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Pediatric cases diagnosed with drug-related acute tubulointerstitial nephritis: a single-center experience

Çocuk hastalarda ilaç ilişkili akut tübülointerstisyel nefritin değerlendirilmesi: tek merkez deneyimi

Özgür Özdemir Şimşek[1] Gökçen Erfidan[1] Caner Alparslan[2] Cemaliye Başaran[1]
Seçil Arslansoyu Çamlar[1] Fatma Mutlubaş[1] Belde Kasap Demir[3] Demet Alaygut[1]

[1] University of Health Sciences Izmir Faculty of Medicine Tepecik Training and Research Hospital Department of Pediatric Nephrology, Izmir, Türkiye

[2] Izmir Demokrasi University Faculty of Medicine Department of Pediatric Nephrology, Izmir, Türkiye

[3] Katip Celebi University Faculty of Medicine Department of Pediatric Nephrology and Rheumatology, Izmir, Türkiye

ABSTRACT

Aim: Acute tubulointerstitial nephritis (TIN) is inflammation of the renal interstitium. It is also a common cause of acute kidney injury (AKI). The aim is to contribute to the literature by evaluating patients diagnosed with drug-induced TIN.

Materials and Methods: 29 Turkish children aged between 3 and 217 months, 5 of whom had undergone a biopsy, were retrospectively analyzed in terms of clinical and laboratory findings.

Results: 29 patients, 19 of whom were girls, were evaluated. The mean age at diagnosis was 161(3-217) months. Nausea-vomiting complaint of 12 cases, 6 under treatment during hospitalization, 4 with headache, 2 with isolated fatigue, and the remaining 5 patients with incidentally detected renal function test disorder, oligo-anuria, urinary incontinence, red urination, and uveitis. At the time of diagnosis, 4 patients had hypertension and 26 patients had AKI. Two of these cases were anuric. The low eGFR values at the time of diagnosis were observed to improve at the end of the follow-up. Hematuria was detected in 18 cases and of them were macroscopic hematuria. 4 patients had pyuria, 19 patients had proteinuria, and 2 of them were nephrotic. Biopsy was performed in 5 cases. While one of the patients presented with uveitis, uveitis developed in 1 patient during the 3rd month of follow-up.

Conclusion: Consequently, although TIN is a reversible disease, its recognition is important in terms of treatment and follow-up.

Keywords: Acute tubulointerstitial nephritis, drugs, uveitis.

ÖZ

Amaç: *Akut tubulointerstisyel nefrit (TIN), renal interstisyumun inflamasyonudur. Aynı zamanda akut böbrek hasarının (ABH) yaygın bir nedenidir. Amaç ilaca bağlı TIN tanısı alan hastaları değerlendirerek literatüre katkıda bulunmaktır.*

Gereç ve Yöntem: *Yaşları 3-217 ay olan 29 Türk çocuğu klinik ve laboratuvar bulguları açısından retrospektif olarak incelendi. 5 hastaya biyopsi yapıldığı görüldü.*

Corresponding author: Özgür Özdemir Şimşek
University of Health Sciences Izmir Faculty of Medicine Tepecik Training and Research Hospital Department of Pediatric Nephrology, Izmir, Türkiye
E-mail: *ozgur_ozdemir_07@hotmail.com*
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Bulgular: *19'u kız olmak üzere 29 hasta değerlendirildi. Ortalama tanı yaşı 161(3-217) ay idi. Başvuru şikayetleri değerlendirildiğinde 12 hastada bulantı-kusma, 4 hastada baş ağrısı ve 2 hastada izole halsizlik olduğu görüldü. 5 hastanın başka sebeplerle hastaneye başvurusu sonucu rastlantısal olarak, 6 ise hastanın farklı nedenlerle hospitalizasyonu sırasında izlemde tanı aldığı belirlendi. 26 hastada ABH bulunmaktaydı ve 4 hasta hipertansifti. İki hasta anürikti. Tanı anında düşük olan eGFR değerlerinin takip sonunda düzeldiği görüldü. Hastalarda idrarda hematüri, piyüri ve proteinüri mevcuttu. 5 olguya biyopsi yapıldı. Hastalardan biri üveit şikayeti ile başvururken, 1 hastanın takibinin 3. ayında üveit gelişti.*

Sonuç: *Sonuç olarak TIN geri dönüşümlü bir hastalık olmasına rağmen tanınması tedavi ve takip açısından önemlidir.*

Anahtar Sözcükler: *Akut tubulointerstisyel nefrit, ilaçlar, üveit.*

INTRODUCTION

Acute tubulointerstitial nephritis (TIN) is a clinical situation that develops secondary to inflammation in the interstitium of the tubules that make up most of the kidney. It is one of the most common causes of acute renal failure in clinical practice. TIN is characterized by interstitial inflammation, interstitial edema, and tubulitis. The term TIN was used for the first time in 1898 by Councilman in this clinical situation in which local edema involving tubules and interstitial inflammation was observed in the histological examination of the kidneys of infected patients.[1] It is a clinic that occurs with an immune mechanism. Infections were considered the primary cause in the past, but recently, immuno-allergic mechanisms, primarily drugs, have been blamed. Medications are the most common cause, antibiotics are the most common. Other causes include, by incidence, autoimmune disorders, infections, and tubulointerstitial nephritis with uveitis (TINU) syndrome. The disease has a sudden onset and, to a lesser extent, can progress to chronic, slow-changing, and rarely even end-stage renal disease. There is no clear data on incidence. The diagnosis is often made clinically and since the disease is self-limiting, patients return to clinical normality with symptomatic treatment, and a biopsy is usually not needed.[2] In pediatric patients, TIN is determined in 3-7% of biopsies performed in acute kidney injury (AKI) (3). This rate is higher in adults, up to 27%.[1] The reasons for this are well-defined and categorized. Determining is well-defined is important in terms of being a marker for treatment and follow-up. This review focuses on TIN secondary to drug use, one of TIN's common etiologies.

MATERIALS and METHODS

The study is a retrospective study in which pediatric patients aged 0-18 years who were followed up in the pediatric nephrology clinic of our hospital between 2015 and 2020 and diagnosed with acute tubulointerstitial (ATIN) nephritis were examined. Ethical committee approval was received from the Ethics Committee of Tepecik Training and Research Hospital (Date: December 23, 2020. Decision No: 2020/14-17). After the approval of the local ethics committee, age, gender, follow-up period, presentation complaint, presence of hypertension and AKI at the time of diagnosis, comorbidities, presence of infection, history of drug use, physical examination findings, and findings were obtained from the files of the patients at the time of diagnosis and follow-up. Final eGFR, laboratory results (complete blood count, biochemical values, tubular tests), eye involvement, renal ultrasonography result, follow-up and treatment (treatment, whether or not received renal replacement therapy (RRT), type of RRT, and duration) were obtained.

Statistical analyses

The SPSS package program (IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp, 2017) was used for statistical analyses. Variables with normal distribution are shown as mean values ± standard deviation (SD), variables with abnormal distribution are shown as median (range), and the rest are expressed as frequency. The chi-square test was used to compare categorical variables between groups. The Kolmogorov-Smirnov test was used to evaluate the normal distribution of continuous variables between groups. All parameters were distributed abnormally, so they were evaluated by the Mann–Whitney U test. For this study, $p < 0.05$ was considered statistically significant.

RESULTS

File information of 29 children, 19 of whom were girls (65.5%), was obtained. The age at diagnosis was 161(3-217) months and the follow-up was 13.7(1-90) months. Considering the complaints of the patients, 41.4% (n=12) of the patients had nausea-vomiting, 20.4% (n=6) had a headache due to the treatment they received during hospitalization, and 13.8% (n=4) had headaches. It was observed that 6.9% (n=2) presented with only weakness, and the remaining 5 patients with incidentally detected renal function test disorder, oligoanuria, urinary incontinence, red urination, and uveitis. At the time of diagnosis, 13.8% (n=4) of the cases had hypertension and 89.7% (n=26) had AKI. 6.9% (n=2) of these cases were anuric. In the anamnesis, 82.8% (n=24) of the cases were using drugs, 17.2% (n=5) had comorbidities that required continuous drug use, and 65.5% (n=19) of the cases were before admission. It was determined that there was drug use in a one-week period. The groups to which the drugs used belong are shown in (Table-1). 31% (n=9) of the cases had concomitant diseases and these were epilepsy (n=3), encephalitis (n=1), hypothyroidism (n=1), hyperlipidemia (n=1), chronic gastritis (n=1), tuberculosis (n=1), ventricular septal defect (n=1). Physical examination revealed positive arthralgia (n=1), high fever (n=1), rash (n=1), and edema (n=1) apart from hypertension.

Considering the laboratory evaluation results, the mean eGFR values of the cases at the time of diagnosis were 55.86±26.74 ml/m/1.73m^2, while the mean final eGFR values were calculated as 116.67± 25.27 ml/m/1.73m^2. The mean values of routine hemograms and biochemistry are shown in (Table-2). In 13.8% (n=4) of patients, acidosis was detected in blood gas. Data on immunoglobulin levels (IgG, A, M, E), vitamin D, PTH, and ANA could not be reached from the file data. Regarding renal involvement, hematuria was found in 62.1% (n=18) of the cases, and two were macroscopic hematuria. Pyuria was present in 13.8% (n=4) of the cases, proteinuria was present in 65.5% (n=19) of the cases, and proteinuria was at a nephrotic level in 2 cases. When tubular tests were evaluated, the most common abnormality was FENA with 4.5%. Renal ultrasonography revealed increased renal echogenicity in 58.6% (n=17) of the cases. It was observed that one patient needed hemodialysis during the follow-up and treatment process. The findings of patients with proteinuria and hematuria are evaluated in (Table-3). Biopsy was performed in 17.2% (n=5) of the patients and the diagnosis of ATIN was proven by biopsy. The data of the patients who performed the biopsy are listed in (Table-4). Anterior-posterior uveitis developed in two patients. While one patient had uveitis at the time of diagnosis, uveitis developed in the third month in the follow-up of the other patient.

Table-1. Proportion of drugs used by patients.

Type of drug	Usage rate (n)
Nonsteroidal anti-inflammatory drugs	N=6 (25%)
Pain relievers other than non-steroidal anti-inflammatory drugs	N=6 (25%)
Antibiotics other than aminoglycosides	N=2 (8.3%)
Anticonvulsant drugs	N=2 (8.3%)
Antifungal drugs	N=2 (8.3%)
Antiviral drugs	N=2 (8.3%)
Aminoglycoside type antibiotics	N=1 (4.1%)
Proton pump inhibitors	N=1 (4.1%)
Antihypertensive drugs	N=1 (4.1%)
Antituberculosis drugs	N=1 (4.1%)

Table-2. Evaluation of the laboratory parameters of the patients.

Laboratory parameters	Mean ± Std.Dev Median (Min-Max)
At the time of the diagnosis	
White blood cells (WBC)	10048.28 ± 3167.43
Neutrophil	6673.10 ± 2765.77
Hemoglobin	11.91 ± 2.01
Hematocrit	35.36 ± 6.09
Eosinophil	100.00 (0.00-500.00)
Percentage of eosinophils	0.92 (0.00-4.50)
Basophil	36.00 (0.00-200.00)
Percentage of basophils	0.55 ± 0.33
Platelets	329689.70 ± 126822.18
Serum urea	54.62 ± 29.85
Serum Creatinine	1.40 (0.70-5.30)
eGFR	55.86 ± 26.74
Uric acid	5.86 ± 1.95
Total protein	7.24 ± 0.79
Albumin	4.05 ± 0.51
Sodium	138.00 (117.00-145.00)
Potassium	4.29 (1.90-6.40)
Calcium	9.31 ± 1.14
Phosphorus	4.30 (1.20-9.40)
C-reactive protein	7.55 (0.20-105.50)
FeNa	2.76 (0.30-22.10)
FeK	16.30 (1.67-69.00)
TPR	85.00 (44.80-98.70)
Spot urine Ca/Crea	0.09 (0.01-0.85)
24-hour urinary proteinuria	5.60 (0.28-40.90)
Spot urine Prot/Crea	0.43 (0.07-2.60)
Urine beta2 microglobulin	0.25 (0.10-15.80)
Urine density	1012.07 ± 6.37
Last visit result	
Serum Creatinine	0.76 ± 0.20
eGFR	116.67 ± 25.57

Table-3. Evaluation of patients with proteinuria and hematuria.

		Hematuria			Proteinuria		
Continuous variables		**positive**	**negative**	**p**	**positive**	**negative**	**p**
Diagnostic creatinine	median (min-max)	1.6 (0.7-4.7)	1.3 (0.8-5.3)	0.238*	2.0 (0.7-5.3)	1.2 (0.8-2.4)	0.006*
Diagnostic uric acid	median (min-max)	6.7 (2.7-8.6)	5.3 (2.3-10.3)	0.159*	6.6 (2.6-10.3)	4.9 (2.3-6.8)	0.024*
White blood cell	median (min-max)	11450 (5500-15500)	8100 (4300-12400)	0.076*	12200 (5500-15500)	8250 (4300-11700)	0.019*
Absolute neutrophil count	median (min-max)	8300 (3200-11600)	4400 (2700-9000)	0.039*	8400 (3200-11600)	4400 (2700-9300)	0.012*
FeNa	median (min-max)	3.4 (0.3-22.1)	1.3 (0.3-22.0)	0.238*	3.5 (0.3-22.1)	1.1 (0.3-4.3)	0.009*
FeK	median (min-max)	18.3 (5.2-69.0)	11.6 (1.7-25.9)	0.102*	18.7 (4.7-69.0)	10.0 (1.7-33.0)	0.035*
TPR	median (min-max)	83.6 (44.8-95.0)	91.0 (54.2-98.7)	0.028*	83.0 (44.8-95.0)	89.6 (76.0-98.7)	0.014*
Spot pr/cre	median (min-max)	0.57 (0.09-2.6)	0.28 (0.07-1.23)	0.033*	0.75 (0.11-2.60)	0.27 (0.07-0.57)	0.009*
Categorical variables		**n(%)**	**n(%)**	**p**	**n(%)**	**n(%)**	**p**
HT	positive	4 (100.0)	0 (0.0)	0.129**	3 (75.0)	1 (25.0)	0.571**
	negative	14 (56.0)	11 (44.0)		16 (64.0)	9 (36.0)	
USG pathology	positive	10 (58.8)	7 (41.2)	0.486**	11 (64.7)	6 (35.3)	0.615**
	negative	8 (66.7)	4 (33.3)		8 (66.7)	4 (33.3)	

Table-4. Evaluation of laboratory and clinical features of biopsy cases.

Age (month)	Gender	Complaint	Hematuria	Proteinuria	Diuresis	Creatinin / eGFR	Dialysis	Systemic treatment
214	Male	hematuria	Gross	nonnephrotic	sufficient	1.3/94.7	-	-
158	Female	vomiting	Gross	nonnephrotic	sufficient	1.3/63.0	-	PMP
207	Male	headache	Gross	nephrotic	sufficient	2.0/60.0	-	Prednisolone
201	Female	vomiting	-	nonnephrotic	sufficient	5.3/16.8	-	-
125	Female	uveitis	-	nonnephrotic	sufficient	1.3/79.1	-	Prednisolone

DISCUSSION

The pathological and clinical condition characterized by decreased renal function and inflammation in the renal interstitium is called TIN (1). The literature studies show that the incidence of TIN is high in elderly patients; this is blamed especially on the increase in the aging population and increasing polypharmacy (4). However, a biopsy is not performed on all patients due to the age of the population and the diagnosis is made clinically because it is reversible (5). For this reason, the data in the literature do not provide precise information in terms of age of incidence. The aim of this study is to make an overall assessment of drug-induced TIN cases in childhood.

Regardless of the cause, it is examined in two groups renal and extrarenal symptoms. Patients with any signs of AKI can apply. The most common renal symptoms are polyuria, nocturia, oliguria, tubular dysfunction, and normal blood pressure; extrarenal symptoms are fever, loin pain, weakness, nausea, vomiting, and arthralgia. Most patients, however, are asymptomatic (6). In our study, the most common reason for admission was nausea and vomiting; contrary to the literature, only 1 patient was asymptomatic. In a study conducted with 60 patients with a diagnosis of TIN, oliguria was demonstrated in 51% of the patients.[7] While 89.7% of our patients had AKI, only 6.9% had oliguria. Renal findings are AKI, Fanconi syndrome, tubular proteinuria,

leukocyturia, isolated glycosuria, microscopic haematuria, eosinophilia, and eosinophiluria (6). Most patients have an increase in plasma creatinine concentration and a decrease in eGFR at presentation (8). Drug-induced TIN, on the other hand, increases with drug administration (9). 4 patients had high blood pressure and 1 patient had edema. In our study, there was a significant difference between the eGFR values at the time of diagnosis and the evaluations made at the last visit (p=0.00). In 2 case series of 121 patients, 40% of the patients required dialysis (7). We received renal replacement therapy for only 1 patient. Since TIN is a reversible disease, short-term dialysis was applied. Urinary eosinophiluria assessment was performed for both kidney biopsy and AKI in 560 patients. Twenty-eight of 179 patients with eosinophiluria had TIN on biopsy. However, 63 of 387 patients without eosinophilia had biopsy-proven TIN (10). Although neither eosinophilia nor eosinophiluria is necessary for TIN, they were absent in any of our patients. Macroscopic and microscopic hematuria is rare in patients (11). In a series of 121 TIN patients, 67% of patients had microscopic hematuria, 93% had non-nephrotic proteinuria and 82% had pyuria (7). Although macroscopic in two of our patients, microscopic hematuria was observed in 18 patients. This finding was confirmed by Praga et al. (7). Similar to his study. Proteinuria may not be present; it may also be observed at the nephrotic level. Although non-nephrotic level proteinuria is usually observed, the risk of nephrotic level proteinuria increases, especially in elderly patients. There are studies showing that NSAIDs cause proteinuria at the nephrotic level (7). There are studies in the literature showing that proteinuria is mild and seen in a limited number of patients (1). Nineteen of our patients had proteinuria and, importantly, 2 had nephrotic proteinuria. Clinical conditions such as Fanconi syndrome and renal tubular acidosis may occur but are rare (12). Four of our patients had metabolic acidosis accompanying the abnormality in renal function tests. Fractional sodium excretion (FENa) may be >1%, partially indicative of tubular damage. Especially in cases without oliguria and milder renal failure findings, lower FeNa can be detected (13) In our study, FeNa was found to be high in accordance with the literature. Renal ultrasonography can show enlarged kidneys, usually with normal renal findings or, rarely, increased echogenicity of the renal parenchyma (14). More than 50% of our patients had increased renal echogenicity.

A male patient presented with uveitis at the time of admission. TINU is observed more frequently in childhood than in adulthood, and its incidence is higher in women (15). In a study, 45% of patients with drug-induced TIN had joint pain, 27% had a fever, and 13% had a rash (7). It was learned that 82.8% of the patients' used drugs. In terms of fever, rash, and eosinophilia, which are classical findings in drug-induced TIN; only 1 patient had a fever, and 1 patient had a rash. Arthralgia was present in 1 patient. It was determined that 17.2% of the patients used drugs regularly, but 65.5% of them used drugs in the period 1 week before admission. The most common causes of drug-related nephritis are antibiotics, proton pump inhibitors, and non-steroidal anti-inflammatories (2). In our study, nonsteroidal anti-inflammatory drugs and pain relievers were the most common causes. In order of frequency, many antibiotics such as penicillin, cephalosporins, sulfonamides, rifampin, and ciprofloxacin are responsible for the development of TIN (2). In our study, there was a patient with TIN related to aminoglycoside, one of the antibiotics.

Since the disease is reversible, clinical and laboratory findings return to normal in a short time, the complaints of the patients are mild, and it is seen especially in the elderly group, the number of biopsies performed is low. TIN occurs in 2% of native kidney biopsies. It is also seen in 27% of cases of unknown cause. TIN in children It constitutes 1-7% of renal biopsy diagnoses (10). Biopsy was performed on 5 patients. The biopsy of 1 patient was found to be compatible with IgA nephropathy, biopsy findings of the remaining 4 patients were compatible with acute TIN. However, if there are no contraindications for biopsy, it is recommended to perform a biopsy before starting the treatment. The biopsy is not required in patients with a preliminary diagnosis of TIN. Steroid therapy can be started without a biopsy. If there is no response to treatment, a biopsy may be performed (9). Steroid therapy was started immediately after the biopsy in 3 of the patients who were biopsied and found to be compatible with acute TIN. In the other 2 patients, clinical and laboratory were normal before treatment started. There is no clear protocol for treatment yet. Clinicians often try to establish treatment protocols based on previous experience. In a study evaluating pediatric

patients with idiopathic TIN and TINU; it has been shown that corticosteroids contribute positively to clinical improvement in patients with severe TIN. However, there was no significant difference in kidney function at 6-month follow-up. At the end of this study, they stated that in long-term uncomplicated cases, steroid treatment could be waited for up to 2 weeks before starting treatment because the disease is self-limiting (16). In a multicenter retrospective adult study, it was shown that in cases of drug-induced TIN, especially early initiation of steroid therapy contributes to kidney recovery (17). Mycophenolate mofetil has also been shown to be a possible option in patients in whom steroid therapy is contraindicated or who are resistant to steroids (18).

One patient had anteroposterior uveitis at admission, and kidney biopsy had 1 granuloma in addition to acute TIN findings. The patient was started on both oral steroids and subcutaneous weekly methotrexate. Anteroposterior uveitis developed in the 3rd month following the discontinuation of steroid therapy in the male patient who underwent another biopsy and was found to be compatible with acute TIN, and methotrexate was added to this patient's treatment. TINU syndrome is an entity in which TIN and uveitis are seen together. TINU syndrome is most commonly seen in female patients and is around the median age of onset of 15 years. Our 2 patients were male. It was present in one patient at the time of admission and appeared in the follow-up in one patient. Patients diagnosed with TINU present in two ways. In patients presenting with renal involvement, vomiting, decreased urine output, flu-like symptoms, and azotemia of unknown origin are observed. In cases presenting with eye involvement, uveitis is diagnosed by presenting with blurred vision and redness in the eyes. Mostly renal manifestations of TINU precede ophthalmologic, but there are also publications in the literature in which the reverse is sometimes possible (19). Since uveitis may develop in the follow-up, patients diagnosed with TIN should have an eye examination annually (20). In TINU, uveitis is usually anterior and bilateral. Middle, posterior and anterior-posterior uveitis can also be seen (21). The prognosis is generally favorable. The disease can completely regress. Sometimes it can be chronic or recurrent. In these cases, the use of immunosuppressive agents comes to the fore. The most important parameter is that both nephrological and ophthalmological follow-up and treatment of the cases are sufficient. Although there is no definitive protocol for the treatment of patients with uveitis, the first step is oral steroid therapy. There is no clear consensus on steroid dose, treatment reduction, and treatment discontinuation (19). Topical steroids are also added to the treatment. Other immunosuppressives should be considered in treatment-refractory or recurrent uveitis and in patients exposed to high doses of steroids. Other agents used by ophthalmologists are cyclophosphamide, cyclosporine, methotrexate, or mycophenolate mofetil. In addition, intravitreal bevacizumab and, in resistant cases, adalimumab, a biological agent, can also be used. TINU is among the treatment options.

CONCLUSION

TIN is a pathology in which inflammation occurs in the renal interstitium and causes a decrease in kidney function. The etiology includes drugs, especially antibiotics, many infections, autoimmune diseases, and TINU. Most of the information we have is from adult studies, with no prospective randomized clinical trials. As with many diseases in the literature, data on childhood are limited. More information is needed in the literature for the disease's diagnosis, follow-up, and treatment. Multicenter prospective studies are needed in this regard.

Main Points:

- TIN is an entity for which there is no consensus on its treatment yet.
- Childhood data are limited.
- In patients with TIN, uveitis can be seen both at the time of diagnosis and before and after diagnosis. For this reason, intermittent ophthalmological examinations are necessary for follow-up.

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