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Tubulointerstitial nephritis and uveitis in children and adolescents

Four new cases and a review of the literature

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Abstract We identified 35 cases of tubulointerstitial nephritis and uveitis (TINU), 31 from a MEDLINE search (1966–1996) of the English literature and 4 from our hospital records (1988–1996). To meet the case definition, the patient had to be less than 18 years old and have TINU of unknown cause. Common presenting symptoms included fatigue, weight loss, fever, and abdominal pain. The uveitis was usually anterior and could occur at any time with respect to the onset of the renal disease. Common laboratory features included anemia, increased erythrocyte sedimentation rate, and decreased creatinine clearance. Most patients (33 of 35) had renal biopsies that commonly revealed an intense inflammatory interstitial infiltrate, glomerular sparing, and negative immunofluorescence studies. Of the 35 patients, 26 received systemic corticosteroid therapy (5 of 26 for eye disease); 22 had follow-up for at least 1 year; 13 of 35 patients had a recurrence of their uveitis. The outcome in all 35 cases was normal renal function with no documented visual loss. In conclusion, TINU is a unique syndrome with characteristic clinical features, laboratory changes, and renal biopsy results. Treatment is controversial, and the outcome in children, even if untreated, is excellent.

Key words Tubulointerstitial nephritis · Uveitis · Systematic review

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Introduction

Tubulointerstitial nephritis and uveitis (TINU) was first described in 1975 by Dobrin et al. [1] in two adolescent female patients with acute eosinophilic interstitial nephritis, anterior uveitis, and noncaseating granulomas in both bone marrow and lymph nodes. A total of 31 pediatric cases have been published in the English literature [1–19]. The differential diagnosis includes infections, drugs, and multisystem illness. We report an additional 4 pediatric cases. Our review suggests that TINU is a benign illness in children and that treatment for renal disease is controversial and may not be necessary.

Methods

We searched MEDLINE (1966–1996) to identify cases of TINU from the literature. Exploding the subject headings *nephritis* (34,286 articles) and *uveitis* (12,836 articles) identified 31 pediatric patients that met our criteria for TINU in the English literature: the patient had to be less than 18 years old at the time of presentation and have both tubulointerstitial nephritis and uveitis without any known cause. We excluded the case described by Guignard and Torrado [2] that had documented toxoplasmosis as a potential etiological agent.

A search of our hospital records (1988–1996) identified 4 cases of TINU. Although there is no classification for TINU in the ICD-9-CM (International classification of diseases, 9th revision, clinical modification) [20], there are codes for acute interstitial nephritis and uveitis. From the charts of the 48 inpatients treated for uveitis at our hospital from 1988 to 1996, we identified 4 patients who met our criteria for TINU.

From the charts of our 4 patients and the 31 reported cases, we recorded signs and symptoms of the disease, laboratory results (serum creatinine, hemoglobin, white blood count, erythrocyte sedimentation rate, total protein, albumin, immunoglobulins, antinuclear antibodies, urinalysis, and chest radiograph), results of renal biopsies, and possible causative infectious agents or drugs. We begin by reporting the 4 cases seen at The Hospital for Sick Children.

Table 1 Summary of laboratory findings for the 4 new cases of tubulointerstitial nephritis and uveitis (TINU)

Case	1	2	3	4
Serum creatinine µmol/l (normal <106)	186	169	257	117
Creatinine clearance (ml/min per 1.73 m^2)	40	48	28	65
Hb (g/l) (normal 120–160)	93	97	98	111
WBC×10^9/l (normal 4–10)	8.3	7	5.4	5.1
Eosinophil count (%) (normal <0.5)	2–4	7–13	4–5	3
ESR mm/h (normal <10)	92	85	62	100
Total protein (g/l) (normal 53–85)	93	ND	78	78
Albumin (g/l) (normal 33–58)	38	ND	41	35
IgG g/l (normal 4–14)	17.8	17.2	17.4	ND
Anti-nuclear antibody	Negative	1:1,280	1:320	Negative
Urinalysis	1+RBC, ketones, protein, glucose	Trace protein, –RBC, glucose	+Glucose, –protein, –RBC	+Protein, RBC
CXR	Normal	ND	Normal	Normal

ND, not done; Hb, hemoglobin; WBC, white blood count; ESR, erythrocyte sedimentation rate; CXR, chest radiograph

Table 2 Summary of renal biopsy results for 3 of the 4 new cases of TINU[a]

Case	1	3	4
Interstitial infiltrate	3+ Lymphocytes, + neutrophils, eosinophils	3+ Lymphocytes, + plasma cells, eosinophils	3+ Lymphocytes, + neutrophils, plasma cells
Interstitial fibrosis	Severe	Severe	Mild
Tubular atrophy	Present	Present	Absent
Granulomas	Absent	Absent	Absent
Vasculitis	Absent	Absent	Absent
Immunofluorescence	Negative	Negative	Negative

[a] No biopsy performed for case 2

Case reports

Case 1

A 15-year-old female presented with a 1-month history of fatigue, anorexia, fever, cough, abdominal pain, and vomiting, with an associated 11-kg weight loss. She was treated with dimenhydrinate. Her only other medication was naproxen for 1–2 days per menstrual cycle for cramps. She described herself as thirsty but denied polyuria. Her past medical history and family history were unremarkable. On admission she was noted to be mildly obese, pale, afebrile, and normotensive. There was diffuse tenderness to palpation and percussion of her abdomen with no organomegaly. The remainder of the physical examination was normal. Her initial laboratory results are presented in Table 1; her renal biopsy results in Table 2 (Fig. 1). Her renal function spontaneously improved over 1 week.

One week after discharge, she developed a red and painful right eye due to nongranulomatous anterior uveitis. She received topical atropine and steroid drops as treatment. At this time her serum creatinine was normal but her urinalysis still revealed hematuria, pyuria, and proteinuria. Prednisone therapy (0.8 mg/kg) was started because of the active nature of her biopsy results. She remained on prednisone for 1 year. The patient's uveitis remained intermittently active for 2 years and was controlled topically with no sequelae. Follow-up 5 years later revealed normal renal function including normal urinalysis. She is on no medications.

Case 2

A 13-year-old female presented with a 3-day history of sore throat and abdominal pain. Over the next month she developed fatigue, malaise, headaches, myalgia, fever, and weight loss. Blood and urine cultures were negative as were investigations for infectious mononucleosis. One month later, she had back pain caused by sacroiliitis and a red and painful eye. Ophthalmological examination revealed bilateral nongranulomatous anterior uveitis. Her eyes were treated with topical steroids and cycloplegics; her systemic disease was treated with indomethacin. On treatment her back pain and fever resolved. Her erythrocyte sedimentation rate fell from 85 to 35 mm/h. Three months after presentation she had an elevated serum creatinine (169 µmol/l). Her urinalysis had trace protein and pyuria. Renal biopsy was refused by the patient's family. The clinical diagnosis was interstitial nephritis due to the presence of renal insufficiency with sterile pyuria and mild proteinuria. At no time did she have mucocutaneous, rheumatological, pleuropulmonary, or neurological symptoms or signs of systemic lupus erythematosus. Although she had a high titer of anti-nuclear antibodies, all specific antibodies (anti-double-stranded DNA/Smith/RNP/Ro/La) were negative; moreover serum complement levels were normal. Her serum creatinine normalized spontaneously within 4 months. Five years of follow-up revealed that she had three relapses of her uveitis, each time treated topically with no sequelae. Her renal function remained normal with normal urinalysis.

Case 3

A 15-year-old female presented with a 2-month history of malaise, anorexia, 4.5-kg weight loss, intermittent headaches, fever, abdominal pain, and backaches. She had had bilateral painful eyes with blurred vision for 4 weeks prior to admission. A diagnosis of anterior nongranulomatous uveitis was made and she was treated with topical steroids and atropine. She was on no other medications. She was admitted to hospital for renal biopsy when her laboratory investigations revealed a high serum creatinine (257 µmol/l). Family history revealed that her sister had ulcerative colitis.

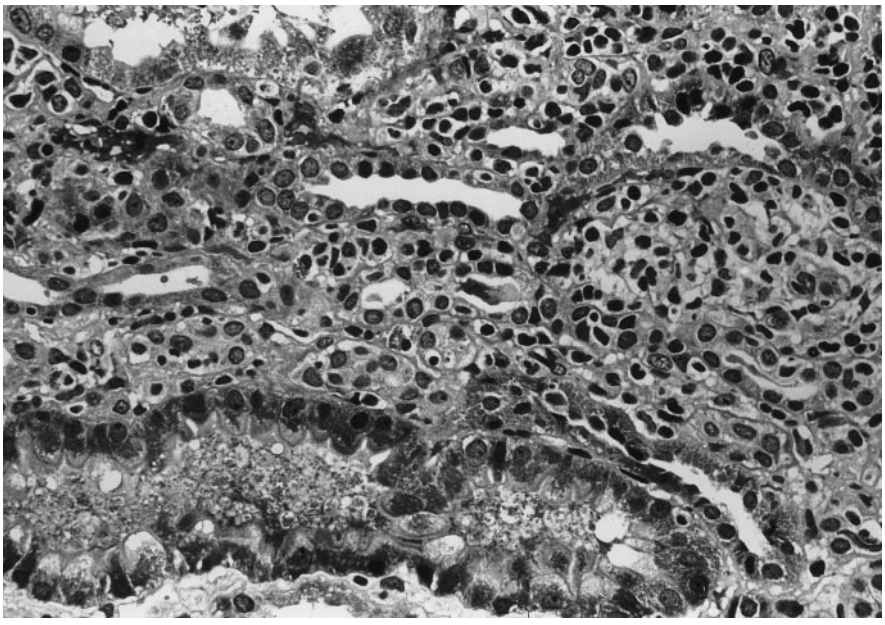

Fig. 1 Cortical lymphocytic interstitial inflammation and tubulitis (original magnification ×67, hematoxylin and eosin stain)

Her laboratory results are summarized in Table 1; her renal biopsy results in Table 2. She was treated with oral prednisone (0.8 mg/kg), which failed to relieve her lower back pain, fatigue, and myalgia. Her serum creatinine levels normalized within a month. Corticosteroid therapy was stopped 4 months later. Fibromyalgia was thought to explain her arthralgia, fatigue, and back pain. Over the next 3 years her uveitis relapsed several times and was treated topically each time without sequelae. Her renal function remained normal with normal urinalysis.

Case 4

A 14-year-old female presented with painful red eyes. A diagnosis of bilateral nongranulomatous anterior uveitis was made and she was started on topical steroids and cycloplegics. She reported a 4.5-kg weight loss over the previous few months. She denied abdominal or joint pain and had no fever or anorexia. She was on no medications. Her past medical history was unremarkable. She was a slim normotensive girl with a normal physical examination. Her laboratory results are presented in Table 1; her renal biopsy results in Table 2.

She was treated with topical as well as systemic steroids (0.6 mg/kg) and her serum creatinine was normal within 2 months. Her uveitis relapsed once. She has no visual sequelae. She has had stable renal function for 3 years of follow-up. Her last urinalysis had trace protein.

Table 3 Summary of symptoms and signs for 35 patients with TINU [1–19]

Weight loss/anorexia	86%
Fatigue/malaise	75%
Fever	64%
Flank/abdominal pain	44%
Polydipsia/polyuria	36%
Arthralgia	33%
Nausea/vomiting	22%
Cough	14%
Rash	0%
Dry eyes	0%
Dysuria	0%

Table 4 Summary of laboratory findings for 35 patients with TINU [1–19]

Decreased creatinine clearance	(mean 33 ml/min per 1.73 m^2)	89%
Increased ESR	(mean 90 mm/h)	83%
Increased IgG	(mean 21.4 g/l)	72%
Anemia	(mean Hb 100 g/l)	66%
Eosinophilia	(mean 7.5% of WBC)	66%

Results

Summary of presenting symptoms and laboratory results

Of the 35 cases of pediatric TINU, 22 were females who presented with nonspecific constitutional symptoms (Table 3) at a mean age of 13.6 years (range 10–18 years) [3–8]. Patients were usually pale, normotensive, and without lymphadenopathy or hepatosplenomegaly. Skin eruptions were rare [3, 9].

Laboratory abnormalities (Table 4) included: increased erythrocyte sedimentation rate, hypergammaglobulinemia, normochromic normocytic anemia, and decreased renal function. Eosinophilia was common although intermittent. Important negative findings included normal serum complement levels and no radiological evidence of sarcoidosis. Investigations for autoimmune diseases were incompletely documented in the literature [1–19]. Potential infectious causes were not found. Of the 35 cases reviewed, only 13 have documented negative cultures for toxoplasmosis. This highlights the needs for a thorough search for potential infectious causes before diagnosing the patient with TINU.

Urinalysis may reveal evidence of tubular dysfunction with aminoaciduria [3, 9], phosphaturia, modest proteinuria (usually <2 g/24 h), normoglycemic glycosuria, and

Table 5 Urinalysis results for 35 patients with TINU [1–19]

Non-nephrotic proteinuria	83%
Normoglycemic glycosuria	58%
Isosthenuria	42%
Pyuria	39%
Microscopic hematuria	28%

isosthenuria (Table 5) [3, 7–9]. Pyuria (rarely eosinophiluria), with or without hematuria, and the presence of white blood cell casts reflect interstitial inflammation [21].

Biopsy findings

Most patients (33 of 35) had renal biopsies. Biopsies taken early in the course of the illness (i.e., within a month of presentation) show acute interstitial nephritis with interstitial edema and a diffuse inflammatory interstitial infiltrate of lymphocytes and plasma cells [1, 2, 4, 6, 9–13]. The presence of interstitial eosinophils was occasionally reported [1, 10, 11, 14, 15]. There was often focal tubular damage with necrosis and atrophy. Some authors have described "tubulitis," a migration of lymphocytes between the tubular basement membrane and the tubular epithelial cells [4, 9, 10, 12, 13]. The glomeruli were normal or had mild proliferation of the mesangial matrix; there was no evidence of vasculitis. Immunofluorescence studies were usually negative [1, 5, 7, 9, 10, 13–15], although nonspecific staining for immunoglobulins on interstitial plasma cells or for IgG and Clq along the glomerular basement membrane has occasionally been reported [3, 22]. Electron microscopy examination of glomerular and tubular basement membranes was normal. Later (i.e., 2–4 months after onset) biopsy results revealed severe focal tubular atrophy and interstitial fibrosis, or resolution of the nephritis [3, 7, 9, 21–23]. Very rarely, renal (3 of 34) or bone marrow (2 of 8) biopsies revealed noncaseating granulomas [1, 19]. On the follow-up biopsies, the granulomas were not found.

Ocular findings

The uveitis was bilateral in 17 of 35 cases and typically followed the onset of systemic symptoms (23 of 35) within 6 months, although it could occur at any time (2 months before to 6 months after). Of the 19 patients in whom ocular signs were described, 17 were symptomatic with red and/or painful eyes; 2 patients had asymptomatic uveitis: 1 bilateral and 1 unilateral.

The eye disease was characteristically a nongranulomatous anterior uveitis (20 of 35) with a surprisingly benign course. In 15 cases no details were reported regarding the location of the uveitis (anterior, posterior, or panuveitis). Only 1 case of posterior uveitis was reported and this was a relapse [3].

Treatment and outcome

One year follow-up data are available for 63% (2-year follow-up data for 53%) of the patients in the literature. Of the 35 patients, 26 received systemic steroids (5 of 26 for eye disease). Half improved in less than 1 month (i.e., normal serum creatinine, rise in hemoglobin, fall in erythrocyte sedimentation rate). One of our patients (case 2) received indomethacin for sacroiliitis and her renal function simultaneously improved. Of the 35 patients, 6 received no therapy; most improved within 2 months [1, 8–10, 12, 13].

All 35 cases had normal renal function at last follow-up. One patient has nephrogenic diabetes insipidus 2 years after onset of acute interstitial nephritis [10]. One patient has developed hypertension but has normal renal function [6]. Both these patients were given systemic steroids to treat their eye disease. While most patients had stable renal function despite ocular relapse, 2 patients did have a simultaneous temporary decline in renal function [11].

The uveitis followed an intermittent relapsing-remitting course in 13 of 35 patients [1, 6, 16]. All patients received topical treatment for uveitis. Only 5 patients required systemic steroids for their eye disease after failing topical treatment, including 2 patients with steroid-dependent ocular disease [3, 6, 7, 18]. Only 1 patient is described with posterior synechiae, a known complication of uveitis [5]. There were no cases of documented visual loss.

Discussion

In the Oregon Health Sciences University uveitic clinic, TINU represents 2% of adult and pediatric patients seen [5]. Our hospital review reveals that TINU represents 8% of pediatric inpatients with uveitis. Patients with uveitis are rarely hospitalized for treatment, and thus the true incidence of TINU remains unknown. It must be part of the differential diagnosis of every patient that presents with either idiopathic interstitial nephritis or uveitis. There are no specific diagnostic tests, therefore TINU is a diagnosis of exclusion.

Major diagnostic features of TINU are the triad of biochemical abnormalities, nephropathy, and uveitis [3]. Its distribution is typically in young girls aged 10–14 years, presenting with symptoms of weight loss, fatigue, and fever. Biochemical abnormalities include increased serum creatinine levels, erythrocyte sedimentation rate, immunoglobulins, and anemia. Bone marrow and other granulomas are rare [1, 19]. The differential diagnosis of TINU is broad, and includes infections, drugs, and systemic illness.

There are a number of infections that can present with renal and/or ocular symptoms (Table 6); however it is unusual for a specific infection to cause both. In particular, toxoplasmosis and tuberculosis must be ruled out as etiological agents. Guignard and Torrado [2] documented

Table 6 Causative infectious agents that can mimic TINU

Causative infectious agents	Interstitial nephritis	Uveitis
Brucellosis	×	×
Leptospirosis	×	
Tuberculosis	×	×
Herpes simplex virus	×	×
Australia AD	×	
Toxoplasmosis	×	×
Cytomegalovirus	×	×
Epstein-Barr virus	×	
Streptococci	×	
Diphtheria	×	
Syphilis	×	×
Salmonella typhi	×	
Legionella	×	
Campylobacter	×	
Mycoplasma	×	
Staphylococci	×	
Yersinia	×	
Hantaan virus	×	
Human immunodeficiency virus	×	
Rubeola	×	
Rickettsii (Rocky Mountain spotted fever)	×	
Nematode infestation		×
Leprosy		×
Histoplasmosis		×
Coccidiodomycosis		×
Chlamydia		×

×, causative agent

toxoplasmosis in their case; thus their patient does not meet our case definition of TINU. One should be careful about the interpretation of PPD tests, because several authors have noted anergy during the acute phase of TINU [3, 7, 9].

Many drugs are known to cause a hypersensitivity reaction with interstitial nephritis [4, 10, 21]. While one-third of the cases reviewed [1, 11, 14, 15, 17] were treated with one of these drugs for their nonspecific symptoms, it is unlikely that TINU is drug induced. Firstly, these drugs do not cause uveitis. Secondly, patients with TINU do not have a rash [1, 24], a common manifestation of drug-induced hypersensitivity reactions.

The differential diagnosis also includes systemic lupus erythematosus and other systemic vasculitides, connective tissue disorders, sarcoidosis, and Sjögren syndrome. TINU lacks the typical features of these illnesses. Unlike systemic lupus erythematosus, patients with TINU have normal serum complement levels and no immune complex deposition in renal biopsies.

Patients with TINU have no other evidence of granulomatous diseases or eosinophilic syndromes, such as Wegener granulomatosis, Churg-Strauss syndrome, or sarcoidosis. The greatest overlap may be with sarcoidosis, in that there may be evidence of local hyperimmune function and systemic anergy. Histamine, antigen-antibody complexes, allergens, and fibrin can all attract eosinophils, therefore it is possible that some antigenic insult within the renal parenchyma leads to an eosinophilic and mononuclear response with concurrent activation of lymphatic and bone marrow histiocytes leading to granuloma formation [1]. However, sarcoidosis is very rare in children and, unlike sarcoidosis, there is no hilar adenopathy or hepatosplenomegaly in children with TINU [1]. Also unique to TINU is that the granulomas disappear. This may reflect sampling error or it may be a variable part of the disease.

Recent observations in TINU show some evidence that it resembles Sjögren syndrome [6, 25]. The presence of immunoglobulins in the tubular basement membrane and interstitial infiltrate in both cases reported by Morino et al. [6] is highly suggestive of an immunological process of tubular damage similar to that seen in Sjögren syndrome. These patients had chronic sialoadenitis on salivary gland biopsy but no symptoms of dry mouth. Dobrin et al. [1] described submandibular swelling and pain in 1 case. However, unlike TINU, the tubulopathy in Sjögren syndrome does not spontaneously resolve.

The uveitis of TINU is most commonly an anterior nongranulomatous inflammation, but can be posterior or panuveitis [9, 14]. It can occur before, during, or after the onset of the renal disease. Although usually symptomatic, it can also occasionally be asymptomatic. The disorder is usually responsive to topical therapy, but systemic steroids may be required. Exacerbations are frequent, but visually significant sequelae do not occur.

Like nephritis, uveitis is associated with a variety of known causes. Systemic causes in children include juvenile rheumatoid arthritis, sarcoidosis, Behcet disease, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease, Sjögren syndrome, Kawasaki disease, leukemia, and lymphoma [26]. In many cases, no etiology is found. While sarcoidosis is an important diagnosis to exclude, the uveitis in TINU is not granulomatous. Other ocular signs of sarcoidosis, such as iris nodules and optic nerve involvement, do not occur. All of the other diseases specified have characteristic clinical features which are not present in patients with TINU.

The theories of etiology and pathogenesis of TINU are varied and range from infection-related etiologies to primary cellular immune-mediated disease [3, 8]. The majority of cells in the interstitial infiltrate are T-lymphocytes, suggesting a cell-mediated response [3, 7, 9, 13, 15, 27–29]. Many of these T-cells are interleukin-2 receptor positive, suggesting they had been induced by antigen activation [12]. The antigenic insult within the renal parenchyma could also attract an eosinophilic and mononuclear response, with concurrent activation of lymphatic and bone marrow histiocytes leading to the granuloma formation found by Dobrin et al. [1] in their initial 2 cases. It does seem that the antigenic stimuli inducing migration and activation of T-cells are transient, because full recovery from the renal disease usually occurs spontaneously [15]. While the inciting antigen is unknown, one may speculate that there are common antigens in the kidney and uvea leading to both nephritis and uveitis [3]. Dobrin et al. [1] suggest that these inflammatory stimuli increase ocular vascular permeability leading to “metastasis” of inflammatory stimuli to the uvea.

The patient may have a genetic predisposition and the expression of antigen on major histocompatibility complex class II antigens through renal tubular epithelium is important in activating the immune response [15].

In support of a cellular immune pathogenesis, Yano et al. [18] reported a predominance of $CD4^+$ (helper/inducer) T-cells in the renal interstitium. This suggests that a delayed-type hypersensitivity reaction may be involved in the development of interstitial nephritis. Bone marrow granuloma formation may also be a manifestation of a delayed-type hypersensitivity.

Anergy has been reported in some patients [3, 7, 9] and may suggest that there is a reduction in T-helper function. Analogous to sarcoidosis, the systemic immune response may be suppressed, while locally there seems to be vigorous immune reactivity in the uvea and kidney. This depression of cellular immunity seems to be limited to the acute phase of the disease. Gafter et al. [7] speculate that the peripheral immune response is suppressed due to the emergence of cells and other factors at inflammatory sites which may suppress the response of peripheral lymphocytes.

An infectious etiology has not yet been firmly excluded. It is possible there is a common antigen that triggers an immune response, but the causative agent has not yet been cultured [4, 6, 8, 15, 17, 30]. Johnson et al. [30] propose an animal model whereby mice eyelids inoculated with human uveitis mycoplasma-like organisms develop chronic progressive tubulointerstitial nephritis.

If a patient presents with acute interstitial nephritis, we recommend a slit lamp examination of their eyes. The uveitis may be asymptomatic; therefore an ophthalmological consultation is mandatory for its diagnosis and treatment [1, 4, 11, 13–15]. If the presenting symptom is uveitis, a thorough evaluation for a systemic disorder is necessary and should include a urinalysis with microscopy and serum creatinine level as a part of the initial work-up. If TINU is diagnosed, the patients should be followed by both a nephrologist and an ophthalmologist, knowing that their eye disease will likely relapse. Treatment should be based on the natural history of the disease process.

Renal function typically improves and the role of systemic steroids in treatment remains unclear [1, 4, 7, 9, 14, 21, 22]. Spontaneous recovery has been reported in 9 patients [1, 3, 8–10, 12, 13, 17]. While systemic steroid therapy does not seem necessary for all patients [28, 31], there is some evidence that renal function may improve more rapidly in steroid-treated patients [10, 15, 21, 22]. Good histological criteria for treatment remain to be established [10, 22, 32, 33]. The renal disease should be followed for 4–6 weeks, including urine microscopy. If the nephropathy has not yet resolved, we recommend a biopsy for diagnosis. Systemic steroids might be restricted to patients who have evidence of significant tubulointerstitial injury. Long-term follow-up of the patients with significant interstitial fibrosis will be important to ensure that progressive renal insufficiency does not occur as a late sequelae.

In contrast, the uveitis must be treated. Cycloplegics alleviate pain and discourage synechiae formation. Topical steroids reduce intraocular inflammation. If topical steroids are ineffective, systemic therapy may be tried with corticosteroids. Other systemic immunosuppressive drugs have not been necessary [26]. Relapse of uveitis is likely, but will respond to renewed treatment. The patient will need ongoing ophthalmological care.

TINU is a unique syndrome, whose features must be recognized early by pediatricians to avoid unnecessary investigation and treatment. Further recognition and study of this disorder will hopefully lead to understanding of its etiology and pathogenesis, which may shed additional light on other causes and mechanisms of uveitis and nephritis in children.

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LITERATURE ABSTRACTS

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Prevalence of bovine verotoxin-producing *Escherichia coli* in Argentina

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Faecal swabs obtained from 126 calves and 118 cows in Argentina were investigated for the presence of verotoxin-producing *Escherichia coli* (VTEC). VTEC strains were recovered from 10 (23%) of 43 calves with diarrhoea, from 24 (29%) of 83 healthy calves, from 40 (44%) of 91 healthy cows waiting at the slaughterhouse, and from 6 (22%) of 27 healthy grazing cattle. PCR showed that 21 (9%) of animals carried VT1+ strains, 49 (20%) VT2+ strains and 10 (4%) VT1+ VT2+ strains. VT1+ strains predominated among calves (16% versus 0.8%; $P<0.001$). The presence of eae gene was significantly more frequent among VTEC strains isolated from calves (78%; 46/59) than from cows (2%; 1/65) ($P<0.001$). Furthermore, eae gene was more prevalent in VT1+ strains (97%; 32/33) than in VT2+ strains (14%; 10/70) $P<0.001$) and in VT1+ VT2+ strains (24%; 5/21) ($P<0.001$). Sorbitol negative high virulent strains serogroups O157 were not detected. This study indicates that cattle are a reservoir of VTEC strains, and that eae gene is associated with VT1+ strains that are predominating among young animals. Fortunately, only adult animals are taken to the slaughterhouse, among which VTEC strains negative for eae gene are predominating.

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Normal growth or prepubertal nephrotic children during long-term treatment with repeated courses of prednisone

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The growth of 21 prepubertal children with steroid-dependent frequently relapsing nephrotic syndrome was studied before and during treatment with repeated courses of oral prednisone for 4 y. The height and height velocity standard deviation scores (HSDS and HVSDS) of the nephrotic children were –0.11 and –0.06, respectively, at the onset of disease and –0.12 and +0.05, +0.14 and +1.02, +0.21 and +0.78 and +0.17 and +0.66, respectively, thereafter yearly during the treatment. The mean yearly cumulative dose of prednisone was 6,300, 3,459, 2,677 and 2,081 mg/body area (m2) at the first, second, third and fourth year, respectively. The nephrotic children grew normally for their age before onset of the disease and growth remained normal despite prednisone treatment.