# Tubulointerstitial Nephritis and Uveitis Syndrome in Children: A Prospective Multicenter Study

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***Purpose:*** To evaluate the occurrence and characteristics of uveitis related to tubulointerstitial nephritis (TIN) in children.

***Design:*** Prospective, observational, multicenter, partly placebo-controlled treatment trial.

***Participants:*** Nineteen children with a biopsy-proven TIN.

***Methods:*** Patients were treated with prednisone or followed without treatment. In addition to the nephrologic evaluations, the prospective follow-up included structured ophthalmological examinations at the onset of TIN and at 3 and 6 months after the diagnosis.

***Main Outcome Measures:*** Occurrence, clinical features, and outcome of uveitis.

***Results:*** Some 84% (16/19) of the patients had uveitis, 83% (5/6) in the nontreatment group and 82% (9/11) in the prednisone-treated group. The remaining 2 patients, originally in the nontreatment group, were switched to the prednisone group after 2 weeks. Both of them developed uveitis. Altogether, 3 patients developed uveitis during prednisone treatment and 2 patients showed worsening of uveitis despite the systemic corticosteroid. Some 50% (8/16) of the patients with uveitis presented with no ocular symptoms; 88% (14/16) of the patients had a chronic course of uveitis. Two patients were diagnosed with uveitis before nephritis; nephritis and uveitis were diagnosed within 1 week from each other in 7 patients, and uveitis developed 1 to 6 months after the diagnosis of TIN in 7 patients.

***Conclusions:*** There was no statistically significant difference in the occurrence of uveitis in patients with TIN in the prednisone and nontreatment groups. In this study, the occurrence of uveitis associated with TIN was considerably higher than previously reported. Uveitis related to TIN may develop late and is often asymptomatic. The ophthalmological follow-up of all patients with TIN is warranted for at least 12 months starting with 3-month intervals.

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Tubulointerstitial nephritis (TIN) is an inflammatory disease of the kidneys. It may be triggered by infectious diseases and numerous medications, including nonsteroidal anti-inflammatory drugs and antibiotics, but in children the cause remains unknown in the majority of cases. The condition may be accompanied by uveitis, in which case it is referred to as "tubulointerstitial nephritis and uveitis" (TINU) syndrome. The uveitis is typically anterior and bilateral.[1]

The incidence of TINU has been reported to be increased in patients with TIN who are younger than 20 years of age.[1–3] The highest occurrence of uveitis in patients with TIN (46%) was reported by the current authors in a retrospective study of pediatric patients in Finland.[3] In children with bilateral sudden-onset uveitis, the incidence of TINU has been reported to be up to 32%.[4] However, in pediatric patients in Finland, the onset of uveitis related to TIN was insidious in the majority.[3]

In a comprehensive review by Mandeville et al,[1] the diagnosis of TINU was considered definite when the typical uveitis was accompanied by a systemic illness with nonspecific laboratory findings and abnormal renal function and urinalysis. Low-molecular-weight (LMW) proteinuria (elevated urine $\alpha$1- or $\beta$2-microglobulin) is considered especially suggestive of TIN,[3,5] but the histopathologic evaluation of a kidney biopsy sample is needed to confirm the diagnosis. It has also been suggested that detection of certain human leukocyte antigen haplotypes could be used to identify patients with increased risk for uveitis.[6,7] The differential diagnosis of TINU includes other causes of uveitis that may have renal manifestations, including sarcoidosis, Wegener's granulomatosis, nephropathia epidemica, Behçet's disease, and juvenile idiopathic arthritis.

Systemic corticosteroids are used in the treatment of TIN.[8,9] However, the need for and efficacy of steroid treatment have not been shown. The purpose of this study was to evaluate the occurrence and characteristics of uveitis related to TIN in a prospective, multicenter treatment trial.

## Materials and Methods

All patients younger than 18 years of age diagnosed with TIN between the years 2008 and 2011 were screened to take part in a

 

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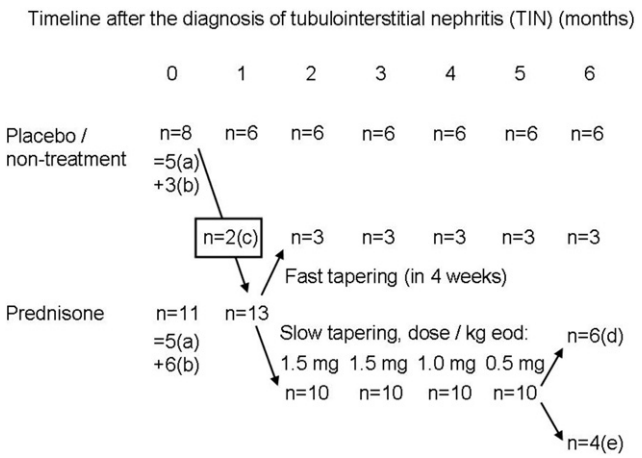


**Figure 1.** Flow of study patients: a = randomized to prednisone or placebo; b = chose prednisone or no treatment; c = switched to prednisone; d = without prednisone after 6 months; e = still receiving prednisone after 6 months; n = number of patients.

partly randomized placebo-controlled study of prednisone treatment for idiopathic TIN. The nationwide screening took place in the 5 university hospitals in Finland. The diagnosis of TIN was based on kidney biopsy. Patients with suspected self-limiting, drug-induced TIN or an underlying disease (e.g., sarcoidosis) were excluded.

The study protocol included a meticulous medical history with specific questions on the typical symptoms of uveitis. The patients were evaluated by a pediatric nephrologist at study inclusion and then at 1 week and 1, 3, and 6 months from the start of medication. Angiotensin-converting enzyme, antinuclear antibody, antineutrophil cytoplasmic antibody, complement components 3 and 4 concentrations, and epidemic nephropathy (Puumala) antibodies were determined and chest x-ray examinations obtained to rule out underlying diseases, including sarcoidosis. The structured ophthalmic examinations to screen for uveitis were scheduled to take place at the onset of TIN and at 3 and 6 months after the diagnosis. The examination included the visual acuity, evaluation of the conjunctiva and cornea including precipitates, grading of cells and flare in the anterior chamber, intraocular pressure, and dilated fundoscopy, also patients with no ocular symptoms were examined. The study adhered to the tenets of the Declaration of Helsinki, and the study protocol was approved by the local ethics committee of each university hospital, the National Agency for Medicines in Finland, and the European Union Drug Regulating Authorities Clinical Trials (EudraCT).

Twenty-one patients were screened during the study period. Two patients were excluded; 1 had diabetes mellitus and 1 was unable to participate because of the tight schedule of the structured protocol. There were no patients excluded because of the failure to obtain informed consent. All 19 patients included in the study completed the follow-up.

Initially, the patients were randomized into the prednisone and the nontreatment groups in a double-blinded manner, and the patients in the nontreatment group were given placebo. Serum creatinine was closely monitored, and if there was a significant increase during the first 2 weeks, the randomization code was opened to ensure that the patient was in the prednisone group. However, the study was changed to an open-label study of treatment versus nontreatment because of the parents' reluctance to enter their children in a blinded, randomized treatment trial. The last 9 patients and their parents were given the opportunity to choose between prednisone and nontreatment. Three of these patients chose follow-up without treatment.

The treatment group received oral prednisone twice per day starting at a dose of 2 mg/kg/day, with a maximum dose of 60 mg. If the nephritis was considered to be fully recovered after 4 weeks, the dose was reduced to 40 mg/m$^2$ every other day for 1 week and tapered by 10 mg/m$^2$ every other day in 1-week steps during the next 3 weeks. If the patient still had LMW proteinuria and elevated serum creatinine at 1 month, the prednisone dose was reduced to 1.5 mg/kg every other day for 2 months and tapered by 0.5 mg/kg every other day in 1-month steps. The study flow is presented in Figure 1.

Uveitis was classified according to Standardization of Uveitis Nomenclature criteria.[10] The onset of uveitis was classified as insidious or sudden onset. The course of uveitis was considered acute if the episode was characterized by a sudden onset and a limited (<3 months) duration. Uveitis that persisted more than 3 months with relapse within 3 months after discontinuing treatment was considered chronic.[10]

The statistical analysis was performed using PASW Statistics 18 (SPSS Inc., Chicago, IL). To compare groups with respect to background characteristics, Wilcoxon rank-sum test, chi-square comparison, or Fisher exact test was used. A $P$ value $<0.05$ was considered statistically significant.

# Results

## Prevalence of Uveitis

Some 84% (16/19) of the patients with TIN had uveitis (TINU). The mean age at the onset of uveitis was 12 years and 9 months, and 50% (8/16) of the patients with TINU were female. Two of the patients with TINU were identical twins. All 16 patients had bilateral anterior uveitis. Eight patients had fine keratic precipitates. Six patients showed mild inflammation in the anterior vitreous, and 1 patient had optic disc swelling (Table 1). None of the patients had sarcoid spots or other retinal findings related to uveitis.

## Onset of Uveitis

Some 50% (8/16) of the patients with uveitis presented with no ocular symptoms. The symptoms related to uveitis included redness, eye pain, photophobia, decreased visual acuity, and itching (Table 1). Two patients were diagnosed with uveitis before nephritis; the nephritis and uveitis were diagnosed within 1 week from each other in 7 patients, and the uveitis developed 1 to 6 months after the diagnosis of TIN in 7 patients (Fig 2).

Table 1. Symptoms and Characteristics of Uveitis (n = 16)

| | No. of Patients | % |
|---|---|---|
| Ocular symptoms | | |
| No ocular symptoms | 8/16 | 50 |
| Photophobia | 6/16 | 38 |
| Redness | 6/16 | 38 |
| Eye pain | 3/16 | 19 |
| Decreased visual acuity | 2/16 | 13 |
| Characteristics of uveitis | | |
| Bilateral anterior uveitis | 16/16 | 100 |
| Keratic precipitates | 8/16 | 50 |
| Vitreous cells | 6/16 | 38 |
| Optic disc swelling | 1/16 | 6 |

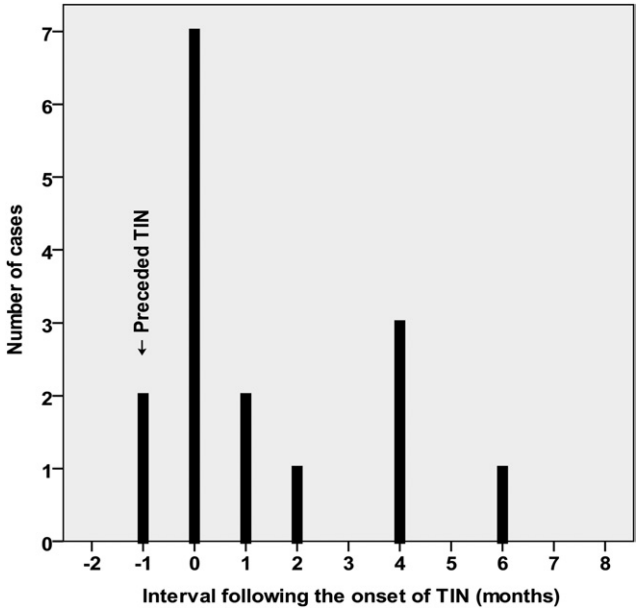


**Figure 2.** The onset of uveitis relative to tubulointerstitial nephritis (TIN) (n = 16).

## Effect of Prednisone versus Nontreatment for Tubulointerstitial Nephritis

Some 83% of patients (5/6) in the nontreatment group and 82% of patients (9/11) in the prednisone-treated group had uveitis. The remaining 2 patients in the nontreatment group were switched to the prednisone group after 2 weeks. Both of them developed uveitis, one before the change in treatment and the other 2 months after the change, while still receiving prednisone. There was no statistically significant difference ($P = 1.0$; n = 17; Fisher exact test) in the occurrence of uveitis in patients with TIN treated with prednisone and those followed without treatment, even when calculated on the basis of intention to treat ($P = 1.0$; n = 19). Altogether, 3 patients developed uveitis during prednisone treatment and 2 patients showed worsening of uveitis despite the systemic corticosteroid. There was no statistically significant difference ($P = 0.85$; n = 17) in the severity of uveitis between the prednisone and nontreatment groups when comparing the highest Standardization of Uveitis Nomenclature gradings of anterior chamber cells during follow-up (Table 2).

## Treatment of Tubulointerstitial Nephritis and Uveitis

All 16 patients with TINU were treated with topical steroids. They initially received topical prednisolone or dexamethasone, but during the course of treatment rimexolone or fluorometholone also was used, especially in patients with ocular hypertension. The initial daily dose was between 1 and 16 drops (mean 9.4). Mydriatics were used in 9 patients (56%). Six patients received antiglaucoma medication. They were treated with topical timolol, and in 3 patients it was combined with dorzolamide or brinzolamide. Five patients (31%) were started on systemic methotrexate as adjunctive or steroid-sparing therapy. Methorexate treatment was initiated 8 to 24 (mean 13.0) months after the diagnosis of uveitis, and the weekly dose was varied from 7.5 to 20 mg. Ocular surgery was not required.

Table 2. Demographic Features, Treatment Group, and Course and Outcome of Uveitis of Patients with Tubulointerstitial Nephritis and Uveitis

| Age at Onset of Uveitis (yrs) | Sex | Treatment of TIN | Onset of Uveitis | Duration of Uveitis (mos) | Course of Uveitis | Duration of Ocular Follow-up (mos) | Maximal Anterior Chamber Cells (SUN) | Complications | Last Reported Visual Acuity | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| 5 | Male | Prednisone | Insidious | >24 | Chronic | 24 | 3+/3+ | OHT, elevated liver enzymes | 1.0/1.0 | Vitreous cells |
| 9 | Male | Prednisone | Insidious | 30 | Chronic | 48 | 1+/1+ | OHT | 0.9/0.8 | |
| 9 | Male | No treatment | Sudden onset | 26 | Chronic | 37 | 1+/2+ | No | 1.2/1.2 | Optic disc edema |
| 9 | Male | No treatment | Sudden onset | >28 | Chronic | 30 | 2+/2+ | No | 1.0/0.9 | Twin |
| 11 | Male | No treatment | Insidious | >6 | Chronic | 10 | 3+/3+ | No | 1.0/1.0 | Twin, vitreous cells |
| 12 | Female | Prednisone | Insidious | 1 | Acute | 10 | 1+/1+ | No | 1.0/0.8 | |
| 12 | Female | No treatment | Sudden onset | 3 | Chronic | 17 | 1+/2+ | OHT | 1.0/1.0 | |
| 12 | Male | Prednisone | Sudden onset | 3 | Acute | 32 | 1+/1+ | OHT | 1.4/1.4 | |
| 13 | Female | Prednisone | Insidious | >2 | Chronic | 6 | 1+/0.5+ | No | 1.0/1.0 | |
| 13 | Female | Prednisone | Insidious | >36 | Chronic | 36 | 1+/1+ | OHT | 1.0/1.0 | Vitreous cells |
| 14 | Female | Switched to prednisone | Insidious | >33 | Chronic | 44 | 2+/2+ | OHT | 0.8/1.0 | Vitreous cells |
| 14 | Female | Prednisone | Sudden onset | 5 | Chronic | 7 | 1+/2+ | No | 0.8/1.0 | Vitreous cells |
| 15 | Female | Switched to prednisone | Insidious | 13 | Chronic | 21 | 0.5+/1+ | OHT | 1.0/1.0 | |
| 15 | Male | Prednisone | Insidious | 24 | Chronic | 36 | 1+/1+ | No | 0.9/1.2 | |
| 15 | Male | Prednisone | Sudden onset | 33 | Chronic | 36 | 3+/3+ | OHT, elevated liver enzymes | 1.2/1.2 | Vitreous cells |
| 17 | Female | No treatment | Insidious | >12 | Chronic | 12 | 1+/1+ | No | 1.2/1.2 | |

OHT = ocular hypertension; SUN = Standardization of Uveitis Nomenclature; TIN = tubulointerstitial nephritis.
The SUN criteria were used to grade anterior chamber cells.

Table 3. Symptoms and Laboratory Findings of Tubulointerstitial Nephritis at the Time of Diagnosis (n = 19)

| Symptom | No. of Patients | % |
|---|---|---|
| Fatigue | 18/19 | 95 |
| Loss of appetite | 16/19 | 84 |
| Weight loss | 12/19 | 63 |
| Fever | 10/19 | 53 |
| Headache | 7/19 | 37 |
| Laboratory findings | | |
| Elevated ESR | 18/19 | 95 |
| Elevated serum creatinine | 17/19 | 89 |
| Glucosuria | 19/19 | 100 |
| LMW proteinuria* | 19/19 | 100 |
| Pyuria | 4/19 | 21 |

ESR = erythrocyte sedimentation rate; LMW = low-molecular-weight proteinuria.
*Elevated urine $\alpha$1- or $\beta$2-microglobulin.

### Complications

Eight patients (50%) with uveitis developed ocular hypertension (24–46 mmHg) during topical steroid therapy. Four (50%) of them were subsequently treated with methotrexate. All patients with ocular hypertension showed reduction of intraocular pressure when the steroid doses were reduced. One of the patients with TIN without uveitis had ocular hypertension during systemic prednisone treatment for TIN and was treated with topical timolol. After the prednisone treatment, timolol was safely discontinued. Two patients had elevated liver enzymes during methotrexate therapy. All complications resolved during the course of treatment, leaving no permanent damage.

### Clinical Course and Outcome

Some 88% (14/16) of patients had a chronic course of uveitis. At the time of writing this article, the mean duration of uveitis was 17 months, but 7 patients still had mild anterior uveitis at their last visit. So far, there have been only 4 patients (25%) with TINU who have shown 3 months of inactivity of uveitis after discontinuing treatment. The last recorded visual acuity was at least 20/25 in both eyes in all patients (Table 2).

### Tubulointerstitial Nephritis

The general symptoms of TIN were unspecific. Most patients had loss of appetite, fatigue, and fever (Table 3), which were in many cases misinterpreted as symptoms of a common cold or other infectious disease. The general outcome of TIN was good. None of the patients developed severe renal insufficiency during the 6-month follow-up time. However, most patients (63%) showed prolonged LMW proteinuria, which suggests tubular dysfunction.

## Discussion

There are approximately 300 cases of TINU reported in the literature. Before the present prospective study, the reports have been based on retrospective analyses of patient records and case reports. A comprehensive review article on TINU summarizes the reported findings of 133 patients.[1]

In a case series of 33 patients, uveitis related to TINU was reported to be sudden onset in 97% of the patients.[4] In a comprehensive review, only 3% (2/71) of the patients with TINU had no symptoms of uveitis.[1] In our retrospective series, 58% of the patients with uveitis were asymptomatic.[3] In the present study, 50% of the patients with uveitis reported no ocular symptoms, despite the specific questions on the symptoms of uveitis. The prospective ophthalmological follow-up may have led to earlier diagnoses of uveitis, that is, before the onset of symptoms. The early diagnosis of uveitis has been related to a more favorable outcome.[11] In 7 patients, uveitis was diagnosed simultaneously with TIN (Fig 2). Because of the high number of patients with asymptomatic uveitis, the onset of uveitis may have been earlier.

In this study, the occurrence of uveitis associated with TIN was considerably higher than previously reported. In retrospective case series, it has been reported to be between 14% and 46%.[2,3] In this study, 84% of the patients with TIN developed uveitis. All of the patients had biopsy-proven TIN. Because TIN may improve without treatment, the patients who are referred to university hospitals may represent the more severe cases of the disease. In theory, this may be related to increased occurrence of uveitis. However, in our earlier retrospective case series, neither the severity nor the prognosis of nephritis was related to the presence of uveitis.[3] Others have also reported that the course of uveitis and nephritis is not related.[1,4] Our study population consisted entirely of pediatric patients, which may have influenced the occurrence of uveitis. Mandeville et al[1] have shown that patients younger than 20 years of age are more prone to chronic uveitis than the adult population.

Kidney biopsy is the only way to confirm the diagnosis of TIN. All patients in this study had biopsy-proven TIN. The ultrasound-guided kidney biopsy is considered to be a safe procedure,[12] and even repeated biopsies in patients with TIN have been recommended if monitoring of renal progression is needed.[13]

We have previously shown in a retrospective study that uveitis related to TIN may develop late, is often initially asymptomatic, and has a tendency to be chronic.[3] This prospective study confirms these findings. The delay from the onset of TIN was up to 6 months, 50% of the patients had no ocular symptoms, and 88% had a chronic course of uveitis. Uveitis related to juvenile idiopathic arthritis also is typically asymptomatic and chronic and may develop years after the onset of arthritis. Repetitive ophthalmological examinations to screen for uveitis are recommended after diagnosing juvenile idiopathic arthritis.[14] To find the asymptomatic cases, ophthalmological screening of patients with TIN also is warranted.

There was no statistically significant difference in the occurrence of uveitis in patients with TIN treated with prednisone and followed without treatment. Systemic corticosteroids are effective in the treatment of uveitis, but in our hospital-referred, biopsy-proven, pediatric patients with TIN, they did not seem to prevent the occurrence of uveitis. Three patients developed uveitis during prednisone treatment. The onset of uveitis during corticosteroid treatment also has been reported in earlier studies.[15,16] Ophthalmological follow-up visits are necessary during systemic steroid treatment, especially when the doses are decreasing. Other immunosuppressive therapy

used in the treatment of TINU includes methotrexate, azathioprine, cyclosporine A, mycophenolate mofetil, and tumor necrosis factor-$\alpha$ inhibitors.[3,17–19] In this study, 5 patients received methotrexate. Adalimumab was under consideration for 1 patient, but the course of uveitis changed for the better before it was started. Altogether, the immunosuppressive treatment should be managed together with the pediatric nephrologists, and the course and severity of both the nephritis and uveitis should be taken into consideration when determining the course of treatment.

All of the complications in this study were treatment related: ocular hypertension due to steroid treatment and elevated liver enzymes due to methotrexate. There were no complications caused by uveitis. For example, none of the patients developed posterior synechiae, which is the most common reported complication of uveitis in TINU.[1] This may be related to the earlier diagnosing of uveitis because of the prospective follow-up.

Four of the patients who developed ocular hypertension subsequently received methotrexate. Steroid-induced hypertension often is resistant to antiglaucoma medications, and the steroid-sparing effect achieved with methotrexate also reduces intraocular pressure. The antiglaucoma medications used in this study included $\beta$-blockers and carbonic anhydrase inhibitors. Prostaglandin analogs are generally not used as first-line treatment of hypertension in the presence of uveitis because there is some concern they may cause activation of the inflammation.[20]

The prognosis of both nephritis and uveitis is good in the majority of patients with TINU. Most studies report a full recovery of visual function in all patients.[3,5,21] However, there are 2 reported cases of severe visual impairment due to TINU. One was caused by bilateral macular edema, and one was caused by rhegmatogenous retinal detachment.[4,22] Tubulointerstitial nephritis rarely causes permanent renal insufficiency.[21,23] The outcome of the nephritis also was good in this study in both the prednisone and nontreatment groups. However, more than half of our patients still showed tubular dysfunction 6 months after the diagnosis. We therefore suggest that urinalysis and quantitation of LMW protein excretion should be considered even in patients with normal serum creatinine concentration during the follow-up of TIN.

In conclusion, the possibility of TINU should be remembered, especially when treating a young patient with bilateral anterior uveitis. Uveitis related to TIN may be more common than previously reported, is often insidious, and may develop late. The treatment of TIN with systemic steroids did not seem to decrease the occurrence of uveitis in this study. Therefore, ophthalmological follow-up is warranted for all patients with TIN, including the asymptomatic patients receiving systemic steroids. We recommend ophthalmic examinations for at least 12 months starting with 3-month intervals.

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