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**CLINICAL CASE** 

# Acute renal damage secondary to acute tubulointerstitial nephritis drug use. Case report

Daño renal agudo secundario a nefritis tubulointersticial aguda por uso de medicamentos. Caso Clínico

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#### **Abstract**

Introduction: Acute tubulointerstitial nephritis (ATIN) is a rare entity in the pediatric age. It is defined by the infiltration of the renal parenchyma by mononuclear and/or polynuclear cells with secondary involvement of the tubules, without glomerular injury. It can be triggered by infections or immunological diseases, drugs like NSAIDs or be of idiopathic origin. Objective: To raise awareness among pediatricians about the prescription of NSAIDs, especially to patients of less than a year old, since they can provoke renal damage. Case report: A ten month old child, with no nephrological antecedents of interest, was transferred to our hospital due to acute renal failure stage 3 KDIGO 2012. The three previous days received treatment with amoxicillin and ibuprofen for acute otitis media. Physical examination revealed mild eyelid edema with normal blood pressure. In the urine analysis, there were non-nephrotic proteinuria with tubular component, microhematuria and leukocyturia. Renal ultrasound showed no abnormalities. ATIN was suspected and so the antibiotic was changed to intravenous cefotaxime and ibuprofen was discontinued, opting for conservative management of acute renal damage. There was an increase in the number of creatinine up to 4.14 mg/dL and eosinophilia, with the immunological study being negative. Treatment with methylprednisolone was initiated, achieving normalization of renal function. Discussion: NTIA can be produced by any medication through an idiosyncratic immune reaction. Among the responsible drugs, there are ones commonly used in the pediatric age, such as NSAIDs. Therefore, the pediatricians should pay special attention during prescriptions and have a high diagnostic suspicion of this disease.

#### **Keywords:**

Acute tubuluinterstitial nephritis, infant, Nonsteroidal antiinflammatory drugs, antibiotics

#### Introduction

Acute tubulointerstitial nephritis (ATIN) is a rare or sub-diagnosed entity in the pediatric age, though in recent studies has been registered an incidence of 3-7%<sup>1</sup>. In the adulthood, it has been communicated an incidence of 24%<sup>2</sup>. At histological level, it is defined by the infiltration of renal parenchyma by predominantly mononuclear cells with secondary affectation of tubules and absent or minor glomerular injury<sup>3</sup>. First described by Councilman in 1898, the etiology of ATIN is very diverse. It can be produced by infections, both viral and bacterial, medicines, immunological disease or idiopathic origin3. Currently, the most frequent causes are drugs, highlighting among them antibiotic and nonsteroidal anti-inflammatory drugs (NSAIDs), of extended use in pediatric age<sup>3,5</sup>. In the light of a diagnosis or a diagnostic suspicion of ATIN, the first step of the treatment is to withdraw the responsible drug as soon as possible. The use of corticoids has been controversial, even when there is recent evidence supporting its use<sup>6</sup>. Usually, the prognosis is good, while a percentage of these children will develop chronic kidney disease (CKD). In the descriptive study carried out by Nikoliv<sup>7</sup>, all the patients recovered a normal renal function. However, in another study performed by Schwarz et al.8, the ATIN a 36% of patients developed CKD. In the same study, the bad prognostic markers were a prolonged use of the responsible drug, the use of NSAIDs and non-acute symptomatology. Regarding histologic findings, it was considered of bad prognosis tubular atrophy, interstitial granuloma, and a marked cell infiltration of renal parenchyma. Clinically, it is not possible to distinguish those patients which will develop CKD, so the long-term follow-up of all patients is essential. The need of ffollow-up is even higher for pediatric patients.

The aim of this article was to describe a case of ATIN secondary to nonsteroidal anti-inflammatory drugs (NSAIDs) in an infant, with emphasis on the pediatricians to consider this association.

#### Clinical case

10-month old female infant, previously healthy, was taken to the Pediatric Intensive Care Unit due to the presentation CKD stadium 3 KDIGO 2012<sup>9</sup>. The child was a product of controlled pregnancy of parents that are not blood relatives, with not relevant nephronurological family history. Her development of weight and height was right.

Three days before her admission, the patient had been diagnosed with acute otitis and she had initiated the treatment with amoxicillin (80 mg/kg/day) and

ibuprofen. Since she started with vomiting, the antibiotherapy was suspended - only two doses were received. At 48 hours, due to the persisting clinic and the associated fever and the decrease of the urinary rhythm, she was revalued in her hospital of origin. Signs of dehydration were not presented and physical examination only highlighted a minor palpebral edema. The blood pressure was adequate for her age (95/55 mmHg, 75-90 percentile for age, gender, and size). She was 77 cm (95 percentile, by the World Health Organization (WHO) curves) and weighted 22.5 lb (10.250 gr) (73 percentile, by the WHO curves). A urine test was carried out by bladder catheterization, highlighting microhematuria and leukocyturia, with no eosinophilia or the presence of cylinders. The blood test was compatible with CKD stadium 3 KDIGO 2012 creatinine 3.7 mg/dL, estimated glomerular filtration rate (eGFR) 9 ml/min/1.73 m<sup>2</sup>, Urea 153 mg/dL) with no evidence of hemolysis or thrombopenia observed in the hemogram. Isotonic intravenous fluids (total: 50 ml/kg) were administered with no improvement in the tests (table 1).

In the renal ultrasound, there were no elements that suggest uropathy or important alterations. In the Doppler, it was appreciated venous and arterial flow in the liver hilum, interlobular, arcuate, and peripheral arteries with resistance rates conserved and adequate speed comparing to the aortic flow. In the light of suspicious of ATIN, she was taken to our Pediatric Intensive Care Unit. It was indicated antibiotic treatment with intravenous cefotaxime adjusted to the glomerular filtrate and the treatment with ibuprofen was suspended, carrying out a conservator management of CKD (fluid restriction, feeding of hypoprotein and low potassium diet, administration of sodium bicarbonate, and potassium and phosphorus chelators). Despite these measures, the oligoanuria persisted and progressive increase of the amount of creatinine up to 4.14 mg/dL was observed. Eosinophilia in peripheric blood (1000 eosinófilos/uL) was detected in her second day, being the immunological study (complement, immunoglobulins, and ANA) and the urine culture normal.

In the third day of admission, it was decided to initiate a treatment with methylprednisolone (three intravenous boluses of 15 mg/kg/day for 3 days) getting a progressive clinical and laboratory parameters improvement until normalize the speed of glomerular filtration nine days after the diagnosis (figure 1). The patient completed the treatment with cefotaxime for 8 days with a full resolution of acute otitis.

After discharge, it was continued a treatment with oral prednisone 1 mg/kg/day and gastric protection with esomeprazole. On an outpatient basis, it was progressively decreasing the dose of prednisone to suspend the treatment at 8 weeks. She did not present steroid-related adverse effects. The recovering of

Table 1. Laboratory data of the blood and urine exams at the moment of admission												
Treatment	Start of fluid therapy	After fluid therapy	Suspension of Ibuprofen. Conservator treatment			Therapy with corticoids						
	Admission	+ 4 h	+ 10 h	+ 17 h	+ 2 d	+ 3 d	+ 4 d	+ 5 d	+ 6 d	+ 7 d	+ 9 d	+ 1 m
Creatinine (mg/dL)	3.7	3.7	3.83	3.92	4.14	3.93	2.87	1.54	0.77	0.61	0.3	0.2
eGFR (ml/min/1,73)	8.6	8.6	8.3	8.1	7.7	8.1	11	20.6	41.3	52.1	85.9	122
Urea (mg/dL)	153	159	138	150	151	162	177	148	104	77	36	15
Phosphate (mg/dL)			8.4	8.8	9.2	6.9	6.1	4.7	5.2	4.3	4.8	5
Potassium (mmol/L)	5.6	6	5.2	5.5	5.3	4.4	3.9	3.5	3.4	4.2	4.1	4.1
Bicarbonate (mmol/L)	22		16	16			23			25	24	25
EFNa	1.84		3.2			10						
Proteins	+		++		++	+	no			no	no	no
Pr <sub>o</sub> /Cr <sub>o</sub>			1.25			1.02	0.67			0.56	0.34	0.34
Hematies (cel/mcL)	isolated		10-15		isolated					isolated	no	no
Leucocytes (cel/mcL)	10-30		10-20		30-40					10-20	5-10	no
Cylinders	hyaline		hyaline		no					no	no	no

Abbreviations: h: hours; d: days; m: month. eGFR: estimated glomerular filtration; Pr<sub>o</sub>/Cr<sub>o</sub>: index proteins/creatinine in urine; FENa: fractional excretion of Sodium.

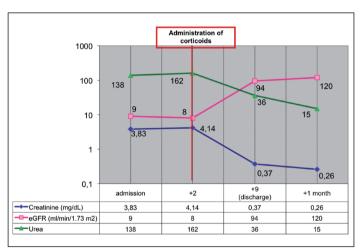
the glomerular and tubular renal function was complete.

The patient is still monitored by Nephrology, maintaining a normal global renal function. The periodic abdominal ultrasound did not show pathological findings. Amoxicillin and NSAIDs were not administered again.

#### Discussion

The ATIN for drugs is produced by an immunological mechanism in which the cellular immunity plays a major role through two mechanisms, the delayed hypersensitivity and the direct cytotoxicity<sup>10</sup>. It occurs regardless the route of drug administration, doses, time used, and it can resort to posterior exposures<sup>11</sup>. Normally, it appears in the first three weeks of the treatment, while it has been described cases of both early onset (first 24 hours) and late onset (months later)<sup>2,11</sup>.

The clinic is so unspecific and its severity is very variable, from asymptomatic urinary alterations to a CKD that indicate of extrarenal depuration. The triad of acute renal damage, exanthema, and eosinophilia is indicative of ATIN produced by drugs. However, in the last studies, it has been seen that only 10% of patients<sup>12</sup> is objectified. In the urine test it can be found proteinuria, hematuria, leukocyturia, eosinophilia, and alterations of tubular damage, while a normal urine sediment is not incompatible with the diagnosis of ATIN<sup>12</sup>. The imaging tests do not tend to show



**Figure 1.** Evolution of the renal function at admission, before and after the administration of corticoids

important alterations. As the histologic diagnosis, the renal biopsy continue to be the reference pattern, but generally, it is reserved for patients that present a topic evolution or when there are diagnostic doubts<sup>3,13</sup>. In the presented case, it was decided not to perform it due to rapid clinic and lab improvement presented after the onset of the corticotherapy. The same decision was taken in other two studies, as the one performed by Nikolic et al.<sup>7</sup> in which a renal biopsy was carried out in 5 out of 21 children diagnosed with ATIN. Regarding our experience, we neither performed a renal biopsy to the other three children who had be treated before in our center, due to the really good clinical evo-

lution presented after being treated with corticoids by the described pattern<sup>14</sup>.

The first measure of the treatment is to withdraw the responsible medicine as soon as possible and offer a proper support treatment adequate to the degree of CKD. The use of corticoids has been very controversial; there are articles in favor<sup>15</sup> and against this type of treatment<sup>16,17</sup>. The most recent studies, as the one carried out by González et al., have proved that the use of corticoids helps to recover the complete renal function, being its early use (in the first 7 days) the principal prognosis marker. In this study, it was analyzed the data of 61 adult patients diagnosticated with ATIN caused by drugs through a histologic study. 52 patients received the treatment with corticoids and compared to the group of patients that did not receive the mentioned treatment they maintained their creatinine values lower, being less frequent the need of dialysis after the acute episode of acute renal insufficiency (3.8% vs 44.4%, p < 0.001).

There are patterns for the treatment with corticoids in this type of patients. In a recent review it is recommended the use of 1 gr/1.73 m<sup>2</sup> of intravenous methylprednisolone once a day during 3 days and after that oral prednisone 2 mg/kg with an decreasing pattern in a 3-6 weeks period. In the current literature, there are no prospective and random studies about the pattern of corticotherapy, so every center has a different pattern. In our case, the most used pattern of corticotherapy in the study of Gonzales et al.6 was adapted to pediatric and 15 mg/kg of methylprednisolone were administered, followed by oral prednisone 1 mg/kg/day with a decreasing pattern in an 8-12 weeks period. The prognosis of patients with ATIN tends to be good, although a percentage of these children will develop CKD.

The importance of this case is related to the age of the patient: a 10-month old infant, being the youngest patient that has presented this pathology in our center. In the reviewed studies, it has not been found a reference of patients of less than 1 year old diagnosticated with ATIN related to ibuprofen and/or beta-lactams. The administration of NSAIDs and antibiotics are subject to risk, reason why pediatrician must be careful when prescribing this type of medicines of frequent use among our population.

## **Conclusions**

In patients with acute renal damage without dehydration signs and echography of the urinary system with no obstruction images, it is very important to research the previous pharmacological treatment. Frequent medicine, as NSAIDs and antibiotics, can be the cause of ATIN even in infants. Withdrawing as soon as possible the suspicious medicine is vital and the early onset of the corticotherapy, since it has been proved a decrease in the percentage of children that will develop a posterior CKD. These children need long-term follow-up and it is discouraged the new administration of the causing medicine.

## **Ethical Responsibilities**

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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#### **Conflicts of Interest**

Authors declare no conflict of interest regarding the present study.

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