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Pediatric

IgA Nephropathies in Children: Epidemiological, Clinical, Histological and Evolutionary Profile: About 31 Cases

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Abstract **Original Research Article**

IgA nephropathy is one of the most common primary glomerulonephritis in children. It is characterized by the presence in the PBR of mesangial deposits of type A immunoglobulins. We report the clinical, biological, histopathological, therapeutic presentation and the evolution, through a retrospective study comprising 31 cases collected in the pediatric IV department of the children's hospital in Rabat from 2007 to 2017. 31 cases have nephropathy in IgA, predominantly male. The average age of our patients at diagnosis was 10 years. Berger's disease was confirmed in 64% of cases, rheumatoid purpura in 30% of cases and 02 cases of secondary IgA nephropathy. Nephrotic proteinuria was present in 80% of cases, associated with hematuria (65%). Hypertension was present in 48% of patients while 32% of cases presented with acute renal failure. Lesions observed by light microscopy were according to the Oxford classification: M1 (61%), E1 (38%), S1 (41%), T1 + T2 (22%), C1 (22%). All the patients were put on corticosteroid therapy, associated with the immunosuppressant in 02 cases. The outcome was favorable for 93% of the patients and two patients progressed to CRF.

Keywords: IgA Epidemiological Evolutionary Profile.

INTRODUCTION

IgA nephropathy is an immune complex glomerulonephritis with the highest response, characterized by heterogeneous glomerular disease, initially described in 1968 by Jean Berger and Nicole Hinglais after the systematic study of renal biopsies in immunofluorescence [1].

There are two main clinical presentations: Berger disease (MB) and Rheumatoid Purpura (RA) which probably involve an autoimmune reaction triggered by variable antigenic stimuli including infectious [2-4]. Kidney complications that affect the long-term prognosis can lead to chronic kidney disease.

The objective of this work is to analyze the epidemiological, clinical, biological, histological, therapeutic and progressive particularities of this disease through a study carried out on 31 Moroccan pediatric cases.

Pathophysiology

The pathophysiological mechanisms of Berger disease remain largely unknown. Their understandings, essential for developing innovative and effective therapeutic strategies, have seen recent progress. The immunological hypothesis of the disease is supported by several clinical observations: The recurrence of IgA deposits after renal transplantation on the graft in patients with N-IgA; and on the contrary, the disappearance of IgA deposits in "non-N-IgA" recipients who received an "N-IgA" kidney [5, 6].

Research has focused mainly on the study of type 1 immunoglobulin A, which is the subclass of IgA exclusively deposited in the mesangium, and the various IgA receptors. Several mechanisms are involved:

- Synthesis of IgA (IgA1)
- IgA1 galactosylation abnormality
- Deposition at the glomerular mesangium
- Inflammatory response
- and genetic susceptibility [7]

A defect in galactosylation of the O-glycosides of the hinge region of IgA1, leads to the formation of circulating nephropathogenic immune complexes and their deposition in the mesangium. It would be the main cause of the stimulation of the mesangial cells, which leads to an inflammatory reaction responsible for irreversible glomerular and tubulointerstitial lesions which then progress to renal sclerosis and chronic renal failure [8].

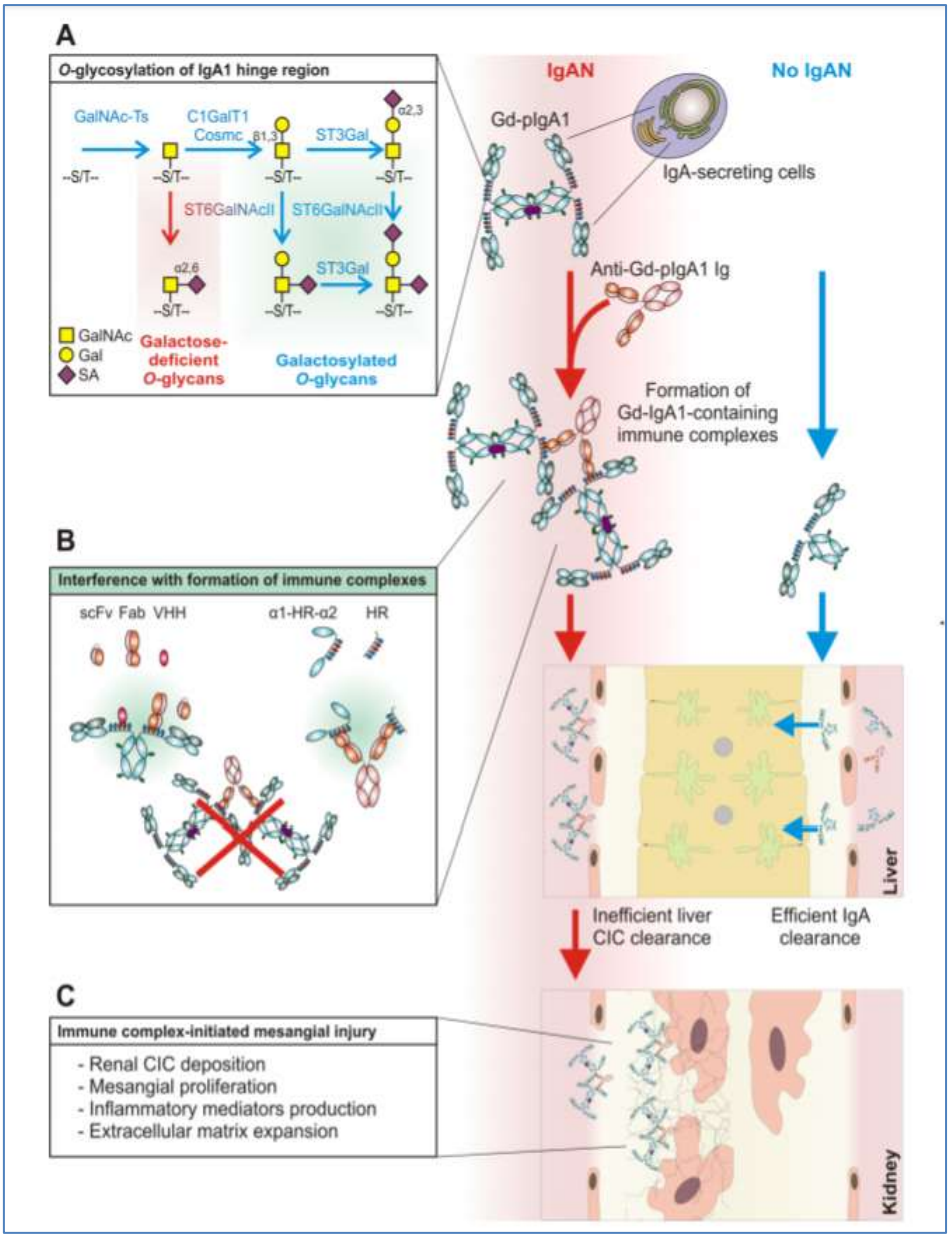

Fig-1[9]: the pathophysiology of IgA nephropathy

MATERIAL AND METHOD

This is a retrospective study, including 31 cases of IgA nephropathy, collected in the pediatric nephrology department of the Rabat Children's Hospital (HER) over an 11-year period, from January 2007 to September 2017.

To carry out this work, we included all children aged under 18, hospitalized for hematuria and/or hypertension and/or petechial purpura or arthralgia, nephrotic proteinuria and/or renal failure. The PBR were examined within the pathological anatomy department of the Rabat children's hospital and revealed an IgA nephropathy such as Berger's disease or Rheumatoid Purpura.

Patients over the age of 18 and those with missing or incomplete records were excluded from our study.

A 03-page operating sheet was established for each patient, allowing the collection of necessary data for the analysis of our series in order to meet our objectives.

Regarding the histological classification, we based ourselves on the classification of Oxford IgA nephropathies.

RESULTS

Epidemiology: 31 cases of IgA nephropathy were identified during the eleven-year period from 2007 to 2017, i.e. 3 cases per year.

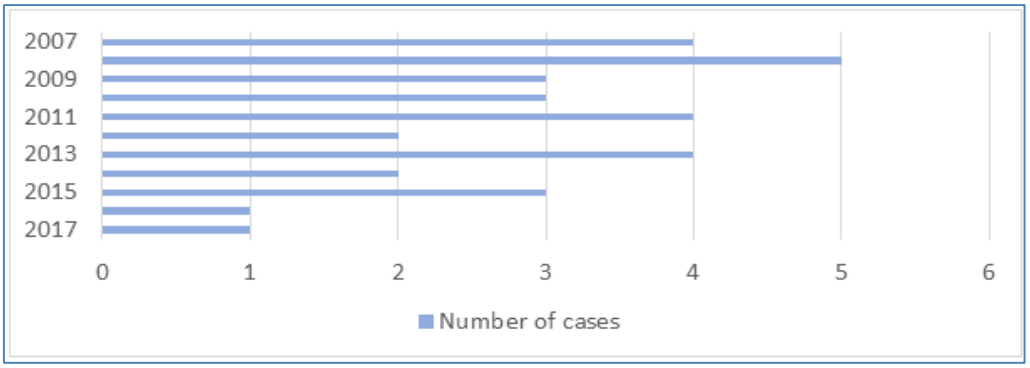

Fig-2: Cases per year

The etiologies are dominated by Berger's disease with a percentage of 64% of cases (20 cases) followed by RA in 29% of cases (9 cases). The remaining 7% (2 cases) are related to IgA nephropathy secondary to celiac disease.

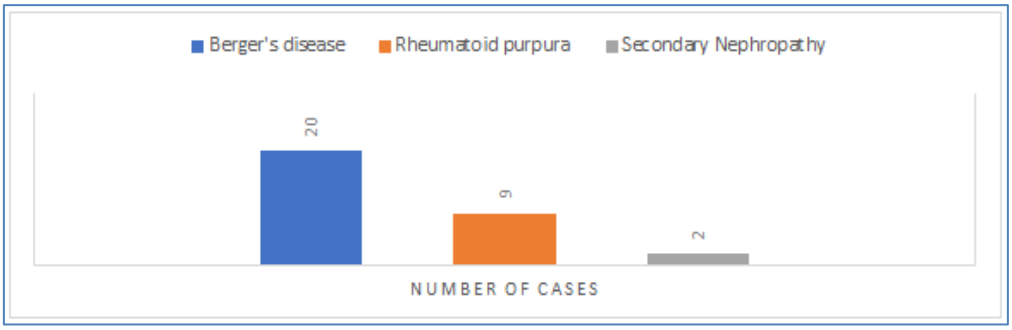

Fig-3: Etiologies of IgA nephropathy

Regarding the sex of our patients, we have a male predominance in Berger's disease with a percentage of 90% of the cases while in rheumatoid purpura, we noted equally predominant characteristics. In the case of celiac disease, the 2 patients were boys.

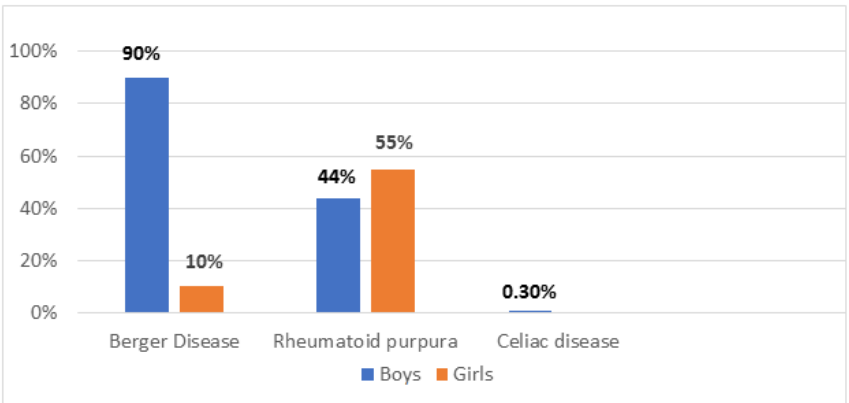

Fig-4: The gender distribution

In our study, the average age of discovery of IgA nephropathy was 9 years. Age extremes range from 4 to 16 years of age. For Berger's Disease, the average age of our patients at the time of diagnosis was 10 years, with extremes of age between 4 and 16 years. For Rheumatoid purpura, the average age was 7.5 years, with extremes of age between 4 and 13 years at the time of diagnosis.

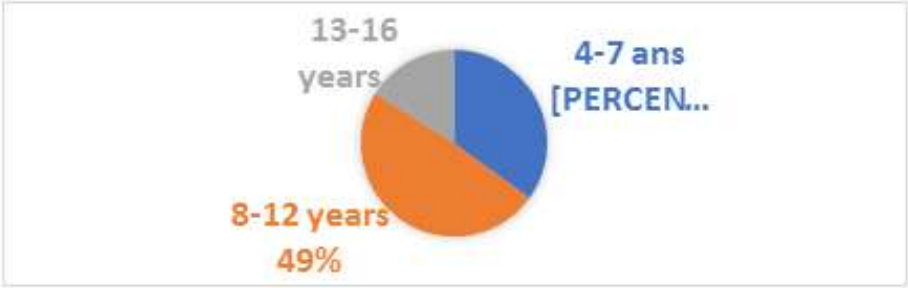

Fig-5: Distribution by age group

Clinical and biological manifestations

The clinical symptomatology of N-IgA is dominated by proteinuria (99%), hematuria (64%) and high blood pressure (48%).

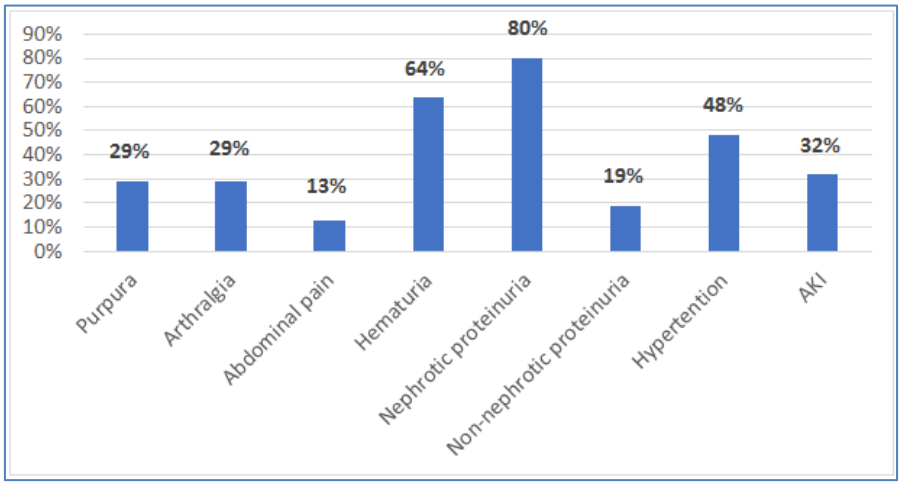

Fig-6: Clinical and biological manifestations of IgA nephropathy

In case of Berger's disease

The clinical picture: An ENT infection or bronchial infection concomitant with clinical manifestations is present in 10 patients (50% of cases). Hematuria was found in 17 cases (85%), associated with edematous syndrome in 14 cases (70%), and isolated in 03 cases. High blood pressure was seen in 10 cases (50%). Acute renal failure at the time of diagnosis was found in 05 cases (25%).

Biology: Proteinuria was positive in 20 cases (100%), nephrotic type in 85% of cases, between 3.2 and 7.8 g / day with an average of 5.4 g / day and non-nephrotic estimated at 0.5 g / d in 15% of the cases. The mean creatinine in patients with acute renal failure is 20 mg / l, with an average creatinine clearance estimated at 40.6 ml / min / 1.73m2. The IgA assay was performed in one patient and returned to normal.

In case of rheumatoid purpura

The clinical picture: Concomitant ENT infection was found in 03 cases (33% of cases), and edematous syndrome in 2 patients (22% of cases). Purpuric lesions and arthralgia were present in all patients (100%), associated with abdominal pain such as epigastralgia in 04 patients (44%). 33% of our patients had gross hematuria. Proteinuria was positive in 06 patients (66%), nephrotic in 04 patients and non-nephrotic in 02 cases. Two patients were hypertensive (22%) and 03 patients presented with acute renal failure.

Biology: The average proteinuria is 6.14 g / d, variant between 1.9 and 12 g / d. The mean creatinine is 24.8 mg / l and the mean clearance is 80 ml / min.

In case of nephropathy secondary to IgA

The 2 patients with nephropathy secondary to celiac disease, are male and between the ages of 4 and 8 years. They had an edematous syndrome associated with chronic diarrhea as well as acute renal failure. The malabsorption balance as well as the anti-transglutaminase antibodies were positive. The intestinal biopsy showed villous atrophy.

Pathology study

To confirm the diagnosis of N-IgA, renal biopsy was essential with an immunofluorescence examination showing mesangial deposits of IgA. It was performed in the event of:

- Nephrotic syndrome associated with hematuria.
- Renal damage associated with extra-renal signs (arthralgia, purpura).
- A patient over 10 years old who presented with nephrological manifestation.
- Unexplained acute renal failure.

In light microscopy, we noted the predominance of hyper-cellularity in glomerular lesions with a percentage of 27% while the interstitium was normal in 71% of cases. In the renal tubules we found that 58% of the cases had a tubular atrophy or necrosis.

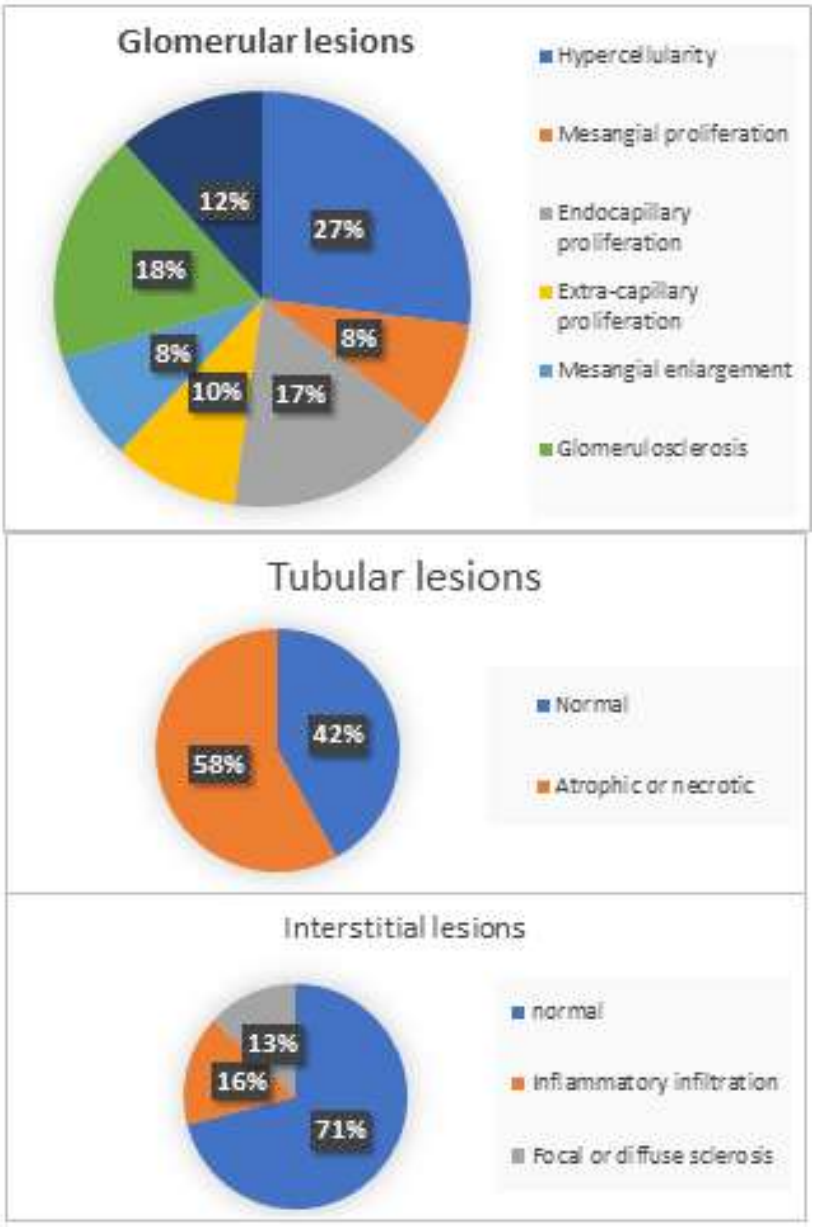

Fig-7: The proportion of histological lesions in light microscopy

Frequency of histological lesions according to the Oxford classification

The Oxford classification of N-IgA [10], devised by a group of more than 40 nephrologists and pathologists representing the International IgA Nephropathy Network and the Renal Pathology Society, is unique as the first scheme based on proofs. [11-14]. It makes it possible to evaluate the prognostic factors and therefore the severity of the pathology and to choose the appropriate therapeutic strategy. The following table shows the proportion of the different histological lesions observed in our series, according to the Oxford classification.

Table-1: Frequency of histological lesions according to the Oxford classification

Variable	Score	PBR	Percentage
Mesangial hypercellularity	M0<=0.5	12	39 %
	M0 >0.5	19	61 %
Endocapillary hypercellularity	E0 : Absent	19	61 %
	E1 : Present	12	39 %
Segmental glomerulosclerosis	S0	18	59 %
	S1: Present	13	41 %
Segmental glomerulosclerosis Interstitial fibrosis / tubular atrophy	T0: 0%--25%	05	16%
	T1:26%--50%	04	13%
	T2: >50%	23	78%
Cellular or fibrocellular crescents	C0: Absent	23	78%
	C1: Present	08	22%

Immunofluorescence (IF): was performed on 21 patients (68% of cases). For the remaining 10 cases, IF was not done because of a fixation defect in one patient, or lack of reagent in 3 patients or aglomerular fragments in the remaining 6 patients. The IF examination objectified the presence of mesangial IgA deposits in 100% of the cases studied.

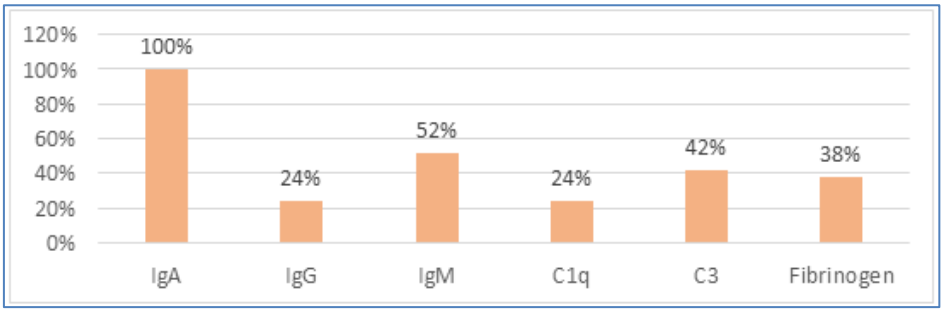

Fig-9: The proportion of deposits to immunofluorescence

Treatment

Blockade of the renin angiotensin system by ACE inhibitors and ARBs II was used in 22 patients, representing a percentage of 71% of cases. This treatment was used in cases of rheumatoid purpura associated with high blood pressure and or residual proteinuria. In the event of Berger disease, this blocking has been recommended in all patients, at a dose of 3 mg / kg for those who have presented with arterial hypertension, and at a dose of 1 mg / kg for others.

Oral corticosteroid therapy, which is the cornerstone of treatment, was used in 100% of patients, preceded in 7 cases by a 3-day intravenous bolus, indicated in nephropathy with massive proteinuria.

An immunosuppressive treatment combining corticosteroid therapy and cyclophosphamide was indicated for 02 patients, justified by persistent proteinuria or serious histological lesions.

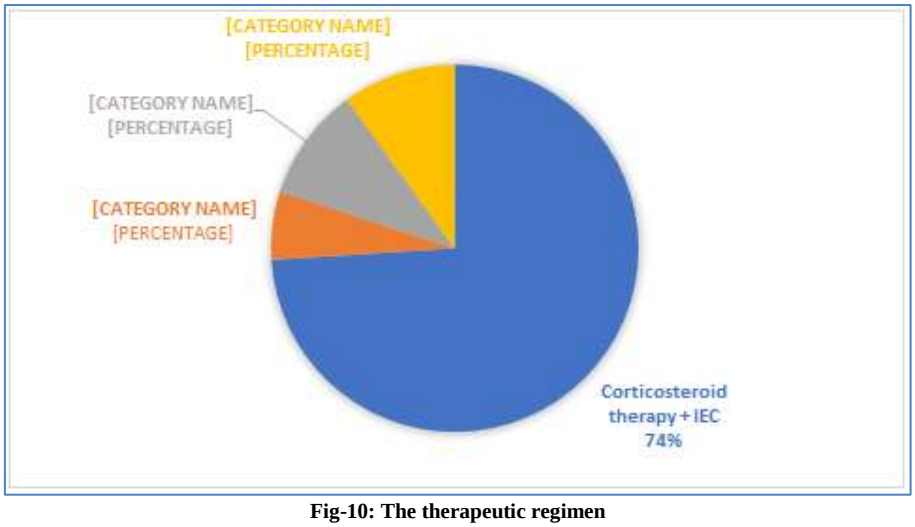

Fig-10: The therapeutic regimen

Evolution

The average duration of follow-up is 3 years, 93% of patients did not present nephrological manifestation at the last follow-up visit.

- 3 children presented recurrent hematuria and proteinuria concomitant with an episode of ENT infection, one of them was proposed a tonsillectomy.
- 2 patients with IgA nephropathy secondary to celiac disease progressed to IRCT stage on dialysis, died after a period.
- The medium-term course is favorable in 93% of the cases in our series.

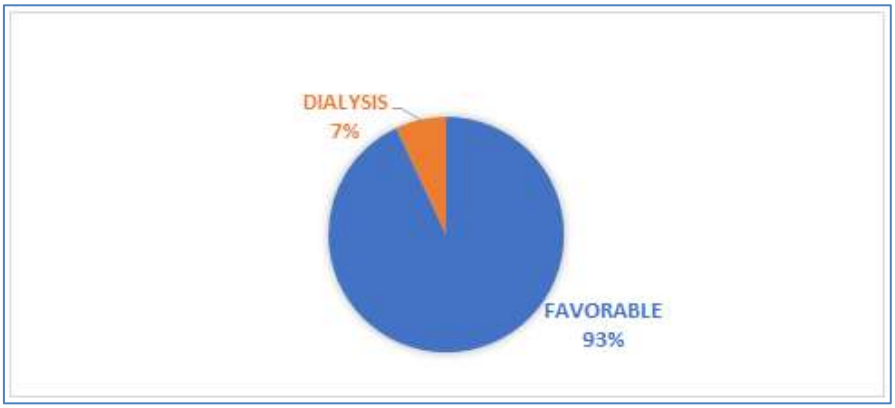

Fig-11: The evolution of our patients

DISCUSSION

Epidemiology

The annual incidence of IgA nephropathies in our series is evaluated at 3 cases per year. This number is identical to the result of the study carried out by Cambier (2017) [15], whereas the study carried out by MIZERSKA [16] displays 9cas per year. Global distribution disparities are explained by genetic influence [17], screening for microscopic hematuria and indications for kidney biopsy.

Table-2: The annual incidence of IgA nephropathy according to the different studies

Study	Cases per year
Chabchoub (2008) (18)	1,7
Figueres (2014) (19)	4
Mizerska Wasi (2016)	9
Cambier (2017) (15)	3
Our study (2017)	3

In Japan, testing for urine sediment abnormalities is a routine in all school children and the presence of isolated microscopic hematuria or low proteinuria leads to kidney biopsy [17]. This explains the high incidence of Berger's disease (10 times higher) in Japanese children, compared to African children [20].

In the United States, Canada or England, renal biopsy is only indicated in the presence of abundant proteinuria and / or renal failure [21]. In our context, the PBR was carried out in cases of Nephrotic syndrome associated with hematuria, renal impairment associated with extra-renal signs (arthralgia, purpura), nephrological manifestations in a child over 10 years of age or in the event of unexplained acute renal failure.

In our series, the mean age of our patients is 10 years in BM and 7.5 in RA, which is consistent with data in the literature. The male predominance has been observed in Berger's disease with a sex ratio of 9, the latter being between 1.5 and 3 in the pediatric literature [16, 19, 22-26].

In case of rheumatoid purpura, we noted a female predominance with a sex ratio of 0.75, a result similar to those of the studies found in the different published series. This divergence between the predominance of women and men in the literature is mainly due to the inclusion criteria in the different studies. Many studies are non-selective and include patients with rheumatoid purpura with or without nephrologic involvement. We find that the selective series, including only children with rheumatoid purpura with renal involvement, like our study, make the same observation of female predominance in cases of rheumatoid purpura nephropathy. This remark could consider the female sex as a factor of poor renal prognosis in patients with rheumatoid purpura.

Table-3: Berger's disease: average age and sex ratio in the different series

Study	Country/City	Number	Sexe ratio	The average age
Levy *et al*. (1985) (22)	United States	91	2,25	10
Linne *et al*. (1991) (23)	Spain	72	3,7	10
Wyatt *et al*. (1995) (24)	Memphis	103	2,6	11
Figueres (2014) (19)	France	29	3	10
Shibano *et al.* (2015) (25)	Japan	37	1,3	10,7
Komatsu *et al.* (2015) (26)	Japan	803	1,3	15
Mizerska wasi (2016) (16)	Poland	140	1,7	11
Notre série (2017)	Rabat	20	9	10

Table-4: Rheumatoid purpura: average age and sex ratio in the different series

Study	City	Number	Sexe ratio	The average age
Abdel-Al *et al*. (1990) [27]	Kuwait	55	-	5,6
Trapani *et al*. (2005) [28]	Italie	150	1,8	6,1
Ben Meriem *et al.* (2006) [29]	Tunisie	67	2,4	7,5
Naija *et al.* (2010) [30]	Tunisie	34	0,61	7,23
O Chen *et al.* (2013) [31]	Chine	120	1,9	6,6
Figueres (2014) [19]	France	33	1,4	7,2
Komatsu *et al*. (2015) [26]	Japon	153	0,9	9
Feng *et al*. (2017) [32]	Chine	54	1,7	8,4
Notre série (2017)	Rabat	09	0,75	7,5

The clinic

Our series and the published ones showed a majority of the macroscopic appearance of hematuria (Table 5), which was concomitant with an ENT or respiratory tract infection (1, 33, 34, 35).

Table-5: Hematuria in IgA nephropathy

Etude	Pays/ville	Nombre	Macro %	Micro %
Levy *et al*. (1985) [22]	Etats-Unis	91	72%	-
Linne *et al*. (1991) [23]	Espagne	72	69%	13%
Wyatt *et al*. (1995) [24]	Memphis	103	77%	16%
Chabchoub (2008) [18]	Tunisie	7	100%	-
Figueres (2014) [19]	Nante	62	51%	4%
Notre étude (2017)	Rabat	31	54%	10%

The data on hypertension vary widely depending on the series (Table 6), and they are due to the difference in definitions given to hypertension in children. In our study we defined hypertension as an increase in blood pressure exceeding the 97.5 percentile for both gender and height.

Table-6: The percentage of arterial hypertension in IgA nephropathy according to different studies

Study	Percentage of hypertension
Yoshikawa [36]	1,5%
Wyatt *et al*. [24]	7%
Kusumoto *et al.* [37]	24%
Komatsu *et al*. [26]	6,5%
Figueres [19]	17%
Mizerska [16]	17%
Notre étude	50%

Biology

In our series, we found that the percentage of patients who presented with nephrotic proteinuria in cases of rheumatoid purpura was 66%, a figure very close to the data found in the literature (figure 12). In the case of Berger's disease, the percentage of nephrotic syndrome is very high compared to data from the Asian literature (figure 13). This difference is probably due to the diagnostic delay up to the stage of renal damage, hence the interest of a systematic examination by urine dipstick in order to detect any abnormalities of urinary sediment in children and to indicate a tonsillectomy in the event of recurrent macroscopic hematuria.

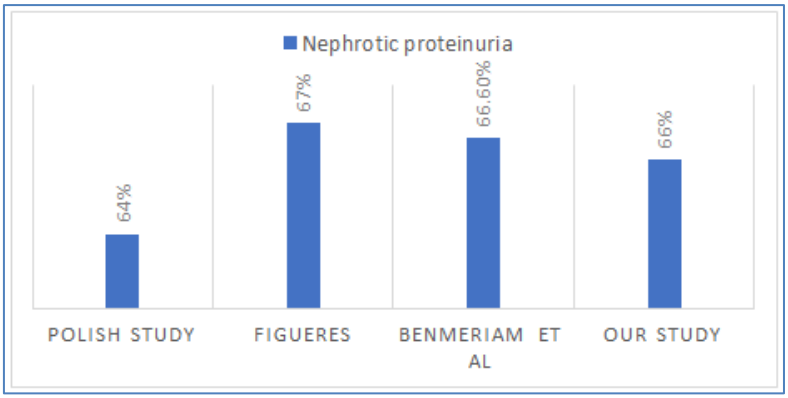

Fig-12: Rheumatoid purpura: the percentage of nephrotic proteinuria according to the different series

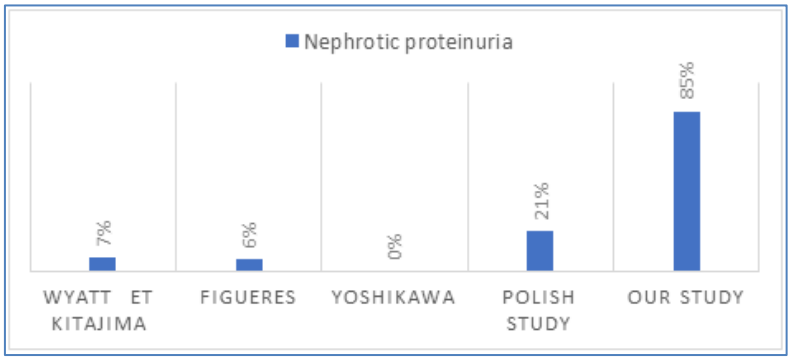

Fig-13: Berger's disease: the percentage of nephrotic proteinuria according to the different series

Chronic kidney disease (CRF) is rarely present in pediatric patients' onset. Acute, mild and transient renal failure is exceptional (10% in cases of Shepherd's disease (24, 36) appearing during an episode of macroscopic hematuria with acute tubular necrosis or in cases of IgA crescent nephropathy (38). Our study revealed acute renal failure in 32% of cases of which 16% had the dominance of histologic lesions of focal segmental hyalinosis and tubular atrophy which is considered to be a histologic factor of poor prognosis (15).

Prognostic factors and evolution

Prognostic, clinical and histological factors were evaluated with conflicting results depending on the authors and the methodology used in these studies [39]. This assessment aims to identify predictive factors for progression to IRCT, in order to isolate patients who require more aggressive treatment.

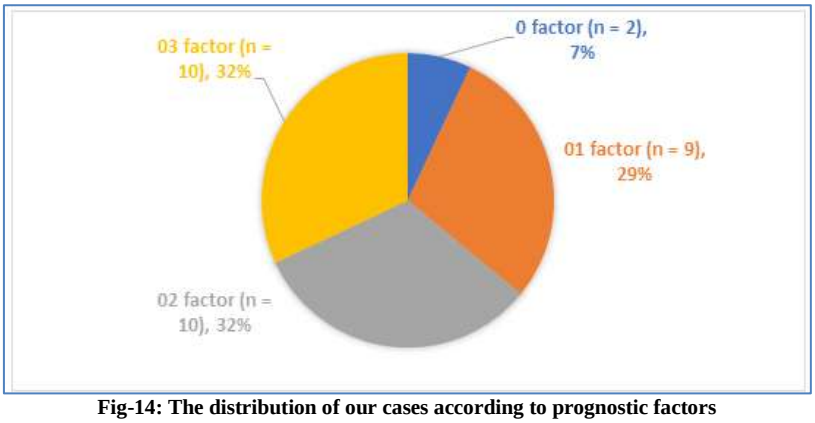

Fig-14: The distribution of our cases according to prognostic factors

After an average of 3 years of follow-up, only 2 patients with nephropathy secondary to celiac disease who progressed to end-stage chronic renal disease and then died after a while. 3 cases presented recurrence of hematuria and proteinuria following an episode of ENT infection, while the outcome was favorable in 93% of patients. Our results are consistent with those of global studies (table 7) where they demonstrated renal survival of 67% to 94% after 10 years of evolution. Other studies [42-45] have shown that progression to end stage renal disease affects 25 to 50% of patients with IgA nephropathy after 20 or 25 years of progression.

Table-7: IgA nephropathy: renal survival at 10 years according to the different studies

Author	Number of patients	Countries	10-year renal survival	Creatinine> 1.5 mg / dL	Arterial hypertension	Proteinuria > 3g / 24h
D'Amico *et al*.1986 [45]	365	Italie	85%	24%	36%	7%
Bogenschutz *et al.* 1990 [46]	239	Allemagne	81%	34%	19%	ND
Alamartine *et al*. 991 [13]	283	France	94%	2%	9%	3%
Katafuchi *et al.* 1994 [47]	225	Japon	74%	36%	22%	16%
Ibels *et al*. 1994 [44]	121	Australie	86%	36%	31%	16%
Radford *et al.*1997 [43]	148	Etats-Unis	67%	59%	47%	30%

Treatment

Currently, there is no curative treatment available to treat IgA nephropathy (38). Interpretation of published studies is difficult due to the small number of large pediatric series, different histological lesions between children and adults, and the lack of homogeneity of the series of children studied with regard to the therapeutic protocol. The therapeutic objective is to decrease the risk of worsening renal function, by keeping blood pressure below normal and proteinuria below 0.5 g / day [48].

Blockage of the renin angiotensin system (ACEI and or ARB II)

Their use as immunosuppressive therapy is recommended as first-line treatment. Several studies have shown their effectiveness, more than any other class of antihypertensive drug, in slowing the progression of renal failure in IgA nephropathy (nephroprotective effect). ENALAPRIL helps preserve kidney function and decrease the flow of proteinuria regardless of blood pressure balance (49).

The combination of ACEI and ARB II is more effective than monotherapy alone [50], allowing a significant reduction (18-25%) in proteinuria compared with monotherapy [51] and therefore preserving renal function (52). It is recommended if the proteinuria target of less than 500 mg / day is not reached in monotherapy at the maximum recommended dose [53].

In our series, we used this monotherapy (ACEI) in 74% of patients and the combination (ACEI + ARBII) in 10% of cases with a good clinical course (normalization of blood pressure figures) and biological (reduction in proteinuria).

Corticosteroid therapy

Corticosteroids have been widely used in pediatric patients with moderate to severe IgA nephropathy. However, it is quite difficult to draw a conclusion about their effectiveness in preserving renal function, as there are discrepancies in studies regarding the duration of follow-up, doses, and routes of administration and the use of concomitant drugs [54, 55].

In severe forms of the disease, corticosteroid therapy plays an important role, especially in children with proteinuria greater than 3g / day, severe histological forms with degradation of renal function [56].

A recent study by Cambier *et al*. which compared two pediatric groups, one under single nephroprotective treatment and the other associated with corticosteroid therapy, they come to the conclusion on the effectiveness of corticosteroid therapy and its major interest in the management of IgA nephropathy in children [15].

In our study where nephrotic proteinuria was frequent, corticosteroid therapy played an important role in the management of our patients and it showed its effectiveness.

Immunosuppressive treatment combining corticosteroid therapy and cyclophosphamide

Only one study has shown its superiority in reducing the rate of proteinuria and improving renal survival [57]. This therapeutic approach was only indicated in 2 of our patients because of persistent proteinuria or severe histological lesions with good improvement.

Tonsillectomy

The tonsils have been proposed to be an abnormal source of IgA which forms immune complexes responsible for deposits in the glomeruli [58]. The role of tonsillectomy in IgA nephropathy remains unclear, but in several studies, tonsillectomy combined with immunosuppressive therapy improved renal outcome in patients with relatively moderate renal impairment [59].

Most of the evidence for tonsillectomy comes from studies in adults. In a retrospective study in Japan with 118 patients who were followed for more than 20 years [60], renal survival in patients with or without a previous tonsillectomy was 90% and 64%, respectively.

In addition, in a recent prospective randomized study by Kawasaki *et al*. [61], the effectiveness of tonsillectomy was studied in 32 Japanese children. Sixteen children who received tonsillectomy and

steroids were compared with 16 other children treated with oral steroids, warfarin, dipyridamole, and mizoribine (PWDM). There were no untreated controls in the study. The authors concluded that tonsillectomy plus steroids is as effective as the PWDM regimen in controlling proteinuria. However, other studies have reported no benefit after tonsillectomy [62]. Until recently, there are not enough data to recommend tonsillectomy as a preventative treatment option for children with IgA nephropathy.

In our series, tonsillectomy was proposed in one of the 3 patients who presented recurrence of hematuria and proteinuria concomitant with an episode of ENT infection, the evolution was marked by the decrease in recurrent episodes of macroscopic hematuria.

CONCLUSION

IgA Nephropathy is an autoimmune disease that can affect people at any age. In the absence of an effective curative treatment, our goal is to underline the importance of screening for this pathology by systematic screening for hematuria in children, in order to avoid its serious progression to chronic renal failure.

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