Acute tubulointerstitial nephritis is a primary injury to renal tubules and interstitium, causing renal impairment. It is characterized by the presence of inflammatory cell infiltration in the interstitium without any significant glomerular lesions. The inflammatory cells are mainly T-lymphocytes and mononuclear cells. Etiologically, TIN can be divided into two main types; infectious and non-infectious. Drugs, mainly non-steroidal anti-inflammatory drugs (NSAID), are the major causes of non-infectious TIN. Viral (CMV, EBV, HIV, hepatitis etc.), bacterial (salmonella, brucella, streptococcus etc.), fungal, parasitic infections are responsible infectious reasons for TIN. Renal manifestations involve polyuria, nocturia and signs of tubular dysfunctions. Patients with drug-induced interstitial nephritis may present with fever, skin rash and mild arthralgia. Renal ultrasound demonstrates normal to enlarged size of kidneys with increased cortical echogenicity. Besides clinical, laboratory and imaging studies renal biopsy is still gold standard for diagnosis.

Elimination of suspected agent, maintaining the fluid-electrolytic balance is the main steps of treatment. There are no controlled clinical trials but corticosteroids are recommended in the case of severe and persistent renal failure. Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare disorder characterized by tubulointerstitial nephritis with bilateral sudden-onset anterior uveitis. The pathogenesis remains poorly understood, but a lymphocyte-mediated immune mechanism has been suggested. For diagnosis of TINU syndrome, sarcoidosis, Sjogren syndrome, Behcet’s disease, granulomatosis with polyangiitis, systemic lupus erythematosus, rheumatoid arthritis, IgG4-related disease, and infectious diseases, such as tuberculosis should be excluded.

This study aimed to describe the demographic features, long-term renal outcomes and treatment modalities of acute TIN in the pediatric age group, based on a retrospective series of nineteen patients.
Material and Methods

We retrospectively reviewed the medical records of 19 acute TIN patients followed by Pediatric Nephrology department between April 1999 and April 2014. Fourteen patients were diagnosed as probable TIN with the history of causative agents, renal symptoms and laboratory findings. Five patients were diagnosed histopathologically. History of drugs and herbal medicine usage and infectious diseases, clinical presentation, estimated glomerular filtration rate (eGFR), serum urea, creatinine, blood sodium bicarbonate and pH, urinalysis, renal biopsy findings and treatment of disease were recorded. Patients were divided into two groups as steroid treated and symptomatically treated. In the steroid treated group, methylprednisolone pulses were initiated for three consecutive days, followed by oral prednisolon twice a day at a dose of 2 mg/kg/day for 1 month, and prednisone was tapered and discontinued in 6 months. One patient whose diagnosis was active tuberculosis, prednisone was initiated at a dose of 1 mg/kg/day then it was tapered and discontinued in 6 months. Anti-nuclear anti body (ANA), anti-double stranded (ds) DNA antibodies, complement factor 3 (C3) and C4 were performed as autoimmune screening. 24-hour urine protein excretion, tubular reabsorption of phosphate, fractionate excretion of sodium were evaluated. An ophthalmologist examined all of these 19 patients at least once during the acute phase of disease. Thereafter, follow-up was continued depending on each patient’s needs. Renal outcomes were evaluated by measuring serum urea, creatinine at first week of illness and, 1, 3 and 6 months after diagnosis.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS/Windows version 22.0, SPSS Inc., Chicago, IL, USA). Numerical data are presented as median (SD; range). Student’s t test and Chi-squared comparison or Fisher’s exact test was used to compare groups with respect to background characteristics. Kaplan–Meier analysis was performed to compare normalisation of plasma creatinine between prednisone and non-treatment groups. Findings were considered statistically significant when the probability of a chance finding was less than 5 % (p<0.05).

Results

Nineteen patients (7 boys and 12 girls) were evaluated. The median age at onset of illness was 14 years (range 7-19). One patient had uveitis. The etiology was drug related in 14 (73.6%) patients and infection related in 3 (15.7%) patients, One patient was developed acute TIN after digestion of a sort of herbal called Rumex patientia (5.3%) and one had undetermined cause (5.3%). The onset of renal symptoms in drug-related acute TIN patients occurred in one week to two months after initiating suspected drugs. The drugs were NSAIDs, cephalosporins, acyclovir and anti-tuberculorous drugs (isoniazid, ethambutol, pyrazinamide and rifampicin). In infection related patients, one patient had common cold, one patient had tonsillitis (throat swab culture was negative) and one patient had helicobacter pylori (HP) infection, diagnosed with 13C- urea breath test. None of them oliguric except patient number 3. Autoimmune screening was normal in all cases. In steroid treated group initial blood creatinine level and initial eGFR level was 2.31±1.63 mg/dl and 52.6±21.3 ml/min/1.73 m² respectively. In symptomatically treated group initial blood creatinine and eGFR level was 2.55±1.8 mg/dl and 51.5±21 ml/min/1.73 m² respectively. There was no statistically significant differences between the prednisone and symptomatically treated groups in age, gender, initial blood creatinine level, initial eGFR and 24- hour proteinuria level.

During the first week of treatment creatinine decreased in all nineteen patients. At the end of the first week the creatinine level in steroid treated and symptomatically treated group was 1.15±0.52 and 1.19±0.71 mg/dl respectively. After one month, plasma creatinine had normalized in all nineteen patients. At the end of the first month the creatinine level in steroid treated and symptomatically treated group was 0.49±0.04 and 0.62±0.41 mg/dl respectively. There was no statistically significant difference between prednisone and symptomatically treated groups in creatinine normalization time (p=0.113).

Demographic and clinical features, initial laboratory findings, treatment, biopsy finding and outcome were listed in Table I.

Renal biopsy was performed in five of
nineteen patients which had renal impairment continued over one week. In all patients’ biopsy revealed diffuse interstitial cellular infiltrate composed predominantly of lymphocytes, normal glomerular structures and negative immunofluorescent staining. There was no interstitial fibrosis and glomeruli showing global sclerosis.

Patient number 2 presented with flank pain and nausea. Two weeks ago cefixime treatment was started with the diagnosis of lower urinary tract infection. Her urinalysis showed 1(+) protein and 1(+) glucose. Serum creatinine level was 1.71 mg/dl, blood urea was 65 mg/ dl, blood gas analysis were normal. Tubular reabsorption of phosphate was 87 % and fractionated excretion of sodium was normal. Biopsy findings were consistent with acute TIN. Her ophthalmological examination revealed anterior uveitis. C3 and C4 were in normal range. ANA and anti-ds DNA was negative. She was diagnosed as TINU syndrome. Methylprednisolone pulses (30 mg/kg) were initiated for consecutive three days, followed by oral prednisolon twice a day at a dose of 2 mg/kg/day for 1 month. Serum creatinine and urine protein excretion reduced within two weeks. Prednisolon dose tapered and discontinued at the end of six months. She was also followed by an ophthalmologist. The patient remained event-free at 5-year follow-up.

Patient number 4 diagnosed as abdominal tuberculosis and he was treated with rifampicin, ethambutol, pyrazinamide and isoniazid. In the first month of treatment, he developed, proteinuria, glucosuria and metabolic acidosis. His laboratory investigation revealed; serum creatinine 0.91 mg/dl, blood urea 52 mg/dl, blood pH 7.28 and bicarbonate 16 mmol/L. His tubular reabsorption of phosphate was 60%. Although the cessation of all drugs, renal improvement was not seen in one week and renal biopsy was performed. Renal biopsy confirmed our clinical diagnosis and prednisolon was initiated at a dose of 1 mg/kg/day. His anti tuberculous treatment was re-arranged as isoniazid (1x300 mg), ethambutol (1x375 mg), and pirazinamid (1x500 mg). After one month from initiating prednisolon therapy his serum creatinine was normal, tubular reabsorption of phosphate was 79% urinalysis showed 1 (+) protein and 1 (+) glucose, his metabolic acidosis improved and alkali therapy was discontinued. He remained event-free at 7-month follow-up.

Patient number 14 who had taken NSAID treatment for acute rheumatic fever (ARF), during the follow up, proteinuria and non oliguric renal failure developed and diagnosed as acute TIN due to NSAID. NSAID treatment discontinued. Prednisolon was started for ARF carditis. Renal failure resolved in one week. All patients showed a rapid recovery as longest in one month and no relapses of TIN/TINU was observed.

Discussion

Acute tubulointerstitial nephritis (TIN) is a primary injury of renal tubules and interstitium, causing renal impairment which is induced most often by drugs, infections and autoimmune disorders\textsuperscript{8,13}. Patients with drug-induced interstitial nephritis may present with triad of fever, skin rash and mild arthralgia in about 20% of patients\textsuperscript{7}. In our study 73.6 % of patients were drug- induced, none of these showed the classical clinic triad, the drugs were NSAIDs, cephalosporins and antituberculous therapy (isoniazid, ethambutol, pyrazinamide and rifampicin). We could not recognize which antituberculous drug was responsible in our case clearly however in the literature there are several studies that emphasis rifampicin as responsible agents of TIN\textsuperscript{14,15}. The mechanism of renal damage is thought to be due to allergic reactions to rifampicin or one of its metabolites causing allergic interstitial nephritis, especially when extra renal manifestations of hypersensitivity exist. This condition has been demonstrated by the presence of rifampicin-dependent antibodies in serum, but the relationship between anti-rifampicin antibodies and renal impairment is not certain, circulating rifampicin antibodies have been observed in patients on rifampicin treatment without any evidence of renal disease\textsuperscript{16}.

Elimination of the suspected agent is the first step in the treatment. The main treatment of TIN is symptomatic, in case of renal failure, maintaining the fluid-electrolytic balance is the most important intervention. The use of glucocorticoids in the treatment of acute TIN has remained controversial. Several retrospective studies have suggested that corticosteroids
Table I. Demographic and Clinical Features, Initial Laboratory Findings, Treatment, Biopsy Findings and Outcome of the Patients

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age (year)</th>
<th>Sex</th>
<th>Clinical feature</th>
<th>Ocular examination</th>
<th>Cause</th>
<th>eGFR (ml/dk/1.73m²)</th>
<th>Cre_1 (mg/dl)</th>
<th>Cre_2 (mg/dl)</th>
<th>Urine analysis/24-hour urine protein</th>
<th>Renal biopsy</th>
<th>Treatment/Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>F</td>
<td>Abdominal pain/ vomiting</td>
<td>Normal</td>
<td>Infection (Common cold)</td>
<td>62</td>
<td>1.39</td>
<td>0.50</td>
<td>3+prt/3+glu</td>
<td>(+)</td>
<td>MP+PD (6 months)</td>
<td>Recovered</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>F</td>
<td>Flank pain/nause</td>
<td>Anterior uveitis</td>
<td>Drug (Cefixime)</td>
<td>40</td>
<td>1.71</td>
<td>0.40</td>
<td>1+prt/1+glu</td>
<td>(+)</td>
<td>MP+PD</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>F</td>
<td>Rash/dyspnea</td>
<td>Hypertensive retinopathy</td>
<td>Infection (Tonsillitis)</td>
<td>16</td>
<td>5.4</td>
<td>0.55</td>
<td>1+prt/1+glu/15mg/m²/h</td>
<td>(+)</td>
<td>MP+PD (6 months)</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>M</td>
<td>Abdominal pain/vomiting</td>
<td>Normal</td>
<td>Drug (Rifampicin?)</td>
<td>61</td>
<td>0.91</td>
<td>0.62</td>
<td>3+prt/4+glu</td>
<td>(+)</td>
<td>MP+PD (6 months)</td>
<td>Recovered</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>M</td>
<td>Flank pain/vomiting</td>
<td>Normal</td>
<td>Undetermined</td>
<td>76</td>
<td>1.48</td>
<td>0.41</td>
<td>5mg/m²/h</td>
<td>(+)</td>
<td>MP+PD (6 months)</td>
<td>Recovered</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>F</td>
<td>Flank pain/nausea</td>
<td>Normal</td>
<td>Drug (NSAID)</td>
<td>55</td>
<td>1.5</td>
<td>0.50</td>
<td>Pyuria/2+prt/22mg/m²/h</td>
<td>(-)</td>
<td>(-)</td>
<td>Recovered</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>F</td>
<td>Abdominal pain</td>
<td>Normal</td>
<td>Drug (NSAID)</td>
<td>46</td>
<td>1.9</td>
<td>0.60</td>
<td>Pyuria/20mg/m²/h</td>
<td>(-)</td>
<td>(-)</td>
<td>Recovered</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>F</td>
<td>Abdominal pain/vomiting</td>
<td>Normal</td>
<td>Drug (NSAID)</td>
<td>30</td>
<td>2.6</td>
<td>0.36</td>
<td>Pyuria/11mg/m²/h</td>
<td>(-)</td>
<td>(-)</td>
<td>Recovered</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>F</td>
<td>Flank pain/nausea</td>
<td>Normal</td>
<td>Drug (NSAID)</td>
<td>31</td>
<td>2.8</td>
<td>0.70</td>
<td>Pyuria/8mg/m²/h</td>
<td>(-)</td>
<td>(-)</td>
<td>Recovered</td>
</tr>
<tr>
<td>10</td>
<td>14</td>
<td>F</td>
<td>Painless hematuria</td>
<td>Normal</td>
<td>Drug (NSAID)</td>
<td>51</td>
<td>1.69</td>
<td>0.52</td>
<td>Pyuria/18mg/m²/h</td>
<td>(-)</td>
<td>(-)</td>
<td>Recovered</td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>M</td>
<td>Abdominal pain/vomiting</td>
<td>Normal</td>
<td>Herbal</td>
<td>101</td>
<td>1.0</td>
<td>0.41</td>
<td>Pyuria/2+prt/23mg/m²/h</td>
<td>(-)</td>
<td>(-)</td>
<td>Recovered</td>
</tr>
<tr>
<td>12</td>
<td>19</td>
<td>M</td>
<td>Abdominal/polyuria</td>
<td>Normal</td>
<td>Infection (HP infection)</td>
<td>68</td>
<td>1.8</td>
<td>0.83</td>
<td>Pyuria/9mg/m²/h</td>
<td>(-)</td>
<td>(-)</td>
<td>Recovered</td>
</tr>
<tr>
<td>13</td>
<td>18</td>
<td>M</td>
<td>Flank pain/vomiting</td>
<td>Normal</td>
<td>Drug (NSAID)</td>
<td>37</td>
<td>3.3</td>
<td>0.74</td>
<td>Pyuria/18mg/m²/h</td>
<td>(-)</td>
<td>(-)</td>
<td>Recovered</td>
</tr>
<tr>
<td>14</td>
<td>16</td>
<td>M</td>
<td>-</td>
<td>Normal</td>
<td>Drug (NSAID)</td>
<td>61</td>
<td>1.89</td>
<td>0.60</td>
<td>Pyuria/10mg/m²/h</td>
<td>(-)</td>
<td>PD*</td>
<td>Recovered</td>
</tr>
<tr>
<td>15</td>
<td>15</td>
<td>M</td>
<td>Flank pain</td>
<td>Normal</td>
<td>Drug (Cefdinir)</td>
<td>67</td>
<td>1.65</td>
<td>0.55</td>
<td>Pyuria/8mg/m²/h</td>
<td>(-)</td>
<td>(-)</td>
<td>Recovered</td>
</tr>
<tr>
<td>16</td>
<td>14</td>
<td>F</td>
<td>Abdominal pain/vomiting</td>
<td>Normal</td>
<td>Drug (Ceftriaxone)</td>
<td>41</td>
<td>2.1</td>
<td>0.58</td>
<td>Pyuria/4mg/m²/h</td>
<td>(-)</td>
<td>(-)</td>
<td>Recovered</td>
</tr>
<tr>
<td>17</td>
<td>15</td>
<td>F</td>
<td>Abdominal pain/vomiting</td>
<td>Normal</td>
<td>Drug (NSAID)</td>
<td>23</td>
<td>3.8</td>
<td>0.47</td>
<td>Pyuria/5mg/m²/h</td>
<td>(-)</td>
<td>(-)</td>
<td>Recovered</td>
</tr>
<tr>
<td>18</td>
<td>11</td>
<td>F</td>
<td>Flank pain/vomiting</td>
<td>Normal</td>
<td>Drug (Cefixime)</td>
<td>51</td>
<td>1.54</td>
<td>0.52</td>
<td>Pyuria/6mg/m²/h</td>
<td>(-)</td>
<td>(-)</td>
<td>Recovered</td>
</tr>
<tr>
<td>19</td>
<td>17</td>
<td>F</td>
<td>Flank pain/nausea</td>
<td>Normal</td>
<td>Drug (Acyclovir)</td>
<td>69</td>
<td>1.3</td>
<td>0.70</td>
<td>Pyuria/20mg/m²/h</td>
<td>(-)</td>
<td>(-)</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

* Prednisolon was started for ARF carditis

PD: Prednisolon, MP: Methylprednisolone pulse, NSAID: non-steroidal anti-inflammatory drugs, Cre_1: Blood creatinine level at diagnose, Cre_2: Blood creatinine level at sixth month
improves clinical outcome\cite{17,18}. On the contrary, Jahnukainen et al.\cite{19} have shown that prednisone treatment speeds up the recovery from renal symptoms of TIN, especially in patients with severe nephritis but the renal function did not differ significantly at the long-term follow-up. At this study prednisolone was given at a dose of 2 mg/kg/day for 1 month and tapered over maximum 6 months\cite{19}. While there were some variations in the dose and length of steroid treatment, typically the regimen is intravenous methylprednisolone 1000 mg per 1.73 m$^2$ body surface on three consecutive days followed by oral prednisolone 2 mg/kg tapered over 3-6 weeks\cite{20}. Except for patients 4 and 14, steroid treatment was given in this manner. Patient 4 had active TB therefore we refrained from giving steroid pulses. However, in our study there was no statistically significant difference between prednisone treated and symptomatically treated groups in creatinine normalisation time (p=0.113).

One of our patients whose initial complaints were stomachache and nausea was diagnosed as helicobacter pylori (HP) with C13 urea breath test. Although we could not determine any other infectious and/or non infectious causes of TIN in this patient, we observed that his renal impairment resolved dramatically in one week after initiation of treatment for HP. HP infections generally affect the gastrointestinal system however, anti-HP antibodies were shown in glomeruli suggested that HP may also be involved in the pathogenesis of membranous nephropathy\cite{21}. Although, Caliskan et al.\cite{22} showed that HP eradication has led to reduction in proteinuria in patients with membranous nephropathy, as far as we know there is not any case reported about the relationship of TIN and HP infection yet.

The diagnosis of TINU syndrome requires the presence of both acute TIN and uveitis. Many bacterial and viral infections, various drugs (especially antibiotics), NSAIDs and purchase over-the-counter drugs such as decongestants, antitussives, expectorants without the need of prescription have been suggested as triggering factors\cite{23,24}. The underlying mechanisms for TINU are not well understood. However limited data suggests that modified C-reactive protein, an auto-antigen common to both the uvea and renal tubular cells, may be involved in the pathogenesis. Also a strong association with HLA-DQA1*01, HLA-DQb1*05, and HLA-DQB1*01 has been observed\cite{25,26}. In our study one patient was diagnosed as TINU syndrome. On admission she had no ophthalmological complaints, however her ophthalmological examination revealed asymptomatic bilateral anterior uveitis. Paladini et al.\cite{27} reported a TINU case which was diagnosed as TINU syndrome. Also Saarela et al.\cite{28} showed that 50% of TINU syndromes had no ocular symptoms. Since corticosteroid therapy does not prevent uveitis, ocular examination should be performed in the follow-up of TINU patients\cite{29}.

In the course of severe acute TIN decreased urine output may emerge, patient number 3 was oliguric and meanwhile due to hypervolemia she became hypertensive. Her initial ophthalmologic examination showed hypertensive changes as bilateral fundus hyperemia, hemorrhage and ischemia. After temporary anti-hypertensive treatment of one month and clinical resolution her blood pressure decreased and ophthalmologic examination improved.

The major limitation of this study is the limited number of the patients. An another important point is, in the patients that were diagnosed clinically, renal damage due to certain drugs can not be ruled out without renal biopsy from acute TIN, however in these patients, because of non-oliguric renal impairment, glucosuria and accurate renal improvement after elimination of suspected agent, we refrained from performing renal biopsy.

In conclusion, it is important to recognize that acute TIN is a common cause of acute renal impairment. Clinical features are often non-specific therefore renal biopsy is recommended especially in persistent renal impairment. Ophthalmological examination is recommended even if there are no ophthalmological complaints. Renal outcome is mostly good with symptomatic treatment but steroids could be preferred in severe nephritis however long-term follow-up showed no differences between the treated and non-treated group.

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REFERENCES


