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Increased prevalence of acute tubulointerstitial nephritis

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Abstract

Acute tubulointerstitial nephritis (ATIN) is a common cause of acute kidney injury (AKI) for which early treatment improves prognosis. The recent increase in prevalence has not been reflected in the literature. The aim of our study was to analyse all native kidney biopsies performed from 1994 to 2009 and included in the Spanish Registry of Glomerulonephritis with a histological diagnosis of ATIN. We assessed the prevalence of ATIN, associated clinical syndromes and urinary sediment abnormalities. We divided the population into two groups according to age: adults (15–65 years) and elderly patients (>65 years). We collected a total of 17 680 native kidney biopsies from 120 hospitals in Spain. The overall prevalence of ATIN was 2.7%. When the analysis was restricted to patients with AKI, the prevalence increased to 12.9%. During the 16 years of follow-up, there was a significant increase in prevalence (from 3.6% in the first 4 years to 10.5% in the last 4 years), which was more marked among elderly patients (from 1.6 to 12.3%). The most common clinical manifestations were AKI, microscopic haematuria, non-nephrotic proteinuria, leucocyturia and arterial hypertension, which were more frequent in the elderly. The prevalence of ATIN has increased in recent years, especially in patients aged >65 years. This could be due to an increase in drug-associated ATIN, which would justify early renal biopsy to identify ATIN and reduce the probability of progression to chronic kidney disease. Although, our data are not able to corroborate this fact.

Keywords: acute kidney injury; acute tubulointerstitial nephritis; renal biopsy

Introduction

Acute tubulointerstitial nephritis (ATIN) is a disorder in which acute kidney injury (AKI) is accompanied by interstitial inflammation, oedema and tubulitis. ATIN is usually caused by drugs or infection and may be idiopathic in origin [including TINU syndrome (ATIN and uveitis) and anti-tubular basement membrane disease] and associated with sarcoidosis or other systemic diseases (e.g. systemic lupus erythematosus, Sjögren's syndrome). Drug-induced ATIN is the most common form of the disease and currently accounts for more than two-third of cases, followed by infection (15%), idiopathic forms (10%) and TINU (4%) [1].

The first description of drug-associated ATIN was published in 1968 by Baldwin *et al.* [2], who reported a series of seven patients with penicillin-induced ATIN. Since then, a large number of cases of drug-induced ATIN have been reported, and most of these were due to antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). Although the prevalence of drug-induced ATIN has increased in recent years [1], mainly due to the widespread use of antibiotics and NSAIDs in the general population, the literature provides very few objective data.

The aim of this study was to identify the changes in the prevalence of ATIN over time and to analyse the associated clinical syndromes in the native kidney biopsies included in the Spanish Registry of Glomerulonephritis over a 16-year period.

Materials and methods

The Spanish Register was established in 1994 and included data on unselected renal biopsies by 120 Spanish centres. We analyse all the native kidney biopsies performed from 1994 to 2009 and included in the Spanish Registry of Glomerulonephritis with a histological diagnosis of ATIN and its clinicopathological correlation. Unfortunately, the date of registration only includes the main diagnosis on biopsy and no data are available about the number of patients with another diagnosis on biopsy in addition to acute ATIN. Patients were divided into three groups according to age: children <15 years; adults (15–65 years) and the elderly (>65 years). In order to study the changes in the prevalence of ATIN, we divided the study period into periods of 4 years: 1994–97, 1998–2001, 2002–05 and 2006–09.

Each sample was analysed by pathologists from the participating hospitals using specific techniques, mainly light microscopy and direct immunofluorescence (IgG, IgA, IgM, C3, C1q, fibrinogen and light chain antibodies). The study was completed by electron microscopy when considered necessary for diagnosis.

Diagnosis of ATIN was based on the presence of oedema and focal cellular infiltrates in the renal interstitium, with preserved glomeruli and vessels. Eosinophils, leucocytes, lymphocytes and plasmatic cells were present in the infiltrates. Confirmation of diagnosis also required the presence of tubular membrane rupture and lymphocytic infiltrates in tubules (tubulitis).

The following definitions were established:

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- AKI: rapid deterioration of glomerular filtration rate (GFR), with or without oligoanuria or rapidly progressive renal failure, including deterioration of chronic kidney disease. These data are from the registry information without more specific GFR data.
- Nephrotic syndrome: proteinuria ≥3.5 g/day/1.73m^2 and serum albumin <2.5 g/dL.
- Acute nephritic syndrome, oliguric AKI with oedema, haematuria and hypertension.
- Asymptomatic urinary abnormalities: proteinuria <3.5 g/day/1.73m^2 and/or haematuria with more than three red blood cells per field and no clinical symptoms.
- Arterial hypertension: blood pressure ≥140/90 mmHg or anti-hypertensive treatment irrespective of blood pressure.
- Chronic kidney disease: persistent serum creatinine ≥1.5 mg/dL.

Each questionnaire included the following information: name, date of birth, sex, hospital, presence of hypertension and/or anti-hypertensive treatment, serum creatinine (mg/dL), creatinine clearance (mL/min) measured in 24-h urine samples, proteinuria (g/day) and urinary sediment. The main syndromic diagnosis, histopathology technique and the number of clusters obtained were also recorded.

Statistical analysis

Data were entered in a database (Microsoft Access®). Statistical analysis was performed using SPSS for Windows V.16.0 (SPSS®, Chicago, IL). The normal distribution of the samples was determined using the Kolmogorov–Smirnov test. Values were expressed as medians (interquartile range) when the parameters did not follow a normal distribution. Qualitative variables were compared using the chi-square test and Fisher's exact test. Quantitative variables were compared using the *t*-test or Mann–Whitney test for non-skewed variables. A P-value <0.05 was considered significant.

Results

Between 1994 and 2009, a total of 17 680 native kidney biopsies from 120 hospitals in Spain were included in the Spanish Registry of Glomerulonephritis. Of all the biopsies performed, 468 met the histological criteria for ATIN (prevalence of 2.7%) and 3059 patients (17.3%) had AKI. Histology revealed ATIN in 392 (12.9%) patients with AKI.

Of the 468 patients with ATIN, 53.2% were male and 46.6% women with a mean age of 58.3 ± 18 years. Adults accounted for 51.2% of cases, elderly patients for 48% and children for 5% cases.

The general characteristics of the patients are shown in Table 1. When dividing the patients by age, we found that serum creatinine at diagnosis was similar in both groups, but creatinine clearance fell significantly with age. Proteinuria was similar in both groups, and 107 patients (25.6%) had proteinuria >1.5 g/day. Only 10 patients had nephrotic proteinuria. Hypertension at diagnosis was much more frequent in elderly patients than in adults.

The clinical syndrome indicating biopsy was AKI in 85.4% of cases. Similar results were observed in adults and elderly patients (Table 2).

Table 3 shows the characteristics of urinary sediment with no significant differences between age groups.

Figure 1 shows the evolution of the prevalence of ATIN during the 16 years of the study. Increased prevalence was observed during the last 4 years. Prevalence increased from 3.6% in the first period to 10.5% in the last. In elderly patients, the prevalence of ATIN during the first period was 1.6%, increasing to 12.3% in the last.

The number of biopsies performed over time has not increased. When we analysed the clinical characteristics of patients with ATIN, we see that age has increased over the time and creatinine levels have been lower (Table 4). These data are not different in total biopsies (the registry data are not shown).

Discussion

Our study describes the largest series to date of renal biopsies used to diagnose ATIN. A histological study of kidney disease and its clinical correlations can provide important information for nephrologists. Renal biopsy plays an important role in the diagnosis of kidney disease. The Spanish Registry of Glomerulonephritis has been collecting data on renal biopsies from 1994, noted precisely because of its contribution to the clinical–pathological correlations [3–5].

ATIN is characterized by the presence of inflammatory infiltrates and interstitial oedema, both of which are normally associated with a sharp decline in kidney function. It accounts for 1–3% of all renal biopsies in some studies [6, 7]. However, when the analysis was restricted to patients who underwent biopsy for diagnosis of AKI, ATIN accounted for 15–27% of cases [8, 9].

In our study, the overall prevalence of ATIN was 2.7%, and when the analysis was restricted to patients with AKI, the prevalence increased to 13%, which is similar to that observed elsewhere [10, 11]. However, no previous studies have shown trends in prevalence in recent years. From our analysis, we draw two important conclusions: the prevalence of ATIN increased during the last 4 years of our study and this increase was striking in elderly patients. In this group, we can observe three phases: (i) low prevalence during the first 4 years (<2%); (ii) a gradual increase to match the prevalence in the adult subgroup during the following 8 years and (iii) an increase in prevalence to >12% during the last 4 years. The increase in prevalence during the third period may be due to two factors: firstly, renal biopsies are performed more frequently in elderly patients than in previous decades, with the result that its prevalence in the early years of the study may be underestimated and secondly, uncontrolled increased use of antibiotics and NSAIDs has been observed in this group of patients [12]. In fact, we observed some changes over time in clinical characteristics of patients presenting with ATIN (Table 4). For instance, the more recent cases (2006–09 period time) presented with a lower serum creatinine (5.2 versus 5.9 mg/dL) and were older (61.4 versus 45.7 years) than the first cases from the 1994 to 1997 time period.

A 1998 report from the UK Medical Research Council (MRC) Glomerulonephritis Register revealed the prevalence of ATIN to be 2.2%. In patients aged >60 years, the prevalence was higher: 3% versus 1.9% in patients aged <60 years ($P < 0.01$) [13]. The authors suggest that increased susceptibility to ATIN in the elderly could be a consequence of a greater sensitivity of ageing kidneys with already diminished renal function. The figures refer to data recorded prior to 1998 and are very similar to

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Table 1. Demographic and biochemical characteristics at presentation according to age[a]

	All ($n = 468$)	Adults, ≤65 years ($n = 239$)	Elderly, >65 years ($n = 223$)	P
Age (years)	58.3 ± 18.2	45.6 ± 14.2	73.2 ± 5.4	0.001
Gender (male, %)	53.2%	55.2%	51.1%	NS
Serum creatinine (mg/dL)	5.2 ± 3.0	5.4 ± 3.5	5.1 ± 2.6	NS
Creatinine clearance (mL/min)	21.2 ± 22.3	25.0 ± 28.3	16.9 ± 12.4	0.001
Proteinuria (g/day)	1.39 ± 2.42	1.46 ± 2.02	1.28 ± 2.37	NS
Hypertension (%)	51.1%	39.3%	62%	NS

[a]Comparison between adult patients and elderly patients.

Table 2. Clinical features at presentation according to age[a]

	All[b] ($n = 468$) % (no. of patients)	Adults[c], ≤65 years ($n = 239$)	Elderly[d], >65 years ($n = 223$)	P
Nephrotic syndrome	2.2% (10)	2.1% (5)	2.2% (5)	NS
Nephritic syndrome	5% (23)	5.9% (14)	4% (9)	NS
Asymptomatic urinary abnormalities	3.5% (16)	4.2% (10)	2.7% (6)	NS
Haematuria	0.4% (2)	0.8% (2)	0% (0)	NS
Hypertension	0.2% (1)	0.4% (1)	0% (0)	NS
AKI	85.4% (392)	82.4% (197)	85.2% (190)	NS
Chronic renal failure	3.3% (15)	2.5% (6)	3.6% (8)	NS

[a]Comparison between adult patients and elderly patients.
[b]Eleven patients (2.3%), data not available.
[c]Four patients (1.7%), data not available.
[d]Five patients (2.2%), data not available.

Table 3. Urinary sediment abnormalities according to age group[a]

% No. of patients	All[b] ($n = 468$)	Adults[c], ≤65 years ($n = 239$)	Elderly[d], >65 years ($n = 223$)	P
Gross haematuria	5.3% (25)	5.4% (13)	5.4% (12)	NS
Microhaematuria	32.8% (154)	32.6% (78)	33.6% (75)	NS
Leucocyturia	21.5% (101)	15.5% (37)	27.4% (61)	NS
Cylindruria	2.3% (11)	3.3% (8)	1.3% (3)	NS
Telescoped sediment	8.1% (38)	11.7% (28)	4.5% (10)	NS
Normal sediment	20% (94)	20.9% (50)	18.8% (48)	NS

[a]Telescopied urinary sediment is one in which red cells, white cells and all types of casts are found in more or less equal profusion. Cylindruria is defined as the presence of all types of casts in the urine.
[b]In 47 patients (10%), data not available.
[c]In 25 patients (10.5%), data not available.
[d]In 20 patients (9%), data not available.

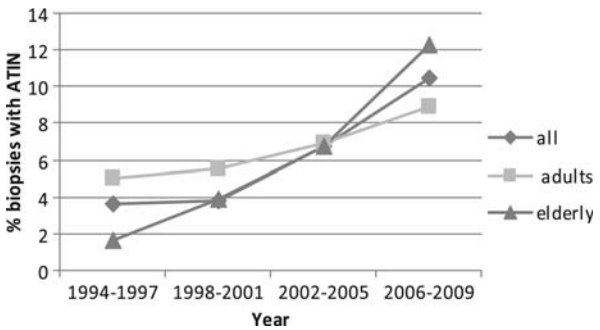

Fig. 1. Prevalence of ATIN during the study period according to age.

ours: 5% in patients aged <65 years compared with 1.6% in elderly patients. However, prevalence in elderly patients increased over time, equalling that of adults in the period 2002–05 and was higher from 2006 onward (8.9 versus 12.3%). Our data are the first to confirm the increased prevalence of ATIN in recent years.

AKI is the syndrome that most often accompanies this condition and is the reason for renal biopsy in most cases. Our study suggests that ATIN is an important cause of AKI, confirming the results of other studies [14, 15], although the true incidence may be underestimated. A significant number of patients in whom ATIN is suspected on clinical grounds do not undergo a confirmatory renal biopsy because empirical treatment is preferred, particularly in elderly patients. Furthermore, mild forms of ATIN can be under-detected either because of the absence or vagueness of clinical symptoms or because AKI is attributed to other causes of renal injury.

Regarding the clinical characteristics of patients, our results are similar to those reported in series such as those by Clarkson *et al.* [14] and Gonzalez *et al.* [15], the most common clinical manifestations being AKI, microscopic haematuria, non-nephrotic proteinuria and leucocyturia.

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Table 4. Clinical characteristics of patients presenting with ATIN over time[a]

Time period	ATIN/total biopsies	Age (years)	Serum creatinine (mg/dL)	GFR (mL/min/1.73m^2)
1994–97	66 (4461)	45.7 ± 20.9	5.9 ± 3.4	22.4 ± 19.8
1998–2001	70 (3979)	58.8 ± 18.8	4.9 ± 2.9	22.5 ± 22.5
2002–05	126 (3967)	60.0 ± 15.2	4.7 ± 2.6	25.5 ± 30.4
2006–09	197 (4690)	61.4 ± 17	5.2 ± 3.1	18.1 ± 15.4
P (ANOVA test)		0.001	0.047	0.073

[a]ATIN/total biopsies: number of patients with ATIN/number of total biopsies from register. ANOVA, analysis of variance.

Although leucocyturia is lower in our series: 20–28 versus 82% in Gonzalez and Clarkson data, one probable explanation for it is that data from these authors are patients diagnosed of ATIN and our data are from a register (data on unselected renal biopsies), where the leucocyturia has probably been underestimated. Moreover, unfortunately, the data of our register only include the main diagnosis on biopsy and no data are available about the number of patients with another diagnosis in addition to acute ATIN. The 476 studied biopsies had ATIN predominantly but we cannot rule out other pathologies that could explain the higher percentage of proteinuria or haematuria. Our data reveal a remarkably high percentage of patients with accompanying arterial hypertension, especially among the elderly. In the only record of renal biopsy with ATIN described in the literature (160 patients, of whom 56 were >60 years [13]), associated hypertension was observed in only 4% of elderly patients compared with 13% of younger patients; these figures are far lower than those found in our study. A striking feature of the UK MRC Glomerulonephritis Register is the low percentage of patients with AKI (48%), which is much lower than in other studies [14, 15], including ours (85.4%). However, the prevalence of chronic kidney disease was 10 times higher (34%) than in our study (3.3%). Regardless of these differences, hypertension is not a common accompanying symptom of ATIN and could only indicate greater vascular damage in elderly patients and probably greater hypersensitivity to certain types of drugs.

Our study has a series of limitations based on its inherent design. Data are collected from a national registry, with the biases that this implies: renal biopsy studied by different pathologists using different methods, heterogeneity in assessing and diagnosing histological entities and lack of data on aetiology, treatment and outcome. Therefore, we cannot conclude that the increased prevalence of ATIN in recent years is associated with drugs and not infection. Data from other studies suggest that drugs are the main cause of ATIN. In a 2004 report including data from three large studies, drugs were the most common cause of ATIN in 91 of 128 patients (71.1%), infection in 20 cases, idiopathic origin in 10 cases, TINU syndrome in 6 cases and sarcoidosis in 1 [16]. In the UK MRC Glomerulonephritis Register, 58% of patients aged ≥60 years and 48% aged <60 years had drug-induced ATIN [13].

The prevalence of ATIN has increased in recent years, especially in elderly patients. Probably, this increased prevalence could be associated with increased drug-induced ATIN, although our data are not able to corroborate this fact. Specific studies in patients with various aetiologies of ATIN are needed to determine if this is the cause of increased prevalence detected in recent years.

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Conflict of interest statement. None declared.

(See related article by Bomback and Markowitz. Increased prevalence of acute interstitial nephritis: more disease or simply more detection? *Nephrol Dial Transplant* 2013; 28: 16–18.)

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