Nephrotic syndrome with Minimal Change Disease and Atopy in North-African adults

Syndrome néphrotique à Lésions Glomérulaires Minimes et atopie chez des adultes Nord-Africains

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Abstract

Background: In adults, minimal change disease (MCD) accounts for 15 to 25% of nephrotic syndrome (NS). Numerous reports have suggested a link between NS and atopy. However, data on treatment and prognosis of NS associated with allergy are limited.

Aim: To examine the presenting characteristics, treatments and outcomes of adults with allergic MCD in a North African center.

Methods: This was an observational study using retrospectively collected data. Patients were recruited from the Nephrology department of Sahloul Hospital (Sousse, Tunisia) from January 2006 to December 2020. Adults with a biopsy proved MCD, which was associated with atopy, were included.

Results: Fifteen patients (eight males, age mean±SD: 34±13 years) were included. High eosinophil and immunoglobulin E (IgE) levels were noted in three and twelve patients respectively. The IgE mean level at the initial presentation was 1431 IU/ml. Allergic skin tests were positive in nine patients. All patients were treated with corticosteroids, five had anti-histamine therapy and five had hyposensitization therapy, which was successful in two patients. Thirteen patients had relapsed during follow-up. Mean eosinophil level was significantly higher in patients with frequent relapses compared to those with infrequent relapses (5415/mm³ vs. 239.12/mm³, respectively, p=0.022). Two patients had progressed to chronic renal failure.

Conclusion: It is important to search for atopic disorders in patients with MCD to better control this disease and use specific treatments. However, the efficacy of anti-allergic therapies has to be proven.

Keywords: Glomerulonephritis, allergens, hypersensitivity, proteinuria, renal disease.

Résumé

Introduction : Les lésions glomérulaires minimes (LGM) représentent 15 à 25 % des syndromes néphrotiques (SN) de l'adulte. Plusieurs rapports ont suggéré un lien entre le SN et l'atopie. Cependant, les données sur le traitement et le pronostic sont limités.

But : Examiner les caractéristiques des adultes atteints de LGM allergique dans un centre nord-africain.

Méthodes : Il s'agit d'une étude rétrospective. Les patients ont été recrutés dans le service de néphrologie de l'hôpital Sahloul (Sousse, Tunisie) de janvier 2006 au décembre 2020. Ceux ayant des LGM prouvées histologiquement, associée à une atopie, ont été inclus.

Résultats : Quinze patients (huit hommes, âge moyen ± ET : 34 ± 13 ans) ont été inclus. Des taux élevés d'éosinophiles et d'immunoglobulines E (IgE) ont été notés chez trois et douze patients respectivement. Le taux moyen d'IgE initialement était de 1431 UI/ml. Les tests cutanés allergiques étaient positifs chez neuf patients. Tous les patients ont été traités avec des corticoïdes, cinq ont eu un traitement anti-histaminique et cinq ont eu un traitement de désensibilisation ayant réussi chez deux patients. Treize patients avaient rechuté ultérieurement. Le taux moyen d'éosinophiles était significativement plus élevé chez les patients avec des rechutes fréquentes par rapport à ceux avec des rechutes peu fréquentes (5415/mm³ contre 239,12/mm³, respectivement, p=0,022). Deux patients avaient évolué vers l'insuffisance rénale chronique.

Conclusion : Une cause allergique doit être recherchée chez les patients avec LGM pour mieux contrôler cette pathologie et utiliser des traitements spécifiques.

Mots clés : Glomérulonéphrite, allergènes, hypersensibilité, protéinurie, maladie rénale.

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INTRODUCTION

Atopy is a predisposition to respond to different antigens/ allergens, leading to the differentiation of CD4+ Th2 lymphocytes with overproduction of immunoglobulin E (IgE) and a propensity to create hypersensitivity responses to allergens (1). Atopy affects a significant proportion of the general population, with estimates ranging from 10 to 30 % in developed countries (1). Many studies have found a strong link between nephrotic syndrome (NS) and atopy in children (2). According to most studies, 30 to 40% of children with steroid-sensitive NS have an allergic disorder (e.g.; fever, asthma, atopic dermatitis) (3, 4).

Minimal change disease (MCD) is the most frequent etiology of steroid-sensitive NS in children (1) causing edema and heavy proteinuria (5, 6) with subtle glomerular lesions on renal biopsy and extensive foot process effacement on electron microscopy (7). Allergic diseases are commonly reported in children with MCD (8) and many studies showed that some children with MCD may present with NS after allergen exposure (9,10). However, few studies (not including the North African population) have investigated the association between atopy and MCD in adults (11–13).

The present study aimed to describe the characteristics of North-African adult patients with biopsy-proven MCD in a context of atopy.

METHODS

Study design

This was a retrospective study performed from January 2006 to December 2020 in the Nephrology department of Sahloul Hospital (Sousse, Tunisia). Ethical approval was obtained from the Institutional Review Board of the University Hospital of Farhat Hached (Sousse, Tunisia) (CEFMS 128/2022), and this study was conducted in accordance with the principles of the Declaration of Helsinki. As the study was retrospective in design and did not involve any interventions, the Institutional Review Board waived informed consent for this study.Patients and public involvement.

Patients: inclusion, non-inclusion, and exclusion criteria

The following inclusion criteria were applied: adult patients over the age of 18, NS and biopsy-proven MCD, and clinical evidence of allergy. The following non-inclusion criteria were applied: idiopathic MCD or secondary MCD from other causes.

Collected data and applied definitions

Data were collected from patient's files on a pre-established form analyzing epidemiological (e.g.; age and sex), clinical (e.g.; personal and familiar history of atopy, presence of functional signs including itching, rhinorrhea, sneezing, cough and joint pain, physical signs including edema, eczema, eye redness, urticaria and contact dermatitis), biological (e.g.; microscopic hematuria, glomerular filtration rate (GFR), plasma eosinophil, IgE, serum albumin and urine protein levels), therapeutic (e.g.; use of corticosteroids, anti-histamine drugs, and hyposensitization), and long-term follow up (e.g.; remission, relapse, steroid dependency, steroid resistance and chronic renal failure) characteristics.

NS was defined as proteinuria ≥ 3 g/day with a hypoalbuminemia < 30 g/l (6, 14). Arterial hypertension was defined as an office systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg (15). Microscopic hematuria was defined as the presence of more than 10 red blood cells per high-power field of urine sediment (16). Creatinine clearance was calculated according to the modification of diet in renal disease (MDRD) formula (6). A serum eosinophil level in the hemogram > 500/mm³, and a serum IgE > 120UI/mL were considered as high (8, 17).

The skin prick test was conducted using a standard allergen extract panel. The latter comprised histamine and saline considered positive and negative controls, respectively. The allergens tested were Dermatophagoïde pteronyssinus, Dermatophagofarinainea, Alternaria, cockroaches, cat dander, dog dander, feathers, olive pollen, four grains, five-grasses, parietary, and cypress. The prick test was considered positive if the diameter of the papule was at least three mm larger than that of the negative control (18).

Patients were considered on complete remission if they had a reduction of proteinuria to less than 0.3 g/day, and on partial remission if they had a reduction of proteinuria to between 0.3 to 3 g/day (14). A relapse was defined, as reappearance of proteinuria > 3 g/day after complete remission has been achieved (14). A frequently relapsing NS was defined by two or more relapses within the first six months after a steroid-induced remission, or four or more relapses within the first year (14). A steroid-dependent NS was defined as a relapse occurring during or within two weeks of completing corticosteroid therapy (6).

Corticosteroid-resistant NS was defined as the persistence of proteinuria > 3g/day despite prednisone 1 mg/kg/day for ≥16 weeks (6, 14).

Statistical analysis

Data were analyzed using SPSS version 20 software. Data were expressed as mean values ± standard deviation. Statistical analysis was carried out using the Chi2 test for the comparison of categorical variables and the Student-test for the comparison of quantitative variables. A difference was considered significant whenever the "p" value was less than 0.05.

RESULTS

Of 1453 renal biopsies carried out between 2006 and 2020, MCD was noted in 184 cases (12.7%) among biopsies showing glomerulonephritis. As seen in Figure 1, among 84 patients with MCD, an allergic cause was noted in 15 patients (18%).

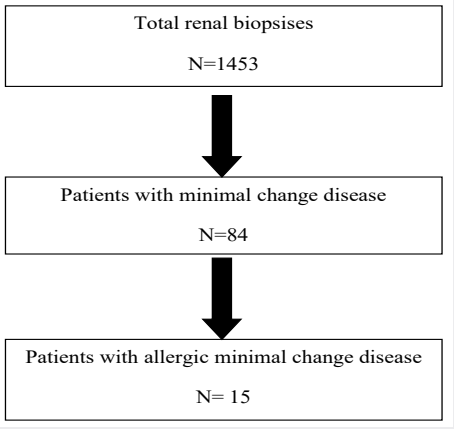

Figure 1. Frequency of allergic minimal change disease.

Clinical and para-clinical presentation

Table 1 exposes the clinical para-clinical characteristics of the 15 patients. High eosinophil levels were found in three patients, while in patients with non-atopic MCD high eosinophil levels were found in only seven patients (p=0.089). One patient had even a very high eosinophil level at 10000/mm³. A sternal puncture was performed for him and showed a normal myelogram. A high level was found in 12 patients with an average of 1431 IU/ml versus 1144 UI/ml in patients with non-atopic MCD (p=0.651).

Table 1. Patients clinical and para-clinical characteristics (n=15)

Age	**At diagnosis (years)**	**34±13**
	Range (years)	**18 to 53**
Sex ratio	Male/female	1.14
Seasonal distribution of Hospitalization	Summer	7
	Spring	4
	Winter	2
	Autumn	2
Familial history of atopy	Yes	3
Personal history of atopy*	Yes	10
Already known allergen**	Yes	6
Arterial hypertension	Yes	3
Functional signs	Itching	3
	Rhinorrhea and sneezing	2
	Cough	2
	Joint pain	2
Physical signs	Edema	15
	Eczema	2
	Eye redness	1
	Urticaria	1
	Contact dermatitis	1
Microscopic hematuria	Yes	2
Glomerular filtration rate	(ml/min/m²)	120.6±48.7
Glomerular filtration rate (range)	(ml/min/m²)	50.1 to 172
Plasma eosinophil	Elements/mm³	988±2602
	High level	3
Plasma IgE	IU/ml	1431±2392
	High level	12
Serum albumin	g/l	19.05±4.13
Urine protein level	g/day	6.21±5.05
Positive allergic skin test***	Yes	9

Quantitative and categorical data were mean±SD and number, respectively.
*Atopic rhinitis (n=3), eczema and asthma (n=2 each), urticaria, contact dermatitis, and allergic conjunctivitis (n=1 each).
**Dust and strawberries (n=2 each), pollen and paint products (n=1 each).
***Pollen (n=4), Acarian (n=3), olive, milk, dust, wool, and cockroaches (n=1 each).

Treatment and outcomes

All patients received corticosteroid therapy with prednisone at the initial dose of 1 mg/kg/day. No one needed immunosuppressive therapy at follow-up. Other

treatments were attempted: anti-histamine therapy (n=5) [cetirizine (n=2), desloratadine (n=2), levocetirizine (n=1)], and hyposensitization therapy (n=5). Among the five patients treated with anti-histamine drugs, two patients with frequently relapsing NS (one treated with cetirizine and one treated with levocetirizine) had a complete remission but subsequently relapsed after one year of remission. Another patient with infrequent relapses who was treated with desloratadine had also a complete remission with no subsequent relapses with a follow-up of three years. Anti-histamine therapy was not successful in the remaining two patients. Two patients had a complete remission after hyposensitization without subsequent relapse with a follow-up of five years for the first patient, and a follow-up of one year and a half for the second patient, while two other patients with multiple allergies, had hyposensitization without success and with subsequent relapses. The fifth patient was still undergoing hyposensitization at the time of data collection. In parallel, eviction of the involved allergen was undertaken in all patients when it was possible and two patients needed a professional re-classification. The mean time to remission in all patients was 1.55±1.1 [range: 0.5-4] months. The average IgE level decreased significantly from 1431±976 UI/ml during the initial presentation to 266±25.4 UI/ml at remission (p= 0.157).

At follow-up, only two patients did not relapse. The remaining patients had experienced relapses, with a mean number of relapses of 4.1±3.8 (range: 1 to 12 relapses), and a mean time to relapse of 1.47±1.40 (range: 0.33 to 4.00) years. Three patients had frequent relapses with a mean number of relapses of 10.5±2.1 (range: 9 to 12), and an average of four relapses/year. These patients with frequent relapses had multiple allergies and the relapse of NS followed exposure to one or more of the allergens.

As seen in Figure 2, the mean eosinophil level was significantly higher in patients with frequent relapses at 5415/mm³ compared to those with infrequent relapses in whom it was at 239/mm³ (p=0.022). However; there was no statistically significant difference in IgE levels between the two groups (p=0.575). Two patients had steroid-dependent NS, and one patient had steroid-resistant NS. Finally, two patients had progressed to chronic renal failure, but no one had an end-stage renal disease.

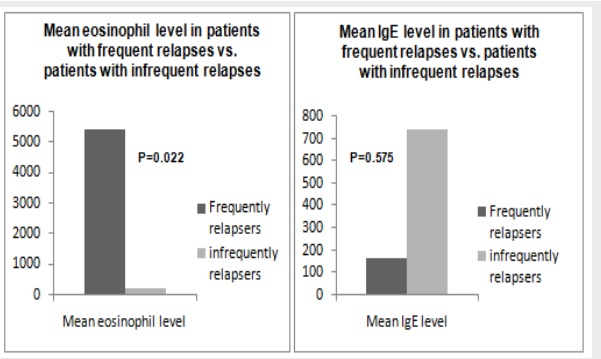

Figure 2. Mean eosinophil and Immunoglobulin E (IgE) levels in patients with frequent relapses (n=3) and those with infrequent relapses (n=10).

DISCUSSION

It is thought to be immunologically mediated, but the underlying mechanism of the etiology of MCD is unknown (19). Strong evidence suggests that it is probably caused by T cell-related circulatory factors, which can lead to podocyte dysfunction resulting in heavy proteinuria (20).

Role of atopy in MCD

There have been numerous reports linking MCD with atopic disorders and an increase in serum IgE levels (21, 22). The incidence of atopy in idiopathic NS patients appears to be higher than in healthy subjects, about 17-40% in MCD patients, compared to 10-23% in age-matched controls (21,22).

In this study, a familial history of atopy was found in 20% of patients and a personal history of atopy was present in 67% of patients suggesting the link between the atopic tendency and the occurrence of NS. This was reported in many series of NS in children (10). In a Chinese study, the occurrence of NS was more frequent in children with a history of atopic dermatitis compared to the control group (23).

As for the involved allergens, in 1959 Hardwicke et al. (11) first reported the case of a patient with NS associated with a pollen allergy. Since then, numerous reports have been published on patients who developed NS secondary to allergic reactions such as insect bites (24), dust (25,26), vaccinations (27), and foods like milk, fish, chicken, gliadin, or ovalbumin (28–31).

In the present study, several types of allergens were also confirmed by allergic tests, such as dust, acarians, pollen,

olive, milk, and wool. Some caution is required when interpreting skin tests, on which the imputability of certain allergens as triggering agents for MCD has been based, as positive skin test in an atopic patient may be related to his pre-existing disease such as asthma, eczema, rhinitis, etc…(3)

Some authors have relied on the argument of seasonality regarding the causal relationship between MCD and allergy, as they noticed an exacerbation of NS due to acariens during autumn (32), and pollen during spring (11,12). However, other observations did not find any causal relationship between seasons and the occurrence of relapse (3). In the present series, there was no particular causal relationship between seasons and NS. In addition, the evidence that eviction of the offending agent can prevent relapse is weak (3,25). This suggests that the allergic response is associated with immune disorders in patients with MCD, rather than having a causal effect. On the other hand, serum IgE levels were found to be more elevated in patients with MCD compared to allergic patients (21). The IgE levels were also found to decrease during remission and ridden up in relapses (33,34). In the present study, 73.3% of patients with non-atopic MCD had high IgE levels versus 80% of patients with atopic MCD. Some authors have debated whether high IgE levels could be correlated to the atopic state or the pathogenic mechanism of lymphocyte regulation resulting in IgE overproduction in MCD (10). Salsano et al. (2) reported that both atopic and non-atopic children with NS developed high IgE levels during relapses.. It is uncertain whether the observed changes are a cause or a result of the nephrotic state since Immunoglobulin and complement components have not been found in the glomeruli of patients with MCD. Patients with MCD may be at increased risk of allergies due to the underlying immune system that makes them more susceptible to both conditions (2).

Treatment

Regarding aeroallergens, some authors have opted for skin hyposensitization therapies for specific allergens. In addition to symptom reduction, allergen immunotherapy may change the course of allergic disease like in allergic rhinitis and asthma (35). Skin hyposensitization was followed by a prolonged remission in one patient described by Hardwicke et al. (11) and another one by Reeves et al. (13). In contrast, it failed to control relapses in two patients reported by Florido et al. (25). Among the patients who responded to hyposensitization, some experienced a relapse, while others remained in remission after the reintroduction of the offending allergen. This hyposensitization strategy was also used in some patients of our series and was successful in 40% of cases. This result remains encouraging. For food allergens, dietetic interventions included the use of elementary diets (e.g.; a liquid diet with 100% free amino acids), limited exclusion diets (e.g.; a diet avoiding specific foods according to the results of allergic tests), or oligo-antigenic diets (e.g.; a diet that allows patients to eat only 4 or 5 foods without caloric or protein restrictions). Some observations initially showed clinical improvement (29), while others showed no benefit from food allergen removal (30, 37, 39).

In this series, an allergen avoidance strategy was attempted in many patients, but there were found difficulties of compliance as allergen avoidance was not always possible, highlighting the difficulty of the application of this therapeutic approach. Disodium cromoglycate has also been used in some series in the treatment of allergic MCD. It is known to be effective in preventing recurrence in patients with allergic asthma, stabilizes mast cells and prevents degranulation when exposed to allergens (39). However, the results of this treatment were not very successful. In the series of patients reported by Florido et al. (25), only three of the 20 patients obtained prolonged remission after the administration of cromoglycate. In another controlled study (3), five patients receiving cromoglycate had a total duration of remission of 33 weeks, while five patients in the control group had a total period of remission of 40 weeks.

In the patients of our series, anti-histamine treatment was also used in five patients. It was beneficial in two patients with frequently relapsing NS treated with cetirizine and levocetirizine as they had a complete remission, but they subsequently relapsed after one year. It was also effective in one patient with infrequent relapses treated with desloratadine who had a complete remission with no subsequent relapses. Trials with other drugs such as mast cell stabilizers (nivimedone and doxantrazole) have also shown no beneficial effect in patients with relapsing NS (3,39).

It is clear that some patients with MCD may present a NS after exposure to certain allergens, and that many patients with MCD have increased serum IgE levels. Nevertheless, specific allergy treatments rarely appear to lead to remission (29), and this has generally been reported in isolated case reports. In this series, only two patients had

positive results after hyposensitization. Further studies elucidating the role of immunity in MCD are needed to lead to new therapies such as the use of soluble "cytotoxic T-lymphocyte-associated protein 4" (CTLA-4) which is a protein receptor that functions as an immune checkpoint and downregulates immune responses specifically targeting the co-stimulatory molecule "cluster of differentiation 80" (CD80) or factors stimulating the expression of CD80 on podocytes which is found to be increased in patients with MCD (9).

CONCLUSION

This study highlighted the frequency and difficulty of managing MCD with atopy in adults as it is a heterogeneous entity with a poorly known mechanism. Atopy should be sought in front of any NS especially when the patient has frequent relapses. History of allergies, elevated levels of eosinophils and IgE as well as positivity of skin tests may support the diagnosis. Anti-allergic therapies including hyposensitization, allergen avoidance, anti-histamine, and disodium cromoglycate could be attempted.

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