies. However, early diagnosis by renal biopsy, detailed history, and withdrawal of the offending agent along with prompt treatment helps in recovery and avoids chronic renal damage.

Key words: *Pediatric, Primary tubulointerstitial nephritis, Renal biopsy*

The term "tubulointerstitial nephritis" (TIN) connotes to inflammatory changes seen predominantly in the interstitium and tubules. In 1869, Biermer first described interstitial inflammation and later in 1898, Councilman reported interstitial edema and inflammation in patients with scarlet fever and diphtheria and termed it as interstitial nephritis. TIN may be primary or secondary. In primary TIN, inflammation is limited to the tubulointerstitial compartment without involving the glomeruli and vessels whereas in secondary TIN, there is tubulointerstitial inflammation along with the glomeruli and/or vessels [1]. It is difficult to estimate the exact prevalence of primary TIN, as all patients may not undergo kidney biopsy. Primary TIN accounts for 3–7% of kidney biopsies performed in children and 27% in adults for acute kidney injury (AKI) [2-5].

There has been a changing pattern observed in the etiologies of primary TIN. Previously, infection was considered as the most common cause of primary TIN; however, later drugs became the more common cause. Certain antibiotics and more recently, non-steroidal anti-inflammatory drugs (NSAIDs) have emerged as the leading cause of drug-induced TIN in adults [3]. There is a paucity of literature on primary TIN in Indian children. Hence, this study was done to study the primary TIN in children to assess the different etiological agents and histomorphological features with clinicopathological correlation in renal biopsies.

MATERIALS AND METHODS

This is a retrospective observational clinicopathological study of kidney biopsies of primary TIN in pediatric patients in Western India. The data were collected from the records in the department of pathology of a tertiary care hospital over a period of 10 years. Secondary TIN, underlying glomerular disease, inherited renal disease, and renal transplants were excluded from the analysis. Clinical findings, laboratory investigations, treatment, and follow-up of patients were obtained from case records. Histomorphological features of tubular changes such as tubular epithelial fraying, denudation, tubular atrophy, necrosis, and interstitial changes such as edema, inflammation, nature of the inflammatory response (acute or chronic), presence of granuloma, and fibrosis were noted. These cases were classified as acute, chronic, and granulomatous TIN depending on clinical presentation and histomorphological features.

RESULTS

There were total of 30 cases of primary TIN during a 10-year period including 18 females and 12 males with a mean of 12.4 years and range from 6 to 18 years. The most common clinical presentation was pedal edema and facial puffiness seen in 80% cases followed by decreased urine output in 66.6% cases (Table 1). Azotemia was seen in almost all cases. Proteinuria was seen in 3 cases, including 2 cases of nephrotic range proteinuria. The majority of these patients presented with a short duration of symptoms; approximately 80% of these were symptomatic for only 1–2 weeks.

The most common cause of primary TIN was drugs followed by infections. Among the drugs, NSAIDs accounted for 67% of cases followed by antibiotics in 33%. Antibiotics included beta-lactams, macrolides, cephalosporins, and rifampicin. The duration, for which all these drugs were taken, was variable, ranging from 5 days to 2 weeks. There were 6 patients with signs and symptoms of infection but without any history of drug intake (Table 2).

All cases were classified as acute, chronic, and granulomatous TIN based on histomorphological features. Acute TIN was most commonly seen in 24 (80%) patients followed by chronic TIN in 6 (16.6%) cases. There was a single case of granulomatous TIN (Table 3).

Leukocytic infiltrate of lymphocytes, plasma cells, and neutrophils was the common findings seen in almost 78% patients. Interstitial edema and neutrophils were predominantly seen in acute TIN. Lymphocytes and plasma cells along with fibrosis were predominant in chronic TIN. Prominent tubular features included tubular damage, atrophy, and necrosis. Occasionally, tubulitis was also seen where inflammatory cells invaded the tubular epithelium. It is stated that eosinophils are a valuable finding in drug-induced TIN, particularly with NSAIDs, but only 3 cases showed eosinophils. Biopsy in 1 case showed granulomatous inflammation without caseation necrosis; however, urinary polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* was positive in that patient, suggesting renal tuberculous.

Table 1: Clinical presentation in drug-induced tubulointerstitial nephritis

Clinical presentation	Number of cases
Pedal edema, puffiness of face	24
Decreased urine output	20
Fever	12
Dysuria	5
Others	6

DISCUSSION

The frequency with which primary TIN affects the kidney is difficult to determine. Retrospective studies of renal biopsies have revealed that 8–22% of patients with kidney injury have primary TIN [3]. In a study by Wilson *et al*., 11% of biopsies of patients with AKI revealed acute TIN [5]. In our study, the age range of patients was from 6 to 18 years (mean – 12.6 years). Most of these patients (60%) had drug-induced TIN. This may be attributed to the common age-related problems such as repeated respiratory and gastrointestinal infections for which antibiotics and NSAIDs are commonly given and are over the counter drugs.

The most common presentation in our study was pedal edema and/or facial puffiness (80%) followed by decreased urinary output (66.6%). Oliguria is considered as one of the common indications for renal biopsies. Drug-induced TIN shows classic triad of low-grade fever (70–100%), fleeting maculopapular skin rash (30–50%), and mild arthralgia (15–20%). The full triad was noted in one-third of the cases of methicillin-induced acute TIN, but only in 5% of the cases of acute TIN in general.

In our study, skin rash was not present in any case, while 17 (31.4%) of 30 cases had a history of fever. We noted proteinuria in 13.3% cases, of which, nephrotic range proteinuria was seen in 6.7% cases. Proteinuria is generally mild and rarely exceeds 2 g/day except in NSAIDs induced TIN which shows nephrotic range proteinuria in 10–12% cases. As studied by Palmer and Henrich, NSAIDs cause minimal change disease; hence, nephrotic range proteinuria is seen in these cases [6,7].

Eosinophiluria is also the characteristic feature seen in drug-induced TIN with 40%–60% sensitivity and 38% positive predictive value as reported by Ruffing *et al*. [8]. In the present study, eosinophiluria was detected in 2 cases. The most common histomorphological form of TIN in our study was acute (74%) followed by chronic (16.8%) and granulomatous TIN (9.2%). The studies by Schwarz *et al*. and Clarkson *et al*. included a total of 124 patients with AIN and found NSAIDs to be the most common culprit class of drugs, whereas Muriithi *et al*. and González *et al*. found antibiotics to be the most common cause [2,9-11]. Other drugs responsible for causing primary TIN were rifampicin, proton pump inhibitors, lithium, and diphenylhydantoin.

In our study, 12 patients gave a history of consuming NSAIDs thus making it the most common cause among drug-induced TIN. There were 8 females taking NSAIDs. These patients were on treatment for joint pains due to osteoarthritis and rheumatoid arthritis, backache, and generalized body ache for a few days to 4 years. A variety of NSAIDs such as salicylates, aspirin,

Table 2: Etiological factors in TIN

Etiological factor	Number	Acute primary TIN	Chronic primary TIN	Granulomatous primary TIN
Drugs (non-steroidal anti-inflammatory drugs and antibiotics)	18	14	4	-
Infections	6	4	1	1
Idiopathic	6	5	1	-

TIN: Tubulointerstitial nephritis

Table 3: Histopathological features in tubulointerstitial nephritis

Histological features	Number of cases
Tubular features	
Tubular damage	24
Tubular atrophy	4
Tubular necrosis	10
Tubulitis	2
Interstitial features	
Leukocytic infiltrate	24
Interstitial edema	24
Interstitial fibrosis	4
Infiltrate showing eosinophils	2
Granuloma	1

diclofenac, indomethacin, ibuprofen, piroxicam, nimesulide, and COX-2 inhibitors is known to be associated with renal damage [6,7]. The histological changes in NSAIDs induced TIN were both acute and chronic. We noted 8 cases of acute TIN and 4 cases of chronic TIN.

It is postulated that NSAIDs induce TIN by inhibiting the synthesis of vasodilatory prostaglandins PGI2 and PGE2 resulting in severe renal vasoconstriction and consequent ischemia. Acute interstitial nephritis may be related to delayed hypersensitive response to NSAIDs. Granulomatous response in NSAIDs induced TIN may be secondary to cell-mediated immune response [6,7].

NSAIDs intake may also result in severe and nephrotic range proteinuria as was noted in 4 (25%) of the 12 cases of NSAIDs induced TIN, where 3 showed acute changes and 1 was chronic TIN. In these cases, glomeruli were normal and showed no pathology on light microscopy but diffuse foot process flattening was observed on electron microscopy. The incidence of NSAIDs induced nephrotic range proteinuria in literature is 10–12% and pathogenic mechanisms include release of lymphokines and cytokines from interstitial inflammatory cells resulting in increased glomerular permeability [6,7].

Interstitial eosinophilic infiltrate, a characteristic histological feature of NSAID-induced TIN, was noted in only 4 cases. This was in accordance with the study by Bender *et al*. [12]. In the Indian adult population, some cases of TIN were also reported due to ayurvedic and indigenous/herbal drugs; however, those are not seen in pediatric patients. These drugs may contain nephrotoxic substances like heavy metals and are commonly used for the treatment of chronic diseases which are unresponsive to routine treatment [13].

In the present study, 6 cases of antibiotic associated TIN were observed. These patients had been taking antibiotics such as ampicillin, gentamycin, macrolides, and cephalosporins for the duration ranging from 5 to 10 days. This is due to an idiosyncratic hypersensitivity reaction, with local activation of drug-specific T cells and release of cytokines as studied by Nast [14].

Infectious TIN presents predominantly as acute TIN due to acute pyelonephritis which may be recognized as localized TIN. All these cases are due to some form of congenital obstructive uropathy. Gram-negative organisms (*Escherichia coli* and *Klebsiella*) were identified in these cases. A single case of chronic TIN was also noted which was not diagnosed and treated at that time. Many infectious agents including viral (cytomegalovirus, hepatitis, HIV, and Epstein-Barr virus), bacterial (*Streptococci, Staphylococci, Salmonella*, and *Brucella*), fungal (*Histoplasmosis*), and parasitic (*Leishmania* and *Toxoplasma*) are known to cause TIN. Rare forms like leptospira-induced TIN have also been reported [15-17].

Granulomatous TIN is noted in tuberculosis, Wegener's granulomatosis, and sarcoidosis and is also associated with some drugs. Hence, special stains for organisms and study of multiple biopsy levels for granulomas around blood vessels and tubules (as seen in Wegener's) are essential. In correlation with this clinical history is essential before the diagnosis of drug-induced TIN as studied by Viero and Cavallo and Shah *et al*. [18,19].

TIN with uveitis (TINU syndrome), sarcoidosis, inflammatory bowel disease, etc., were not seen in the present study. No identifiable cause or predisposing factor was found in 6 cases (20%). This may be due to strict criteria of 1 week for history of drug intake or proven infection followed in this study. This is also significantly high as compared to other studies where definitive cause was established in almost 90% cases. Patient referral, willingness for biopsy, and early recovery after withdrawal of drug or treatment of infection may be some speculated reasons for this difference.

One of the limitations of this study is that we have selected only biopsy-proven primary TIN in this retrospective study. Renal biopsy is commonly done in patients with more severe and long duration of AKI, and as not all AKI patients undergo kidney biopsy, we could not determine the exact prevalence of primary TIN.

CONCLUSION

In the pediatric age group, acute TIN is one of the common causes of acute renal failure resulting from drug-induced hypersensitivity reaction. NSAIDs are a more common cause of TIN in the pediatric population in India as compared to antibiotics in the Western world. Early biopsy with early withdrawal of potential offending agents and prompt treatment will help in renal recovery.

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