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HAL Id: hal-03636866
https://hal.umontpellier.fr/hal-03636866v1

Submitted on 11 Apr 2022

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Introduction: Tubulointerstitial nephritis (TIN) and uveitis (TINU) syndrome is a rare disease. The renal prognosis is generally thought to be better in children with TINU syndrome than in adults. However, data are scarce. We aimed to investigate the long-term renal prognosis in a French cohort of children with TINU syndrome.

Methods: We performed a national retrospective study including 23 French pediatric nephrology centers enrolling patients with TINU syndrome diagnosed between January 2000 and December 2018.

Results: A total of 46 patients were included (52% female, median age 13.8 years). At diagnosis of TIN, the median estimated glomerular filtration rate (eGFR) was 30.6 ml/min per 1.73 m^2 (4.9–62.8). The median time between diagnosis of uveitis and TIN was 0.4 months (−4.1; +17.1). All patients had anterior uveitis, but 12 (29%) were asymptomatic. Nearly all patients (44 of 46) received steroid treatment, and 12 patients (26%) received a second-line therapy. At last follow-up (median 2.8 years), the median eGFR was 87.5 ml/min per 1.73 m^2 (60.3–152.7) and <90 ml/min per 1.73 m^2 in 20 patients.

Conclusion: In our study, nearly half of the patients had renal sequelae at last follow-up. Given the possible progression to chronic kidney disease, long-term monitoring of children with TINU syndrome is mandatory. Approximately a quarter of the children had asymptomatic uveitis suggesting all children presenting with TIN should undergo systematic ophthalmologic screening even in the absence of ocular signs.

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TINU syndrome is a rare disease that was first described by Dobrin in 1975.[1] It is defined as a combination of acute TIN and uveitis. In 2001, Mandeville et al.[2] proposed diagnostic criteria and classified TINU syndrome into 3 categories—"definite," "probable," or "possible" (Supplementary Table S1). TINU syndrome may be triggered by infectious diseases or medications (nonsteroidal anti-inflammatory drugs or antibiotics), but its physiopathology remains unclear to date.[3–5]

The median age at diagnosis of TINU syndrome is from 15 to 17 years, but the exact incidence and prevalence remain undetermined and are probably underestimated as the condition could be underdiagnosed.[2] A recent review estimated the prevalence of TINU syndrome to be of 2.3% in children diagnosed with having uveitis.[6] Others estimate the prevalence to be from 5% to 28% in children diagnosed with having TIN.[7–9] In Japan, TINU syndrome is the second etiology of pediatric uveitis after sarcoidosis and is found in up to a third of patients with bilateral acute anterior uveitis.[10] Therefore, TINU syndrome seems to be a significant part of etiology in children with isolated TIN or uveitis at presentation.

The renal prognosis of TINU syndrome is usually described as favorable: recent data from Hayashi et al.[11] revealed a good renal outcome in a series of 29 children. The same conclusion was drawn from data collected recently by Regusci et al.[12] in a systematic review of the literature. Nevertheless, recent studies have highlighted that 70% to 96% of adult patients with TINU have chronic kidney failure on long-term follow-up.[13,14] These conflicting results highlight the weakness of the literature and require confirmation of the general supposition that the outcome of pediatric patient with TINU is generally good.[7,11]

Therefore, the aims of our study were to describe the clinical and biological data, therapeutic management, and renal outcome in a cohort of French pediatric cases of TINU syndrome diagnosed in the past 18 years and to highlight risk factors of poor renal prognosis.

METHODS

A national retrospective study was performed including all 23 pediatric nephrology units in France. To improve the completeness, patients were identified by crossing data from the following 3 different registries: the common nomenclature of medical treatment (patients <18 years, diagnosed with having TIN), the National Rare Disease Registry (CEMARA/BAMARA: TINU or Dobrin syndrome), and local registers specific to each center.

Approval to perform the study was obtained from the Ethics Committee of Montpellier (no. 2019_IRB-MTP_02-22).

Patients had to meet the following inclusion criteria: at least 1 attack corresponding to TINU syndrome according to the criteria of Mandeville's classification ("definite" and "probable" TINU [Supplementary Table S1]), aged <18 years, and diagnosed between January 2000 and December 2018. Exclusion criteria were "possible" TINU syndrome according to Mandeville's TINU classification, <12 months of follow-up, or an incomplete medical file not allowing collection of data. After patient identification, data were collected in each center by means of a standardized form. Differential diagnosis, such as sarcoidosis, Sjogren syndrome, and lupus, was ruled out for all patients.

Clinical and Biological Data at Presentation

The following data were collected for each patient: personal and family history of autoimmune diseases, medication during preceding month, age at diagnosis, and sex.

The time to onset between uveitis and TIN was calculated in months. Ophthalmologic symptoms, such as follows, during the first attack of uveitis were collected: red eye, painful eye, reduced visual acuity, and photophobia. The clinical features of uveitis on diagnosis were described by the report of the ophthalmologist and included uveitis type (anterior, intermediate, posterior, or panuveitis; unilateral or bilateral; granulomatous) and uveitis complications.

The general symptoms at the first attack of TIN were as follows: weight loss (in kg), fever ($>38\ ^{\circ}C$), vomiting, abdominal or lumbar pain, headache, arthralgia or myalgia, dyspnea on exertion, polyuropolydipsic syndrome, and skin rash.

The following biological parameters were assessed: enzymatic-assessed serum creatine level, eGFR (using 2009 Schwartz's formula with $k = 36.5$, in ml/min per 1.73 m^2), and serum electrolytes.[15,16] Hypokalemia was defined as <3.1 mmol/l, hypophosphatemia was defined as <1.16 mmol/l in patients from 6 to 12 years old or <0.74 mmol/l in patients >13 years old, and acidosis was defined as bicarbonatemia <20 mmol/l. Biological inflammatory syndrome was defined as CRP >10 mg/l and/or erythrocyte sedimentation rate >40 mm, and/or plasma protein electrophoresis with hypergammaglobulinemia, α-1 or α-2 hyperglobulinemia, and/or IgG >17.2 g/l. Anemia was defined as hemoglobin concentration <11.1 g/dl in patients 6 to 12 years old or <12.1 g/dl in patients >12 years old, lymphopenia as <1500/mm^3, and hypereosinophilia as >800/mm^3. Significate proteinuria was defined as proteinuria/creatinuria >20 mg/mmol,

Table 1. Symptoms at first attack of TIN and uveitis

	Patients/population (%)			
Initial symptoms	CoR at 1 year n = 11, n (%)	InR at 1 year n = 34, n (%)	P	Total, n/N (%)
General				
Weight loss kg, median (range)	9 (82)	23 (68)	0.83	33/44 (75) 5 (2–17)
Fever[a]	4 (36)	18 (53)	0.34	22/46 (48)
Abdominal pain	4 (36)	16 (47)	0.73	20/46 (44)
Vomiting	4 (36)	12 (35)	1	16/46 (35)
Polyuropolydipsic syndrome	5 (45)	11 (32)	0.65	17/43 (40)
Headache	5 (45)	9 (26)	0.28	14/46 (30)
Dyspnea on exertion	3 (27)	7 (21)	0.61	11/43 (26)
Arthralgia/myalgia	4 (36)	5 (15)	0.19	9/46 (20)
Absence of general symptoms	MD	MD	MD	4/46 (9)
Eye				
Uveal symptoms				
Asymptomatic	3 (27)	10 (29)	0.49	12/46 (26)
Red eye	7 (64)	22 (65)	0.36	30/42 (71)
Painful eye	6 (55)	22 (65)	0.49	29/42 (69)
Reduced visual acuity	2 (18)	8 (24)	1	11/38 (29)
Photophobia	2 (18)	4 (12)	0.41	7/39 (18)
Ophthalmologic examination				
Anterior uveitis	11 (100)	34 (100)	1	46/46 (100)
Intermediate uveitis	0 (0)	5 (15)	0.31	4/46 (9)
Posterior uveitis	0 (0)	4 (12)	0.56	3/46 (7)
Panuveitis	0 (0)	3 (9)	0.57	3/46 (7)
Unilateral uveitis	2 (18)	9 (26)	0.70	11/46 (24)
Bilateral uveitis	9 (82)	25 (74)	0.70	35/46 (76)
Granulomatous uveitis	2 (18)	4 (12)	0.62	6/40 (2)
Complication at diagnosis[b]	1 (9)	8 (24)	0.65	9/35 (26)

CoR, complete recovery; InR, incomplete recovery; MD, missing data; TIN, tubulointerstitial nephritis.
[a]Fever defined as body temperature >38 °C.
[b]Iris synechiae or cystoid macular edema.

urinary β2-microglobulin (β2m) was positive if >0.2 mg/l, glycosuria was defined as urine glucose level >0.2 mmol/l, aseptic leukocyturia was defined as leukocytes >10,000/ml with sterile culture, and hematuria was defined as erythrocyte count >10,000/ml.[17,18]

Kidney ultrasound findings such as increase in kidney size and cortical hyperechogenicity were collected. Histologic description of kidney biopsy samples was recorded.

Follow-Up

Data regarding renal and ophthalmologic outcome (number of relapses) were collected for all patients at 1 year and at last follow-up. Details of therapies administered were recorded.

Data at 1 year (±3 months) and at last follow-up included the following: eGFR, blood pressure (high blood pressure [HBP] was defined as a blood pressure >95th percentile by ag, sex, and size[19] or patient treated with an antihypertensive drug), and proteinuria (positive proteinuria was defined as a value >20 mg/mmol or positive result from urine dipstick test at ≥1+).

The persistence of ophthalmologic involvement was defined by the presence of uveitis and/or treatment with a topical corticosteroid and/or ophthalmologic complications (chronicity of uveitis, elevated intraocular pressure, cataract).

At 1 year and at last follow-up, the patients were categorized into the following 2 groups according to renal progression: "incomplete recovery" (InR) group defined by an eGFR <90 ml/min per 1.73 m^2 and/or proteinuria and/or HBP and/or treatment with an antiproteinuric or antihypertensive drug and "complete recovery" (CoR) group defined by the absence of these criteria. A patient was defined as being in remission if there was no uveitis recurrence for 1 year without local or systemic treatment and with CoR at last follow-up.

Statistical Analysis

Statistical analysis was computed using SAS 9.4, GraphPad Prism version 5.04 for windows (La Jolla, CA, www.graphpad.com). Quantitative variables are expressed as medians and ranges (minimum and maximum) and compared using nonparametric Wilcoxon–Mann–Whitney U test or Student t test.

Table 2. Abnormal biological and urinary findings at the first attack

| Abnormal findings | Patients/population (%) | | | | |
	CoR 11, n (%)	InR 34, n (%)	*P*	Total, n/N (%)	Median (range[a])
Biological					
eGFR <30 ml/min per 1.73 m^2	2 (18)	20 (59)	0.04	22/46 (48)	30.6 (4.9–62.8)
Hypokalemia (mmol/l)	2 (18)	8 (24)	1	10/46 (22)	3.8 (2.7–4.6)
Hypophosphatemia (mmol/l)	3 (27)	7 (21)	0.66	10/45 (22)	1.13 (0.64–1.75)
Acidosis (bicarbonates mmol/l)	6 (55)	18 (23)		25/45 (56)	20.5 (12–28)
Biological inflammatory syndrome	MD	MD	MD	41/45 (91)	
CRP (mg/l)	MD	MD	MD	30/44 (68)	25.8 (2–161)
ESR (mm/h)	MD	MD	MD	24/32 (75)	73 (22–128)
Anemia (g/dl)	9 (82)	25 (74)	0.70	35/46 (76)	10.5 (6.9–14.5)
Lymphopenia (/mm^3)	1 (9)	4 (12)	0.82	5/43 (12)	2400 (1000–6410)
Hyperleukocytosis (/mm^3)	3 (27)	5 (15)	0.48	8/43 (19)	8870 (4540–19,960)
Hypereosinophilia (/mm^3)	0 (0)	0 (0)		0/39 (0)	341 (40–644)
Urinary					
Increase of β2m (mg/l)	MD	MD	MD	28/28 (100)	19.3 (1.05–72.2)
Proteinuria (mg/mmol)	10 (91)	30 (88)	1	41/46 (89)	93 (8–279.8)
Normoglycemic glycosuria	8 (73)	25 (74)	0.52	33/37 (89)	
Aseptic leukocyturia	9 (82)	18 (53)	0.26	28/41 (68)	
Hematuria	2 (18)	6 (18)	1	8/41 (20)	

CoR, complete recovery; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; InR, incomplete recovery; MD, missing data; β2m, β2-microgluobulin.
[a]Range from minimum to maximum.

Qualitative variables are expressed as number and percentage and were compared using the Fisher exact test or χ^2 test as appropriate. Univariate and multivariate correlation analyses were performed to determine risk factors. Primary outcome was defined by InR at 1 year and at last follow-up. A $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics
Of the 58 patients identified as having TINU syndrome from the databases of the participating pediatric nephrology centers, 46 were included in the study (Supplementary Figure S1). According to Mandeville's criteria, 36 patients (78%) had definite TINU syndrome and 10 (22%) had probable TINU syndrome. The main clinical and biological findings at diagnosis, treatments received, and progression were summarized in Supplementary Table S2 (Supplementary Material). The female-to-male sex ratio was 1.1:1 (24 female and 22 male). The median age at diagnosis was 13.8 years (range 7.2–17.0). There was 1 patient who had type 1 diabetes mellitus diagnosed at 5 years of age. Furthermore, 7 patients had a family history of autoimmune disease: TINU syndrome (classified as "possible") in his twin brother for 1 patient (2%), 4 patients (9%) had thyroid disease in first-degree relative family, 1 patient (2%) had a mother with juvenile idiopathic arthritis, and 1 patient (2%) had a father with type 1 diabetes mellitus. In addition, 19 patients (41%) had received

medication in the previous month: 7 (15%) received antibiotics (cephalosporins, macrolides, or penicillin), 6 (13%) nonsteroidal anti-inflammatory drugs, 4 (9%) proton pump inhibitors, and 3 (7%) other medications, such as anticonvulsant or colchicine.

The median time between uveitis diagnosis and TIN was 0.4 months (range −4.1 to 17.1). Uveitis preceded TIN diagnosis in 11 patients (24%), and TIN preceded uveitis diagnosis in 26 (57%). Uveitis and TIN occurred simultaneously in the remaining 9 patients (20%).

Initial Presentation
The general and ocular symptoms at the first attack are summarized in Table 1. There were 4 patients who had no general symptoms but were diagnosed with having TINU syndrome by means of a blood test performed during uveitis management. Conversely, 12 patients (29%) had no ocular signs and were diagnosed during systematic ophthalmologic screening after TIN diagnosis.

All patients had impaired kidney function (i.e., an eGFR <90 ml/min per 1.73 m^2). The median eGFR at diagnosis was 30.6 ml/min per 1.73 m^2 (4.9–62.8 ml/min per 1.73 m^2) (Table 2).

Kidney ultrasound result was abnormal in 14 patients (30%): 5 (11%) had enlarged kidneys and 12 (26%) had renal cortical hyperechogenicity. Kidney biopsy was performed in 44 patients (96%). The most frequent histologic findings were interstitial infiltration with a predominance of lymphocytes and plasma cells for 82% of the patients. Of these patients, 10 (23%) had

Table 3. Comparison of initial clinical and biological characteristics between patients with InR and CoR at 1 year and at last follow-up

Characteristics	At 1 year			At last follow-up		
	CoR (n = 11)	InR (n = 34)	P value	CoR (n = 14)	InR (n = 24)	P value
Female sex	4 (36%)	19 (56%)	0.26	7 (50%)	13 (54%)	0.80
Age (yr)	11.9 (7.2–15.9)	13.9 (8.6–15.6)	0.38	10.8 (7.2–15.9)	13.9 (8.6–15.6)	0.06
At diagnosis						
Creatininemia (µmol/l)	136 (82–727)	231 (90–1110)	0.01	134 (82–386)	226.5 (90–1110)	0.05
eGFR (ml/min per 1.73 m^2)	42 (±15.6)	29.8 (±15.4)	0.03	37.8 (±16.7)	28.9 (±14.8)	0.10
eGFR >30 ml/min per 1.73 m^2	9 (82%)	14 (42%)	0.02	8 (57%)	10 (42%)	0.36
eGFR <30 ml/min per 1.73 m^2	2 (18%)	20 (59%)	0.02	6 (43%)	14 (58%)	0.36
Hemoglobin (g/dl)	10 (±1.5)	10.6 (±1.7)	0.29	10.5 (±1.5)	10.4 (±1.9)	0.84
CRP (mg/l)	14 (2–82)	30 (2–161)	0.08	39.5 (2–137)	22.7 (2–161)	0.35
ESR (mm/h)	62.2 (±25.7)	72.1 (±29)	0.48	71 (±26.1)	70.6 (±31.7)	0.97
Albuminemia (g/l)	41.1 (±4.5)	37.3 (±4.6)	0.03			
Uveitis complications	1 (9%)	8 (24%)	0.65	2 (14%)	6 (25%)	0.35
Granuloma on kidney biopsy	3 (27%)	4 (12%)	0.32	5 (36%)	1 (4%)	0.02
Fibrosis on kidney biopsy	6 (55%)	13 (38%)	0.59	6 (43%)	10 (42%)	1.00
Occurrence of uveitis after TIN	5 (45%)	20 (59%)	0.72	4 (29%)	18 (75%)	<0.01
Progression						
Methylprednisolone pulses	2 (18%)	17 (50%)	0.09	5 (36%)	10 (42%)	0.72
Second-line therapy	3 (27%)	9 (27%)	1.00	4 (29%)	5 (21%)	0.70
Kidney relapses	0 (0%)	5 (15%)	0.31	2 (14%)	3 (13%)	1.00
Uveitis relapses	6 (55%)	19 (56%)	1.00	12 (86%)	10 (42%)	<0.01
Ophthalmologic involvement at 1 year	4 (36%)	10 (29%)	0.72	6 (43%)	4 (17%)	0.13
Ophthalmologic involvement at last follow-up				4 (29%)	7 (29%)	1.00
Treatment[a] at 1 year	6 (55%)	17 (50%)	0.79	7 (50%)	14 (58%)	0.62
Treatment[a] at last follow-up				4 (29%)	4 (17%)	0.43
Median time to follow-up (yr)				3.2 (1.1–8.3)	2.5 (1.2–9.5)	0.23

CoR, complete recovery, InR, incomplete recovery, eGFR, estimated glomerular filtration rate, ESR, erythrocyte sedimentation rate, TIN, tubulointerstitial nephritis.
[a]Corticotherapy or second-line therapy.
Data presented as median and rank (minimum and maximum), mean ± SD, or number and percentage.

rare eosinophils. Fibrosis was found in 19 patients (43%). Using the Banff classification on interstitial fibrosis and tubular atrophy, repartition of patient was as follows: grade III: 0, grade II: 3, grade I: 3, and grade 0: 13. A granuloma was found in 8 patients (18%). None had glomerular disease.

Treatments
No patient required dialysis. At TIN diagnosis, 44 patients (96%) were treated by corticosteroids and 20 of these (44%) were started with 3 pulses of methylprednisolone. Pulse posology was 500 mg/m^2 for 5 of 20 patients (25%), 1 g per 1.73 m^2 for 11 of 20 (55%), and 500 mg per 1.73 m^2 for 4 of 20 (20%). Oral steroid dosage ranged from 0.5 to 2 mg/kg per day (range: 30–120 mg/d). The median duration of steroid therapy was 8.2 months (range 2–62 months), and 3 patients were still receiving corticosteroid therapy at the last follow-up (median 2.9 years).

Treatment for uveitis included topical or subconjunctival steroids for 42 patients (91%) and combined with mydriatic for 26 (57%).

There were 12 patients (26%) who received a second-line immunosuppressive drug. Indications for this second-line treatment were the following: uveitis recurrence for 7 patients (4 received methotrexate and 3 azathioprine), TIN recurrence for 4 (treated with mycophenolate mofetil), and resistant TIN and uveitis recurrence for 1 (treated with mycophenolate mofetil). Among these 12 patients, 2 received another immunosuppressive drug (adalimumab) for uveitis recurrence despite methotrexate or mycophenolate mofetil treatments. The median immunosuppressive therapy duration was 18 months (range 4.1–40.9 months). At the last follow-up, 7 patients (15%) were still receiving an immunosuppressive treatment with a median duration of 2.4 years.

Clinical Progression
At 1 Year
Data were available for 45 patients at 1 year. Their median eGFR was 82.8 ml/min per 1.73 m^2 (60.2–129.6). There were 11 patients who were considered as having a CoR at this time, with a median eGFR of 96.1 ml/min per 1.73 m^2 (90.7–114.3) without proteinuria or HBP. The remaining 34 patients were defined as belonging to the InR group with either a median eGFR <90 ml/min per 1.73 m^2 (32 patients), proteinuria (1 patient), or HBP (3 patients). In the InR group, the median eGFR was 77.5 ml/min per 1.73 m^2 (60.2–129.6). There were 14 patients (30%) who had active uveitis. There were 23 patients (50%) who had an ongoing treatment:

corticosteroids for 18 (39%) and second-line immunosuppressive drugs for 8 (17%).

There were 14 patients (30%) who still had ophthalmologic involvement at 1 year: 11 had an active or chronic uveitis, 1 had a corticosteroid-induced cataract, and 2 were treated for elevated intraocular pressure (Table 3).

At Last Follow-Up

Data were available for 42 patients (91%) with a median follow-up of 2.8 years (range 1.1–9.6 years). The median eGFR, available for 40 patients, was 87.5 ml/min per 1.73 m^2 (60.3–152.7).

At this time, 24 patients were classified in the InR group with a median eGFR of 79.8 ml/min per 1.73 m^2 (60.3–152.8). In this group, 20 patients (20 of 40, 50%) had a median eGFR <90 ml/min per 1.73 m^2, 6 had proteinuria, and 2 had HBP. In addition, 9 patients (21%) were still on treatment: oral steroid therapy for 3 and a second-line treatment for 7. There were 14 patients (43%) who were classified in the CoR group at the last follow-up with an eGFR >90 ml/min per 1.73 m^2 without proteinuria or HBP. There were 4 patients who were not classified in either the InR or the CoR group because of missing eGFR, blood pressure, or proteinuria data.

There were 26 patients (57%) who had experienced uveitis relapses (range 1–5, median 2) and 5 (12%) who had TIN relapses. A total of 11 patients (26%) still had active ophthalmologic involvement. In addition, 9 had active or chronic uveitis treated with intravitreal corticosteroid injections for 1 patient, with a topical steroid for 6, and with an oral steroid for 2. Furthermore, 1 patient had a corticosteroid-induced cataract and 1 was treated for elevated intraocular pressure. Of 42 patients, 12 (29%) had neither ophthalmologic nor kidney impairment at the last follow-up (Table 3).

Comparison of Clinical and Biological Characteristics at Diagnosis Between Patients With InR and CoR: At 1 Year and at Last Follow-Up

At 1 Year

Impaired kidney function at diagnosis was significantly more severe in the children classified in the InR group than for those in the CoR group at 1 year with a significantly higher median creatinine plasma level of 231 versus 136 μmol/l ($P = 0.01$) and a lower median eGFR of 29.8 versus 42 ml/min per 1.73 m^2 ($P = 0.03$), respectively (Table 3). Albuminemia at diagnosis was also significantly lower in the InR group (37.3 g/l vs. 41.1 g/l, respectively, $P = 0.03$). There were no significant differences between the 2 groups in terms of uveitis complications, time between uveitis and TIN diagnosis, uveitis or TIN relapses, corticosteroid

regimen, or use of immunosuppressive drugs during the first year (Table 3).

At Last Follow-Up

The median time of follow-up was not statistically different between InR and CoR groups at last follow-up: 2.5 and 3.2 years, respectively ($P = 0.23$).

The median creatinine plasma level at diagnosis was higher in the children classified in the InR group at last follow-up without reaching significance: 134 versus 226.5 μmol/l respectively ($P = 0.05$) (Table 3). The median eGFR at baseline was similar in both groups at 28.9 versus 37.8 ml/min per 1.73 m^2 for the InR and CoR groups, respectively ($P = 0.10$). Nevertheless, the median eGFR at 1 year was significantly different for the InR and CoR groups (77.2 vs. 89.1 ml/min per 1.73 m^2, respectively, $P = 0.01$]).

Although uveitis occurred after TIN in more patients in the InR group compared with those in the CoR group (75% vs. 29%, respectively, $P < 0.01$), follow-up revealed that uveitis relapses were significantly more frequent in the CoR than in the InR group at 86% versus 42%, respectively ($P < 0.01$) (Table 3).

DISCUSSION

We describe the clinical and biological characteristics, treatment regimens, and medium-term prognosis in a cohort of 46 children with TINU syndrome. To the best of our knowledge, this study constitutes the largest series of pediatric patients published to date. Despite the retrospective design of the study, many observations can be drawn and we specifically highlight the possibility of poor renal prognosis.

Diagnostic criteria for TINU syndrome were first established by Mandeville in 2001 based on a literature review.[2] According to these criteria, TINU syndrome can be diagnosed into the following 3 categories: "possible," "probable," and "definite." TINU syndrome described as "possible" by Mandeville has limited diagnostic criteria based on incomplete clinical and biological findings without histologic evidence of TIN, associated with an atypical uveitis (Supplementary Table S1). Several studies concerning TINU have chosen to include only patients with "definite" TINU syndrome (i.e., with histologic evidence of TIN[13,14,20,21]), which may generate a selection bias concerning the initial severity of TIN and its long-term prognosis. Indeed, a patient suspected of having TIN does not systematically undergo a kidney biopsy if initial kidney involvement seems limited. For these reasons, we decided to include in our study patients with "definite" and "probable" TINU syndromes even in the absence of kidney biopsy, corresponding to 2 patients.

We found that children with TINU syndrome may have a poor renal prognosis. Although TINU syndrome is usually described as having a favorable renal outcome,[2,12,13,22] several recent studies suggest that a full kidney recovery is not always achieved especially in adult patients. Indeed, Legendre et al.[14] reported that two-thirds of their patients (24 of 35) had abnormal kidney function (eGFR <90 ml/min per 1.73 m^2) at 1 year of follow-up. According to Li et al.,[13] only 1 of 25 adult patients with TINU syndrome had an eGFR >90 ml/min per 1.73 m^2 at 1 year of follow-up, and for Su et al.,[20] 22 of 35 patients (63%) had an eGFR <60 ml/min per 1.73 m^2 at 3 years of follow-up. The second point that could explain the differences between our results and those from other studies on renal outcome is that our patients have a higher rate of renal fibrosis at diagnosis compared with other pediatric cohorts (43% of patients vs. 24% for the Finnish cohort published by Rytkönen et al.).[23] This could be explained by a delayed diagnosis leading to a late-onset treatment. At last, our criteria for a total renal recovery based on the guidelines of Kidney Disease: Improving Global Outcomes for the evaluation of chronic kidney disease are more stringent than those from other studies in which an eGFR >70 ml/min per 1.73 m^2 was considered as a total recovery.[24,25]

Renal outcomes in children have been poorly described in the literature to date. Hayashi et al.[11] recently reported a good renal prognosis with 100% of their patients having an eGFR >90 ml/min per 1.73 m^2 with a follow-up of 5 years. It is worth noting that the mean eGFR at diagnosis in their patients was normal (98.1 ml/min per 1.73 m^2) and significantly higher when compared with the initial median eGFR found in our study which was only 30.6 ml/min per 1.73 m^2. This suggests that the severity level was not identical in the 2 cohorts of patients explaining the difference observed at last follow-up. The discrepancy may also be explained by the fact that in their study 22 of the 29 patients (75%) were defined as having "probable" TINU syndrome as opposed to 22% of our patients.

In our study, 34 of the 45 patients (75%) were in the InR group at 1 year of follow-up and 24 of 38 patients (63%) were at the last follow-up. The lack of recovery of full kidney function can be explained either by sequelae of TIN or by persistence of an active kidney disease.

The poor renal outcome in children with TINU syndrome may be underdiagnosed for the following several reasons:

First, TINU syndrome can be tricky to diagnose as revealed in the study of Su et al.[20] in which 21 patients with TINU syndrome (21 of 35, 60%) were classified as having another TIN etiology at the time of kidney biopsy. Similarly, Li et al.[13] reported that 18 of their 31 patients (58%) with TINU syndrome were initially diagnosed with having immunoallergic TIN. Nevertheless, medication, which often consists of potentially nephrotoxic drugs administered during the prodromal phase of TIN, is a possible trigger for TINU syndrome and can lead to confusion.2 In our study, 19 patients (41%) received such treatment in the month before diagnosis, including 12 (26%) for whom uveitis appeared after the TIN diagnosis. Treatment could therefore represent a confounding factor for an immunoallergic TIN diagnosis especially if uveitis is not initially present.

Second, uveitis can be diagnosed sometime after TIN. It is typically diagnosed between 2 months before and 12 months after the TIN diagnosis.[2] In our study, 57% of uveitis cases occurred after the TIN diagnosis. Uveitis can also be asymptomatic. Indeed, in more than a quarter of our patients (12 of 46), uveitis was diagnosed on a systematic eye examination after a TIN diagnosis. The prospective pediatric study by Saarela et al.,[21] which included children diagnosed with having TIN with a systematic ophthalmologic assessment at diagnosis and after 3 months and 6 months, revealed the occurrence of uveitis in 16 of 19 patients, and 50% (8 of 16) of their patients were asymptomatic. The retrospective study by Jahnukainen et al.,[26] which analyzed children with idiopathic TIN, found that 12 of their 26 patients had bilateral anterior uveitis and 7 of these were asymptomatic. For these reasons, systematic ophthalmologic screening is essential for any child diagnosed with having TIN to detect associated uveitis both at diagnosis and at 6 months after if the first examination result is normal.

Third, and less frequently, patients with TIN can present with very mild symptoms: 4 patients in our cohort had no general symptoms and were diagnosed after a systematic laboratory workup after being diagnosed with having uveitis, although there was a biopsy-proven TIN result. This was also found in the study of Legendre et al.[14] in adults with TINU syndrome: 10 of 41 of their patients (24%) had no general symptoms at the time of TIN diagnosis. Urinary β2m dosage in patients presenting with uveitis can also be useful to diagnose TIN and is part of Mandeville's diagnostic criteria.[2] Hettinga et al.[17] reported a negative predictive value of 96% for a normal urinary β2m (<0.2 mg/l) and a positive predictive value of 100% by combining the elevation of creatinine and urinary β2m. Provencher et al.[27] reported a correlation between elevated urinary β2m, presence of cells in the anterior chamber, and a Tyndall effect in 9 patients. Thus, all children presenting with anterior uveitis without

obvious etiology should systematically be screened for kidney involvement.

We found that the severity of kidney involvement at diagnosis was a risk factor for an InR at 1 year of follow-up. Hypoalbuminemia in the absence of heavy proteinuria also seems to be a risk factor for InR and can be interpreted as an indirect marker of a prolonged inflammatory syndrome, and possibly of a late-diagnosed TINU syndrome. These differences were not found to be statistically significant in our study, but this may be due to the small number of patients in each group.

In the study of Li et al.,[13] significant risk factors of poor renal outcome in 25 adults (defined as an eGFR <60 ml/min per 1.73 m^2) were as follows: older patients, increased erythrocyte sedimentation rate, lower eGFR at diagnosis, and presence of leukocyturia. It should be noted that in our study there were more patients with elevated CRP at diagnosis in the InR group without reaching significance ($P = 0.09$). Indeed, presence of biological inflammatory syndrome (elevated erythrocyte sedimentation rate or CRP) could be a sign of a greater level of kidney inflammation leading to kidney damage. In the study of Jahnukainen et al.,[26] which included 26 children with idiopathic TIN (including 12 with TINU syndrome), no risk factors for poor renal outcome were found for TINU syndrome.

We also found that the patients in the InR group at the last follow-up already had a significantly lower eGFR at 1 year when compared with the patients in the CoR group (77.2 vs. 89.1 ml/min per 1.73 m^2, respectively, $P = 0.01$). These data suggest that the challenge of improving kidney function in patients lies in the first few months after diagnosis. In the study of Clavé et al.,[7] early treatment was significantly associated with a better eGFR at 6 months. Renal function tends to improve after the diagnosis of TIN but with possible sequelae at distance. This is of concern for patients with a short follow-up in nephrology, for whom kidney prevention should be implemented.

The presence of recurrent uveitis was not associated with poor renal outcome. By contrast, there were significantly more patients with uveitis recurrence in the CoR group at the last follow-up ($P < 0.01$). This surprising finding could be explained either by use of more intensive treatments and a closer monitoring in children with recurrent uveitis or by an independent kidney and eye involvement.

On the basis of the results of our study, diagnosis of TINU syndrome could be improved by systematic biological assessment of kidney function in all children with isolated uveitis at diagnosis and then after 2 months, including eGFR, proteinuria/urinary creatinine, and urinary β2m. Conversely, all children diagnosed with having TIN should systematically undergo ophthalmologic screening for uveitis at diagnosis and then after 3 and 6 months.

In conclusion, multidisciplinary care including nephrology, ophthalmology, and internal medicine specialists is essential for the timely diagnosis of TINU syndrome. The aim is to diagnose the syndrome early as the long-term renal prognosis seems to be strongly correlated with kidney impairment at diagnosis. Long-term kidney monitoring is then necessary to detect potential evolution to chronic kidney failure.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Diagnostic criteria for TINU syndrome, adapted from Table 5 of Mandeville's article. "(PDF)".

Table S2. Patient characteristics, progression, and treatments.

Figure S1. Flow chart.

STROBE Statement (PDF).

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