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

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Abstract

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].
**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.
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.

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.
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.

Clinical and biological manifestations

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

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 / d day with an average of 5.4 g / d 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 celiac disease

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           | T0: 0%--25% | 05  | 16 %       |
| Interstitial fibrosis / tubular atrophy| 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 agglomerular fragments in the remaining 6 patients. The IF examination objectified the presence of mesangial IgA deposits in 100% of the cases studied.

**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.
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.

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 9 cases 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)     | United States| 91     | 2,25       | 10             |
| Linne et al. (1991)    | Spain        | 72     | 3,7        | 10             |
| Wyatt et al. (1995)    | Memphis      | 103    | 2,6        | 11             |
| Figueres (2014)        | France       | 29     | 3          | 10             |
| Shibano et al. (2015)  | Japan        | 37     | 1,3        | 10,7           |
| Komatsu et al. (2015)  | Japan        | 803    | 1,3        | 15             |
| Mizerska wasi (2016)   | 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) | Kuwait   | 55     | -          | 5,6            |
| Trapani et al. (2005)  | Italie   | 150    | 1,8        | 6,1            |
| Ben Meriem et al. (2006)| Tunisia | 67     | 2,4        | 7,5            |
| Naija et al. (2010)    | Tunisia  | 34     | 0,61       | 7,23           |
| O Chen et al. (2013)   | Chine    | 120    | 1,9        | 6,6            |
| Figueres (2014)        | France   | 33     | 1,4        | 7,2            |
| Komatsu et al. (2015)  | Japon    | 153    | 0,9        | 9              |
| Feng et al. (2017)     | 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)      | Etats-Unis | 91     | 72%     | -       |
| Linne et al. (1991)     | Espagne    | 72     | 69%     | 13%     |
| Wyatt et al. (1995)     | Memphis    | 103    | 77%     | 16%     |
| Chabchoub (2008)        | Tunisie    | 7      | 100%    | -       |
| Figueres (2014)         | 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 (2017)      | 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.
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.

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.
Series of children studied with ACEI system (ACEI and ARB II), which regarding effectiveness of therapy, 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 came 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

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**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. 1991 [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%                   |
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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