


Biopsy-proven paediatric tubulointerstitial nephritis

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Abstract

Background Tubulointerstitial nephritis (TIN) is an uncommon condition in which the aetiology, treatment and outcome is not well defined. We describe a large series of children with biopsy-proven TIN.

Methods All children with biopsy-proven TIN presenting to our institution during a 23-year period were retrospectively reviewed for aetiology, symptoms, treatment, and long-term outcome.

Results A total of 27 children (16 girls) were described. Median age was 12 years (range 8 months to 15 years). A potentially adverse drug reaction was found in 12 (44 %) and infection in 8 (30 %). In 13 (48 %) no initiating factor was identified. All but 1 patient were treated with corticosteroids owing to worsening kidney function and 4 patients with other immunosuppressive agents. Fifteen children (56 %) had an estimated glomerular filtration rate (eGFR) of less than 80 ml/min/1.73 m² at last follow-up. Fifteen of the 23 children investigated (65 %) had coexistent uveitis.

Conclusion This series represents a subset of paediatric TIN patients in whom there was a clinical indication for a renal biopsy, hence presenting with more severe disease than previously reported. This group were more likely to have no identifiable underlying cause and an increased requirement for corticosteroid treatment. Furthermore, more than half of the cases developed chronic kidney disease (CKD) with impaired kidney function.

Keywords Tubulointerstitial nephritis · TIN · Uveitis · Prednisolone · Outcome

Introduction

Acute tubulointerstitial nephritis (TIN) was first described by Biemer in 1860, and defined as a disease entity by Councilman in 1898, noting histopathological changes in autopsy specimens of patients with diphtheria and scarlet fever (described in Kodner and Kudrimoti and Schwarz et al. [1, 2]).

Tubulointerstitial nephritis is a significant cause of acute kidney injury (AKI) among children and adults that accounts for 5–15 % of cases of acute kidney injury (AKI), in some patients leading to chronic kidney disease (CKD) [3]. Approximately 1 % of renal biopsies performed for the evaluation of haematuria or proteinuria show TIN and it was reported in 3–7 % of biopsies from children with AKI [4, 5].

One major cause of acute TIN is as a complication of drug treatment, often antibiotics, mainly β -lactam and rifampicin, but also analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics [2]. Acute TIN has also been described in association with infections, autoimmune or collagen vascular disorders and systemic diseases. It may present as granulomatous inflammation in sarcoidosis or as part of the syndrome of TIN and uveitis (TINU) [6, 7].

The original description of TIN included the triad of fever, eosinophilia and a rash. Recent studies suggest that this triad might be present in only around 30 % of cases [8]. Acute TIN is often associated with non-specific signs and symptoms, such as low-grade fever, maculopapular rash, mild arthralgia, anorexia, nausea, vomiting, abdominal or loin pain and malaise [1, 5].

Information on aetiology, clinical presentation and outcome of acute TIN in the paediatric setting is limited. The

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aim of this study is therefore to describe the clinical features and outcomes of children with biopsy-proven TIN.

Materials and methods

We performed a retrospective review of the case notes of all children younger than 18 years, with a proven histological diagnosis of TIN at Great Ormond Street Hospital GOSH for Children, London, between January 1990 and November 2012. Patients with a kidney transplant, a defined underlying glomerular disease or inherited renal disease were excluded.

Data on previous infections and medications, clinical signs and symptoms, ultrasound features and abnormalities on urinalysis and tubular function tests at presentation were collected. Maximum serum creatinine and estimated glomerular filtration rate (eGFR) at the time of presentation and at the latest clinical control, treatment received and concurrence of uveitis were also recorded. The eGFR was determined according to the Schwartz formula, using a k value of 33 [9].

The indication for kidney biopsy was impaired kidney function that did not improve on stopping the suspected causative drug. The database and descriptive statistics were created in Microsoft Excel for Mac 2011. Linear regression was performed on Infostat 2007 and Wilcoxon signed rank test was performed on Prism 6. The study was registered with the clinical governance and safety team at Great Ormond Street Hospital for Children.

Results

There were 27 children with biopsy-proven TIN during the 23-year study period including 11 boys and 16 girls, aged between 8 months and 15 years (median 12 years; Table 1).

Potential causative factors

Twenty-five of the children (93 %) had an unremarkable previous medical history. One patient, who had been previously diagnosed with an undefined immunodeficiency, developed bronchiectasis (patient number 7, Table 1). Another patient, whose mother had been diagnosed with sarcoidosis during childhood, had been followed for erythema nodosum and chronic uveitis during infancy and had been later diagnosed with sarcoidosis on renal biopsy (patient number 20, Table 1).

Twelve (44 %) of the children had recently received one or more medications, including non-steroidal anti-inflammatory drugs, aspirin, paracetamol, antibiotics, H2 blockers and proton pump inhibitors. Of those patients, 1 was receiving chronic omeprazole and antibiotic prophylaxis because of immunodeficiency and bronchiectasis (patient number 7). The other 11 children had 1–12 weeks between the drug exposure and the

development of symptoms. Eight children had a previous infection: 6 (24 %) had a respiratory tract infection, 1 had diarrhoea and another had endocarditis caused by *Staphylococcus aureus*. This latter child was treated for 6 weeks with vancomycin. Thus, in 13 children (48 %) no potential causative factor could be identified.

Clinical presentation

The duration of the symptoms before the presentation at GOSH was a median of 5 (range 0.3–12) weeks. Twenty-six patients showed non-specific symptoms, the most common being anorexia, malaise and vomiting (Table 2). The boy with uveitis and a family history of sarcoidosis was the only child who was asymptomatic at the time of diagnosis.

Proteinuria was found in 96 % of the children. Only patient number 7 developed a nephrotic range of 698 mg/mmol without other features of nephrotic syndrome. The other children had a median urine albumin/creatinine ratio of 16.5 (range 4.4–43.7) mg/mmol. Pyuria and microscopic haematuria were present in 21 out of 27 (each) patients (78 %) and glycosuria was found in 17 out of 21 of the children tested (81 %). Urine potassium wasting was present in 7 out of 10 children, phosphorus tubular reabsorption was less than 85 % in 8 out of the 13 evaluated patients and metabolic acidosis was present in 7 out of 26 of the children tested. Low molecular weight urine proteins, the urinary N-Acetyl-beta-D-glucosaminidase:creatinine ratio (U-NAG/Cr) and retinol binding protein:creatinine ratio (U-RBP/Cr), were abnormally high in 17 of the 18 children tested. Median U-NAG/Cr was 189 (range 7–378; normal range 3.5–27.3) U/mmol and the median U-RBP/Cr was 4, 257 (range 87–21,827; normal range 1.9–42.6) μ g/mmol (Table 3).

Twenty-six patients had been investigated using renal ultrasound, 14 of whom had abnormal findings, including kidney enlargement and/or increased echogenicity (Table 2).

Initial kidney function

The maximum serum creatinine was a median of 263 (35–1,143) μ mol/l, median eGFR was 20 (4.6–103.7) ml/min/1.73 m². The eGFR was less than 10 ml/min/1.73 m² in 5 patients and 4 of them required renal replacement therapy (1 peritoneal dialysis and 3 haemodialysis). We found no relation between the time to onset of treatment or if the steroids were given orally or as large intravenous doses and the outcome regarding kidney function. There was no difference in the severity of disease between the children with and those without uveitis.

Table 1 Demographic features, treatment and follow-up

Patient number	Gender	Age (years)	Maximum SCr ($\mu\text{mol/l}$)	Lowest eGFR (ml/min/1.73 m^2)	Treatment	Uveitis	Follow-up time (months)	SCr at follow-up ($\mu\text{mol/l}$)	eGFR at last visit (ml/min/1.73 m^2)
1	Female	15	145	39	MP, P	–	22	70	81
2	Male	8	193	23	MP, P	–	70	120	44
3	Female	8	375	13	P	+	31	59	92
4	Female	15	263	20	P	ND	7	84	63
5	Male	8	354	13	MP, P	+	27	49	106
6	Female	10	139	34	MP, P	+	17	44	116
7 ^a	Male	4	35	69 ^b	P, AZA	–	1	35	82
8 ^c	Male	12	100	53	MP, P, AZA, MMF	+	21	67	85
9	Female	13	1,143	5	MP, P	–	4	56	94
10	Female	14	230	25	MP, P	+	3	84	69
11	Male	0.6	336	7	PD	ND	2	38	63
12	Female	9	202	24	P, MTX, CSA, ADA	+	21	61	83
13	Male	7	345	12	MP, P	+	508	108	54
14	Male	14	480	12	MP, P	+	25	95	61
15	Male	13	819	7	HD, MP	+	NA ^d		
16	Female	13	283	17	MP, P	+	18	70	76
17	Female	14	120	44	MP, P	+	12	62	87
18	Female	11	201	26	MP, P	–	44	69	78
19	Female	15	310	18	MP, P	–	NA		
20	Male	4	124	25	P, AZA	+	92	81	51
21	Female	15	230	23	MP, P	+	14	80	66
22	Female	15	673	7	HD, MP	–	18	46	110
23	Female	13	205	26	P	+	18	73	72
24	Female	13	376	14	MP, P	+	32	127	46
25	Male	15	323	17	MP, P	–	24	83	69
26	Female	12	200	26	MP, P	ND	16	70	76
27	Male	11	966	5	HD, MP, P	ND	70	99	56

eGFR estimated glomerular filtration rate, SCr serum creatinine, MP methylprednisolone, P prednisone, AZA azathioprine, MMF mycophenolate mofetil, PD peritoneal dialysis, HD haemodialysis, MTX methotrexate, CSA cyclosporine, ADA adalimumab, ND not documented, NA not available

^a Patient with unexplained immunodeficiency

^b Estimated with iohexol clearance

^c Patient with suspected Cogan syndrome

^d Deceased patient

Treatment

Twenty-six children received steroid therapy: 18 received intravenous methylprednisolone followed by oral prednisone, 6 were given oral prednisone from the beginning and 2 received intravenous methylprednisolone as the only steroid treatment (Table 1). Only 1 child did not receive any steroid therapy; he was admitted after 1 week of diarrhoea and vomiting after treatment with ceftriaxone and metronidazole and developed anuric AKI requiring peritoneal dialysis for 5 days. When the biopsy result was available he had recovered and did not need any further therapy. Three patients required further immunosuppressive therapy with azathioprine.

Follow-up

Twenty-five children were followed for a median of 21 (1–128) months. The kidney function improved in all children to a median eGFR of 75.7 (44.4–116.3) ml/min/1.73 m². Fifteen patients had an eGFR below 80 ml/min/1.73 m² at last follow-up (Table 1). Figure 1 shows the improvement in kidney function on treatment (p value <0.0001). Two children showed one relapse each, 2 and 4 months after the first episode respectively. Four patients had low-grade proteinuria (urine albumin/creatinine ratio range of 4.3–9.2 mg/mmol), 1 child had high-grade proteinuria (urine albumin/creatinine ratio of 310 mg/mmol) and 3 children had hypertension at follow-

Table 2 Clinical signs and symptoms and ultrasound features upon presentation ($N=27$)

Feature	Number	Percentage
Asymptomatic	1	4
General symptoms	26	96
Anorexia	22	81
Malaise	19	70
Vomiting	16	59
Nausea	13	48
Fever	11	41
Loin pain	9	33
Arthralgia	6	22
Hypertension	5	18
Polyuria	5	18
Rash	4	15
Oliguria	4	15
Oedema	3	11
Uveitis ^a	15	65
Asymptomatic	8	53
Red eye	6	40
Photophobia	5	33
Ocular pain	2	7
Decreased visual acuity	1	13
Ultrasound ^b		
Normal	12	44
Increased echogenicity	11	41
Kidney enlargement	9	33

^a 23 patients were examined by an ophthalmologist

^b 26 patients were investigated using ultrasound

up. Fourteen of the 18 patients were tested for low molecular weight urine proteins with follow-up ranging from 2 months to 10 years. Those 14 children showed lower but not normalised urinary levels of NAG, with a median NAG/Cr of 30 (7–148) U/mmol, and RBP with a median RBP/Cr of 31.5 (2–524) $\mu\text{g}/\text{mmol}$ (Table 3).

Uveitis

Twenty-three children were examined by an ophthalmologist and 15 (65 %) were diagnosed with uveitis. Eight of these did not have any eye symptoms. The uveitis was diagnosed at onset in 6 children, in 3 children, 3 to 12 months before TIN and in 6 children 1 to 20 months after TIN. Eleven children were treated with steroid eye drops and 4 with systemic steroids, which had already been given for the TIN. Two children also required other immunosuppressant therapies because of active uveitis. One boy developed sensorineural hearing loss, confirming the diagnosis of atypical Cogan syndrome, and received further treatment with azathioprine followed by mycophenolate mofetil. Another girl had a recurrent course of

Table 3 Urinary findings and results of tubular function tests

Patient number	U-NAG/Cr at onset (U/mmol)	U-RBP/Cr at onset ($\mu\text{g}/\text{mmol}$)	Follow-up time (months)	U-NAG/Cr at follow-up (U/mmol)	U-RBP/Cr at follow-up ($\mu\text{g}/\text{mmol}$)
1	177	1,493	11	13	6
2	53	7,256	58	48	232
3	217	812	10	25	76
6	115	177	17	31	83
7	271	502			
8	251	988	21	70	
10	202	10,621			
12	102	9,286	21	30	40
13	378	21,827	128	148	524
14	115	3,544			
16	208	6,443	18	16	6
17	317	3,943	2	30	10
18	140	1,781	4	18	35
20	348	16,015	83	83	2
21	127	9,302	14	25	34
23	161	4,571	18	25	29
26	215	4,704	16	33	16
27	7	87			

U-NAG/Cr urinary N-Acetyl-beta-D-glucosaminidase:creatinine ratio (normal range 2–12 U/mmol), *U-RBP/Cr* retinol binding protein:creatinine ratio (normal range 3.9–32 $\mu\text{g}/\text{mmol}$)

uveitis and was treated with local and systemic steroids followed by methotrexate, cyclosporine and adalimumab (Table 1). In 5 children the uveitis resolved, and 6 had a relapsing course, including the patient diagnosed with sarcoidosis and the child with atypical Cogan syndrome.

Discussion

We describe a series of 27 children with biopsy-proven TIN from a specialist centre. A potential cause was found in only 13 (48 %) patients. Sixty per cent of the children had an eGFR of less than 80 ml/min/1.73 m² at the last available follow-up.

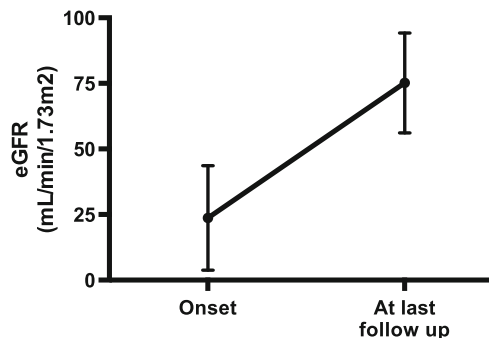


Fig. 1 Estimated glomerular filtration rate (eGFR) at onset and at last follow-up

Acute TIN is characterized by the presence of inflammatory infiltrates and oedema within the interstitium, usually associated with an acute deterioration in renal function. It is found in around 15–30 % of biopsies in adults with AKI, and of course, this is likely to be an underestimation, as many patients with typical features are not subjected to a biopsy [4]. The aetiology and clinical presentation of TIN in the paediatric setting has not been described very often, as it is a rare condition, which may require a renal biopsy to make a definitive diagnosis, especially in atypical cases. The current series therefore represents a preselected group of cases undergoing renal biopsy, by definition, representing either clinically atypical or severe cases.

Drugs, in particular antibiotics and NSAIDs, are the most commonly identified causes of TIN in the literature, accounting for 75–90 % of cases [8, 10, 11]. In our series of children with TIN, almost half had received a medication (including non-steroidal anti-inflammatory drugs, antibiotics, H2 blockers, proton pump inhibitors, aspirin and paracetamol), and 30 % had had a recent infection. It is of course difficult to define the cause of TIN in patients with previous infections who have been given antibiotic treatment.

No identifiable predisposing factor was found in around half of the children in our series, if drug use up to 12 weeks before presentation was considered. This is significantly less common compared with other studies where a likely cause of the TIN has been found in the vast majority (>90 %) of cases [8, 10–12]. We can only speculate about the reason for this difference, but it is most likely simply that the majority of patients with suspected TIN with a clear suggested predisposing cause are managed clinically and do not undergo biopsy if their kidney function improves on withdrawal of the drug.

Uveitis with TIN, TINU syndrome, accounts for 4 % of TIN in adults [1, 5], whereas in this series, 65 % of the 23 patients who received an ophthalmology review showed uveitis. Similarly, a recent Finnish case series reported uveitis in 84 % of children with TIN [13], and such patients are less likely to have any other identifiable cause [14]. The ocular lesions are bilateral in 77 % of cases [15]. The pathogenesis is not known, but there is an association with certain human leukocyte antigen types [16]. The outcome seems to be generally good [14].

The treatment of TIN is based on clinical experience and data from case series. The most common approach is corticosteroid therapy. Buysen et al. treated 10 adult patients who had not improved spontaneously on drug discontinuation from a larger group of 27 patients [17]. All 10 showed improvement in renal function and 6 recovered fully [17]. However, in another report, there was no difference in outcome between adult patients who were treated and those who were not treated with prednisolone [8]. In our study all children but 1 received steroid treatment [11].

Only 10 of the 27 children in this series regained normal kidney function, despite active treatment. This outcome is significantly worse than those reported from other case series. For example, 20 children from two series combined reported that all but 1 recovered normal kidney function [12, 18]. In adults, a 60 % recovery of kidney function has been reported [10]. Furthermore, 2 of our children relapsed, a feature that is uncommon in other case series.

In conclusion, we describe a large group of children with biopsy-confirmed TIN in whom a defined cause of the disease was less common than previously reported. Nearly all children required treatment with prednisolone. A new finding is that as many as 60 % of the children showed signs of CKD with impaired kidney function and increased excretion of low molecular weight urine proteins at follow-up.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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