Clinicopathological Study of Non-Lupus Full-House Nephropathy

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Abstract

Background: Non-lupus full-house nephropathy is defined as “full-house” immunofluorescence pattern in patients without systemic lupus erythematosus. We compiled our adult case series with non-lupus full-house nephropathy evaluating etiology, clinical presentation and outcomes and in addition comparing them with lupus nephritis patients from our base records.

Methods: We included patients with full-house immunofluorescence pattern in renal biopsies collected between January 2000 and January 2017, excluding lupus nephritis. Patients with Non-lupus full-house nephropathy that did not show any underlying disease (the idiopathic group) were compared with a group of lupus nephritis patients extracted from our database (n=20).

Results: Non-lupus full-house nephropathy was identified in 20 patients (14 males) with mean age, 40.05 ± 12.37 years; mean serum creatinine, 1.63 ± 1.41 mg/dl and mean proteinuria, 6.35 ± 4.48 g/day. The most common light microscopy pattern was membranoproliferative glomerulonephritis in 9 cases (45%). During follow-up 4 patients met the criteria for systemic lupus erythematosus; 5 with others systemic diseases and 11 with idiopathic form. On last follow-up visit serum creatinine was higher in idiopathic non-lupus full-house nephropathy group compared to full-house lupus nephritis.

Conclusion: Non-lupus full-house nephropathy is a rare condition, affecting mainly males, with the predominance of the idiopathic form and this form showing higher final creatinine levels compared to full-house lupus nephritis.

Keywords: Lupus nephritis; Systemic lupus erythematosus; Renal lupus; Immunofluorescence; Full-house nephropathy; Epidemiology; Outcomes

Introduction

Full-house nephropathy (FHN) is characterized by immunofluorescence pattern of concomitant deposition of immunoglobulins - IgG, IgA, and IgM - and two complement system components - C3 and C1q - in renal tissue [1]. Glomeruli are ever the site of deposition although tubules and vessels could be occasionally involved [1]. Light microscopy features can show varied patterns [1].

The main etiology of FHN is lupus nephritis, although it has also been described in other diseases, such as in infection associated glomerulopathies (hepatitis C virus or HIV), cryoglobulinemia, Henoch-Schönlein purpura, and in idiopathic forms [2]. Ojemakinde et al. found a full-house pattern on immunofluorescence in 20% of patients with cryoglobulinemia [3].

In the literature, patients with FHN who do not meet the criteria for the diagnosis of systemic lupus erythematosus (SLE) and who test negative for anti-nuclear antibody (ANA) and serum anti-DNA antibodies are usually referred to as patients with lupus-like renal disease [2]. In a recent study, Rijnink et al. suggested that, those who present a full-house pattern on immunofluorescence without any associated disease should be classified as having "idiopathic non-lupus full-house nephropathy" [4].

Records of non-lupus FHN in children series showed light microscopy pattern of acute diffuse glomerulonephritis, membranous glomerulopathy, membranoproliferative glomerulonephritis and focal segmental glomerulosclerosis [1]. Another study involving 50 children followed for 68 months, focusing on the evolution of the disease, showed that 5 (10%) of the children came to meet the criteria for SLE, although only 2 (4%) had an unfavorable renal outcome [5].

Wen et al. studied 24 adult patients with non-lupus FHN found that 2 (8.3%) patients developed SLE during the 24 months of follow-up [2]. In the remaining 22 patients, the initial histological diagnoses were as follows: membranous glomerulopathy (n=9); membranous glomerulopathy associated with hepatitis B virus (n=1); IgA nephropathy (n=4); membranoproliferative glomerulonephritis (n=3); post infectious glomerulonephritis (n=3); C1q glomerulopathy (n=1); and unclassified glomerulopathy (n=1) [2].

Sam et al. evaluated 23 adult patients with non-lupus FHN reported that their light microscopy findings were of membranous glomerulopathy in all 23 cases, although 12 of these patients were ANA-positive and should therefore, on the basis of the current criteria, should have been classified as having SLE [6]. Huerta et al. also described 4 patients with non-lupus FHN with no extra renal manifestations of SLE with 2 patients presenting positive ANA in low
Rijnink et al. described a larger case series of 32 patients with non-lupus FHN [4]. Twelve patients were characterized as "secondary non lupus FHN" (positive antibodies M-Type phospholipase A2 receptor - PLA2R- membranous nephropathy n=1; cancer n=3; IgA nephropathy n=4; infections related glomerulonephritis n=2 and ANCA associated glomerulonephritis n=2), while 20 patients were diagnosed as idiopathic non-lupus FHN and compared with 117 classes III, IV and V "full-house" lupus nephritis patients. After analysis the authors conclude that idiopathic non-lupus FHN was an independent risk factor for ESRD [4].

Considering that there is a scarce literature on this subject, we compiled our adult case series describing clinical presentation and outcomes of non-lupus FHN. In addition, we compared idiopathic non-lupus FHN patients with those full-house lupus nephritis from our lupus nephritis base records.

Methods

Patients with renal biopsies collected between January 2000 and January 2017 in the Department of Nephrology and Pathology at the University of São Paulo School of Medicine Hospital das Clínicas that showed a "full-house" pattern on immunofluorescence were retrieved. The diagnosis of SLE was based on the criteria established by the Systemic Lupus International Collaborating Clinics (SLICC) [8]. We included idiopathic forms of FHN as well as those associated with diseases other than lupus, evaluating clinical and biochemical data obtained at the time of renal biopsy, during medical visits, and at the end of follow-up. Patients that did not show any underlying disease (the idiopathic non-lupus FHN group) were compared with a group of lupus nephritis patients extracted from our database (n= 20), matched by age and serum creatinine level on diagnosis. Treatment for both groups was determined by the attending physician.

Analysis of clinical and biochemical parameters

Ethnicity ancestry was assessed by self-denomination extracted from the medical record. On renal biopsy and during follow-up, patients were evaluated by 24 h proteinuria, determined by the automated colorimetric method; urinalysis findings; serum creatinine, determined by kinetic colorimetric assay; glomerular filtration rate (GFR), determined by the Modification of Diet in Renal Disease equation [9]; C3 and C4 complement fractions, determined by immunoturbidimetry (reference ranges of 90–180 mg/dl and 10–40 mg/dl, respectively); serology for hepatitis B virus, hepatitis C virus, and HIV; ANA, determined by immunofluorescence in Hep-2 cells; anti-DNA antibodies by enzyme immunoassay (ELISA); complete blood count; and blood pressure. The end of follow-up was defined as doubling of serum creatinine or ESRD.

Hard renal outcome was defined as doubling of serum creatinine or ESRD. Hematuria was defined as >10 red blood cells per field in two first-morning urine specimens. Hypertension was defined as arterial blood pressure > 140/90 mmHg, in two measurements on different days [10], or previous use of antihypertensive drugs, regardless of blood pressure levels.

Renal biopsy parameters

Diagnosis of FHN on a renal biopsy sample, was in accordance with the following criteria: more than 6 glomeruli on light microscopy sample and a "full-house" immunofluorescence pattern-concomitant deposition of IgG, IgA, IgM, complement C3, and complement C1q, each with a minimum intensity of 1+ on a 0-3 + scale. Only biopsies showing granular fluorescent staining along the capillary walls, in the mesangium or both were included.

Compliance with ethical standards

The procedures involved in this study have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The Research Ethics Committee of the University of Sao Paulo School of Medicine Hospital das Clínicas approved the study with protocol number 73240217.90000.0068. For this type of study formal consent is not required.

Statistical Analysis

Data related to numerical variables are expressed as mean ± standard deviation, whereas data related to categorical variables are expressed as absolute and relative frequencies. Comparison between idiopathic non-lupus FHN and lupus nephritis for numerical variables were done by unpaired t-test, whereas categorical variables were compared by Fisher's exact test. Values of p< 0.05 were considered statistically significant.

Results

During the study period, 367 renal biopsies met the criteria for FHN and 347 (94.5%) were classified as lupus nephritis while 20 (5.5%) were classified as non-lupus FHN. Main characteristics of patients with non-lupus FHN were predominance of males (70%), white race (80%), mean age of 40.05 ± 12.37 years, serum creatinine of 1.63 ± 1.41 mg/dl, MDRD GFR 68.05 ± 35.56 ml/min/1.73m², serum albumin of 2.31 ± 0.68 g/dl, proteinuria of 6.35 ± 4.48 g/day, and mean hemoglobin level of 11.22 ± 1.69 g/dl (Table 1). Serum complement (C3 and C4) levels were evaluated in 19 patients and were below normal in 11 (57.8%), hematuria occurred in 15 (75%) patients and high blood pressure records were detected in 11 patients (57.8%) out of 19 that had this record.

| Patient | Age (years) | Gender | Serum creatinine (mgdl) | Proteinuria (g/day) | Serum albumin (g/dl) | Haemoglobin (gdl) |
|---------|-------------|--------|-------------------------|--------------------|---------------------|------------------|
| 1       | 46          | F      | 1.1                     | 0.98               | 3.3                 | 12.4             |
| 2       | 25          | F      | 0.73                    | 10.33              | 1.7                 | 12.8             |
| 3       | 34          | F      | 0.9                     | 3.13               | ND                  | 12.3             |
Table 1: Clinical and biochemical characteristics at diagnosis of 20 patients with non-lupus full-house nephropathy.

| Patient | Light microscopy pattern | Immunoglobulin | Complement | Site |
|---------|--------------------------|----------------|------------|------|
| 1       | Acute diffuse GN         | ++            | +          | ++   | ++  | Capillary loop |
| 2       | Mesangial GN             | +             | +          | +    | +   | Mesangium; capillary loop |
| 3       | Mesangial GN             | ++            | +          | ++   | +   | Mesangium |
| 4       | MGN                      | +++           | +          | +    | +   | Capillary loop |
| 5       | MGN                      | +++           | +          | +    | +   | Capillary loop |
| 6       | MGN                      | +++           | +          | +    | +   | Mesangium; capillary loop |
| 7       | MGN                      | +++           | +          | +    | +   | Capillary loop |
| 8       | MGN                      | +++           | ++         | +    | +   | Mesangium; capillary loop |
| 9       | MGN                      | +++           | ++         | +    | +   | Mesangium; capillary loop |
| 10      | MPGN                     | ++            | +          | +    | +   | Capillary loop |

Light microscopy diagnoses were as follows: membranoproliferative glomerulonephritis (45%); membranous glomerulopathy (30%); mesangial glomerulonephritis (10%); acute diffuse glomerulonephritis (5%); cryoglobulinemic vasculitis (5%); and crescentic glomerulonephritis (5%) (Table 2).
Immunofluorescence studies showed more intense glomerular staining of IgG over IgM or IgA. IgG 3+ was present in 10 patients (50%) while IgM 3+ in 3 (15%) and IgA 3+ in 2 (10%) patients. Complement C3 staining compared to C1q was largely over expressed: 8 patients (40%) graded 3+ on C3 while no patients grade 3+ on C1q (Table 2).

Patients associated diseases clinical parameters on follow-up and treatment are depicted on Table 3. After a mean follow-up of 64.32 ± 55.26 months, 4 patients (20%) developed criteria for SLE, with ANA positivity along 2 to 12 years; 3 (15%) were diagnosed with schistosomiasis, 1 (5%) with cryoglobulinemia, 1 (5%) with HIV and 11 (55%) were classified as idiopathic form.

Fourteen patients received immunosuppressive therapy immediately after diagnosis: 2 with Tacrolimus, 1 cyclosporine, 1 Mycophenolate mofetil with prednisone and 10 with cyclophosphamide plus prednisone that was combined with rituximab in 2 and plasmapheresis in one (Table 3). Considering outcomes, 1 patient (5%) died, 3 (15%) progressed to ESRD, and 1 was lost to follow-up. Among the remaining patients (n= 15), the mean serum creatinine level was 1.99 ± 1.38 mg/dl (Table 3).

| Patient | Initial diagnosis         | Treatment            | Final diagnosis         | Final creatinine (mg/dl) | Follow-up (months) |
|---------|---------------------------|----------------------|-------------------------|-------------------------|--------------------|
| 1       | Acute diffuse GN          | No IS                | SLE/ANA+ after 2 years  | 0.73                    | 144                |
| 2       | Mesangial GN              | CP + prednisone      | Idiopathic GN Mesangial| 1.29                    | 120                |
| 3       | Mesangial GN              | No IS                | SLE/ANA+ after 12 years | 0.90                    | 144                |
| 4       | MGN                       | No IS                | Schistosomiasis         | 3.60                    | 49                 |
| 5       | MGN                       | CP + prednisone      | Idiopathic MGN          | 0.98                    | 72                 |
| 6       | MGN                       | No IS                | Idiopathic MGN          |                          | lost               |
| 7       | MGN                       | Tacrolimus           | Idiopathic MGN          | 0.90                    | 6                  |
| 8       | MGN                       | Tacrolimus           | Schistosomiasis         | 0.90                    | 6                  |
| 9       | MGN                       | Cyclosporine         | Idiopathic MGN          | 1.50                    | 24                 |
| 10      | MGN                       | No IS                | Idiopathic MGN          | 1.70                    | 132                |
| 11      | MPGN                      | CP + prednisone      | Idiopathic MPGN         | 2.44                    | 132                |
| 12      | MPGN                      | CP + prednisone      | Idiopathic MPGN         | 5.50                    | 48                 |
| 13      | MPGN                      | No IS                | Schistosomiasis         | 2.8/Death               | 48                 |
| 14      | MPGN                      | CP + prednisone      | SLE/ANA+ after 4 years  | 2.40                    | 132                |
| 15      | MPGN                      | CP + prednisone      | Idiopathic MPGN         |                          | Hemodialysis       |

Table 2: Renal biopsy data of 20 patients with non-lupus full-house nephropathy.
Table 3: Associated disease, treatment and outcomes of 20 patients with non-lupus full-house nephropathy.

| Patient | Disease | Treatment | Outcome | Follow-up (months) | Hemodialysis |
|---------|---------|-----------|---------|--------------------|--------------|
| 16      | MPGN    | CP + prednisone | Idiopathic MPGN | 108 |
| 17      | MPGN    | CP + prednisone + RTX | SLE/ANA+ after 2 years | 24 |
| 18      | MPGN    | MMF + prednisone | HIV | 6 |
| 19      | GN cryoglobulinemia; crescents | CP + prednisone + RTX + plasmapheresis | Cryoglobulinemia | 6 |
| 20      | GN crescents; TMA | CP + prednisone | Idiopathic GN crescents; TMA | 6 |

GN: Glomerulonephritis; MPGN: Membranoproliferative glomerulonephritis; CP: Cyclophosphamide; IS: immunosuppression; MGN: Membranous glomerulopathy; RTX: Rituximab; MMF: Mycophenolate mofetil; TMA: Thrombotic microangiopathy

Table 4: Clinical and biochemical data at diagnosis and renal outcomes of patients with idiopathic non-lupus full-house nephropathy compared to those with lupus nephritis.

| Variable | Idiopathic non-lupus FHN (n=11) | Lupus nephritis (n=20) | p |
|----------|---------------------------------|------------------------|---|
| Age (years) | 33.18 ± 9.13 | 31.50 ± 10.10 | 0.89 |
| Gender (M/F) | 8/3 | 1/19 | 0.0002 |
| Initial Serum creatinine (mg/dl) | 1.69 ± 1.89 | 1.81 ± 1.69 | 0.94 |
| Initial Proteinuria (g/day) | 8.40 ± 3.65 | 6.34 ± 5.86 | 0.04 |
| Initial Serum albumin (g/dl) | 2.17 ± 0.54 | 2.60 ± 0.83 | 0.22 |
| Initial Hemoglobin (g/dl) | 11.30 ± 1.55 | 11.9 ± 2.10 | 0.60 |
| Arterial hypertension (%) | 45.4 | 60 | 0.20 |
| Hematuria (%) | 45.4 | 52 | 0.88 |
| C1q n (%) | 9 (81.8) | 16 (80) | 1 |
| 2 (18.2) | 2 (10) |
| 0 | 2 (10) |
| Follow up (months) | 64.50 ± 54.90 | 105.8 ± 2.62 | 0.0043 |
| Dialysis (n%) | 2/18.1 | 6/30 | 0.06 |
| Doubling of serum creatinine n% | 3/27.2 | 1/5 | 0.115 |
| Final Proteinuria g/day | 2.42 ± 2.56 | 0.80 ± 0.96 | 0.016 |
| Final serum creatinine | 2.28 ± 1.64 | 1.10 ± 1.08 | 0.012 |

FHN: Full-house nephropathy; C1q: Complement component 1q; IF: Immunofluorescence; RTT: Renal replacement therapy

Regarding renal survival there was a tendency to dialysis, ESRD, in lupus nephritis 30% compared with 18.1% of the patients with idiopathic non-lupus FHN (p=0.06), although the follow-up time was longer for the patients with lupus nephritis (Table 4). There was a difference in final creatinine levels and proteinuria when only out of dialysis patients were included, showing higher levels of both in non-lupus FHN (p= 0.012 and 0.016 respectively), without difference in doubling of serum creatinine (Table 4).
Considering treatment, idiopathic non-lupus FHN were submitted to immunosuppressive drugs as used in lupus nephritis mainly with corticosteroids and cyclophosphamide as induction therapy without difference between both groups (Table 5). However, on maintenance, patients with no immunosuppression were predominant in idiopathic non-lupus FHN (54.5 vs. 10%, p = 0.012).

Table 5: Immunosuppressive treatment of patients with idiopathic non-lupus full-house nephropathy and lupus nephritis.

| Immunosuppression       | Idiopathic non-lupus FHN (n=11) | Lupus nephritis (n=20) | P     |
|-------------------------|---------------------------------|------------------------|-------|
|                         |                                 |                        |       |
| Induction               |                                 |                        |       |
| Cyclophosphamide + corticosteroids n (%) | 7 (63.6) | 16 (80) | 0.4   |
| Corticosteroids n (%)   |                                 | 4 (20)                 |       |
| Calcineurin Inhibitor n (%) | 2 (18.2) |            |       |
| No immunosuppression n (%) | 2 (18.2) |            |       |
| Maintenance             |                                 |                        |       |
| Azathioprine + corticosteroids n (%) | 4 (36.4) | 10 (50) | 0.7   |
| Mycophenolate mofetil + corticosteroids n (%) | 1 (9.1) | 8 (40) | 0.10  |
| No immunosuppression n (%) | 6 (54.5) | 2 (10)  | 0.012 |

Table: Immunosuppressive treatment of patients with idiopathic non-lupus full-house nephropathy and lupus nephritis.

**Discussion**

In our adults patients report, we found 20 patients with non-lupus FHN (5.5%) out of 367 with full-house immunofluorescence-staining. However, this proportion of distribution is variable in the literature with some authors reporting higher frequencies as 20% of non-lupus FHN over all FHN [2,4].

About sex distribution in non-lupus FHN, we showed a higher frequency of male over female (70 vs. 30%) such as Rijnink et al. [4], while publications by Ruggiero et al. [5] in children and Wen et al. [2] in adults showed an equal sex distribution. Age presentation of our patients with non-lupus FHN mean of 40 years is not different from those of Rijnink et al. [4] 37.3 years and Wen et al. [2] 47 years, considering only publications on adults.

On clinical presentation, 14 patients out of 20 had nephrotic syndrome with mean proteinuria of 8.37 ± 3.80 g/day and mean of serum albumin of 2.06 ± 0.56 g/dl not different from Wen et al. [2] that describes 13 patients out of 24 and protein excretion rate of 5.6 ± 2.2 g/ day. There is scarce information in literature of renal function of patients with non-lupus FHN but some authors report normal or near normal renal function on presentation [4] while our patients showed lower renal function with a mean creatinine of 1.63 mg/dL.

Associated diseases are well described in non-lupus FHN such as cancer, infection-related glomerulonephritis, ANCA associated glomerulonephritis, hepatitis B virus, C1q nephropathy [2,4]. In our casuistic, we highlighted 3 patients with Schistosomiasis that is a chronic infectious disease endemic in Northeast Brazil, caused by Schistosoma mansoni that may affect migrated populations. Its pathogenesis relies on polyclonal lymphoproliferative stimulation and immune-complex deposition in the kidney. Histological diagnosis on light microscopy of affected kidneys is mainly of Membranoproliferative glomerulonephritis or Focal Segmental Glomerulosclerosis [11,12]. Our 3 patients with Schistosomiasis and non-lupus FHN were diagnosed with Membranoproliferative glomerulopathy (n=1) and membranous glomerulopathy (n=2) and on follow-up one died of no renal causes, one progressed to chronic kidney disease and one, who was treated with tacrolimus, stabilized renal function on serum creatinine of 0.9 mg/dL.

Light microscopy histopathological findings of our entire sample showed that membranoproliferative glomerulonephritis and membranous glomerulopathy were the most common forms of non-lupus FHN accounting for 75% of the cases. Similar results were obtained in the study conducted by Wen et al. [2], who reported that 14 (58.3%) of 24 patients with FHN received clinicopathological diagnoses of membranoproliferative glomerulonephritis or membranous glomerulopathy.

Excluding patients with associated diseases and those that developed criteria for SLE on follow-up, we characterized a group of 11 patients with idiopathic non-lupus FHN and compared them with 20 patients class IV (n=10) and class V (n=10) lupus nephritis retrieved from our archives (Table 4). Our patients with idiopathic form were more often male and showed a higher protein excretion rate, similar as described by Rijnink et al. [4]. Although, no differences on C1q staining by immunofluorescence were identified in our study some authors have called attention to the higher intensity of C1q deposition in cases with non-lupus FHN, suggesting that genetic alterations involving C1q structure or function as well as the presence of anti-C1q antibodies could create patterns indistinguishable from those of lupus nephritis [13].

Considering outcomes, our patients with idiopathic non-lupus FHN compared to lupus nephritis showed higher final serum creatinine levels and final proteinuria while a borderline significance was obtained, on benefit of idiopathic non-lupus FHN, on dialysis outcome (18% vs 30%, p = 0.06) although, lupus nephritis group had a lower follow-up time. Rijnink et al. [4] showed that idiopathic non-lupus FHN progressing significantly more rapidly to ESRD than lupus nephritis. They speculate that this poor outcome may well be related to their lack of cytotoxic therapy: 11 out of 20 patients (55%) did not receive any immunosuppressive drug while 5 (25%) received corticosteroids alone and none received cyclophosphamide [4]. This contrasts with a minority (18.2%) of our patients with idiopathic non-lupus FHN not receiving any immunosuppressive drug as induction treatment while the majority (63.6%) received corticosteroids plus cyclophosphamide. Ruggiero et al. [5] in a recent study of pediatric non-lupus FHN patients who received intensive cytotoxic immunosuppression and had a favorable renal outcome raises the possibility that those patients may benefit from immunosuppression.

The etiology and pathogenesis of idiopathic non-lupus FHN remain to be elucidated. Full-house glomerular deposits in the absence of a clinical diagnosis of SLE may be seen as defective immune complex clearance following abnormal immune complex overload or handling as in full-house lupus nephritis. Unidentified endogenous or exogenous antigens as well as genetic factors resulting in defective clearance of immune complexes may underlie idiopathic non-lupus FHN. It is a matter of debate in literature the real meaning of "seronegative lupus nephritis" and its course. Usually this term is used to describe patients in whom the renal histology is typical of lupus nephritis, even with immunofluorescence “full-house” staining.
there is no clinical or serological evidence of SLE at the time of renal biopsy. It has been proposed that a significant proportion of patients with such "seronegative lupus nephritis" will develop overt SLE fulfilling clinical criteria but, in fact, only approximately 10% of such patients are subsequently diagnosed with SLE in some publications [2,3]. In our report 4 patients (20%) developed clinical criteria for SLE along follow-up time of 2 to 12 years, allowing us to speculate that they could have been "seronegative lupus nephritis" on presentation. Appearance of symptoms and auto antibodies suggestive of SLE in long time follow-up, up to 10 years as in our patients, are reported by several authors [1,2,4].

In summary, full-house immunofluorescence per se is a far from optimal indication of lupus nephritis and must be interpreted in light of clinical features. Non-lupus FHN is a rare condition, affecting mainly males patients in different ages that could be associated to systemic diseases or totally idiopathic while a minority could evolve into SLE if more long-term follow-up data are available. When treated with immunosuppressants, non-lupus FHN showed hard renal outcomes (dialysis and doubling of serum creatinine) not different from that of lupus nephritis, although higher serum creatinine levels and protein excretion were found. Nevertheless, further studies are needed in order to corroborate that conclusion and to establish better approaches to the treatment of non-lupus FHN.

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